PART I
Coronary Artery Disease

CHAPTER 1
Acute Coronary Syndromes

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Chapter Overview

- Acute coronary syndromes (ACS) are the acute manifestation of atherosclerotic coronary artery disease. Based on different presentations and management, patients are classified into non–ST-segment elevation ACS (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI).
- In western countries, NSTE-ACS is more frequent than STEMI.
- Even if the short-term prognosis (30 days) for NSTE-ACS is more favorable than for STEMI, the long-term prognosis is similar or even worse.
- Early invasive strategy is the management of choice in patients with NSTE-ACS, particularly in high-risk subgroups.
- Primary percutaneous coronary intervention (PCI) is the treatment of choice for STEMI. Facilitated PCI is of no additional benefit.
- The reduction of door-to-balloon time in primary PCI is critical for improved outcomes in STEMI patients.
- If fibrinolytic therapy is administered in STEMI, then patients should be routinely transferred for immediate coronary angiography, and if needed, percutaneous revascularization.
- High-risk ACS patients (eg, elderly patients, those in cardiogenic shock) have the greatest benefit from PCI.
- Antithrombotic therapy in ACS is getting more and more complex. The wide spectrum of antiplatelet agents and anticoagulants requires a careful weighing of ischemic and bleeding risks in each individual patient.

ST-Segment Elevation Myocardial Infarction

The term acute coronary syndrome (ACS) has emerged as useful tool to describe the clinical correlate of acute myocardial ischemia. ST-segment elevation (STE) ACS includes patients with typical and prolonged chest pain and persistent STE on the ECG. In this setting, patients will almost invariably develop a myocardial infarction (MI), categorized as ST-segment elevation myocardial infarction (STEMI). The term non–ST-segment (NSTE) ACS refers to patients with signs or symptoms suggestive of myocardial ischemia in the absence of significant and persistent STE on ECG. According to whether the patient has at presentation, or will develop in the hours following admission, laboratory evidence of myocardial necrosis or not, the working diagnosis of NSTE-ACS will be further specified as NSTE-MI or unstable angina.

Recently, MI was redefined in a consensus document [1]. The 99th percentile of the upper reference limit (URL) of troponin was designated as the cut-off for the diagnosis. By arbitrary convention, a percutaneous coronary intervention (PCI)-related MI and coronary artery bypass grafting (CABG)-related MI were defined by an increase in cardiac enzymes more than three and five times the 99th percentile URL, respectively. The application of this definition will undoubtedly increase the number of

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events detected in the ACS and the revascularization setting. The impact on public health as well as at the clinical trial level of the new MI definition cannot be fully foreseen.

The extent of cellular compromise in STEMI is proportional to the size of the territory supplied by the affected vessel and to the ischemic length of time. Therefore a quick and sustained restoration of normal blood flow in the infarct-related artery is crucial to salvage myocardium and improve survival.

Primary PCI Versus Thrombolytic Therapy

Primary percutaneous coronary intervention became increasingly popular in the early 1990s. Evidence favoring this strategy in comparison with thrombolytic therapy is substantiated by a meta-analysis of 23 randomized trials demonstrating that PCI more efficaciously reduced mortality, nonfatal reinfarction, and stroke (Fig. 1.1) [2]. The advantage of primary PCI over thrombolysis was independent of the type of thrombolytic agent used, and was also present for patients who were transferred from one institution to another for the performance of the procedure. Therefore, primary PCI is now considered the reperfusion therapy of choice by all the guidelines [3,4]. With respect to bleeding complications, a recent meta-analysis demonstrated that the incidence of major bleeding complications was lower in patients treated with primary PCI than in those undergoing thrombolytic therapy [2]. In particular intracranial hemorrhage, the most feared bleeding complication, was encountered in up to 1% of patients treated with fibrinolytic therapy and in only 0.05% of primary PCI patients. The algorithm for treatment of patients admitted for a STEMI is presented in Fig. 1.2 [5].

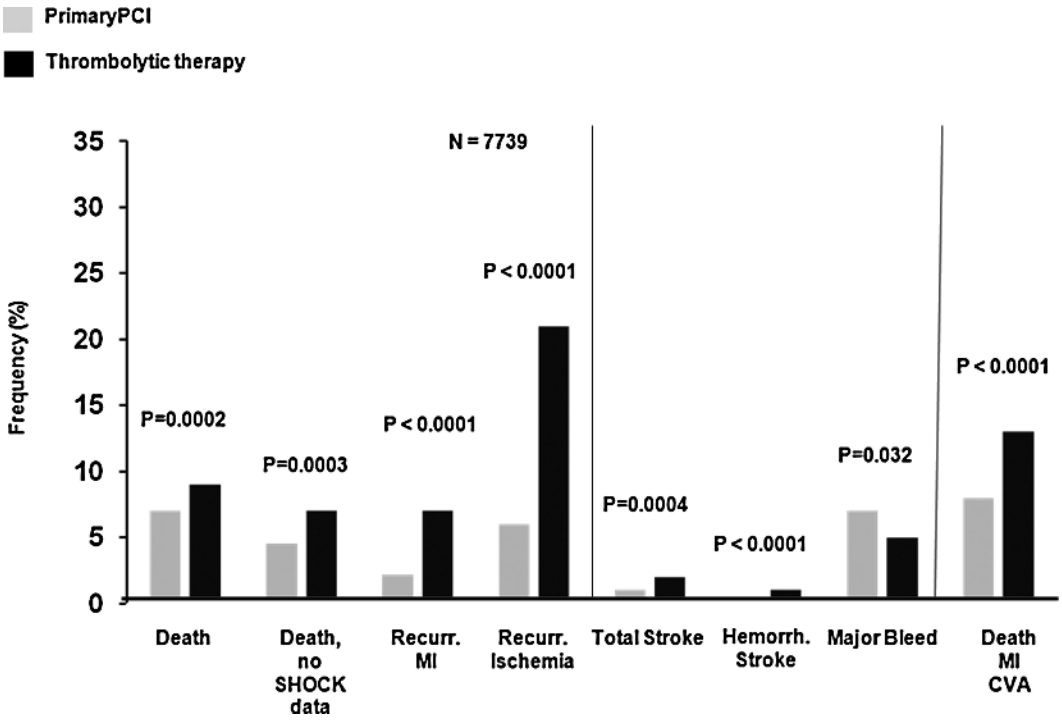
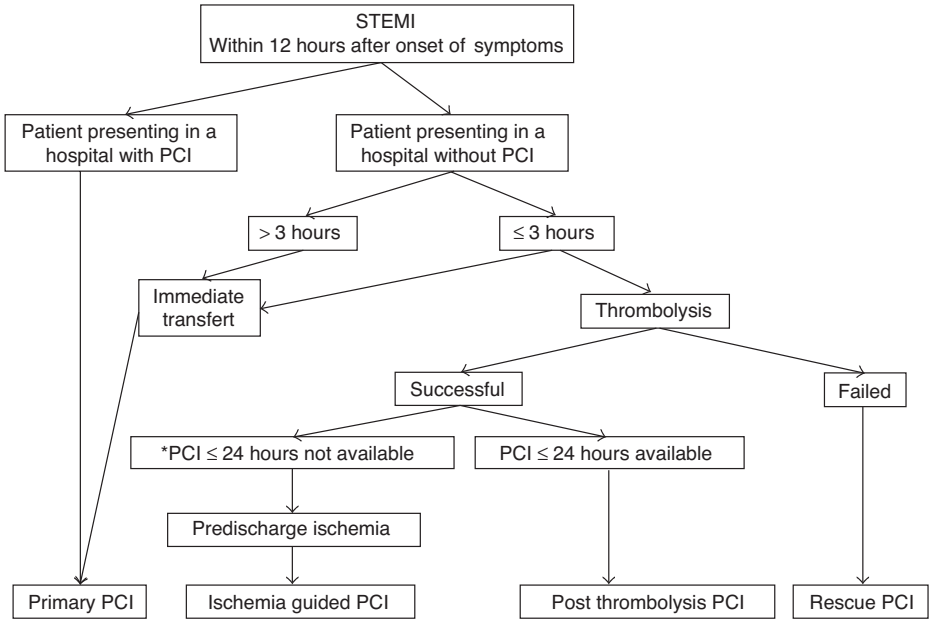


Figure 1.1 Short-term clinical outcomes of patients in 23 randomized trials of primary PCI versus thrombolysis. (Reproduced with permission from [2] Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13–20.)



†*If thrombolysis is contraindicated or the patient is at high risk, immediate transfer should be considered*
**Even after successful thrombolysis, adjunctive PCI should be considered*

Figure 1.2 Algorithm for revascularization in STEMI patients with less than 12 hours from symptom onset according to the 2005 ESC guideline for PCI. (Reproduced with permission [5] from Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J.* 2005;26:804–847.)

Advantages of Primary PCI

More than 90% of patients treated by primary PCI achieve normal flow (thrombosis in myocardial infarction [TIMI] grade flow 3) at the end of the intervention, while only 65% of patients treated by thrombolytic therapy benefit from this degree of reperfusion (Table 1.1) [6–8]. In addition, thrombolyis is characterized by a rapidly decreased efficacy after 2 hours of symptom onset (Fig. 1.3) [9]. There is a close relationship between the quality of coronary flow obtained after reperfusion therapy and mortality, and the prognosis of patients in whom flow normalization is not achieved is similar to that of patients with persistent vessel occlusion. The classification of TIMI myocardial blush grade allows an estimate of the tissue-level perfusion (Table 1.1). A critical link between lower TIMI myocardial blush grade, expression of a microcirculatory compromise, and mortality has been demonstrated in patients with normal epicardial flow following reperfusion therapy [10]. The improvement of clinical outcomes with primary PCI versus thrombolysis is also the consequence of a lower rate of reocclusion (0–6%). Accordingly, with thrombolytic therapy, reocclusion may occur in over 10% of cases even among patients presenting within the first 2 hours of symptom onset.

Mechanical complications of STEMI, such as acute mitral regurgitation and ventricular septal defect, were reduced by 86% by primary PCI compared with thrombolytic therapy in a meta-analysis of the GUSTO-1 and PAMI trials [11]. Free wall rupture was also significantly reduced by primary PCI [12]. Finally, primary PCI may allow earlier discharge (2–3 days following PCI versus 7 days following fibrinolytic therapy for uncomplicated courses).

Table 1.1 TIMI Classification of Coronary Flow and Perfusion

Flow Grade Classification	
TIMI Flow Grade	Definition
0	No antegrade flow beyond the point of occlusion.
1	Faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete.
2	Delayed or sluggish antegrade flow with complete filling of the distal territory.
3	Normal flow that fills the distal coronary bed completely.
Perfusion Grade Classification	
Perfusion Grade	Definition
0	Minimal or no myocardial blush is seen.
1	Dye stains the myocardium; this stain persists on the next injection.
2	Dye enters the myocardium but washes out slowly so that the dye is strongly persistent at the end of the injection.
3	There is normal entrance and exit of the dye in the myocardium so that the dye is mildly persistent at the end of the injection.

Adapted with permission from [7] Gibson CM, Schomig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. *Circulation.* 2004;109:3096–3105; and [8] Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA.* 2005;293:2865–2872.

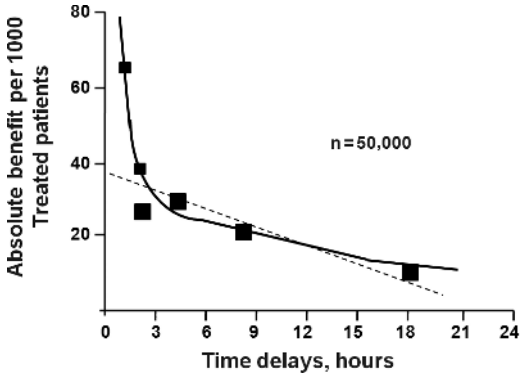


Figure 1.3 Time delays to thrombolysis in STEMI and the absolute reduction in 35-day mortality. (Reproduced with permission from [9] Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996;348:771–775.)

Decreasing the Time to Reperfusion in Primary PCI

The survival benefit of reperfusion associated with thrombolytic therapy shrinks with increasing delay in the administration of the agent. For stable patients undergoing primary PCI, no association between symptom-onset-to-balloon time and mortality was observed in the U.S. NRMI registry [13]. In contrast, a significant increase in mortality was detected for patients with a door-to-balloon-time greater than 2 hours [14]. Therefore, the findings of primary PCI trials may be only applicable to hospitals with established primary PCI programs, experienced teams of operators, and a sufficient volume of interventions. Indeed, an analysis of the NRMI-2 registry demonstrated that hospitals with less than 12 primary PCIs per year have a higher rate of mortality than those with more than 33 primary PCIs per year [13]. Useful tools to decrease the door-to-balloon time are described in Table 1.2 [15].

Challenging Groups of Patients

Concomitant High-Grade Non-Culprit Lesions

The timing of revascularization of severe non-culprit lesion treatment in patients with multivessel

Table 1.2 Strategies to Reduce the Door-to-Balloon Time in Primary PCI

- Emergency medicine physicians activate the catheterization laboratory (mean reduction in door-to-balloon time, 8.2 minutes)
- Having a single call to a central page operator activate the laboratory (13.8 minutes)
- Having the emergency department activate the catheterization laboratory while the patient is en route to the hospital (15.4 minutes)
- Expecting staff to arrive in the catheterization laboratory within 20 minutes after being paged (vs. >30 minutes) (19.3 minutes)
- Having an attending cardiologist always on site (14.6 minutes),
- Having staff in the emergency department and the catheterization laboratory use real-time data feedback (8.6 minutes).

From [15] Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med.* 2006;355:2308–2320.

disease undergoing primary PCI has long been debated. Multivessel PCI in stable STEMI patients was found to be an independent predictor of major adverse cardiac events (MACE) at 1 year [16]. However, a recent study suggested that systematic revascularization of multivessel disease at the time of primary PCI in contrast to ischemia-driven revascularization may be of advantage because incomplete revascularization was found to be a strong and independent risk predictor for death and MACE [17]. Another study supported the notion that complete revascularization improved clinical outcomes in STEMI patients with multivessel disease [18]. Accordingly, the study showed a significant lower rate of recurrent ischemic events and acute heart failure during the indexed hospitalization. Nevertheless, current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that PCI of the non-infarct artery should be avoided in the acute setting in patients without hemodynamic instability [19].

Cardiogenic Shock

The incidence of cardiogenic shock in acute MI patients is in decline, accounting for approximately 6% of all cases [20]. As the result of the increasing use of primary PCI, the shock-related mortality has decreased. Accordingly, a U.S. analysis showed mortality rates in shock of 60% in 1995 and 48% in 2004, while the corresponding primary PCI rates were 27% to 54% [21]. In the SHOCK trial, early revascularization was associated with a significant survival advantage [22]. In the study, approximately two-thirds of patients in the invasive arm were revascularized by PCI and one-third by CABG surgery. Thrombolysis was administered in 63% of patients allocated to the medical stabilization arm. Early revascularization is strongly recommended for shock patients younger than 75 years. In older patients, revascularization may be considered in selected patients [23].

In the last two decades, hemodynamic support devices have been developed to limit end-organ failure in the setting of cardiogenic shock. The intraaortic balloon pump (IABP) is the most commonly used mechanical support device. Percutaneous left atrial-to-femoral arterial bypass assistance, and more recently the Impella Recover microaxial left ventricular and/or right ventricular assist device, have been developed to increase cardiac output. However, no randomized clinical data exist to support the benefit of this device. Percutaneous cardiopulmonary bypass support using extracorporeal membrane oxygenation (ECMO) can be used in cardiogenic shock for a longer period of time than the other devices just described. However, while ECMO has excellent oxygenation properties, it provides only limited cardiac output support.

Elderly Patients

Elderly patients present more frequently with non–ST-segment elevation myocardial infarction (NSTEMI) than with STEMI. As many as 80% of all deaths related to MI occur in persons older than 75 years of age. With respect to STEMI, up to two-thirds may occur in patients older than 65 years of age. Although, fibrinolytic therapy has been shown to be as effective in the elderly as in younger patients for achieving TIMI-3 flow, the percentage of patients eligible for this therapy decreases with advancing age due to comorbid conditions. The Senior PAMI trial randomized 483 patients $\geq$ 70 years old who were eligible for thrombolysis to primary PCI versus thrombolytic therapy [24]. A substantial benefit of PCI was seen in patients aged 70 to 80 with a 37% reduction in death, and a 55% reduction in the composite end point of death, MI, or stroke. Among patients older than 80 years of age, the prognosis was poor in both the PCI and thrombolytic arms. Based on these findings and on the increased delay of reperfusion observed in this population, primary PCI is the preferred revascularization approach.

Late Presentation

Few studies have evaluated whether mechanical reperfusion is beneficial in patients presenting >12 hours from symptom onset. The OAT trial demonstrated in patients randomized to conservative medical therapy or late PCI that stable patients do not clinically benefit from late invasive strategy after MI [25]. This was confirmed with the DECOPI trial [26]. However, in the latter trial at 6 months, left ventricular ejection fraction was 5% higher in the invasive compared with the medical group ($p = 0.013$), suggesting that mechanical revascularization may improve ventricular remodeling and function. The BRAVE-2 investigators randomized 365 patients with STEMI (between 12 and 48 hours from symptom onset) to PCI with abciximab versus conservative care [28]. Infarct size measured by sestamibi was smaller in the invasive group, with a favorable trend with respect to composite clinical end points. These data suggest that the benefit of primary PCI may extend beyond the traditional 12-hour window.

Rescue and Urgent PCI Following Thrombolytic Therapy

Because of the high rate of primary failure of fibrinolysis, in the absence of reperfusion rescue PCI must be considered 60 to 90 minutes after thrombolytic therapy [27]. Suggestive of primary failure are persistent, severe, or worsening chest pain, dyspnea, diaphoresis, persistent or worsening ST segment elevation, and hemodynamic or rhythmic instability. According to the ACC/AHA guidelines, reduction of $>$ 50% of the initial ST segment elevation on ECG at 60 to 90 minutes after thrombolytic therapy is suggestive of reperfusion, and $>$ 70% reduction is considered as complete resolution [4]. Among 1398 STEMI patients presenting within 6 hours of symptom onset, the 35-day mortality rate for complete, partial (30–70%), or no resolution of ST segment elevation at 3 hours was 2.5%, 4.3%, and 17.5%, respectively ($p < 0.0001$) [28]. This relationship was observed in both anterior and inferior wall infarction. In the study, the degree of ST segment resolution was the most powerful clinical predictor of 35-day mortality. In the InTIME-II trial, the prognostic impact of ST segment resolution at 60 versus 90 minutes was compared among 1797 patients [29]. Patients with ST segment resolution at 60 minutes had a lower mortality rate at 30 days and 1 year compared to those with resolution at 90 minutes. These findings suggest that ST segment should be routinely reassessed at 60 minutes and, in the absence of reperfusion, patients should undergo rescue PCI.

Facilitated PCI

Facilitated PCI refers to the administration of an urgent pharmacologic therapy (ie, thrombolysis, GP IIb/IIIa inhibitor, or a combination) followed by systematic early PCI. Although the international European Society of Cardiology (ESC) and ACC/AHA guidelines recommended a door-to-balloon time for primary PCI of less than 90 minutes, a survey of 4278 patients transferred for primary PCI from the U.S. NRMI registry found that only 4% and 15% of them were treated within 90 and 120 minutes, respectively [30]. In the CAPITAL AMI trial, 170 high-risk STEMI patients were randomized to full-dose tenecteplase or full-dose

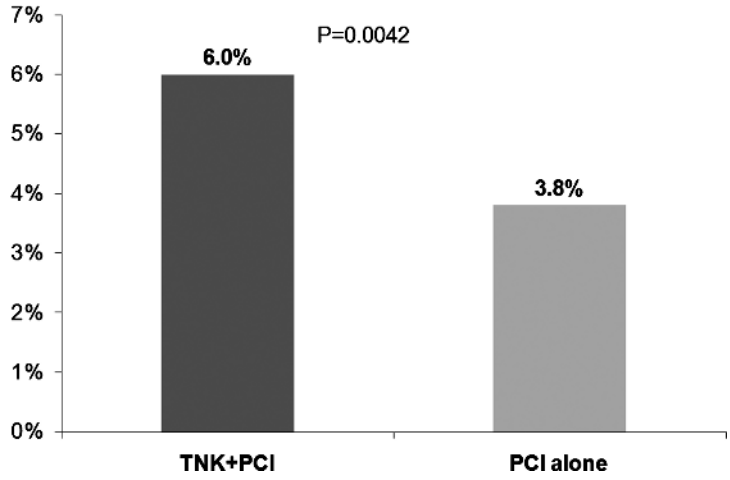


Figure 1.4 Thirty-day mortality following primary or facilitated PCI by using tenecteplase [TNK] among the 1663 patients involved in the ASSENT-4 trial. (Data extracted with permission from the ASSENT-4 investigators [32].)

tenecteplase followed by immediate transfer for PCI [31]. The composite primary end point of death, recurrent MI, recurrent unstable ischemia, or stroke at 6 months was significantly decreased by facilitated PCI (11.6% vs. 24.4 %, $p = 0.04$). The reduction was driven by a decrease in recurrent ischemia.

The ASSENT-4 trial randomized 4000 patients with STEMI of less than 6 hours from symptom onset to full dose tenecteplase or placebo prior to primary PCI. The composite primary end point was death, heart failure, or shock within 90 days. The study was stopped prematurely because of a significant increase in mortality in the tenecteplase group (6% vs. 3%, $p = 0.0105$) (Fig. 1.4) [32]. A meta-analysis of facilitated PCI trials showed that GP IIb/IIIa inhibitor-facilitated PCI had no advantages in term of post-procedure TIMI 3 grade flow and clinical end points [33]. Similarly, no benefit in terms of ischemic event reduction but a greater bleeding risk was observed in facilitated PCI with abciximab and half-dose reteplase compared with primary PCI. Therefore, facilitated PCI should be avoided.

Adjunctive PCI After Successful Thrombolysis

In the CARESS-in-AMI trial, among 600 high-risk STEMI patients treated with reteplase, randomization to immediate transfer for urgent PCI was associated with a significant decrease in the composite end point of death, reinfarction, or refractory ischemia at 30 days compared to a conservative approach [34]. In the TRANSFER-AMI trial, high-risk STEMI patients were randomized to tenecteplase or tenecteplase and transfer for PCI within 6 hours of fibrinolysis [35]. The 30-day composite primary end point of death, recurrent MI, congestive heart failure, severe recurrent ischemia, or shock occurred in 16.6% of patients in the control group and in 10.6% of patients in the invasive group ($p = 0.0013$). No difference was noted in bleeding complications. The optimal timing of routine angiography and possible PCI after fibrinolytic therapy for STEMI has not been determined. Evidence from the GRACIA-2 trial suggests that PCI within 3 to 12 hours after fibrinolysis is both safe and effective [36]. Therefore following fibrinolytic therapy, patients should be routinely transferred for immediate coronary angiography.

Transfer for Primary PCI

The DANAMI-2 trial compared primary PCI and fibrinolysis, specifically addressing the impact of patients transferred to primary PCI centers [37]. The primary composite end point of death, reinfarction, or disabling stroke was significantly decreased by primary PCI compared with fibrinolysis in the overall study cohort (13.7% vs. 8%, $p < 0.001$) as well as among patients treated in centers without catheterization facilities. The greatest benefit

of primary PCI was found in patients with a delay of more than 4 hours from symptom onset to reperfusion. The mean duration of inter-hospital transportation by ambulance was short (32 minutes). These benefits of primary PCI over thrombolytic therapy persisted at 3 years [38]. Overall, primary PCI is to be considered superior to thrombolytic therapy if it can be performed within 110 minutes of admission to the first hospital.

Delayed PCI

It has been suggested that delayed reperfusion compared to medical therapy prevents unfavorable ventricular remodeling. However, the TOAT study (N = 66) suggested that late recanalization of occluded infarct-related arteries (1 month post STEMI) in symptom-free patients had an adverse effect on remodeling despite showing a trend to improved exercise tolerance and quality of life [39]. The recent OAT study (N = 2166) demonstrated that late PCI (3 to 28 days post STEMI) in stable patients did not reduce the occurrence of death, reinfarction, or heart failure compared to medical management, with a trend toward an excess of reinfarction in the intervention group at 4-year follow-up [25]. The BRAVE-2 trial including 365 asymptomatic patients found a significant smaller infarct size by scintigraphy among individuals randomized to PCI between 12 and 48 hours following a STEMI compared to those treated optimal medical therapy alone (infarct size 8% vs. 13%, $p < 0.001$) [28]. In conclusion, delayed PCI following a STEMI should be considered in patients at high risk such as those with heart failure, left ventricular dysfunction, or moderate to severe ischemia.

Techniques of Reperfusion and Adjunctive Pharmacologic Treatments

Bare-Metal and Drug-Eluting Stents

The CADILLAC trial compared balloon angioplasty and stenting in the setting of STEMI [40]. No difference in mortality or reinfarction rates was noted, but a significant decrease in ischemic target vessel revascularization (TVR) at 6 months favored stenting. The TYPHOON study randomized 712 patients to sirolimus-eluting stents or bare-metal stents (BMS) [41]. The composite primary end point defined as target vessel–related death, recurrent MI, or TVR was significantly lower in the drug-eluting stent (DES) group than in the BMS group at 1 year (7.3% vs. 14.3%, $p = 0.004$). There was no significant difference between the two groups in the rate of death, reinfarction, or stent thrombosis. At 2 years, the benefit persisted. A similar benefit was observed in the MULTISTRATEGY trial comparing sirolimus-eluting stents and bare-metal stents among 672 STEMI patients. Therefore, drug-eluting stents appear to be beneficial also in the STEMI setting [42].

Embolic Protection Devices and Thrombus Aspiration

Distal embolization, a frequent phenomenon in the setting of primary PCI, is associated with reduced epicardial and/or tissue-level perfusion and late mortality. Neverthelesss, a strategy based on distal emboli protection did not reduce events in the STEMI setting in two randomized trials (EMERALD [43] and PROMISE [44]). The use of thrombectomy with the AngioJet device was not beneficial in the AiMI trial but the strategy will be assessed again in the JETSTENT trial in patients with large thrombotic burden [45]. The TAPAS study randomized 1701 STEMI patients prior to angiography to thrombectomy with an aspiration catheter or conventional primary PCI [46]. The study demonstrated a significant increase in rate of complete resolution of ST-segment elevation with the use of aspiration catheters. While the use of distal protection devices is not recommended, aspiration catheter-based thrombectomy should be routinely performed in the presence of a sizable thrombus.

Antithrombotic Therapy

A detailed description of antithrombotic agents will follow in the NSTEMI section of the chapter. With respect to STEMI, an initial loading dose of 162 to 325 mg of uncoated acetylsalicylic acid should be given immediately and continued indefinitely at a dose of 75 to 162 mg/day [3]. The recommendations for clopidogrel were extrapolated from the PCI and the NSTEMI setting because no randomized trial has been performed in the primary

PCI setting. Patients should be loaded with 300 to 600 mg of clopidogrel prior to PCI, and the treatment should be continued for up to 1 year at 75 mg/day. Prasugrel is discussed below.

Glycoprotein IIb/IIIa Inhibitors

The use of glycoprotein (GP) IIb/IIIa receptor inhibitors is well established and supported by a meta-analysis demonstrating a MACE reduction at 30 days and 6 months [47]. In addition, multiple registries have shown a mortality reduction associated with the use of this class of agents [48,49]. Although the most-studied compound in STEMI has been abciximab, a high-bolus dose of tirofiban may be equally effective [42]. Recently however, the BRAVE-3 study questioned the value of GP IIb/IIIa inhibitors in STEMI patients pretreated with clopidogrel [50]. Among 800 patients there was no difference in left ventricular infarct size assessed by nuclear imaging. The HORIZONS AMI trial studied 3602 patients with STEMI randomized to either bivalirudin with provisional use of a GP IIb/IIIa inhibitor, or to unfractionated heparin (UFH) plus a GP IIb/IIIa inhibitor prior to primary PCI [51]. There was a significant reduction in the primary end point of net adverse clinical events in the group receiving bivalirudin at 30 days, and even a reduction in 30-day mortality. Bivalirudin appears to be a valid alternative to UFH plus GP IIb/IIIa inhibitors in selected patients.

Summary of Guidelines

Primary PCI, if performed in a timely fashion, is the reperfusion therapy of choice in patients with STEMI. However, since not all hospitals have the ability to perform primary PCI, the choice of reperfusion strategy should take into account the delay between primary PCI in another institution and immediate thrombolysis. PCI should be considered as the preferred strategy if it can be achieved within 90 minutes from the first medical contact. The 2007 ACC/AHA/SCAI PCI guidelines concluded that facilitated PCI is harmful. However, facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered in patients with a low bleeding risk and if PCI is not available within 90 minutes. The optimal timing of routine angiography and possible PCI after fibrinolytic therapy for STEMI has not been determined, though a procedure at 3 to 12 hours appears to be both safe and effective. Mechanical thrombectomy using an aspiration catheter at the time of primary PCI is recommended.

Non–ST-Elevation Acute Coronary Syndromes

Epidemiology and Risk Stratification

In western countries, the ratio between NSTE-ACS and STEMI has switched over time, and currently NSTE-ACS is more frequent than STEMI. Registries and surveys have estimated that the annual incidence of hospital admissions for NSTE-ACS is in the range of 3 per 1000 inhabitants. With respect to gender, approximately 40% of ACS patients in the United States are women. Overall, the in-hospital mortality is generally higher for STEMI than for NSTE-ACS (approximately 7% and 5%, respectively). However, while in STEMI most events occur before or shortly after presentation, in NSTE-ACS adverse events continue over days and weeks. As a consequence, the mortality rates at 6 months of both conditions become comparable (approximately 12% and 13%, respectively). At 4 years, a two-fold higher rate in the NSTE-ACS population compared to STEMI has been reported. The difference in mid- and long-term evolution may be due to different patient profiles. NSTE-ACS patients are generally older, have more comorbidities such as diabetes and renal failure, and may have a more advanced stage of CAD and vascular disease.

A variety of parameters have been shown to have independent predictive power for long-term ischemic events in patients with ACS. Clinical parameters include age, heart rate, blood pressure, Killip class, diabetes, history of prior MI, history of CAD, ECG changes such as ST-depression, laboratory parameters such as troponin, measurements of renal function, BNP or NT-proBNP, and high-sensitivity CRP. Some of them have been grouped to form multiple risk stratification scores. However, only a limited number of scores are simple enough to be useful in everyday practice. The GRACE risk score, recommended by the ESC 2007 ACS

guidelines as the preferred risk stratification tool, is based upon a large unselected international population of patients presenting with NSTE-ACS and STEMI and has been validated in several registries for prediction of in-hospital deaths and postdischarge deaths at 6 months [52,53]. However, score calculation is complex and hardly doable at the bedside. As alternative is the TIMI risk score, which includes 7 variables: age $>$ 65 years; $>$ 3 risk factors for coronary artery disease; prior coronary stenosis $>$ 50%; ST-segment deviation on ECG at presentation; $>$ 2 anginal events in the 24 hours prior to admission; use of acetylsalicylic acid in the 7 days prior to admission; and elevated serum cardiac biomarkers [54].

Anti-Ischemic Medications

Independently of the revascularization strategy chosen, pharmacologic options in ACS include antianginal medication, anticoagulants, and antiplatelet agents. The role of antianginal medications in the acute setting of NSTE-ACS is limited. No randomized data support the use of nitrates for prognostic reasons. Two randomized trials have compared beta-blockers to placebo in unstable angina, showing a modest 13% reduction in the risk of progression to STEMI. The value of beta-blockade in the acute phase of ACS was further shaken by the recent COMMIT study, a mega-trial showing no benefit of an early and aggressive beta-blocker treatment in STEMI patients [55]. Only small randomized studies have tested calcium channel blockers in NSTE-ACS, and a meta-analysis failed to document a reduction in the progression to STEMI or mortality. Nicorandil and ivabradine have not been tested in ACS.

Anticoagulants

A pooled analysis of six trials testing UFH or low-molecular-weight heparin (LMWH) versus placebo or untreated controls in the setting of NSTE-ACS demonstrated a significant 33% risk reduction at 7 days for death or MI. [56] A meta-analysis of the six trials comparing UFH and enoxaparin including almost 22,000 patients found no difference in mortality but a modest, though statistically significant based on the large sample size, 9% relative risk reduction in the combined end point of death or MI at 30 days in favor of enoxaparin [57]. No significant differences in blood transfusions or in major bleeding were observed.

Fondaparinux is the only selective factor Xa inhibitor approved for ACS. In the OASIS-5 trial, among 20,078 patients with NSTE-ACS, fondaparinux or enoxaparin conveyed similar reduction in ischemic events at 9 days [58]. However, fondaparinux therapy was associated with halving in major bleeding episodes. As a result, the composite outcome of death, MI, refractory ischemia, or major bleeding was significantly reduced with fondaparinux (7.3% vs. 9.0%). In addition, the mortality was lower in the fondaparinux group both at 30 days (2.9% vs. 3.5%, HR 0.83, $p = 0.02$) and at 6 months (5.8% vs. 6.5%, HR 0.89, $p = 0.05$). In the study most of the patients were treated conservatively. However, also among the 6238 patients who underwent PCI, fondaparinux halved major bleeding compared to enoxaparin (2.4% vs. 5.1%, HR 0.46, $p < 0.00001$) [59]. In the presence of similar rates of ischemic events among the two arms, this resulted in a superior net clinical benefit for fondaparinux (death, MI, stroke, major bleeding: 8.2% vs. 10.4%, HR 0.78, $p = 0.004$). A source of great concern was the observation that catheter thrombus formation was more common in patients receiving fondaparinux (0.9%) than enoxaparin (0.4%), despite an additional intravenous dose of fondaparinux at the time of cardiac catheterization.

The direct thrombin inhibitor bivalirudin was assessed in 13,819 patients with moderate- to high-risk NSTE-ACS undergoing early angiography within the ACUITY trial, a randomized, open-label study [60]. Three primary 30-day end points included composite ischemia (death from any cause, MI, or unplanned revascularization for ischemia), major bleeding, and net clinical outcome (composite of ischemic events and major bleeding). Patients were randomized to one of three treatment groups: UFH or LMWH with GP IIb/IIIa inhibitors; bivalirudin with GP IIb/IIIa inhibitor; or bivalirudin alone. In a subsequent randomization process, GP IIb/IIIa inhibitors were administered either upstream or at the time of PCI. There was no significant difference between standard UFH/LMWH

plus GP IIb/IIIa inhibitors and the combination of bivalirudin and GP IIb/IIIa inhibitors for the composite ischemia end point at 30 days (7.3% vs. 7.7%, respectively), or for major bleeding (5.7% vs. 5.3%). Bivalirudin alone was shown to be noninferior to the standard UFH/LMWH combined with GP IIb/IIIa inhibitors as to the composite ischemia end point (7.8% vs. 7.3%, respectively) in the presence of a significantly lower rate of major bleeding (3.0% vs. 5.7%, RR 0.53, $p < 0.001$). As a consequence, the rate of 30-day net clinical outcome was significantly lower (10.1% vs. 11.7%, RR 0.86, $p = 0.015$) with bivalirudin alone versus UFH/LMWH plus GP IIb/IIIa inhibitors.

In both the 2007 ESC and the 2007 ACC/AHA guidelines on ACS, the use of an anticoagulant drug (UFH, enoxaparin, bivalirudin, or fondaparinux) is a class IA recommendation. In the context of early invasive or conservative strategy, fondaparinux was given a prominent place (class I recommendation) by both societies, notably in patients at risk of bleeding. Fondaparinux was preferred over enoxaparin (class IA vs. IIa-B) in the ESC guidelines, regardless of initial strategy (excluding urgent revascularization for life-threatening conditions). In the ACC/AHA guidelines, fondaparinux was considered the drug of choice in conservative strategy. In fondaparinux patients undergoing invasive procedures, it was recommended to add unfractionated heparin. For patients taken immediately to the catheterization laboratory, the ESC 2007 guidelines recommend either UFH or bivalirudin as first choice [53]. In patients treated with a therapeutic dose of enoxaparin, PCI can be safely performed within 6 to 8 hours following the last subcutaneous dose. If a longer delay is present, then an additional intravenous bolus of enoxaparin is recommended.

Antiplatelet Agents

Acetylsalicylic Acid and Clopidogrel

Acetylsalicylic acid reduces the risk of MI, ischemic stroke, and cardiovascular death in patients with NSTE-ACS and is recommended in all patients as acute and long-term treatment. Clopidogrel has an established role in NSTE-ACS based on results of the CURE trial, which randomized 12,562 patients with NSTE-ACS to receive clopidogrel or placebo in addition to acetylsalicylic acid [61]. Clopidogrel was administered in a loading dose of 300 mg, followed by 75 mg/day for 3 to 12 months. The composite of cardiovascular death, nonfatal MI, or stroke occurred significantly less often in the clopidogrel group (9.3% vs. 11.4%, RR 0.80, $p < 0.001$). Major bleeding occurred in 3.7% of patients in the clopidogrel group and 2.7% of patients in the placebo group (RR 1.38, $p = 0.001$). Among the 2658 patients in the CURE trial who underwent PCI, the incidence of cardiovascular death or MI was reduced by one-third in the clopidogrel group [62].

The appropriate loading dose of clopidogrel before PCI has been the subject of debate. In the ARMYDA-2 study, 255 patients undergoing planned PCI were randomized to loading doses of 300 or 600 mg of clopidogrel. Patients allocated to the higher dose had a $> 50\%$ risk reduction in the 30-day incidence of MI, a difference due entirely to a reduction in periprocedural MI, with no excess of bleeding [63]. A pharmacologic study failed to prove that a 900-mg loading dose offers an additional advantage over the 600-mg dose in terms of platelet aggregation inhibition [64].

GP IIb/IIIa Receptor Inhibitors

In the pre-clopidogrel era, the administration of GP IIb/IIIa inhibitors has been associated with a 30-day mortality reduction compared with placebo in a meta-analysis involving 20,186 patients undergoing PCI (OR 0.73, $p = 0.024$) [65]. In the setting of NSTE-ACS, the degree of benefit derived from these agents has been related to the revascularization strategy used. For patients treated mainly conservatively, the benefit of GP IIb/IIIa inhibitors has been modest. Accordingly, a meta-analysis detected a 9%, albeit statistically significant, relative risk reduction in death or nonfatal MI at 30 days compared with placebo [66]. However, in the subgroup of patients undergoing PCI while on study drug in this analysis, a significant 26% reduction in death or MI was detected. A far greater benefit was observed in the subgroup of diabetic patients, with a significant mortality reduction at 30 days associated with active treatment [67]. With respect to interventional studies in the setting of ACS, the most

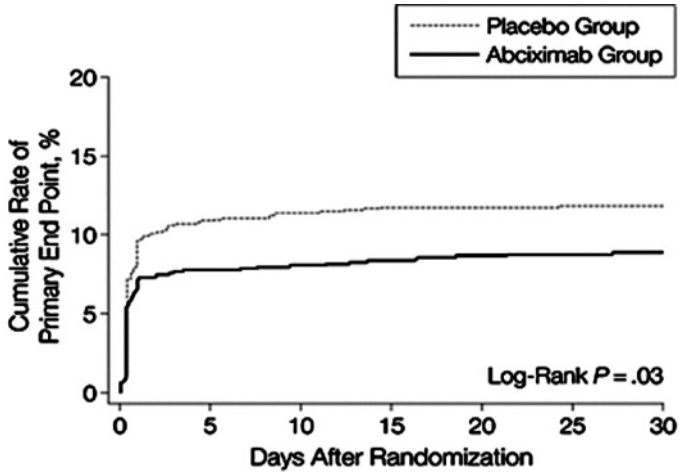


Figure 1.5 Kaplan-Meier analysis of cumulative incidence of death, myocardial infarction, or urgent target vessel revascularization in the ISAR-REACT 2 trial. (Reproduced with permission from [70] Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA.* 2006;295:1531–1538.)

studied agent has been abciximab. Among 7290 patients enrolled in three trials, allocation to abciximab was associated with a significant reduction in cardiac events at 30 days as well as a significant late mortality benefit (HR 0.71, $p = 0.003$) [68].

The benefit of GP IIb/IIIa receptor inhibitors in the clopidogrel era has been recently questioned [69]. However, the ISAR-REACT-2 study demonstrated among 2022 high-risk NSTE-ACS patients that abciximab was beneficial in patients pretreated with clopidogrel 600 mg [70]. Accordingly, the 30-day composite end point of death, MI, or urgent TVR occurred significantly less frequently in abciximab-treated patients versus placebo (8.9% vs. 11.9%, RR 0.75, $p = 0.03$) (Fig. 1.5). The effect was more pronounced in troponin-positive patients (13.1% vs. 18.3%, RR 0.71, $p = 0.02$). The benefit of abciximab in addition to acetylsalicylic acid and clopidogrel was sustained at 1 year, with a combined incidence of death, MI, or TVR of 23.3% in the abciximab group and 28.0% in the placebo group (RR 0.80, $p = 0.012$). The combined incidence of death or MI was 11.6% and 15.3%, respectively (RR 0.74, $p = 0.015$) [71].

The value of upstream versus in-laboratory GP IIb/IIIa inhibitor therapy still needs to be fully elucidated. In the ACUITY trial, upstream use of GP IIb/IIIa inhibitors resulted in a lower rate of ischemic events but a higher rate of bleeding such that the net clinical benefit was similar for the two strategies [72]. However, the major limitation of this analysis is that the time of administration prior to PCI in the upstream group was short (median 5 hours). The EARLY ACS trial demonstrated that high dose regiment fo GP IIb/IIIa receptor inhibitors eptifibatide 12 hours or more before angiography was not superior to the provisional use of eptifibatide after angiography (insert Ref: [Giugliano RP, White JA, Bode C, et al.; EARLY ACS Investigators. *N Engl J Med.* 2009 May 21:360(21):2176–2190]).

Prasugrel

In the TRITON-TIMI 38 trial, 13,608 moderate- to high-risk patients with NSTE-ACS or STEMI undergoing PCI were randomized to receive prasugrel or clopidogrel for 6 to 15 months [73]. The composite end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in 12.1% of patients randomized to clopidogrel and 9.9% of patients randomized to prasugrel (HR 0.81, $p < 0.001$). There were also significant reductions in the rates of MI, urgent TVR, and stent thrombosis among patients randomized to prasugrel. The rate of major bleeding was higher in the prasugrel group (2.4% vs. 1.8%, HR 1.32, $p = 0.03$). The somewhat overdosed prasugrel and underdosed clopidogrel may account for most of the difference.

Recommendations

The ESC 2007 guidelines have made following recommendations [53]. Acetylsalicylic acid is recommended as acute and long-term treatment for all patients with NSTE-ACS, independently of the chosen revascularization strategy. Clopidogrel is recommended for acute treatment at a dose of 300 mg, followed by 12 months of treatment at 75 mg/day. Treatment with eptifibatide or tirofiban in addition to oral antiplatelet therapy is recommended for initial early treatment in patients at intermediate to high risk; in high-risk patients undergoing PCI not pretreated with a GP IIb/IIIa inhibitor, abciximab is recommended immediately following angiography. Bivalirudin may be considered an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH.

Invasive Versus Conservative Strategy

The more recent meta-analysis of randomized trials comparing early invasive versus conservative strategy including six studies and 7962 patients demonstrated a significant 16% reduction at 1 year in death or MI associated with the early invasive treatment (Fig. 1.6) [53]. This analysis also included the ICTUS trial, a study that challenged the paradigm of superior outcome with routine invasive strategy. In this trial, 1200 patients were randomized to an early invasive strategy versus a more conservative (selective) approach [74]. In the routine invasive arm, revascularization was performed within 48 hours of randomization in 56% of patients and during initial hospitalization in 76% of cases. While there was no difference in the incidence of the

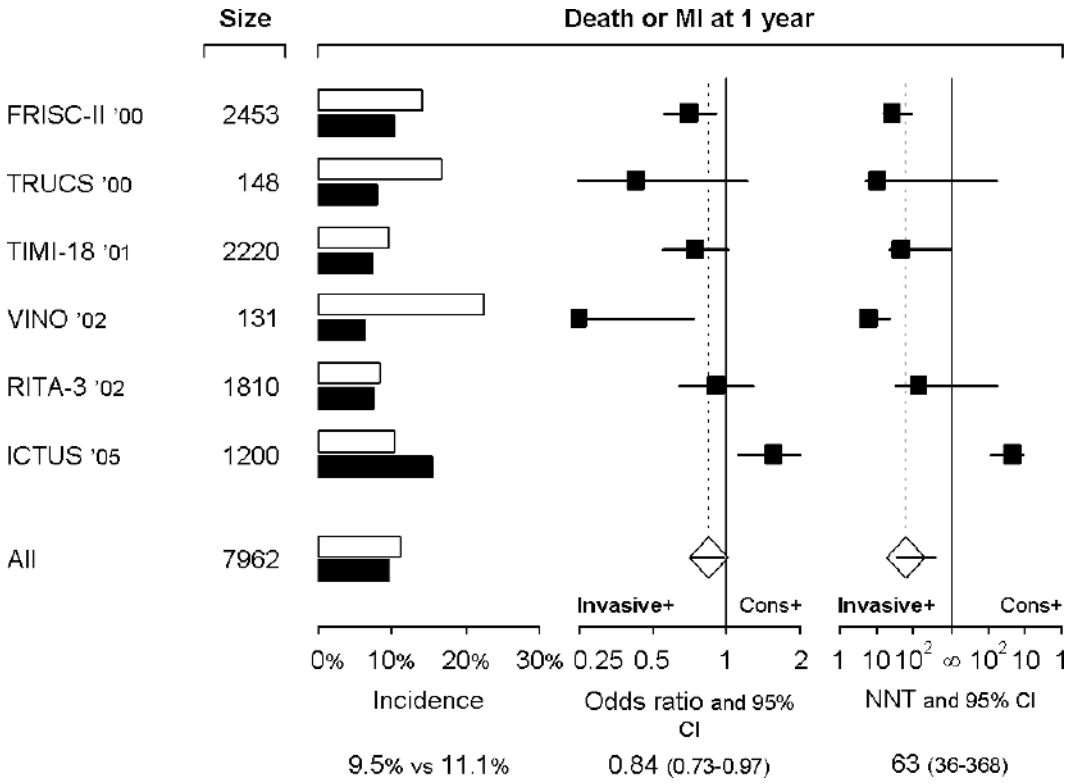


Figure 1.6 Meta-analysis of randomized trials comparing early invasive strategy (*dark bars*) versus conservative strategy (*open bars*). (Reproduced with permission from [53] Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J.* 2007;28:1598–1660.)

primary composite end point of death, MI, or rehospitalization for angina within 1 year (22.7% in the early invasive vs. 21.2% in the selective invasive arm), routine angiography was associated with a significant early hazard. Accordingly, MI was significantly more frequent in the early invasive group (15.0% vs. 10.0%, RR 1.5, $p = 0.005$) and in two-thirds of cases was a periprocedural event. The discrepancy between this and previous trials could be attributed in part to the small difference in revascularization rates between the two study groups and the high overall rate of revascularization before discharge (76% in the routine invasive and 40% in the selective group). In addition, the criterion for diagnosis of MI (any CK-MB elevation above ULN as opposed to more than three times ULN) differs between studies. Furthermore, the selection of patients may have been biased, as some studies included all consecutive patients admitted while others did not enter severely unstable patients.

Additional data supporting the long-term benefit of an early invasive strategy come from the RITA-3 trial. At 5 years, 16.6% of patients in the invasive arm and 20.0% of patients in the conservative arm died or had nonfatal MI (OR 0.78, $p = 0.044$), with a similar benefit for cardiovascular death or MI (OR 0.74, $p = 0.030$) [75]. The mortality reduction associated with an invasive treatment barely missed statistical significance (2% vs. 15%, OR 0.76, $p = 0.054$). In the highest-risk group, a highly significant 56% reduction in death or nonfatal MI was observed. The 5-year follow-up of the FRISC-II study confirmed a benefit of an early invasive strategy in terms of death or MI 19.9% in the invasive arm and 24.5% in the conservative arm (RR 0.81; $p = 0.009$) [76]. While mortality did not differ among the groups, the rate of MI was 12.9% in the invasive arm and 17.7% in the conservative group (RR 0.73; $p = 0.002$). In all randomized trials, a large proportion of patients in the conservative arm eventually underwent revascularization (crossover). This phenomenon represents a failure of conservative therapy and dilutes the benefit of revascularization. Even in the FRISC-2 study, a study with hard requirements for the conservative arm to get investigated with coronary angiography and if needed revascularization, 43% of patients in the conservative arm had to be revascularized in the first year.

Timing of Angiography

The ESC ACS 2007 guidelines stratify the degree of urgency of an early invasive strategy depending on the risk of the patient into urgent, early, or elective (Fig. 1.7) [53]. In low-risk patients, either an elective angiography or a noninvasive assessment of inducible ischemia may be performed. While the time window in the American and previous European guidelines to perform early invasive strategy was 48 hours, it has been extended to 72 hours in the current ESC guidelines. However, controversy remains as to the optimal timing between hospital admission, initiation of medical therapy, and invasive evaluation. Support for immediate angiography came from the small ISAR-COOL study [77]. In 410 consecutive high-risk patients with either ST-segment depression (65%) or elevated troponin (67%) enrolled in the trial, deferral of intervention did not improve outcome. On the contrary, patients randomized to immediate PCI (on average 2.4 hours after admission) had a lower incidence of death or MI at 30 days than patients randomized to deferred PCI (86 hours after admission and medical therapy) (5.9% vs. 11.6%, RR 1.96, $p = 0.04$). No early hazard was observed among patients undergoing PCI in ISAR-COOL as well as in TACTICS-TIMI-18, in which the mean delay for PCI was 22 hours and all patients had upstream treatment with GP IIb/IIIa inhibitors [78]. The timing issue was investigated retrospectively in the SYNERGY trial (N = 9978) [79]. In the study 92% of patients underwent coronary angiography, 63% within 48 hours. Unadjusted and adjusted rates of death/MI increased with increasing time to angiography. The adjusted odds ratio for death/MI in patients receiving angiography in ≤ 6 hours was 0.56 (95% CI 0.41 to 0.74), whereas after 30 hours, there was no significant benefit compared with further delayed angiography.

Bleeding Complications and Outcomes

It is estimated that 2% to 8% of patients with NSTE-ACS suffer a major bleeding episode during

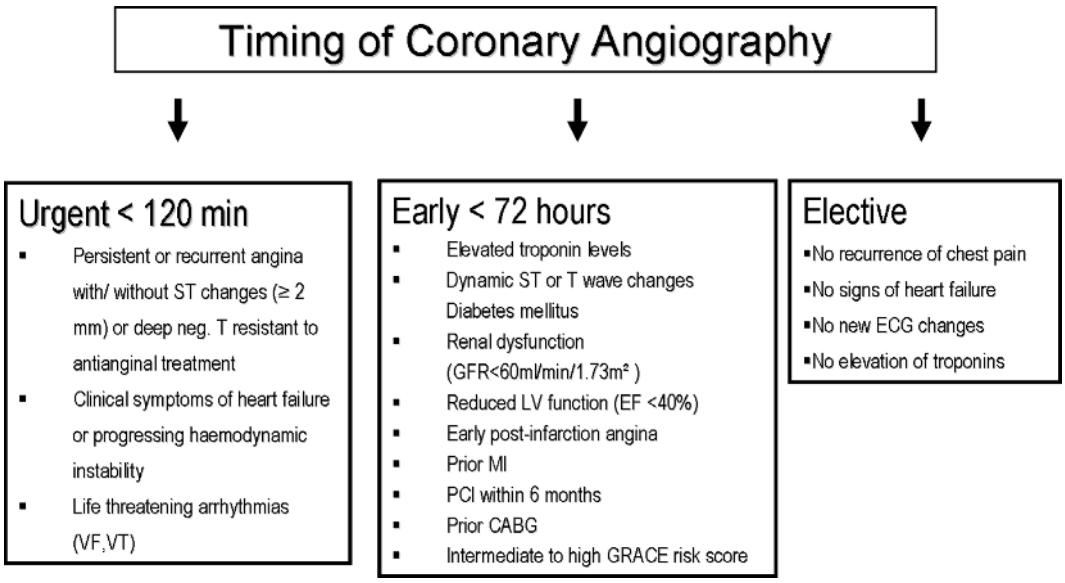


Figure 1.7 Timing of coronary angiography according to the 2007 Guidelines of the European Society of Cardiology. (VF, ventricular fibrillation; VT, ventricular tachycardia; GFR, glomerular filtration rate; LV, left ventricular; EF, ejection fraction; MI, myocardial infarction; CABG, coronary artery bypass surgery.) (Modified with permission from [53] Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J.* 2007;28:1598–1660.)

hospitalization. The main predisposing factors are the type and dose of antithrombotic and antiplatelet therapies and whether or not the patient underwent an invasive procedure. With respect to clinical variables, advanced age, female gender, renal insufficiency, and history of bleeding have all been shown to independently predict a bleeding event. In recent years, the link between bleeding and poor outcomes in ACS patients has become evident. Pooled data from four multicenter randomized clinical trials of patients with ACS documented a stepwise increase in the risk of death at 30 days and 6 months, according to the severity of bleeding. At 1 month, the hazard ratios for death were 1.6, 2.7, and 10.6 for mild, moderate, and severe bleeding, and at 6 months, the hazard ratios were 1.4, 2.1, and 7.5, respectively [80]. In the OASIS-5 trial, the risk of ischemic events was strongly influenced by major bleeding. The rate of 30-day death was 12.9% versus 2.8%, the risk of MI 13.9% versus 3.6%, and the risk of stroke 3.6% versus 0.8% for patients who suffered major bleeding versus no bleeding, respectively [58]. Nonpharmacologic strategies to reduce access site bleeding complications include the use of closure devices and the radial approach.

Secondary Prevention

Measures and therapies that may reduce the risk of recurrence of events after ACS include lifestyle changes such as smoking cessation; regular physical exercise; and a healthy diet based on low salt intake, reduced intake of saturated fats, and regular intake of fruit and vegetables. Additional measures include weight reduction and optimal blood pressure, diabetes mellitus, and lipid control. The ESC guidelines recommend that beta-blocker therapy should be initiated in all ACS patients and maintained indefinitely in the case of reduced LV function, with or without symptoms of heart failure, unless formal contraindications exist [81]. In other patients, beta-blockers may be useful, but evidence of their long-term benefit is not established. ACE inhibitors have, in addition to the beneficial properties for patients with heart failure or left ventricular dysfunction, anti-atherogenic properties,

quantified in meta-analyses in a 14% risk reduction for death at 4 years. The applicability of these findings, although documented in the context of stable coronary artery disease, has been extended to all ACS. A meta-analysis including 13 trials and 17,963 patients revealed that early initiation of statin therapy reduced major cardiovascular events at 2 years (HR 0.81, $p < 0.001$) [82]. The advantage of early initiation of aggressive (atorvastatin 80 mg) vs. moderate (pravastatin 40 mg) lipid-lowering therapy in ACS was assessed in the PROVE-IT trial [83]. At 2 years, the primary composite end point (death, MI, unstable angina requiring rehospitalization, revascularization, or stroke) was significantly reduced by 16% in the atorvastatin arm compared with the pravastatin arm. Current recommendations support early initiation of statin therapy for all ACS patients.

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