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ESC Guidelines

Guidelines for Percutaneous Coronary Interventions

The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology

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Summary

In patients with stable CAD, PCI can be considered a valuable initial mode of revascularization in all patients with objective large ischaemia in the presence of almost every lesion subset, with only one exception: chronic total occlusions that cannot be crossed. In early studies, there was a small survival advantage with CABG surgery compared with PCI without stenting. The addition of stents and newer adjunctive medications improved the outcome for PCI. The decision to recommend PCI or CABG surgery will be guided by technical improvements in cardiology or surgery, local expertise, and patients' preference. However, until proved otherwise, PCI should be used only with reservation in diabetics with multi-vessel disease and in patients with unprotected left main stenosis. The use of drug-eluting stents might change this situation.

Patients presenting with NSTE-ACS (UA or NSTEMI) have to be stratified first for their risk of acute thrombotic complications. A clear benefit from early angiography ($<$48 h) and, when needed, PCI or CABG surgery has been reported only in the high-risk groups. Deferral of intervention does not improve outcome. Routine stenting is recommended on the basis of the predictability of the result and its immediate safety.

In patients with STEMI, primary PCI should be the treatment of choice in patients presenting in a hospital with PCI facility and an experienced team. Patients with contra-indications to thrombolysis should be immediately transferred for primary PCI, because this might be their only chance for quickly opening the coronary artery. In cardiogenic shock, emergency PCI for complete revascularization may be life-saving and should be considered at an early stage. Compared with thrombolysis, randomized trials that transferred the patients for primary PCI to a 'heart attack centre' observed a better clinical outcome, despite transport times leading to a significantly longer delay between randomization and start of the treatment. The superiority of primary PCI over thrombolysis seems to be especially clinically relevant for the time interval between 3 and 12 h after onset of chest pain or other symptoms on the basis of its superior preservation of myocardium. Furthermore, with increasing time to presentation, major-adverse-cardiac-event rates increase after thrombolysis, but appear to remain relatively stable after primary PCI. Within the first 3 h after onset of chest pain or other symptoms, both reperfusion strategies seem equally effective in reducing infarct size and mortality. Therefore, thrombolysis is still a viable alternative to primary PCI, if it can be delivered within 3 h after onset of chest pain or other symptoms. Primary PCI compared with thrombolysis significantly reduced stroke. Overall, we prefer primary PCI over thrombolysis in the first 3 h of chest pain to prevent stroke, and in patients presenting 3–12 h after the onset of chest pain, to salvage myocardium and also to prevent stroke. At the moment, there is no evidence to recommend facilitated PCI. Rescue PCI is recommended, if thrombolysis failed within 45–60 min after starting the administration. After successful thrombolysis, the use of routine coronary angiography within 24 h and PCI, if applicable, is recommended even in asymptomatic patients without demonstrable ischaemia to improve patients' outcome. If a PCI centre is not available within 24 h, patients who have received successful thrombolysis with evidence of spontaneous or inducible ischaemia before discharge should be referred to coronary angiography and revascularized accordingly—independent of 'maximal' medical therapy.

Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organizations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilization of health resources.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups, or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the Level of Evidence as indicated in the tables that follow:

Classes of recommendations	
Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.

Levels of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

1. Introduction and definitions

With the tremendous increase in publications available, guidelines become more and more important to make available to clinicians the most relevant information while simultaneously improving patient care on the basis of evidence.[1,2] Furthermore, guidelines are increasingly used by health care providers and politicians to assess the 'appropriate use' and develop disease management programmes. The European Society of Cardiology (ESC) has a tradition—initiated in 1992—of publishing annual reports and analyses regarding interventional cardiology.[3] ESC Guidelines for percutaneous coronary interventions (PCI), however, have not been established. It is the purpose of these guidelines to give practically oriented recommendations on when to perform PCI on the basis of currently available published data derived from randomized and nonrandomized clinical studies.

1.1. Method of review

A literature review was performed using Medline (PubMed) for peer-reviewed published literature. The use of abstracts should be avoided in guidelines. According to the ESC recommendations for task force creation and report production, clinical trials presented at a major cardiology meeting were included for decision-making on the condition that the authors provided a draft of the final document to be submitted for publication.[4]

1.2. Definition of levels of recommendation

The levels of recommendations were graded on the basis of the ESC recommendations.[4] In contrast to the ACC/AHA levels of recommendations,[5] class III ('conditions for which there is evidence and/or general agreement that the procedure is not useful/effective and in some cases may be harmful') is discouraged by the ESC[4] (*Table* on Classes of recommendations). Consensus could be achieved for all recommendations on the basis of evidence (*Table* on Levels of evidence). To verify the applicability of the recommendations to a specific area, the expert panel emphasized the importance of the primary endpoint for the randomized trials, giving high priority to the importance of significantly improving patients' outcome as the primary endpoint investigated in an adequately powered sample size.

2. Indications for PCI

2.1. Indications for PCI in stable coronary artery disease

2.1.1. General indications for PCI in stable coronary artery disease

2.1.1.1. PCI vs. medical therapy. Three randomized studies compared PCI with medical treatment. The ACME study[6,7] was designed to evaluate whether PCI was superior to optimized medical therapy in relieving angina in patients with single and double-vessel disease. PCI offered earlier and more complete relief of angina than medical therapy and was associated with a better exercise tolerance and/or less ischaemia during exercise testing.[6] Some of the early benefits from PCI in patients with single-vessel disease are sustained, making it an attractive therapeutic option for these patients.[7] The ACIP trial[8] focused on patients with severe daily-life ischaemia. Patients had both stress-inducible ischaemia and at least one episode of silent ischaemia on 48 h Holter monitoring (*Table 1*). Two years after randomization, the total mortality was significantly reduced from 6.6% in the angina-guided to 4.4% in the ischaemia-guided and to 1.1% in the revascularization strategy.[9] *(Recommendation for PCI to treat objective large ischaemia: I A).*

In patients with no or mild symptoms, however, the scenario is different and unlikely to be improved by PCI, as shown by the AVERT trial.[10,11] At 18 months, 13% of the patients who received aggressive lipid lowering had ischaemic events, compared with 21% of the patients who underwent PCI as planned. This difference was initially statistically significant, but lost its significance after being adjusted for interim analysis. There are two major limitations in AVERT: (i) it is not a fair comparison of medical treatment with PCI because a more aggressive lipid-lowering treatment was used in the medical arm; stenting was used in only 30% and restenosis requiring re-intervention is more likely to happen in the PCI than in the conservative group. (ii) AVERT did not show the anti-ischaemic effect of statins, but it did show that statins may prevent acute coronary events. RITA-2 was a randomized trial comparing the long-term effects of PCI with conservative (medical) care in patients with CAD considered suitable for either treatment option.[12] After a median follow-up of 2.7 years, death or definite myocardial infarction occurred in 6.3%

Table 1 Recommendations of PCI indications in stable CAD

Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Objective large ischaemia	I A	ACME[a] ACIP[b]
Chronic total occlusion	IIa C	–
High surgical risk, including LV-EF < 35%	IIa B	AWESOME
Multi-vessel disease/diabetics	IIb C	–
Unprotected LM in the absence of other revascularization options	IIb C	–
Routine stenting of *de novo* lesions in native coronary arteries	I A	BENESTENT-I STRESS
Routine stenting of *de novo* lesions in venous bypass grafts	I A	SAVED VENESTENT

Assuming that the lesions considered most significant are technically suited for dilatation and stenting, the levels of recommendation refer to the use of stainless steel stents.

[a]The benefit was limited to symptom improvement and exercise capacity.

[b]ACIP is not a pure trial of PCI vs. medical treatment as half of the revascularization patients were treated with bypass graft surgery. Drug-eluting stents are discussed subsequently.

treated with PCI and in 3.3% with medical care ($P = 0.02$). On the other hand, PCI was associated with greater symptomatic improvement, especially in patients with more severe angina. RITA-2, however, cannot be applied to today's modern PCI. Only 7.6% of the patients received stents. Ticlopidine, clopidogrel, or GP IIb/IIIa inhibitors were not even mentioned in the study.

A meta-analysis of randomized controlled trials found that PCI may lead to a greater reduction in angina compared with medical treatment, although the trials have not included enough patients for informative estimates of the effect of PCI on myocardial infarction, death, or subsequent revascularization.[13] Regardless of assignment to invasive or medical treatment (TIME study[14]) and medication with at least two antianginal drugs, long-term survival was similar in patients aged 75 years or older presenting with Canadian Cardiac Society (CCS) class II or greater angina. The benefits of both treatments in angina relief and improvement in quality of life were maintained, but nonfatal events occurred more frequently in patients assigned to medical treatment. Irrespective of whether patients were catheterized initially or only after drug therapy failure, their survival rates were better if they were revascularized within the first year.[14] Costs should not be an argument against invasive management of elderly patients with chronic angina.[15]

2.1.1.2. PCI vs. CABG surgery. Data comparing PCI with coronary artery bypass graft (CABG) surgery are derived from 13 trials, randomizing 7964 patients between 1987 and 1999. For a follow-up period of 8 years, there was no statistically significant risk difference for death between the two revascularization strategies at 1, 3, or 8 years (except at year 5).[16] The use of stents plays a major role: in early trials without stents, there was a trend favouring CABG surgery over PCI at 3 years that was no longer present in more recent trials with stents.[16] The trend in favour of CABG surgery disappeared despite a reduction in mortality in the CABG surgery arm from 5.2% in trials without stents to 3.5% in the more recent trials with stents.[16] Stenting halved the risk difference for repeat revascularization.[16] Both PCI and CABG surgery provided good symptom relief.

2.1.2. Indications for PCI in special subsets of stable patients

2.1.2.1. Chronic total occlusions. Chronic total occlusion (CTO) still represents the anatomical subset associated with the lowest technical success rates with PCI. When the occlusion can be crossed with a guide wire and the distal lumen has been reached, satisfactory results are obtainable with stent implantation, as shown by several trials with primarily angiographic primary endpoints (GISSOC,[17] PRISON,[18] SARECCO,[19] SICCO,[20] SPACTO,[21] STOP,[22] and TOSCA[23]), albeit at the expense of a high restenosis rate ranging from 32 to 55%. The value of drug-eluting stents in this respect is currently under evaluation. In the PACTO study, the treatment of CTOs with the Taxus stent considerably reduced major adverse cardiac events (MACE) and restenosis and almost eliminated reocclusion—all typically frequent occurrences with bare metal stents.[24] First results from a Cypher stent registry were encouraging.[25] Before approaching CTOs, one has to keep in mind the possibly increased risk of side branch occlusion or perforation. *(Recommendation for PCI in patients with chronic total occlusion: IIa C).*

2.1.2.2. PCI in high surgical risk patients. The AWESOME trial[26] tested the hypothesis that PCI is a safe and effective alternative to CABG surgery for patients with refractory ischaemia and high risk of adverse outcomes. In a subgroup analysis of patients with prior CABG surgery, the repeat CABG and PCI 3-year survival rates were 73 and 76%, respectively.[27] Patients with severely depressed left ventricular function seem to benefit from revascularization by PCI, in

particular when there is evidence for residual viability of the dysfunctional myocardium. The 'patient choice registry' revealed that PCI is preferable to CABG surgery for many post-CABG patients.[27] The conclusions of the AWESOME randomized trial and registry are also applicable to the subset of patients with low left ventricular ejection fractions (LVEFs).[28] *(Recommendation for PCI in patients at high surgical risk: IIa B).*

2.1.2.3. PCI in patients with multi-vessel disease and/or diabetes mellitus. In patients with multi-vessel CAD and many high-risk characteristics, CABG was associated with better survival than PCI after adjustment for risk profile.[29] Early differences in cost and quality of life between CABG and PCI, however, were no longer significant at 10–12 years of follow-up in patients with multi-vessel disease.[30] The decision to perform either culprit vessel or complete revascularization can be made on an individual basis.[31]

Although a formal trial evaluating the value of PCI vs. CABG surgery in diabetics is not yet available, every subgroup or *post hoc* analysis has invariably shown that the outcome for diabetics was worse following PCI than after CABG surgery. In the ARTS trial[32,33] comparing PCI with surgery in patients with multi-vessel disease, the outcome for diabetics was poor in both treatment arms, but even more so following PCI. After 3 years, mortality was 7.1% in the PCI and 4.2% in the CABG group with a still significant difference in event-free survival of 52.7% in the PCI group and 81.3% in the CABG surgery group.[33] In patients with multi-vessel disease, PCI in those with one or two haemodynamically significant lesions as identified by an FFR <0.75 (see section 4.6.2) yielded a similar favourable outcome as CABG in those with three or more culprit lesions despite a similar angiographic extent of disease.[34] *(Recommendation for PCI in patients with multi-vessel disease and/or diabetes mellitus: IIb C).* Upcoming data on the use of drug-eluting stents in patients with multi-vessel disease and/or diabetes mellitus may change this situation.

2.1.2.4. PCI of unprotected left main disease. The presence of a left main (LM) coronary artery stenosis identifies an anatomic subset still requiring bypass surgery for revascularization. PCI of protected left main disease (i.e. partially bypass protected) can be performed, although a 1-year MACE of 25% is still rather high, which may reflect an increased mortality in patients with severe CAD who have previously undergone CABG surgery.[35,36] The 2% periprocedural mortality and 95% 1-year survival for protected LM stenting appear comparable to outcomes for a repeat coronary bypass surgery while avoiding potential morbidity associated with a repeat operation.[36]

Stenting for unprotected LM disease should only be considered in the absence of other revascularization options.[36] Therefore, PCI can be recommended in these subsets when bypass surgery has a very high perioperative risk (e.g. EuroSCORE $>10\%$). Initial data on the use of drug-eluting stents in unprotected LM disease seem promising.[37,38] *(Recommendation for PCI in patients with unprotected left main stenosis in the absence of other revascularization options: IIb C).*

2.1.3. Provisional or elective stenting in stable CAD?

There is no doubt that stents are a valuable tool in dissections with threatening vessel closure or insufficient results after balloon angioplasty. In general, stents are superior to balloons (BENESTENT-I,[39] STRESS,[40] REST,[41] and others[42–45] for the following reasons:

- Plaque fracture and dissection caused by balloon angioplasty often result in a pseudo-successful procedure and limited luminal enlargement is obtained.
- While abrupt closure within 48 h following balloon treatment is not uncommon (up to 15% in the presence of severe residual dissection), the treated lesion shows greater acute and subacute stability after stenting.
- The angiographic results that can be obtained after stenting are predictable irrespective of the stenotic complexity.
- In the medium-long term, stent implantation results in fewer vessel occlusions or reocclusions and lower rates of clinical restenosis.

In a meta-analysis of 29 trials involving 9918 patients, coronary stenting, compared with balloon angioplasty, reduced the rate of restenosis and the need for repeated PCI for about 50%.[46] A recent meta-analysis[47] showed that stenting is associated with reduced mortality compared with balloon angioplasty and patients who underwent stent placement had a significantly lower risk of MACE when target revascularization is included as an endpoint.[48] The benefit of routine stenting is even more evident in smaller coronary arteries.[49] A similar benefit could be shown in saphenous venous bypass grafts (SAVED,[50] VENESTENT[51]). After bare metal stent implantation, the 5-year clinical outcome is related to disease progression in segments other than the stented lesion, which itself remains relatively stable.[52,53] *(Recommendation for routine stenting of de novo lesions in native coronary arteries or venous bypass grafts in patients with stable CAD: I A).*

2.1.4. Troponin elevation after PCI in stable CAD

Troponin release is relatively common after PCI in stable CAD and associated with procedural complications, including side branch occlusions, thrombus formations, saphenous vein graft interventions, multi-stent use, and glycoprotein IIb/IIIa use.[54,55] In patients without acute myocardial infarction, troponin I elevation after PCI did not predict mortality[56] and a post-PCI elevation of more than three times the normal limit had no incremental risk of adverse 8 months clinical outcomes.[57] A meta-analysis of 2605 patients suggested that the use of low cutoff concentrations after PCI does not correlate with an increased incidence of composite adverse events (cardiac death, myocardial infarction bypass surgery, or repeat PCI of the target vessel) and some multiple of the cutoff may be more appropriate for the prediction of adverse events.[58] In a recent study, even troponin-I elevations five times above the upper limit of normal did not predict events after hospital discharge.[59] Therefore,

with respect to periprocedural elevations of cardiac markers, increasing evidence exists that only an increase in CK-MB of more than five times normal (and not any level of troponin I elevation) is associated with a higher mortality at follow-up, whereas mild (one to five times normal) CK-MB elevation is increasingly regarded as a common procedure-related event with little prognostic relevance.[56]

In summary, PCI can be considered a valuable initial mode of revascularization in all patients with stable CAD and objective large ischaemia in the presence of almost every lesion subset, with only one exception: CTO that cannot be crossed. In early studies, there was a small survival advantage with CABG surgery compared with PCI without stenting. The addition of stents and newer adjunctive medications improved the outcome for PCI. The decision to recommend PCI or CABG surgery will be guided by technical improvements in cardiology or surgery, local expertise, and patients' preference. However, until proved otherwise, PCI should be used only with reservation in diabetics with multi-vessel disease and in patients with unprotected LM stenosis. The use of drug-eluting stents might change this situation.

2.2. Indications for PCI in acute coronary syndromes without ST-segment elevation

The ESC recently published guidelines for the general management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation.[60] The present guidelines focus on PCI to optimize the management of patients presenting with NSTE-ACS. Patients demonstrating elevated serum markers [troponin (Tn)-I, Tn-T, or CK-MB] will be subsequently considered to have non-ST-segment elevation myocardial infarction (NSTEMI).

2.2.1. Risk stratification in NSTE-ACS

The importance of stratifying patients with unstable angina (UA) or NSTEMI in high-risk vs. low-risk groups applies to the fact that a clear benefit of early angiography and, when needed, PCI, has been reported only in high-risk groups.[61–65]

According to the ESC NSTE-ACS guidelines,[60] the characteristics of patients at high risk for rapid progression to myocardial infarction or death who should undergo coronary angiography within 48 h are given in *Table 2*.[66–76]

Furthermore, the following markers of severe underlying disease, i.e. a high long-term risk, might also be helpful for risk assessment in NSTE-ACS:[63–73,77–80]

- age >65–70 years,
- history of known CAD, previous MI, prior PCI, or CABG,
- congestive heart failure, pulmonary oedema, new mitral regurgitation murmur,
- elevated inflammatory markers (i.e. CRP, Fibrinogen, IL 6),
- BNP or NT-proBNP in upper quartiles,
- renal insufficiency.

Table 2 Characteristics of patients with NSTE-ACS at high acute, thrombotic risk for rapid progression to myocardial infarction or death that should undergo coronary angiography within 48 h

(1)	recurrent resting pain
(2)	dynamic ST-segment changes: ST-segment depression ≥0.1 mV or transient (>30 min) ST-segment elevation ≥0.1 mV
(3)	elevated Troponin-I, Troponin-T, or CK-MB levels
(4)	haemodynamic instability within the observation period
(5)	major arrhythmias (ventricular tachycardia, ventricular fibrillation)
(6)	early post-infarction unstable angina
(7)	diabetes mellitus

A *post hoc* analysis of TACTICS-TIMI 18 suggested that routine early invasive strategy significantly improves ischaemic outcomes in elderly patients with NSTE-ACS.[81]

2.2.2. Conservative, early invasive, or immediately invasive?

Recently published surveys revealed that less than 50% of the patients with NSTE-ACS are undergoing invasive procedures (GRACE[82] and CRUSADE[83]). Proponents of a conservative strategy in the management of UA and NSTEMI base their suggestions on the results of the TIMI IIIB trial,[84] the MATE trial,[85] and the VANQWISH trial.[86] Several methodological flaws arise in these studies (high crossover rates, no or minimal usage of stenting, no usage of GP IIb/IIIa inhibitors), making their conclusions not contemporary. In GUSTO IV-ACS, revascularization within 30 days was associated with an improved prognosis.[87] The relative high mortality in medically treated patients might have been related in part to patient selection.

Besides two smaller European studies (TRUCS[88] and VINO[89]), the preference for an early invasive vs. an initially conservative approach is based on the results of 6487 patients in three trials: FRISC II,[90] TACTICS-TIMI 18,[91] and RITA-3[92] (*Tables 3* and *4* and *Figure 1*). (*Recommendation for early PCI in patients with high-risk NSTE-ACS: I A*).

Although caution is needed in interpretation, gender differences may exist.[93] There are more studies underway (e.g. ICTUS) that include a more potent antiplatelet regime and therefore may challenge the currently recommended invasive strategy. ISAR-COOL[94] compared a medical ('cooling') strategy vs. immediate PCI in patients at high risk with either ST-segment depression (65%) or elevated troponin T (67%). The median time to catheterization was 86 h in the cooling off group and 2.4 h in the immediate group. Only 5.8% of the deferred group had to be catheterized earlier. The primary endpoint, defined as death from any cause and large nonfatal MI at 30 days, occurred in 11.6% of patients randomized to the cooling-off group ('prolonged antithrombotic pre-treatment') vs. 5.9% of patients randomized to the immediate invasive strategy ($P = 0.04$). This outcome was attributable to events occurring before catheterization. The investigators concluded that in patients with

Table 3 The three randomized, controlled trials comparing initially conservative (catheterization as needed) with initially invasive (routine catheterization with revascularization as needed) strategies in patients with NSTE-ACS

	FRISC II	TACTICS-TIMI 18	RITA 3
Enrolment period	1996–1998	1997–1999	1997–2001
Number of patients	2457	2220	1810
Patients' characterization (inclusion criteria)	UA/NSTEMI	UA/NSTEMI	UA/NSTEMI
Anticoagulation	Initially open label (UFH or LMWH dalteparin) up to 72 h, later randomization into four groups	All UFH	Before randomization: 84% LMWH (enoxaparin) 11% UFH (equal in both groups); After randomization: all enoxaparin
GP IIb/IIIa usage (%) based on PCI cases only (early conservative/ early invasive)	Abciximab 10/10	Tirofiban 59/94	Any 25
Strategies	Early conservative (selectively invasive) vs. routine invasive: (PCI <7 days of the start of open treatment)	Early conservative (selectively invasive) vs. early routine invasive (<4–48 h after randomization and revascularization when appropriate)	Early conservative (selectively invasive) vs. routine invasive (coronary angiography <72 h after randomization); most patients were transferred to PCI centres
Catheterizations performed (%) (conservative/invasive at 4 or 6 months)	47/98	61/98	16/96
PCI performed (%) (conservative/invasive at 4 or 6 months)	37/77	29/42	7/33
Stent usage (%) (conservative/invasive at 4 or 6 months)	70/61	86/83	90/88
Any revascularization (%) (conservative/invasive at 4 or 6 months)	37/77	45/64	10/44
Primary endpoint defined	Death/MI	Death/nonfatal MI/ rehospitalization for ACS	Death/MI/refractory angina
At time	6 months	6 months	4 months
Result of primary endpoint (%) (conservative/invasive)	12.1/9.4[a]	19.4/15.9[a]	14.5/9.6[a]
Primary endpoint reached	Yes	Yes	Yes

All three studies reached their primary endpoint.
[a]$P < 0.05$.

Table 4 Recommendations for PCI indications in NSTE-ACS (UA or NSTEMI)

Procedure	Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Early PCI (<48 h)	High-risk NSTE-ACS	I A	FRISC-II, TACTICS-TIMI 18, RITA-3
Immediate PCI (<2.5 h)	High-risk NSTE-ACS	IIa B	ISAR-COOL
Routine stenting in *de novo* lesions	All NSTE-ACS	I C	—

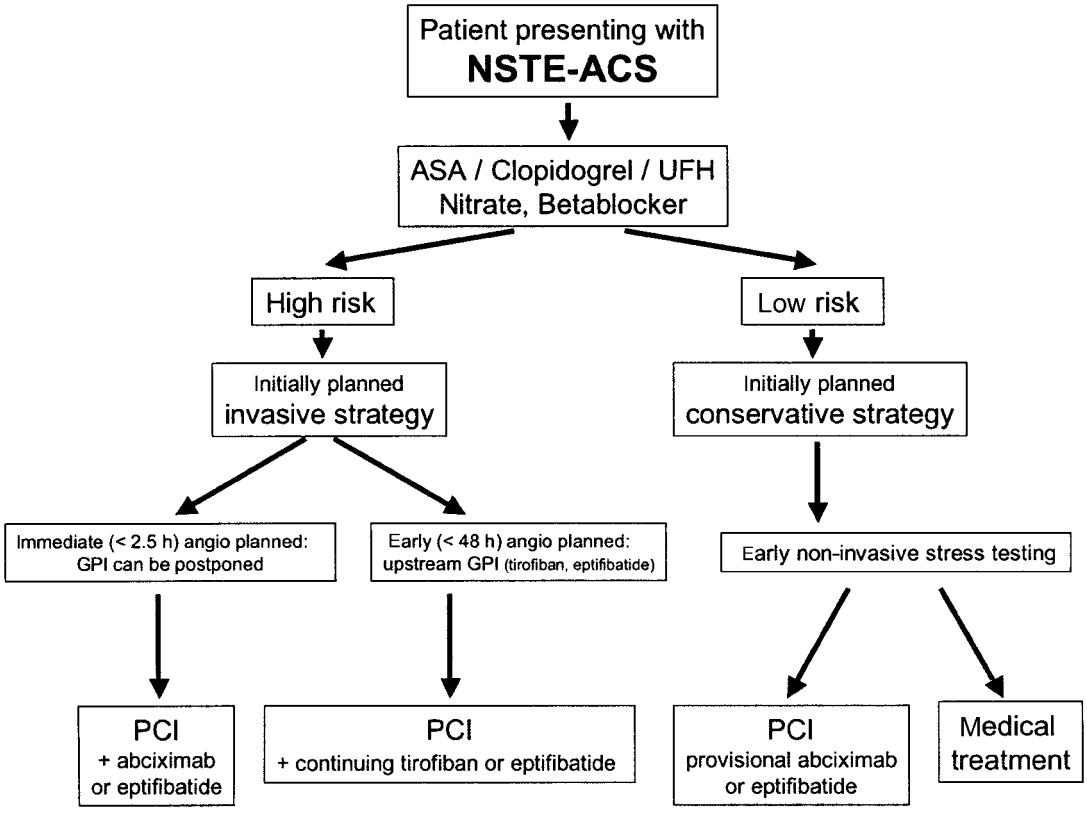

Figure 1 Flow-chart for planning coronary angiography and PCI, if appropriate, according to risk stratification in patients with NSTE-ACS (unstable angina or NSTEMI). GPI, Glycoprotein IIb/IIIa inhibitor. If for some reason the delay between diagnostic catheterization and planned PCI is up to 24 h, abciximab can also be administered. Enoxaparin may be considered as a replacement for UFH in high-risk NSTE-ACS patients, if invasive strategy is not applicable. Levels of recommendation are given in *Tables 4*, *8*, and *13*).

NSTE-ACS at high risk, deferral of intervention does not improve outcome and antithrombotic pre-treatment should be kept to the minimum duration required to organize cardiac catheterization and revascularization. (*Recommendation for immediate, i.e. <2.5 h PCI in patients with high-risk NSTE-ACS: IIa B*).

In most of the studies utilizing PCI in UA or NSTEMI, stenting was the most frequently applied final treatment. (*Recommendation for routine stenting in de novo lesions of patients with high-risk NSTE-ACS: I C*).

In summary, patients presenting with NSTE-ACS (UA or NSTEMI) have to be first stratified for their risk of acute thrombotic complications. A clear benefit from early angiography (<48 h) and, when needed, PCI or CABG surgery has been reported only in the high-risk groups. Deferral of intervention does not improve outcome. Routine stenting is recommended on the basis of the predictability of the result and its immediate safety.

2.3. Indications for PCI in ACS with ST-segment elevation

The ESC recently published guidelines for the general management of patients presenting with STEMI, i.e. patients with history of chest pain/discomfort associated with persistent ST-segment elevation or (presumed) new bundle-branch block.[95] The present guidelines focus more specifically on the use of PCI in this condition (*Figure 2*).

PCI for STEMI requires an experienced team of interventional cardiologists working together with a skilled support staff. This means that only hospitals with an established interventional programme should use PCI for STEMI instead of intravenous thrombolysis. Most of the trials comparing thrombolysis vs. primary PCI were carried out in high-volume centres by experienced operators with short response times. Therefore, the results do not

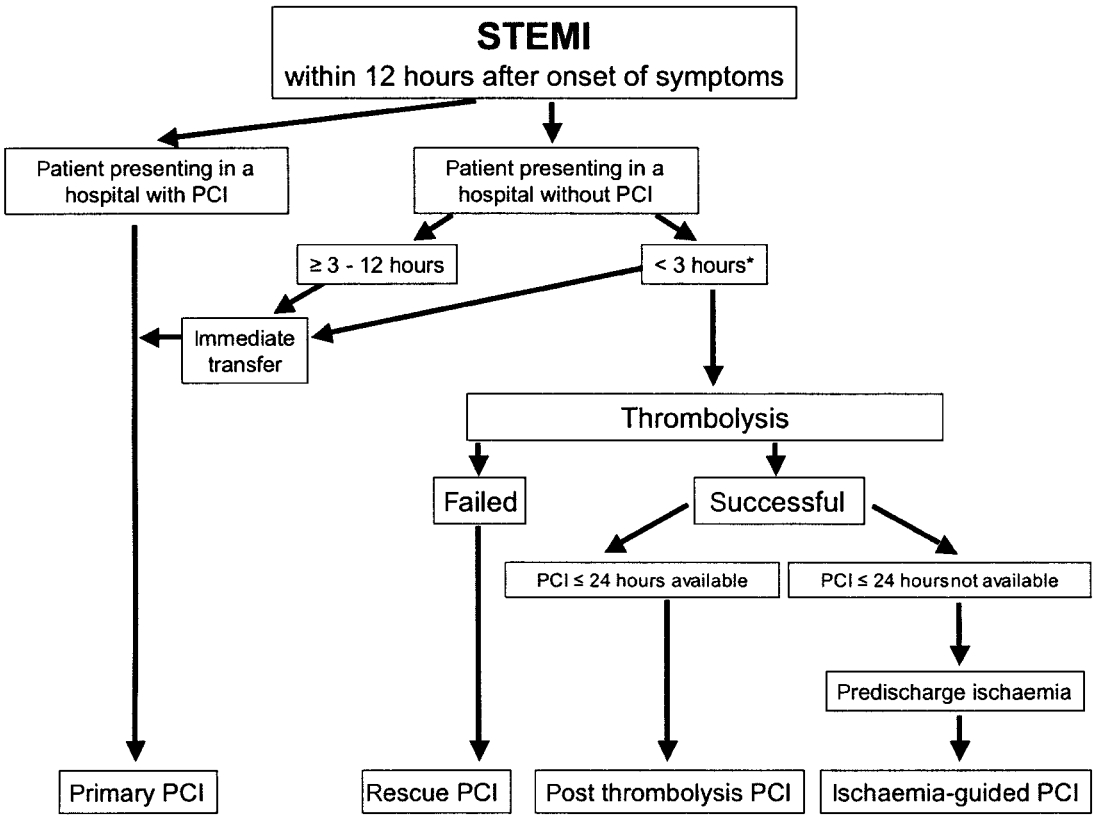

Figure 2 Within the first 3 h after onset of chest pain or other symptoms, thrombolysis is a viable alternative to primary PCI. *If thrombolysis is contraindicated or the patient is at high risk, immediate transfer for primary PCI is strongly advised. The main rationale for possible preference of primary PCI over thrombolysis within the first 3 h is stroke prevention. The main rationale for preference of primary PCI over thrombolysis within 3–12 h is to salvage myocardium and to prevent stroke. If thrombolysis is preferred, it should not be considered to be the final treatment. Even after successful thrombolysis, coronary angiography within 24 h and PCI, if applicable, should be considered. Cardiogenic shock is discussed in section 2.3.4. Levels of recommendation are given in *Table 7*.

necessarily apply in other settings. Large variations between individual institutions have been documented.[96–104] In general, for primary PCI, a higher level of experience and patient volume is required than for PCI in patients with stable coronary artery disease.[104] In patients with multi-vessel disease, primary PCI should be directed only at the infarct-related coronary artery (culprit vessel), with decisions about PCI of non-culprit lesions guided by objective evidence of residual ischaemia at later follow-up.[105]

Fortunately, the implementation of guidelines for patients with acute MI has shown to improve the quality of care.[106] In one study, patients treated during off-hours had a higher incidence of failed angioplasty and consequently a worse clinical outcome than patients treated during routine duty hours.[107] In another study, patients who underwent primary PCI during off-peak hours achieved rates of TIMI grade 3 flow, 30-day and 1-year mortality and improvement in ejection fraction and regional wall motion similar to those presenting on weekdays.[108]

2.3.1. Primary PCI

Primary PCI is defined as intervention in the culprit vessel within 12 h after the onset of chest pain or other symptoms, without prior (full or concomitant) thrombolytic or other clot-dissolving therapy. Primary PCI was first performed in 1979,[109] i.e. only 2 years after the introduction of PCI.[110] Ever since, many randomized controlled trials have documented that primary PCI is superior to intravenous thrombolysis for the immediate treatment of STEMI (more effective restoration of coronary patency, less recurrent myocardial ischaemia, less coronary reocclusion, less recurrent MI, improved residual left ventricular function, and better clinical outcome including strokes). It seems that women[111] and elderly patients[112] particularly benefit from primary PCI vs. thrombolysis.

A meta-analysis of 23 randomized trials,[113] which together assigned 7739 thrombolytic-eligible patients with STEMI to either primary PCI or thrombolytic medication, revealed the following findings: primary PCI was better than thrombolytic therapy at reducing overall short-term (defined as 4–6 weeks) death (9.3 vs. 7.0%, $P = 0.0002$), non-fatal re-infarction (6.8 vs. 2.5%, $P < 0.0001$), total stroke (2.0 vs. 1.0%, $P = 0.0004$), and the combined endpoint of death, non-fatal re-infarction, and stroke (14.5 vs. 8.2%, $P < 0.0001$). During long-term follow-up (6–18 months), the results seen with primary PCI remained better than those seen with thrombolytic therapy with 12.8 vs. 9.6% for death, 10.0 vs. 4.8% for

non-fatal MI, and 19 vs. 12% for the combined endpoint of death, non-fatal re-infarction, and stroke.[113–116]

The most impressive difference between thrombolysis and primary PCI was the significant reduction of recurrent ischaemia from 21% with thrombolysis to 6% following primary PCI during short-term ($P < 0.0001$), and also during long-term follow-up (39 vs. 22%, $P < 0.0001$).[113] *(Recommendation for primary PCI in STEMI: I A)*.

The pivotal studies contributing to level of evidence A for primary PCI were PAMI,[117] GUSTO-IIb,[118] C-PORT,[119] PRAGUE-1,[120] PRAGUE-2,[121] and DANAMI-2[122] (*Table 7*).

2.3.1.1 Transfer of patients for primary PCI. There is no doubt that patients presenting within 12 h after onset of chest pain or other symptoms in hospitals without PCI facilities and having contra-indications to thrombolysis should be immediately transferred for coronary angiography and, if applicable, primary PCI in another hospital, because PCI might be their only chance for quickly opening the coronary artery. Absolute contra-indications to thrombolysis are the following conditions: aortic dissection, status post haemorrhagic stroke, recent major trauma/surgery, GI bleeding within the last month or a known bleeding disorder.[95] Patients with a contra-indication to thrombolysis are known to have a higher morbidity and mortality than those who are eligible.[123] Primary PCI has not been formally evaluated by a randomized controlled trial in this subset of patients, but it has been shown to be safely feasible in a large majority of cases.[124] *(Recommendation for primary PCI in patients with contra-indications to thrombolysis: I C)*.

The decision for transferring a patient to a PCI facility will also depend on the individual clinical risk assessment. The choice between PCI and thrombolysis is often dictated by logistic constraints and transport delays.[125] The trials that have investigated the possible superiority of primary PCI despite the need for patient transfer from a non-PCI hospital to a PCI hospital are Limburg (LIMI),[126] PRAGUE-1,[120] PRAGUE-2,[121] Air-PAMI,[127] and DANAMI-2.[122] Their details are listed in *Table 5*.

The DANAMI-2 trial[122] was the first to show a significant reduction in the primary endpoint of death, re-infarction, and stroke after 30 days with primary PCI, despite the transfer-induced delays (*Table 5*). The PRAGUE-2 trial[121] was prematurely stopped because of a 2.5-fold excess mortality in the thrombolysis group among patients treated after >3 h from symptom onset. In patients randomized >3 h after the onset of symptoms, the mortality of the thrombolysis group reached 15.3% compared with 6% in the PCI group ($P < 0.02$). Patients randomized within <3 h of symptom onset had no difference in mortality whether treated by thrombolysis (7.4%) or transferred to primary PCI (7.3%). Approximately two-thirds of the patients were randomized within <3 h after onset of chest pain, so PRAGUE-2 had no chance of reaching the primary endpoint.

Within the first 3 h after onset of chest pain, thrombolysis is a viable alternative as indicated by PRAGUE-2,[121] STOPAMI-1 and -2,[128] MITRA, and MIR[129] as well as CAPTIM[130] with pre-hospital thrombolysis[131] (*Figure 2*). Therefore, within the first 3 h after onset of chest pain, both reperfusion strategies seem equally effective in reducing infarct size and mortality. This questioned superiority of primary PCI vs. thrombolysis within the first 3 h can be additionally addressed by a combined analysis from STOPAMI-1 and -2.[128] However, the 'myocardial salvation index' was not statistically different between thrombolysis and primary PCI within the first 165 min (0.45 vs. 0.56); it showed a highly significant superiority of primary PCI after 165–280 min (0.29 vs. 0.57, $P = 0.003$) and after 280 min (0.20 vs. 0.57). This time-dependent superiority of primary PCI compared with thrombolysis (i.e. with increasing time to presentation, MACE rates increase after thrombolysis but appear to remain relatively stable after PCI) has also been previously observed in the PCAT meta-analysis of 2635 patients[132] and in patients with a pre-hospital delay of >3 h (MITRA and MIR registries[129]). Thus, 'late is perhaps not too late'.[133]

The major reason why one could possibly prefer primary PCI over thrombolysis even within the first 3 h after onset of chest pain is stroke prevention. The meta-analysis of 23 randomized trials[113] showed that primary PCI as compared with thrombolysis significantly reduced total stroke (2.0 vs. 1.0%). According to the PCAT[132] meta-analysis, the advantage of stroke reduction by primary PCI vs. thrombolysis is 0.7% in patients presenting within 2 h, 1.2% in patients presenting 2–4 h, and 0.7% in patients presenting 4–12 h between onset of chest pain and presentation. These data are consistent with the CAPTIM study, with 1% (4/419) strokes in the thrombolysis and 0% (0/421) in the primary PCI group.[130] A meta-analysis focusing on the transfer trials revealed a significant 1.2% reduction of stroke from 1.88% (thrombolysis) to 0.64% (primary PCI).[134] Therefore, the major rationale for preference of primary PCI over thrombolysis for patients presenting 3–12 h after onset of chest pain is not only to salvage myocardium but also prevent stroke. *(Recommendation for primary PCI in patients presenting within 3–12 h after onset of chest pain: I C)*.

The PRAGUE-2 and DANAMI-2 trials are especially important as they show that primary PCI for STEMI can be applied in large areas of partly urbanized Europe with good results.[135] Primary PCI in high-risk STEMI patients at hospitals with no cardiac surgery on-site appears to be safe and effective.[136,137]

2.3.1.2. Routine stenting in STEMI. One trial has suggested that direct stenting (without prior balloon dilatation) is associated with a more complete ST-segment resolution.[138] Three studies have documented the usefulness of stenting in patients with STEMI: Zwolle,[139] Stent-PAMI,[140] and CADILLAC.[141] *(Recommendation for routine stenting in patients with STEMI: I A)*.

2.3.2. Facilitated PCI

Facilitated PCI is defined as planned intervention within 12 h after onset of chest pain or symptoms, soon after clot-dissolving medication to bridge the delay between first medical contact and primary PCI. However, the

Table 5 Clinical outcome in patients transferred for primary PCI compared with thrombolysis initiated in-hospital

	Limburg	PRAGUE-1	PRAGUE-2	Air-PAMI	DANAMI-2
Enrolment period	1995–1997	1997–1999	1999–2002	2000–2001	1997–2001
Number of patients	224	300	850	138	1572
Inclusion criteria	STEMI presenting within <6 h	STEMI presenting within <6 h (including new LBBB)	STEMI presenting within <12 h	High risk STEMI presenting within <12 h (including new LBBB)	STEMI presenting within <12 h
Number of patients (thrombolysis/PCI)	75/75	99/101	421/429	66/71	782/790
Time from onset of symptoms to admission or randomization (min)	125 ± 80 130 (no SD)	110 (122) 120 (135)	173 ± 119 183 ± 162	N/A	105–107 (54–202)
Thrombolytic drug	Alteplase (t-PA)	Streptokinase	Streptokinase	Streptokinase (32%) or alteplase/reteplase (68%)	Alteplase (t-PA)
Stent usage (%)	21	79	63	34	93
Distance for transfer of patients to primary PCI	25–50 km	5–74 km	5–120 km	51 ± 58 km; Air: 92 ± 80 km; Ground: 42 ± 45 km	50 (3–150) km
Transport time of patients transferred to primary PCI (min)	20 (maximum 30)	35	48 ± 20	33 ± 29	32 (20–45)
Mean delay from emergency room or randomization to PCI (min)	85 ± 25	95	94 (20 ± 9 + 48 ± 20 + 26 ± 11)	174 ± 80	Referral hospital: 90 (74–108) PCI centres: 63 (49–77)
Mean delay from emergency room or randomization to start of thrombolysis (min)	10	22	12 ± 10	63 ± 39	Referral hospital: 20 (15–30) PCI centres: 20 (13–30)
Primary endpoint defined	Death and recurrent MI (secondary endpoint)	Death (any cause)/ re-infarction/stroke	Death (any cause)	Death/non-fatal re-infarction/disabling stroke	Death/clinical evidence of re-infarction/disabling stroke
At time	42 days	30 days	30 days	30 days	30 days
Result of primary endpoint (thrombolysis/PCI, %)	16/8	23/8[a]	10.0/6.8	13.6/8.4	13.7/8.0[a]
Primary endpoint reached	N/A (pilot study)	N/A (no power calculation)	N/A (prematurely terminated)	N/A (prematurely terminated)	Yes

Times are listed as mean values ± SD (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant, and only one trial reached the primary endpoint.

[a] $P < 0.05$.

N/A = not applicable.

term 'facilitated PCI' is not uniformly used for identical settings: it should be used as initially planned PCI, following shortly after initiating thrombolysis and/or GP IIb/IIIa inhibitors. Therefore, in randomized studies testing the concept of facilitated PCI, all patients (with or without pre-treatment) should undergo planned primary PCI.

2.3.2.1. Thrombolysis-facilitated primary PCI. Facilitated PCI was tested in smaller subgroups of PRAGUE-1 study[120] and SPEED (GUSTO-4 Pilot[142]). Newer concepts with administration of a half dose of t-PA prior to systematic primary PCI have shown to be associated with improved TIMI-3 flow rates upon arrival at the catheterization laboratory, but this did not translate into a relevant clinical benefit (PACT study[143]). In BRAVE,[144] randomizing to either half dose reteplase plus abciximab or abciximab alone before they were transferred for planned PCI with stenting, early administration of reteplase plus abciximab did not lead to a reduction of infarct size compared with abciximab alone. Although the concept of 'low-dose thrombolysis'[145] combined with clopidogrel and GP IIb/IIIa inhibitors shortly before stenting in STEMI is an interesting one, the studies dedicated to facilitated PCI suggest no benefit and even potential harm.[116] More data will be available from the currently ongoing ASSENT-4 trial (randomizing TNK-facilitated primary PCI vs. primary PCI with GP IIb/IIIa inhibitor as needed) and from FINESSE[146] (randomizing reteplase-facilitated vs. abciximab-facilitated vs. unfacilitated primary PCI). But at the moment, there is no evidence for the recommendation of thrombolysis-facilitated PCI.

2.3.2.2. GP IIb/IIIa inhibitor-facilitated primary PCI. In the ADMIRAL study,[147] the analysis of the pre-specified subgroup that received abciximab in the emergency department or in the ambulance showed better outcomes than the group of patients receiving the drug later, suggesting an advantage of 'facilitation'. In the ON-TIME trial,[148] patients were prospectively randomized to early, pre-hospital initiation of tirofiban (early) or to initiation in the catheterization laboratory (late). At initial angiography, TIMI 3 flow was present in 19% of the early group and in 15% of the late group (not significant). No beneficial effect on post-PCI angiographic or clinical outcome was found. Although the TIGER-PA[149] pilot and the BRIDGING[150] studies suggested that early administration of tirofiban or abciximab improves angiographic outcomes in patients undergoing primary PCI and although in a meta-analysis of six randomized trials[151] early administration of GP IIb/IIIa inhibitors in STEMI appeared to improve coronary patency with favourable trends for clinical outcomes, no evidence-based recommendation for GP IIb/IIIa inhibitor-facilitated primary PCI can be made at the present time to improve patients' outcome.

2.3.3. Rescue PCI after failed thrombolysis

Rescue PCI is defined as PCI in a coronary artery that remains occluded despite thrombolytic therapy. Failed thrombolysis is generally suspected when persistent chest pain and non-resolution of ST-segment elevation are evident 45–60 min after starting the administration. It is then confirmed angiographically (significant epicardial coronary lesion together with impaired flow $<$ TIMI 3). A Cleveland Clinic Study investigated the value of rescue PCI after failed thrombolysis.[152] The patients were randomized to ASA, heparin, and coronary vasodilators (conservative therapy) or to the same medical therapy and PCI. The occurrence of the primary endpoint (either death or severe heart failure) was significantly reduced by rescue PCI from 17 to 6%. A meta-analysis from the RESCUE I, RESCUE II, and other clinical experiences suggested a probable benefit of rescue PCI.[153] On the other hand, in the MERLIN trial,[154] rescue PCI did not improve survival by 30 days, but improved event-free survival almost completely due to a reduction in subsequent revascularization. The most serious limitation of MERLIN, however, was that it was considerably underpowered.[155] The recently finished REACT trial[156] (enrolling patients who, after a 90-min ECG, failed to achieve a $>$50% resolution of ST changes) indicates that rescue PCI is superior to repeat thrombolysis or conservative treatment in patients who failed to achieve reperfusion after thrombolysis. At 6 months, the incidence of any event was reduced by almost half in the rescue PCI group, compared with either the repeat lysis or conservative therapy groups (death: 18 vs. 9%). As compared with MERLIN, the use of GP IIb/IIIa inhibitors and stents was higher; and in REACT, the time delays for rescue PCI were shorter. As in primary PCI, stenting is superior to balloon-only angioplasty in rescue PCI.[157] (*Recommendation for rescue PCI in patients with failed thrombolysis: I B*).

2.3.4. Emergency PCI in cardiogenic shock

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic blood pressure $<$90 mmHg and a capillary wedge pressure $>$20 mmHg or a cardiac index $<$1.8 l/min m^2 (ESC Guidelines on STEMI[95]). Emergency PCI or surgery may be life-saving and should be considered at an early stage.[95] If neither PCI nor surgery is available or can only be provided after a long delay, thrombolytic therapy should be given.[95] Women have a higher mortality than men, regardless of the treatment received.

Two randomized, controlled trials (SHOCK[158,159] and SMASH[160]) have evaluated early revascularization (PCI or CABG surgery) in patients with shock because of left ventricular dysfunction following STEMI. PCI in patients with cardiogenic shock is characterized by two differences in comparison to 'normal' STEMI patients: the usually recommended time window of 12 h after onset of chest pain is wider[161] and multi-vessel PCI should be strongly considered. All trials of primary PCI have evaluated a strategy of limiting the acute revascularization procedure to the culprit vessel. Only in the setting of cardiogenic shock is there a consensus for attempting multi-vessel PCI in selected patients with multiple critical lesions. The use of intra-aortic balloon pump (IABP) should be strongly considered. If the multivessel disease is not amenable to relatively complete

percutaneous revascularization, surgery should be considered in these patients.[161] In the Benchmark Counterpulsation Outcomes Registry (25 136 patients), in-hospital mortality was higher in patients who received only medical interventions (32.5%) than in those who underwent percutaneous (18.8%) and surgical (19.2%) interventions.[162] One should keep in mind that patients with cardiogenic shock and NSTEMI have an in-hospital mortality similar to shock patients with STEMI.[163] In-hospital mortality in patients with acute MI complicated by cardiogenic shock remains high, even with early PCI.[164] Among patients older than 75 years with MI complicated by cardiogenic shock, outcomes may be better than previously believed when early revascularization is performed. In this population, 56% of patients survived to be discharged from the hospital, and of the hospital survivors, 75% were alive at 1 year.[165] Within the last few years, an increase in revascularization of patients with acute MI complicated for cardiogenic shock was observed, probably due to more frequent admission of eligible patients to hospitals capable of this service.[166] (*Recommendation for emergency PCI in patients with cardiogenic shock: I C*).

2.3.5. Routine angiography early post thrombolysis

The ALKK study[167] randomized 300 patients (initially planned were 800) to either PCI or medical therapy. Before randomization, 63% of the PCI and 57% of the medical group received thrombolysis. PCI was performed at a mean of 24 days after STEMI. The event-free survival at 1 year showed a trend in favour of PCI (90 vs. 82%). This difference was mainly due to the difference in the need for (re)interventions (5.4 vs. 13.2%, $P = 0.03$). A multi-level analysis of patients in ASSENT-2 showed a lower mortality in the countries with the highest rates of PCI after thrombolytic treatment.[168] A meta-analysis of 20 101 patients from the TIMI 4, 9, and 10B and InTIME-II trials revealed that PCI during hospitalization was associated with a lower rate of in-hospital recurrent MI (4.5 vs. 1.6%, $P < 0.001$) and a lower 2-year mortality (11.6 vs. 5.6%, $P < 0.001$).[169] A prospective cohort study from the Swedish National Cause of Death registry supported the use of an invasive approach early after an acute myocardial infarction.[170] In GUSTO-I, the rates of cardiac catheterization and revascularization during the index hospitalization among US patients were more than twice those among Canadian patients.[171] The 5-year mortality rate was 19.6% among US patients and 21.4% among Canadian patients ($P = 0.02$). Thus, a more conservative pattern of care with regard to early revascularization had a detrimental effect on long-term survival.[171]

Four randomized studies have contributed to recommend routine coronary angiography and—if applicable—PCI early post-thrombolysis: SIAM III,[172] GRACIA-1,[173] CAPITAL-AMI,[174] and the Leipzig Prehospital Lysis Study (LPLS[175]). The details of these four studies are listed in *Table 6*.

Thus, SIAM III, GRACIA-1, and CAPITAL-AMI together with LPLS, the ALKK study, the ASSENT-2 analysis, the meta-analysis of the TIMI 4, 9, and 10B, and InTIME-II trials as well as GUSTO-I have contributed to the solution of an old but still pivotal problem: the incidence of re-infarction, the 'Achilles' heel' of thrombolysis. Thus, thrombolysis, even if successful, should not be considered as the final treatment: 'lyse now, stent later'.[176] (*Recommendation of routine coronary angiography and PCI, if applicable, in patients after successful thrombolysis: I A*).

2.3.6. Ischaemia-driven PCI after thrombolysis

The DANAMI-1 trial[177] was the first and only prospective, randomized study comparing an invasive strategy of PCI/CABG surgery with a conservative strategy in patients with pre-discharge inducible myocardial ischaemia after thrombolytic treatment for a first STEMI. The occurrences of the primary endpoint (mortality, re-infarction, and admission with unstable angina) were significantly reduced with 15.4 vs. 29.5% at 1 year, 23.5 vs. 36.6% at 2 years, and 31.7 vs. 44.0% at 4 years. Thus, patients who have received treatment with thrombolytics for their first STEMI with inducible ischaemia before discharge should be referred to coronary angiography and revascularized accordingly—independent of maximal medical therapy. (*Recommendation for ischaemia-driven PCI after successful thrombolysis: I B*).

2.3.7. PCI for patients not having received reperfusion within the first 12 h

Patients often seek medical attention too late and either do not receive reperfusion therapy or reperfusion therapy fails to successfully recanalize the artery. Late reperfusion therapy is defined as thrombolysis or PCI starting >12 h after onset of symptoms (for late PCI in cardiogenic shock please see section 2.3.4.). Thrombolytic therapy for the late treatment of patients with STEMI does not reduce infarct size or preserve left ventricular function, probably because it is ineffective in establishing coronary patency.[178]

Cautious interpretation of PCAT,[132] PRAGUE-2,[121] and CAPTIM[130] might consider a possible beneficial effect of late PCI. This, however, is inconsistent with the smaller TOAT trial,[179] with late PCI having an adverse effect on LV remodelling. In DECOPI,[180] 212 patients with a first Q-wave MI and an occluded infarct vessel were randomized to PCI, carried out 2–15 days after symptom onset or medical therapy. The primary endpoint was a composite of cardiac death, non-fatal MI, or ventricular tachyarrhythmia. Although at 6 months, LV-EF was significantly higher (5%) in the invasive compared with the medical group and significantly more patients had a patent artery (82.8 vs 34.2%), at a mean of 34 months of follow-up, the occurrence of the primary endpoint was similar in the medical and PCI groups (8.7 vs. 7.3%, respectively). Because recruitment and event rates were lower than planned, the study is markedly underpowered. Thus, although the 'late open artery hypothesis' seems appealing,[181] we will have to wait for the results of the OAT trial. Currently, there is no agreement on treatment recommendations for this group of patients.

2.3.8. Minimization of time delays

For all forms of PCI in STEMI (*Table 7*) there is unanimous agreement that every effort must be made to minimize

Table 6 Clinical outcome and infarct size in patients routinely transferred for coronary angiography and, if applicable, routine PCI after thrombolysis as compared with thrombolysis alone and an ischaemia-driven invasive strategy

	SIAM-III	GRACIA-1	CAPITAL-AMI	LPLS
Number of patients	197	500	170	164
Inclusion criteria	STEMI presenting within <12 h	STEMI presenting within <12 h	STEMI presenting within <6 h	STEMI presenting within <4 h
Thrombolysis performed	In-hospital	In-hospital	In-hospital	Pre-hospital
Thrombolytic drug	Full-dose reteplase	Accelerated dose of alteplase	Full-dose tenecteplase	Half-dose reteplase with abciximab
Time between thrombolysis and routine coronary angiography in the PCI group	<6 h	<24 h	Immediate transfer	Immediate transfer
Primary endpoint	Combination of death, re-infarction, ischaemic events, TLR	Combination of death, re-infarction, TLR	Combination of death, re-infarction, recurrent ischaemia, stroke	Infarct size, determined by MRI
At time	6 months	12 months	30 days	6 months
Result of primary endpoint (thrombolysis alone/thrombolysis + routine coronary angiography ± PCI	50.6/25.6%[a]	21/9%[a]	21.4/9.3%[a]	11.6/6.7%[a]
Primary endpoint reached	Yes	Yes	Yes	Yes

All four trials reached their primary endpoint.
[a]$P < 0.05$.
TLR = target lesion revascularization.

Table 7 Recommendations for PCI in STE-ACS (STEMI)

Procedure	Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Primary PCI	Patients presenting <12 h after onset of chest pain/other symptoms and preferably up to 90 min after first qualified medical contact; PCI should be performed by an experienced team	I A	PAMI GUSTO-IIb C-PORT PRAGUE-1 and -2 DANAMI-2
Primary stenting	Routine stenting during primary PCI	I A	Zwolle Stent-PAMI CADILLAC
Primary PCI	When thrombolysis is contra-indicated	I C	—
Primary PCI	Preferred more than thrombolysis for patients presenting within >3 h and <12 h after onset of chest pain/other symptoms	I C	—
Rescue PCI	If thrombolysis failed within 45–60 min after starting the administration	I B	REACT
Emergency (multi-vessel) PCI	Cardiogenic shock in association with IABP even >12 to <36 h	I C	—
Routine post-thrombolysis coronary angiography and PCI, if applicable	Up to 24 h after thrombolysis, independent of angina and/or ischaemia	I A	SIAM III GRACIA-1 CAPITAL-AMI
Ischaemia-guided PCI after successful thrombolysis	Pre-discharge angina and/or ischaemia after (first) STEMI treated with thrombolysis	I B	DANAMI-1

any delays between onset of chest pain/other symptoms and the initiation of a safe and effective reperfusion strategy in patients with STEMI.[182,183] Shortening the total ischaemic time is pivotal, not only for thrombolytic therapy but also for primary PCI.[184] (*Figure 3*). Minimizing presentation and treatment delays significantly improves clinical outcome, whereas prolonged symptom-to-treatment times are associated with

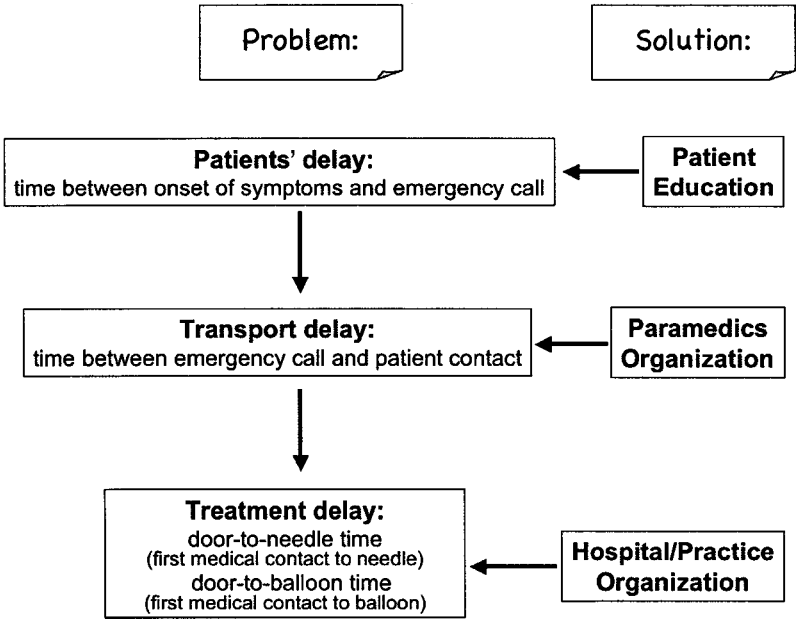

Figure 3 Sources of possible time delays between onset of symptoms and start of reperfusion therapy in patients with STEMI. Solutions to keep the sum of these delays ('total ischaemia time') as low as possible include improvements in the organization of ambulance services as well as optimization of organization within the hospitals or private practices. Most importantly, patients have to be better educated to minimize the time delay between onset of symptoms and the emergency call.

impaired myocardial perfusion independent of epicardial flow.[185] The effort starts with patient education and includes improvements in organization of ambulance services as well as optimizing procedures within the hospital or private practice (*Figure 3*). As far as primary PCI is concerned, all efforts should be made to keep the average time between first medical contact and PCI below 90 min, including door to balloon time. Skipping the emergency room and directly transferring STEMI patients to the cath lab additionally reduces door to balloon times. However, patients with longer delays should also be treated by primary PCI even when presenting 3 h after onset of symptoms. Only when a substantial delay (e.g. >2–3 h) in initiating primary PCI is likely, reperfusion therapy with second or third-generation fibrinolytic agents should be considered.[186]

In summary, primary PCI should be the treatment of choice in patients presenting with STEMI in a hospital with PCI facility and an experienced team. Patients with contra-indications to thrombolysis should be immediately transferred for primary PCI, because this might be their only chance for quickly opening the coronary artery. In cardiogenic shock, emergency PCI for complete revascularization may be life-saving and should be considered at an early stage. Compared with thrombolysis, randomized trials that transferred the patients for primary PCI to a 'heart attack centre', observed a better clinical outcome, despite transport times leading to a significantly longer delay between randomization and start of the treatment. The superiority of primary PCI over thrombolysis seems to be especially clinically relevant for the time interval between 3 and 12 h after onset of chest pain or other symptoms on the basis of its superior preservation of myocardium. Furthermore, with increasing time to presentation, MACE rates increase after thrombolysis, but appear to remain relatively stable after primary PCI.

Within the first 3 h after onset of chest pain or other symptoms, both reperfusion strategies seem equally effective in reducing infarct size and mortality. Therefore, thrombolysis is still a viable alternative to primary PCI, if it can be delivered within 3 h after onset of chest pain or other symptoms. Primary PCI compared with thrombolysis significantly reduced stroke. Overall, we prefer primary PCI over thrombolysis in the first 3 h of chest pain to prevent stroke and, in patients presenting 3–12 h after the onset of chest pain, to salvage myocardium and also prevent stroke. At the moment, there is no evidence to recommend facilitated PCI.

Rescue PCI is recommended, if thrombolysis failed within 45–60 min after starting the administration. After successful thrombolysis, the use of routine coronary angiography within 24 h and PCI, if applicable, is recommended even in asymptomatic patients without demonstrable ischaemia to improve outcomes. If a PCI centre is not available within 24 h, patients who have received successful thrombolysis with evidence of spontaneous or inducible ischaemia before discharge should be referred to coronary angiography and revascularized accordingly—independent of maximal medical therapy.

3. Adjunctive medications for PCI

A routine pre-treatment with an intracoronary bolus of nitroglycerin (NTG) is recommended to unmask

vasospasm, to assess the true vessel size, and to reduce the risk of vasospastic reactions during the procedure (*Recommendation for NTG: I C*). The bolus may be repeated during and at the end of the procedure, depending on the blood pressure. In the rare case of spasm resistant to NTG, verapamil is a useful alternative.

In the setting of 'no/slow reflow' (see 4.5.), many reports investigated the intracoronary application of verapamil and adenosine in various dosages.[187] The direct nitric oxide donor nitroprusside (NPN) seems also to be an effective and safe treatment of reduced blood flow or no-reflow associated with PCI.[188,189] In addition, IABP might be helpful. The combination of adenosine and nitroprusside provided an improvement in coronary flow that was better than the improvement with intracoronary adenosine alone.[190] (*Recommendation for adenosine, verapamil and NPN for no/slow reflow: IIa C*).

3.1. Acetylsalicylic acid

Since the beginning of interventional cardiology, antiplatelet drugs are a cornerstone of the adjunctive medication because the trauma induced by PCI to the endothelium and deeper layers of the vessel wall regularly results in platelet activation. The basic pharmacology and general clinical application of antiplatelet agents in patients with atherosclerotic cardiovascular disease have been recently elaborated in an ESC consensus document.[191] The PCI guidelines address their indications more specifically to the setting of PCI.

3.1.1. Acetylsalicylic acid in stable CAD

In the 'Antithrombotic Trialists' Collaboration meta-analysis, acetylsalicylic acid (ASA) reduced vascular death, MI, or stroke among all patients who were at high risk for vascular events in 22% as compared with placebo.[192] M-HEART II[193] was the only placebo-controlled PCI study with ASA alone showing a significant improvement of clinical outcome in comparison to placebo (30 vs. 41%). MI was significantly reduced by ASA from 5.7 to 1.2%. Today, ASA continues to play an important role in reducing ischaemic complications related to PCI. If patients are not chronically pre-treated or when there is doubt about medication compliance, a loading dose of 500 mg orally should be given more than 3 h prior or at least 300 mg intravenously directly prior to the procedure. Only in patients with known allergy against ASA, should it be omitted. As pointed out in the ESC consensus document, for chronic use, there is no need for doses higher than 100 mg daily.[191] (*Recommendation for ASA in PCI for stable CAD: I B*).

3.1.2. ASA in NSTE-ACS

The 'Antithrombotic Trialists' Collaboration meta-analysis revealed a 46% reduction of vascular death, MI, or stroke (from 13.3 to 8.0%).[192] Although these studies were performed before the widespread use of PCI, they have led to the universal recommendation of ASA as standard therapy in NSTE-ACS with and without PCI. (*Recommendation for ASA in PCI for NSTE-ACS: I C*).

3.1.3. ASA in STE-ACS (STEMI)

ASA has proved its efficacy compared with placebo in the ISIS-2 trial, showing ASA to be almost as effective as Streptokinase.[194] The administration of both drugs was additive. Despite the limitations and side effects of ASA, it should be given to all patients with STEMI (if clinically justifiable) as soon as possible after the diagnosis is established.[95] (*Recommendation for ASA in PCI for STEMI: I B*).

Recently, the problem of 'aspirin resistance' has arisen.[195] However, more prospective studies are needed to correlate ASA non-responsiveness to adverse clinical events.

3.2. Ticlopidine and clopidogrel

3.2.1. Thienopyridines (ticlopidine/clopidogrel) in stable CAD

Ticlopidine and clopidogrel are potent antiplatelet compounds. There is a compelling evidence that for a reduction in acute and sub-acute stent thrombosis following PCI with stent implantation, the combination therapy of a thienopyridine plus ASA is superior to ASA alone or ASA plus an oral anticoagulant (Milan/Tokyo,[196] ISAR,[197] STARS,[198] FANTASTIC,[199] and MATTIS[200]). According to three randomized, controlled studies (CLASSICS,[201] TOPPS,[202] Bad Krozingen,[203]) and several registries and meta-analyses,[204–209] clopidogrel seems to be at least as effective as ticlopidine. Compared with ticlopidine, clopidogrel has fewer side-effects and is better tolerated. *(Recommendation for 3–4 weeks of ticlopidine or clopidogrel in addition to ASA after bare metal stent implantation in stable CAD: I A)*.

At present, as the vast majority of PCI procedures eventually conclude with stent implantation, every patient scheduled for PCI should be considered for pre-treatment with clopidogrel, regardless of whether stent implantation is intended or not.[210] A pre-treatment with 300 mg within 2.5 h, however, may not be sufficient.[211] To ensure full antiplatelet activity, clopidogrel should be initiated at least 6 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI (CREDO trial[212] and TARGET analysis[213]). If this is not possible, a loading dose of 600 mg should be administered at least 2 h before PCI, but no fully published (ARMYDA-2-study) randomized data exist.[94,214–216] If diagnostic angiography is negative or no stenting was performed, or if early heart surgery is indicated, clopidogrel can be stopped. Patients unable to be pre-treated with clopidogrel should receive the (possibly higher) loading dose immediately following the procedure. (*Recommendation for pre-treatment with 300 mg clopidogrel at least 6 h before PCI: I C*).

After stenting, there is no need to recommend prolonged (>4 weeks) treatment in patients with stable angina—except after brachytherapy or after implantation of a drug-eluting stent (*Table 8*, see also Chapter 5). *(Recommendation for clopidogrel administration after brachytherapy for 12 months or drug-eluting stents for 6–12 months: I C)*.

Table 8 Recommendations for clopidogrel as adjunctive medication for PCI

Indication	Initiation and duration	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Pre-treatment of planned PCI in stable CAD	Loading dose of 300 mg at least 6 h before PCI, ideally the day before	I C	—
Pre-treatment for primary PCI in STEMI or immediate PCI in NSTE-ACS or ad hoc PCI in stable CAD	Loading dose of 600 mg, immediately after first medical contact, if clinically justifiable	I C	—
After all bare metal stent procedures	3–4 weeks	I A	CLASSICS TOPPS Bad Krozingen
After vascular brachytherapy	12 months	I C	—
After drug-eluting stents	6–12 months	I C	—
After NSTE-ACS	Prolonged for 9–12 months	I B	CURE

3.2.2. Clopidogrel in NSTE-ACS

The optimal time for initiating clopidogrel therapy in patients with NSTE-ACS is a matter of discussion: on the one hand, the CURE trial[217] revealed that the frequency of adverse events was significantly reduced within the first hours of entry into the trial.[218] On the other hand, in patients referred to cardiac surgery while on clopidogrel, perioperative blood loss during surgery is a concern. In CURE, no overall significant excess of major bleeding episodes occurred after CABG surgery (1.3 vs. 1.1%). In the patients who did not stop study medication until 5 days before surgery, the rate of major bleeding was higher in the clopidogrel group (9.6 vs. 6.3%).[217] Overall, the benefits of starting clopidogrel on admission appear to outweigh the risks even among those who proceed to CABG surgery during the initial hospitalization.[219] In several cases, platelets have to be substituted. A clear increase in bleeding risk occurred as the dose of ASA increased from 100 to 100–200 mg or $\geq$200 mg in patients treated with both ASA alone (1.9, 2.8, 3.7% major bleedings) and ASA plus clopidogrel (3.0, 3.4, 4.9%).[220] The available data suggest that in patients treated for NSTE-ACS, a daily dose of ASA in the range of 75–100 mg may be optimal.[220]

According to the ACC/AHA guidelines for the management of patients with NSTE-ACS,[221] in many hospitals in which patients with UA or NSTEMI undergo diagnostic catheterization within 24–36 h of admission, clopidogrel should not be started until it is clear that CABG surgery will not be scheduled within the next several days. Today's preference for an early invasive strategy, combined with stenting and GP IIb/IIIa inhibitors, lowers the likelihood of urgent bypass surgery for the majority of these high-risk patients. On the basis of the very early positive effects of clopidogrel[218] we therefore recommend initiating clopidogrel administration as soon as possible, if clinically justifiable. (*Recommendation for the immediate clopidogrel administration in NSTE-ACS: I B*).

After the acute phase of NSTE-ACS, the continuation of ASA plus clopidogrel over 9–12 months is beneficial (CURE,[217] PCI-CURE[222]). (*Recommendation for prolonged clopidogrel administration for 9–12 months after NSTE-ACS: I B*).

3.2.3. Clopidogrel in STE-ACS (STEMI)

Although not being PCI-studies, CLARITY (loading dose: 300 mg) and COMMIT/CCS-2 (no loading dose) showed that ASA + clopidogrel was more effective in STEMI than ASA alone. With primary PCI and stenting in STEMI, clopidogrel will be additionally administered in these patients, preferably with a loading dose of 600 mg. Regarding the duration of clopidogrel prescription, the results from NSTE-ACS may be extrapolated to STE-ACS, but this has yet to be scientifically proven.

Some initial laboratory findings warned of the combination of clopidogrel with statins metabolized in the liver, especially atorvastatin,[223] but it does not seem to play a clinical role.[224] The emerging question about possible clopidogrel resistance requires more investigation.[225,226]

In summary, the 'double' antiplatelet therapy with ASA and clopidogrel is standard for the pre-treatment of patients with stable CAD undergoing PCI—with or without planned stent implantation. After implantation of a bare metal stent, clopidogrel must be continued for 3–4 weeks and ASA lifelong. In patients presenting with NSTE-ACS, ASA and, if clinically justifiable, immediate administration of clopidogrel, is the basic standard antiplatelet regimen. After the acute phase, the continuation of 100 mg/d ASA + clopidogrel 75 mg/d over 9–12 months is beneficial. ASA should be given i.v. to all patients with STEMI as soon as possible after the diagnosis is established, if clinically justifiable. With the concept of primary PCI and primary stenting in STEMI, clopidogrel will be additionally administered in these patients. After brachytherapy, clopidogrel should be administered in addition to ASA for 12 months and after drug-eluting stents for 6–12 months to avoid late vessel thrombosis.

3.3. Unfractionated heparin

3.3.1. Unfractionated heparin for PCI in stable CAD

Since the beginning of PCI, unfractionated heparin (UFH) has been used to prevent thrombosis on the instrumentarium and to minimize thrombus formation at the site of iatrogenic vessel wall injury/plaque rupture. There are obviously no placebo-controlled trials specifically

addressed to PCI, as the omission of anticoagulation would be prohibitive in the setting of any coronary interventions. UFH is given as an i.v. bolus either under activated clotting time (ACT) guidance (ACT in the range of 250–350 s or 200–250 s, if GP IIb/IIIa receptor inhibitor is given) or in a weight-adjusted manner (usually 100 IU/kg or ~50–60 IU/kg, if GP IIb/IIIa receptor inhibitor is given). Because of marked variability in UFH bio-availability, ACT-guided dosing is advocated, especially for prolonged procedures when additional bolus (-es) may be required. The therapeutic response to UFH in general is difficult to predict. There is evidence that its benefit is linked to an effective dose, although low doses (5000 IU or lower) have been used in routine procedures.[227] Continued heparinization after completion of the procedure, either preceding or following arterial sheath removal is not recommended.

3.3.2. UFH for PCI in NSTE-ACS

Adding UFH as a standard regimen is usually recommended on the basis of a meta-analysis of six smaller randomized trials showing a 7.9% rate of death/MI in patients with unstable angina treated with ASA plus heparin compared with 10.3% in those treated with ASA alone.[228] Discontinuation of UFH in patients with unstable angina carries the inherent risk of a rebound effect.[229]

3.3.3. UFH for PCI in STE-ACS (STEMI)

UFH is the standard therapy in patients with STEMI, especially for those undergoing primary PCI. UFH served as control for many studies investigating LMWHs (see 3.4.3.) or bivalirudin. (*Recommendation for unfractionated heparin for all PCI procedures: I C*).

3.4. Low-molecular weight heparins

Both UFH and LMWHs act by binding to antithrombin-III (AT-III) and thereby accelerating the AT-III inhibition of thrombin. UFH, however, involves several disadvantages: owing to its strong binding to plasma proteins, the antithrombotic effects of UFH are variable, leading to unpredictable levels of free heparin. Although UFH inhibits factors Xa and thrombin to the same extent, LMWHs predominantly and more intensely inhibit factor Xa. Because of their more consistent plasma levels, LMWHs are considered to be more predictable anticoagulants, not requiring laboratory monitoring.

3.4.1. LMWHs for PCI in stable CAD

The data on LMWHs as sole anticoagulant during PCI in stable CAD patients are limited. To be on the safe side, it is suggested that UFH should be added in patients arriving on pre-treatment with LMWHs, according to the interval of the last LMWH dose.

3.4.2. LMWHs for PCI in NSTE-ACS

The clinical outcome as primary endpoint comparing LMWHs with UFH was investigated in four major trials, randomizing altogether 12 048 patients with NSTE-ACS. These four studies have been extensively reviewed in the ESC NSTE-ACS Guidelines[60] and other reviews.[230] It is important to emphasize, however, that these trials do not apply to coronary interventions, as PCI was excluded (dalteparin, FRIC[231]), not recommended within 24 h (enoxaparin, TIMI-11B[232,233]), or left at the discretion of the physicians (enoxaparin, ESSENCE[233,234] and nadroparin, FRAXIS[235]).

Dalteparin was superior to UFH in unstable patients (FRISC-II[236]). This advantage, however, was demonstrable only in the non-invasive arm; in patients with early revascularization, dalteparin was no longer superior.[90] The ESSENCE[234] and TIMI 11B[232] studies showed a superiority of enoxaparin over UFH in a predominantly conservative strategy of high-risk NSTE-ACS patients at the cost of a significant increase in minor bleeding.[64] In the SYNERGY trial,[237] 9978 NSTE-ACS patients were randomized to either UFH or enoxaparin (plus ASA) with an early invasive strategy. Inclusion criteria (high-risk) were ischaemic symptoms lasting at least 10 min occurring within 24 h before enrolment and at least two of the following: age 60 years or older, troponin or creatine kinase elevation above the upper limit of normal, or ST-segment changes on electrocardiogram. The combined endpoint of death and MI after 30 days was 14.5 vs. 14.0%. Major bleeding (TIMI criteria), however, was significantly increased by enoxaparin (7.6 vs. 9.1%). These results are consistent with the A to Z trial,[238] where patients with NSTE-ACS and early invasive strategy receiving ASA and tirofiban had no clinical benefit from enoxaparin vs. UFH, but the bleeding rate was significantly higher in the PCI groups with enoxaparin (4.4 vs. 2.8%).

Switching from UFH to LMWH and vice versa should generally be avoided.[239] If LMWH has been administered prior to PCI, the administration of additional anticoagulant therapy depends on the timing of the last dose of LMWH.[240]

Combining the results of ESSENCE, TIMI 11 B, SYNERGY, and A to Z, UFH should be preferred in high-risk NSTE-ACS patients with planned invasive strategy (*Figure 1*). Furthermore, although enoxaparin can be administered before PCI in NSTE-ACS,[241] the Task Force recommends UFH because of its easier reversibility by the administration of protamine. There is no firm evidence that enoxaparin can be used safely in the cathlab, but this possibility is currently being explored.

If an invasive strategy is, for some reason, not applicable in a high-risk NSTE-ACS patient, enoxaparin could be preferred for reducing ischaemic complications.[242] (*Recommendation for LMWHs as a replacement for UFH in high-risk NSTE-ACS, if invasive strategy is not applicable: I C*).

3.4.3. LMWHs for PCI in STE-ACS (STEMI)

Several angiographic trials investigated LMWHs in STEMI. The HART II trial[243] found a trend towards improved effectiveness with the immediate use of enoxaparin in conjunction with tissue plasminogen activator (t-PA) compared with UFH in achieving infarct-related artery patency (TIMI-2 and -3 flow) 90 min after the start of treatment. Patients in the enoxaparin group had a significantly lower re-occlusion rate at days 5–7, with no increase in major bleeding. In patients with full-dose

tenecteplase (TNK) and half-dose TNK plus abciximab, enoxaparin is associated with similar TIMI-3 flow rates as UFH (ENTIRE-TIMI-23 trial[244]). The PENTALYSE study[245] investigated the efficacy and safety of fondaparinux in patients with evolving STEMI. In patients undergoing coronary angiography at 90 min and on days 5–7, TIMI flow grade 3 rates at 90 min were similar. Unless more data from pivotal studies are provided, there is no evidence to support the preference of LMWHs over UFH for PCI in STEMI.

In summary, UFH is given as an i.v. bolus under ACT guidance. Because of their pharmacologic advantages, LMWHs are considered to be more predictable anticoagulants, not requiring laboratory monitoring. However, the data on LMWHs as sole anticoagulant during PCI in stable CAD patients is limited. UFH is to be preferred in high-risk NSTE-ACS patients with planned invasive strategy and in lower-risk patients with planned conservative strategy. If in high-risk NSTE-ACS patients an invasive strategy is not applicable for some reason, enoxaparin may be preferred, taking into account an increase in minor bleeding. In patients with STEMI undergoing primary PCI, UFH is the standard therapy.

3.5. Glycoprotein IIb/IIIa inhibitors

GP IIb/IIIa inhibitors are the most potent antiplatelet drugs that block the fibrinogen receptor.

3.5.1. GP IIb/IIIa inhibitors for PCI in stable CAD

The ISAR-REACT study[215] randomly assigned abciximab or placebo in low-risk CAD patients, with exclusion of ACS, insulin-dependent diabetes, or visible thrombus (*Table 10*). Abciximab did not reach the primary endpoint in these low-risk patients undergoing elective stenting.

Although the retrospective analysis of the EPISTENT diabetics substudy[246] with a mixed patient population of stable and unstable CAD (*Table 10*) suggested a prognostic benefit of abciximab in the stent group, the prospective ISAR-SWEET trial in patients with stable CAD excluding patients with ACS and/or a visible thrombus could not corroborate this concept.[247] Given the overall low risk of PCI in stable CAD patients, the potential of GP IIb/IIIa receptor inhibitors of increasing the risk of bleeding complications and the considerable cost of their use, they are not a part of standard periprocedural medication. Despite a large cumulative meta-analysis in 20 186 patients suggesting the routine administration of GP IIb/IIIa inhibitors in PCI,[248] and despite a recent meta-analysis in 8004 patients suggesting a mortality reduction with GP IIb/IIIa inhibitors for stenting patients with non-acute coronary artery disease (non-acute CAD),[47] the use of GP IIb/IIIa inhibitors in PCI for stable angina should be considered case by case. Whenever there is a higher than average risk of complications in stable CAD, GP IIb/IIIa inhibitors are helpful in unstable lesions, as bail-out medication in case of threatening/actual vessel closure, visible thrombus, or no/slow-reflow phenomenon. GP IIb/IIIa inhibitors are also useful in complex interventions.[249] (*Recommendation for* GP IIb/IIIa inhibitors *in stable CAD PCI with complex lesions, threatening/actual vessel closure, visible thrombus, no/slow reflow: IIa C*).

3.5.2. GP IIb/IIIa inhibitors for PCI in NSTE-ACS

The individual studies investigating GP IIb/IIIa inhibitors in patients with NSTE-ACS have been discussed in detail in the ESC NSTE-ACS guidelines.[60]

With respect to PCI, the studies investigating the usefulness of GP IIb/IIIa inhibitors in NSTE-ACS can be divided into those in which PCI was planned per protocol and into those discouraging an invasive strategy. PCI was not scheduled or even discouraged in GUSTO-IV-ACS with abciximab,[250] PRISM[251] and PRISM-PLUS[252] with tirofiban, and PARAGON-A[253] with lamifiban. PCI was left at the discretion of the physicians in PURSUIT[254] with eptifibatide and PARAGON-B[255] with lamifiban. Therefore, the PCI rates in these studies are low, varying between 1.6 and 30.5% (*Table 9*).

The GP IIb/IIIa inhibitor studies with planned PCI are listed in *Table 10*. In general, use of any of the three GP IIb/IIIa inhibitors is recommended in patients undergoing PCI at high risk for acute thrombotic complications in NSTE-ACS[60] (*Figure 1*). Abciximab given shortly before the intervention is superior to placebo in reducing the acute risk of ischaemic complications (CAPTURE,[256] EPIC,[257] EPILOG,[258] EPISTENT[259]). Although these studies were 'PCI studies', one has to keep in mind that planned stenting was an exclusion criterion in EPILOG and the stent rate was quite low with 7.6% in CAPTURE and below 2% in EPIC, where stenting was discouraged (*Table 10*). In EPISTENT, 43% of the patients had stable angina and in ERASER[260] with planned stenting, patients with an evident intracoronary thrombus were excluded (*Table 10*).

Similar results can be concluded from retrospective subgroup analyses of studies performed with eptifibatide (ESPRIT,[261] IMPACT-II[262]), whereas the evidence for tirofiban is less well established (RESTORE[263]). Eptifibatide offers antiplatelet efficacy beyond ASA and clopidogrel in NSTEMI patients (PEACE study).[264] However, routine early administration of eptifibatide in the emergency department with a low PCI rate did not modulate serologic measurements of infarct size in patients with NSTE-ACS (EARLY study).[265]

In the TARGET trial,[266,267] the direct comparison of abciximab with tirofiban in patients undergoing PCI revealed less effectiveness of tirofiban in the high-risk subset. The primary endpoint, the composite of death, nonfatal MI, or urgent target-vessel revascularization at 30 days occurred significantly more frequent among the patients in the tirofiban group than in the abciximab group (7.6 vs. 6.0%). At 6 months, however, there was no statistical difference any more between abciximab and tirofiban. It has been proposed that this may be related to an under dosing of the bolus of tirofiban, which could be overcome by increasing the dose 2 to 2.5 times.[268–270] The TENACITY trial will study a higher bolus dose of tirofiban than in TARGET and compare it head to head with abciximab.

For contemporary PCI, a trial investigating the usefulness of either upstream (i.e. before diagnostic angiography) or in-lab (i.e. before PCI) initiation of a GP IIb/IIIa

Table 9 Prospective randomized trials investigating the usefulness of GP IIb/IIIa inhibitors in patients with NSTE-ACS when PCI was not planned in all patients

	GUSTO-IV ACS	PRISM	PRISM-PLUS	PURSUIT	PARAGON-A	PARAGON-B
Drug	Abciximab	Tirofiban	Tirofiban	Eptifibatide	Lamifiban	Lamifiban
Enrolment period	1998–2000	1994–1996	1994–1996	1995–1997	1995–1996	1998–1999
Number of patients	7800	3232	1915	10 948	2282	5225
Patients characterization	No persistent ST-elevation ACS	Unstable angina	Unstable angina and non-Q-wave MI	No persistent ST-elevation ACS	Unstable angina and non-Q-wave MI	No persistent (<30 min) ST-elevation ACS
Drug administration related to PCI	Not scheduled	N/A	At least 48 h before PCI (upstream)	<72 h before PCI (upstream)	At least 3–5 days in stable patients	Average 3 days before PCI
Heparin with drug	Yes (UFH or LMWH)	No	No/Yes	Yes	No/Yes (in low and high dose)	Yes (UFH or LMWH)
PCI	Discouraged, performed in 1.6% within 48 h, in 19% within 30 days	Not scheduled (performed in only 1.9% of patients)	When necessitated by refractory ischaemia or by a new MI, encouraged to postpone after 48 h, performed in 30.5%	At the discretion of the treating physician, performed in 11.2% within 72 h	Not to be performed during the first 48 h unless clinically necessitated, performed electively in 10–15% and emergent in 1.5–2.4%	Performed in 28%
Stent usage (including non-urgent)	N/A	N/A	N/A	ca. 50%	N/A	76%
Primary endpoint defined	Death/MI	Death/MI/ re-intervention	Death/MI/ re-intervention	Death/MI	Death (any cause)/MI	Death/MI/severe recurrent ischaemia
At time	30 days	48 h	7 days	30 days	30 days	30 days
Result of primary endpoint (placebo/drug, %)	(Placebo/drug for 24 h/drug for 48 h) 8.0/8.2/ 9.1	5.6/3.8[a]	Hep/tirof/hep + tirof 16.9 (17.9)/17.1/11.6 (12.9)[a]	15.7/14.2[a]	Placebo/low dose ± heparin/high dose ± heparin: 11.7/10.3/10.8/12.3/11.6	12.8/11.8
Primary endpoint reached	No	Yes (tirofiban alone)	Yes (tirofiban + heparin)	Yes	No	No

PCI was left at the discretion of the physicians, discouraged or not scheduled.
[a] $P < 0.05$.

Table 10 Prospective randomized PCI trials investigating the usefulness of GP IIb/IIIa inhibitors in patients with stable angina and/or NSTE-ACS

	CAPTURE	EPIC	EPILOG	EPISTENT	ERASER	ISAR-REACT	ESPRIT	IMPACT-II	RESTORE
Drug	Abciximab	Abciximab	Abciximab	Abciximab	Abciximab	Abciximab	Eptifibatide	Eptifibatide	Tirofiban
Enrolment period	1993–1995	Before 1994	1995	1996–1997	1996–1997	2002–2003	1999–2000	1993–1994	1995
Number of patients	1265	2099	2792	2399	225	2159	2064	4010	2212
Patients' characterization	Refractory unstable angina, enrolled within 24 h of angiography	Severe unstable angina, evolving acute MI, or high-risk coronary morphology	Urgent or elective PCI, STEMI, and NSTEMI excluded	43% stable angina, 57% UA or recent MI	Lower-risk population; MI and evident coronary thrombus excluded	Low risk (excluded were ACS, MI <14 days, insulin-dependent diabetes, visible thrombus)	Stable CAD: 49%; UA/NQMI: 46%; STEMI: 5%	Elective, urgent, or emergency PCI	UA or acute MI, (68% UA, primary PCI for AMI in 6%)
Drug administration related to PCI	18–24 h before PCI	At least 10 min before PCI	10–60 min before PCI	Up to 60 min before PCI	Immediately before PCI	Immediately before PCI	Immediately before PCI	10–60 min before PCI	At beginning of PCI
Stent usage (placebo/drug, %)	7.4/7.8	0.6–1.7 (stenting discouraged)	N/A (planned stenting was exclusion criteria)	Stenting in 67% (stenting was randomized to placebo or drug). All balloons (33%) had drug	Planned in all patients	91%	Planned in all patients	3.6/4.5 (stenting was permitted only if required to treat an abrupt closure event)	N/A (stenting discouraged)
Primary endpoint defined	Death (any cause)/MI/ re-intervention	Death (any cause)/ MI/ re-intervention/ unplanned stent/IABP	Death (any cause)/ MI/ urgent unplanned revascularization	Death/MI/ urgent unplanned revascularization	Percent in-stent volume obstruction (IVUS)	Death/MI/ urgent TVR	Death/MI/ urgent TVR/ bailout GP IIb/IIIa	Death/MI/urgent unplanned revascularization/ bailout stenting	Death (any cause)/ MI/ re-interven-tion/bailout stenting
At time	30 days	30 days	30 days	30 days	6 months	30 days	48 h	30 days	30 days
Result of primary endpoint (placebo/drug, %)	15.9/11.3[a]	Placebo/bolus/ bolus + infusion: 12.8/ 11.4/8.3[a]	Placebo/drug + low dose hep/drug + standard dose hep 11.7/5.2[a]/ 5.4[a]	Stent + placebo/ stent + drug/ balloon + drug: 10.8/5.3[a] /6.9[a] balloon angio-plasty with abciximab is safer than stenting without abciximab	Placebo/12 h infusion/ 24 hr infusion 25.1/ 27.04/29.15	4.0/4.2	10.5/6.6[a]	Placebo/bolus + lower dose infusion/bolus+ higher dose infusion 11.4/9.2/9.9	12.2/10.3
Primary endpoint reached	Yes	Yes	Yes	Yes	No	No	Yes	No	No

Although PCI was planned in all patients, these trials do not reflect contemporary PCI.
[a]$P < 0.05$.

inhibitor, the following study design would be required: inclusion of only high-risk NSTE-ACS patients, PCI planned in all patients with stenting planned in all patients. Because such a trial does not exist (*Tables 9* and *10*), the following recommendations had to be derived from non-contemporary trials: for upstream management (i.e. initiating therapy when the patient first presents to the hospital, before diagnostic catheterization), tirofiban and eptifibatide clearly show benefit.[271,272] Abciximab was effective in a predominantly non-stented population when administered within 24 h between diagnostic catheterization and planned PCI.[256] When PCI was not scheduled in an unselected UA/NSTEMI patient population, abciximab was of no benefit.[250] Abciximab is in fact unnecessary for patients treated with a non-invasive strategy.[221,273] If cardiac catheterization is unlikely to be performed within 2.5 h in high-risk NSTE-ACS patients, tirofiban or eptifibatide should be initiated ('drip and ship'),[274–276] (*Figure 1*). If cardiac catheterization is likely to be performed within 2.5 h, GP IIb/IIIa inhibitors can be postponed and abciximab or eptifibatide initiated in the catheterisation laboratory,[274,275,277] (*Figure 1*). Generally, abciximab is administered for 12 h and eptifibatide for 16 h after PCI.[278] (*Recommendation for GP IIb/IIIa inhibitors in high-risk NSTE-ACS patients with planned or performed PCI: I C*).

3.5.3. GP IIb/IIIa inhibitors for PCI in STE-ACS (STEMI)

Compared with NSTE-ACS, tirofiban and eptifibatide are less well investigated in patients with STEMI. Abciximab has been evaluated in five randomized, controlled trials (RAPPORT,[279] ISAR-2,[280] CADILLAC,[141] ADMIRAL,[147] and ACE[281]) in association with primary PCI (*Table 11*). A recent meta-analysis[282] including also a smaller study with rescue PCI[283] concluded that abciximab, as adjunctive therapy to PCI, reduces mortality, TVR, and MACE at 6 months after STEMI. The long-term benefits of abciximab administered during coronary artery stenting in patients with STEMI require more investigation.[284] (*Recommendation for abciximab in primary PCI: IIa A*).

3.6. Direct thrombin inhibitors

3.6.1. Direct thrombin inhibitors for PCI in stable CAD

In contrast to the analogues of hirudin (desirudin and lepirudin), the inhibition of thrombin by the polypeptide bivalirudin is reversible with its effects lasting for ~25 min. However, hirudin trials have repeatedly shown increases in haemorrhagic risks, but the results for bivalirudin in PCI are quite encouraging.[287] CACHET[288] was the first randomized trial to suggest that in stable patients a provisional abciximab strategy with bivalirudin as the underlying antithrombin agent may be at least equivalent to the administration of abciximab and heparin to all patients undergoing PCI. Today, bivalirudin is suggested as a replacement for UFH[289] because of significantly less bleeding compared with UFH alone (BAT trial[290]). Furthermore, the bivalirudin arm of REPLACE-2 was indirectly but prospectively compared to an imputed heparin control:[291] relative to heparin alone, the imputed odds ratio was 0.62, satisfying statistical criteria for superiority of bivalirudin to heparin alone.[291] Patients who received bivalirudin took significantly less time for the ACT to normalize despite significantly higher average ACTs and significantly fewer sub-therapeutic ACTs.[292] (*Recommendation for bivalirudin to replace UFH or LMWHs to reduce bleeding complications: IIa C*).

At present, bivalirudin is unanimously recommended as a replacement for UFH (and LMWHs) in patients with heparin-induced thrombocytopenia (HIT). In the ATBAT study in which 52 patients with HIT underwent PCI with bivalirudin, no patient had significant thrombocytopenia (platelet count $<$150 000/100 mL). Bivalirudin appeared safe and provided effective anticoagulation during PCI in this special subset of patients.[293] (*Recommendation for bivalirudin to replace UFH or LMWHs in patients with HIT: I C*).

3.6.2. Direct thrombin inhibitors for PCI in NSTE-ACS

Two randomized studies comparing a direct thrombin inhibitor with UFH were 'pure' PCI studies (*Table 12*). In the HELVETICA study, the primary endpoint (reduction of event-free survival after 7 months) was not reached by hirudin as compared to UFH.[294] The results of the bivalirudin angioplasty trial (BAT[290]) were initially published for the per protocol analysis. According to this analysis, the primary endpoint (death in the hospital, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin) was not reached. Bivalirudin significantly reduced bleeding complications from 9.8 to 3.8%. The final report was published as an intention-to-treat analysis of the entire dataset using adjudicated endpoints.[295] The combined endpoint of death, MI, or repeat revascularization (defined at 7, 90, and 180 days) was reached at day 7 and 90. Thus, the final report supports the hypothesis that bivalirudin reduces ischaemic complications and bleeding after PCI as compared to high-dose UFH (*Table 13*).

REPLACE-1[296] compared the efficacy of bivalirudin and heparin, randomizing patients for elective or urgent revascularization. The composite efficacy endpoint of death, MI, or repeat revascularization before hospital discharge or within 48 h occurred in 6.9 and 5.6% of patients in the heparin and bivalirudin groups, respectively (not significant). REPLACE-2[291] determined the efficacy and safety of bivalirudin monotherapy compared with heparin plus GP IIb/IIIa blockade with regard to protection from periprocedural ischaemic and haemorrhagic complications in patients undergoing PCI. By 30 days, the primary composite endpoint (death, MI, urgent repeat revascularization or in-hospital major bleeding) had occurred among 9.2% of patients in the bivalirudin group vs. 10.0% of patients in the heparin-plus-GP IIb/IIIa group (not significant). Despite the initial trend towards a higher frequency of (enzymatically determined) MI in the bivalirudin group, after 1 year, mortality showed a lower trend in the bivalirudin group (1.89%) compared with the heparin plus GP IIb/IIIa group (2.46%, $P = 0.16$).[297] Thus, long-term clinical outcome with bivalirudin and provisional GP IIb/IIIa blockade is

Table 11 Prospective randomized trials investigating the usefulness of abciximab in patients with planned PCI for STEMI

	RAPPORT	ISAR-2	CADILLAC	ADMIRAL	ACE	Pooled
Enrolment period	1995–1997	1997–1998	1997–1999	1997–1998	2001–2002	
Number of patients	483	401	2082	300	400	
Patients' characterization	STEMI <12 h	STEMI <48 h (including cardiogenic shock)	STEMI <12 h	STEMI <12 h (including cardiogenic shock)	Admission either <6 h of symptom onset or >6 <24 h, if evidence of continuous ischaemia (including cardiogenic shock)	
Stent usage	Discouraged, performed in 14.5%	Planned in all patients	Planned in 50% 18.1/14.0 in balloon groups, 98.0/97.7 in stent groups	Planned in all patients	Planned in all patients	
Primary endpoint defined	Death (any cause)/ re-infarction/any TVR	Late lumen loss	Death (any cause)/re-infarction/ ischaemia-driven TVR/disabling stroke	Death /MI/urgent TVR	Death (any cause)/ re-infarction/TVR/ stroke	
At time	6 months	6 months	6 months	30 days	30 days	
Result of primary endpoint (placebo/drug, %)	28.1/28.2	1.21 mm/1.26 mm	Balloon/balloon + drug/stent/stent + drug 20.0/16.5[a]/11.5[a]/10.2	14.6/6.0[a]	10.5/4.5[a]	
Primary endpoint reached	No	No	Yes (balloon only), No (stenting)	Yes	Yes	
Death, re-infarction, TVR (%) (control/abciximab)	11.3/5.8[a]	10.5/5.0[a]	6.8/4.5[a]	14.6/6.0[a]	10.5/4.5[a]	8.8/4.8[a]
Death, re-infarction (%) (control/abciximab)	5.8/4.6	6.0/2.6	3.2/2.7	7.9/4.7	8.55/4.0	4.8/3.2[a]
Death (%) (control/abciximab)	2.1/2.5	4.5/2.0	2.35/1.9	6.6/3.4	4.0/3.5	3.1/2.3

The pooled analysis for the clinical outcome relates to 30 days.[285,286]
[a]$P < 0.05$.
TVR = target vessel revascularization.

Table 12 Randomized PCI studies with direct thrombin inhibitors in predominantly NSTE-ACS patients

	HELVETICA	BAT per protocol	BAT intention to treat
Drug	Hirudin (i.v/i.v. + s.c.)	Bivalirudin	Bivalirudin
Administered related to PCI	Before PCI	Immediately before PCI	Immediately before PCI
Randomized to control	Heparin (UFH) bolus: 10 000 U 24 h inf. 15 U/kg/h	Heparin (UFH) bolus: 175 U/kg 18–24 h inf. 15 U/kg/h	Heparin (UFH) bolus: 175 U/kg 18–24 h inf. 15 U/kg/h
Patients' characterization	UA	UA/post-MI angina	UA/post-MI angina
Enrolment period	1992–1993	1993–1994	1993–1994
Number of patients	1141	4098	4312
PCI	Planned in all patients	Planned in all patients	Planned in all patients
Stent usage	Planned stenting was exclusion criteria	Planned stenting was discouraged	Planned stenting was discouraged
Major bleeding (control/drug, %)	6.2/5.5/7.7	9.8/3.8[a]	7 days: 9.3/3.5[a], 90 days: 9.3/3.7[a], 180 days: 9.3/3.7[a]
Primary endpoint defined	Event-free survival	Death/MI/abrupt vessel closure/rapid clinical deterioration of cardiac origin	Death/MI/revascularization
At time	7 months	In-hospital	7, 90, 180 days
Result of primary endpoint (control/drug, %)	67.3/63.5/68.0	12.2/11.4	7 days: 7.9/6.2[a], 90 days: 18.5/15.7[a], 180 days: 24.7/23.0
Primary endpoint reached	No	No	Yes (7 and 90 days)

[a] $P < 0.05$.

Table 13 Recommendations for GP IIb/IIIa inhibitors and bivalirudin as adjunctive medications for PCI

Medication	Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Abciximab, eptifibatide, tirofiban, in stable CAD	Complex lesions, threatening/actual vessel closure, visible thrombus, no/slow reflow	IIa C	—
Abciximab, eptifibatide in NSTE-ACS	Immediately before PCI in high-risk patients	I C	—
Tirofiban, eptifibatide in NSTE-ACS	Pre-treatment before diagnostic angiography and possible PCI within 48 h in high-risk patients (upstream)	I C	—
Abciximab in NSTE-ACS	In high risk patients with known coronary anatomy in the 24h before planned PCI	I C	—
Abciximab in STEMI	All primary PCI (preferably in high-risk patients)	IIa A	ADMIRAL, ACE
Bivalirudin	Replacement for UFH or LMWHs (± GP IIb/IIIa inhibitors) to reduce bleeding complications	IIa C	—
Bivalirudin	Replacement for UFH in HIT	I C	—

comparable with that of heparin plus planned GP IIb/IIIa inhibition during contemporary PCI.[297] For final recommendations regarding bivalirudin in NSTE-ACS, the ongoing ACUITY trial will provide further information.

3.6.3. Direct thrombin inhibitors in STE-ACS (STEMI)

At present, even when analysing the PCI subgroups, there is no evidence-based recommendation to use direct thrombin inhibitors for PCI in STEMI.[298,299]

In summary, given the overall low risk of PCI in stable CAD patients, the potential of GP IIb/IIIa inhibitors to increase the risk of bleeding complications, and the considerable cost of their use, they are not a part of standard periprocedural medication. The use of GP IIb/IIIa inhibitors for PCI in stable angina should be considered on an elective basis: whenever there is a higher than average risk of acute thrombotic complications in stable CAD (complex interventions, unstable lesions, as bail-out medication in case of threatening/actual vessel closure, visible thrombus, or no/slow-reflow phenomenon), GP IIb/IIIa inhibitors are helpful.

In NSTE-ACS, GP IIb/IIIa inhibitors should be added only in high-risk patients, in whom an invasive strategy is planned. For 'upstream' management (i.e. initiating therapy when the patient first presents to the hospital and catheterization is not planned or available within 2.5 h), tirofiban and eptifibatide show benefit. If cardiac catheterization is likely to be performed within 2.5 h, GP IIb/IIIa inhibitors could possibly be postponed and abciximab or eptifibatide initiated in

the catheterization laboratory. If, for some reason, the delay between diagnostic catheterization and planned PCI is up to 24 h, abciximab can also be administered.

In patients with STEMI, the GP IIb/IIIa inhibitors tirofiban and eptifibatide are less well investigated. In STEMI, stenting plus abciximab seems to be a more evidence-based reperfusion strategy. Bivalirudin is suggested today as a replacement for UFH (or LMWHs) because of significantly less bleeding compared with UFH alone or UFH + GP IIb/IIIa inhibitors. Bivalirudin is unanimously recommended for PCI as a replacement for UFH (and LMWHs) in patients with HIT.

4. Adjunctive devices for PCI

4.1. Intracoronary brachytherapy for in-stent restenosis

In-stent restenosis is based on intimal hyperplasia within the stent and often including its edges. Although balloon angioplasty is safe for the treatment of in-stent restenosis, it is associated with high recurrence rates up to 80%.[300,301] For in-stent restenosis, the risk factors are well delineated: mainly, longer lesion length (>30 mm), longer stent length, smaller vessel diameter (<2.5 mm), smaller post-treatment lumen diameter, reopened chronic total occlusions, ostial/bifurcations location, and the presence of diabetes mellitus.[302–304]

In several randomized, placebo-controlled trials, intracoronary brachytherapy showed significant improvement in angiographic and clinical outcome in native coronary arteries (GAMMA-I,[305] WRIST,[306] LONG-WRIST,[307] START,[308] INHIBIT[309]) and in saphenous venous bypass grafts (SVG-WRIST[310]). These results reflected the 'real world' situation as confirmed by the European RENO registry.[311] Restenosis observed at the stent edges was a major concern in the beginning of the brachytherapy era. The risk of the edge phenomenon is minimized by the use of long sources (or a sequential, i.e. pull-back technique) that effectively irradiate the complete vessel segment of interest. The clinical long-term results with a remaining significant reduction in MACE with beta radiation in START[312] was comparable to those obtained by gamma radiation in SCRIPPS-I,[313] GAMMA-1,[314] and WRIST[315] (*Table 14*).

For gamma radiation, good long-term results after 3 and 5 years have been reported.[316,317] To prevent late vessel occlusion, a prolonged intake of clopidogrel for 1 year after radiation therapy is widely accepted.[318,319] (*Recommendation for brachytherapy to treat in-stent restenosis in native coronary arteries: I A; Recommendation for brachytherapy to treat in-stent restenosis in saphenous venous bypass grafts: I B*).

Table 14 MACE after 2 years in randomized, controlled studies with intracoronary brachytherapy for in-stent restenosis

Study	Type of radiation	MACE (%) control	MACE (%) brachytherapy
SCRIPPS-I	Gamma	72.4	38.5[a]
GAMMA-1	Gamma	72.0	48.0[a]
WRIST	Gamma	52.0	41.0[a]
START	Beta	40.1	31.3[a]

[a]$P < 0.05$.

4.2. Cutting balloon

The cutting balloon (CB) is fitted lengthwise with three or four metal razors, making longitudinal plaque incisions at dilatation. The incisions theoretically encourage favourable plaque redistribution at lower inflation pressures compared with balloon angioplasty.

The 'cutting balloon global randomized trial' tested the concept of 'controlled dilatation' in 1238 patients with a *de novo* stenosis.[320] However, the primary endpoint, the 6-month binary angiographic restenosis rate, was 31.4% for the CB and 30.4% for the balloon angioplasty. Thus, the proposed mechanism of controlled dilatation did not reduce the rate of angiographic restenosis for the CB compared with conventional balloon angioplasty. According to several retrospective studies and small randomized trials, the CB has also been suggested for the treatment of in-stent restenosis. However, data from the randomized RESCUT trial[321] do not justify the use of the CB for in-stent restenosis. The CB may still be useful in the treatment of in-stent restenosis, because avoiding balloon slippage reduces vessel trauma. In combination with brachytherapy, the cutting balloon is a logical choice for reducing the likelihood of 'geographical miss' on the basis of reduced slippage. (*Recommendation for the cutting balloon to avoid slipping-induced vessel trauma during PCI of in-stent restenosis: IIa C*).

4.3. Rotablation

High speed (140 000–180 000 rpm) diamond-burr rotablation (ROTA, PTCR, or PRCA) 'pulverizes' the atheroma. Because of the more frequent occurrences of spasm and no/slow-flow phenomenon, one must know how to manage these complications (CARAFE study[322]), especially those related to its proprietary technology. The COBRA trial[323] was designed to prove the efficacy of rotablation in complex *de novo* lesions compared to balloon angioplasty. The results, however, could not show any long-term benefits. STRATAS[324] found no advantages of a more aggressive rotablation and the CARAT trial[325] showed that aggressive debulking with bigger burr sizes led to a higher complication rate and worse clinical outcome compared with smaller-size burrs. Rotablation has also been suggested for the treatment of in-stent restenosis, because tissue ablation with ROTA may be more efficacious compared with tissue compression or extrusion with plain balloon angioplasty. This strategy, however, is still a matter of controversy. The ARTIST trial[326] revealed a significantly worse outcome for ROTA when compared with balloon angioplasty. On the other side, in ROSTER,[327] MACE at 1-year follow-up was significantly better in the ROTA group. In ROSTER, IVUS was mandatory for excluding patients with

underdeployed stents. In general, we do not support the use of rotablation for in-stent restenosis.

With the increasing use of drug-eluting stents and its need for a homogeneous drug release based on an optimal apposition of the stent struts in calcified lesions, rotablation might again be increasingly used. For practical clinical use it is well known that wired lesions, which cannot be crossed by a balloon or cannot be adequately dilated with an even non-compliant balloon, may occasionally be better treated by rotatablation.[328] (*Recommendation for rotablation of fibrotic or heavily calcified lesions that cannot be crossed by a balloon or adequately dilated before planned stenting: I C*).

4.4. Directional coronary atherectomy

The concept of removing obstructive coronary plaque by directional coronary atherectomy (DCA) to obtain a large vessel lumen (rather than compressing the plaque with balloons/stents) appears attractive; CAVEAT-I,[329] however, resulted in higher rates of early complications at a higher cost and with no clinical benefit. CAVEAT-II[330] compared DCA and balloon angioplasty in vein grafts with no difference in 6-month restenosis rates. The BOAT,[331] the CCAT,[332] and the OARS studies[333] had no impact on clinical outcome over a period of 18 months after DCA. In the AMIGO trial,[334] considerable interinstitutional differences existed, possibly explaining some of the negative results. For research, atherectomy is the only percutaneous method available to retrieve tissue safely from obstructive atheromatous plaques or restenotic lesions for histology. (*Recommendation for DCA of de-novo ostial or bifurcational lesions in experienced hands: IIb C*).

4.5. Embolic protection devices

Most patients undergoing PCI are potentially exposed to distal coronary embolization,[335] especially in interventions of saphenous vein graft (SVG).[336] PCI of *de novo* stenoses in SVG must be considered a high-risk intervention.[337,338] A pooled analysis of five randomized clinical trials revealed that GP IIb/IIIa inhibitors do not improve outcomes after PCI of bypass grafts.[339] The use of membrane-covered (PTFE) stents did not reduce clinical event rates resulting from distal embolisation (STING,[340] RECOVERS,[341] and SYMBIOT-III).

The no-reflow phenomenon is characterized by inadequate flow at tissue level despite a fully dilated/reopened epicardial coronary artery. These myocardial areas of 'no-reflow' may be caused by microvascular disruption, endothelial dysfunction, myocardial oedema, or embolization of thrombotic or atheromatous debris. It may result in critical haemodynamic deterioration.[342] Therefore, different approaches are being evaluated to prevent distal embolisation. Several devices aiming at filtering[343] or aspirating[344] embolic particles in the target vessel are currently undergoing randomized controlled evaluation.

4.5.1. Distal protection (blocking, filter) devices

A protection system using an obstructing balloon placed distally to the lesion and an aspiration catheter (GuardWire) significantly improves myocardial perfusion grade in SVG PCI.[345] It was investigated in the SAFER trial in patients having PCI of a SVG.[346] The primary endpoint [death, MI, emergency bypass, or target lesion revascularization (TLR) by 30 days] was significantly reduced from 16.5 to 9.6%. This 42% relative reduction in MACE was driven by MI (14.7 vs. 8.6%) and 'no-reflow' phenomenon (9 vs. 3%).[346] In contrast to such an occlusive device, distal protection with catheter-based filters offer the inherent advantage of maintained antegrade perfusion. The FIRE trial was a randomized, controlled 'non-inferiority' study, comparing two different concepts of peripheral protection devices in SVG lesions.[347] The composite incidence of death, MI or TVR at 30 days, occurred in 9.9% of FilterWire EX patients and in 11.6% of GuardWire patients. In CAPTIVE, the CardioShield failed to demonstrate a non-inferiority benefit as compared to the GuardWire in reducing emboli during PCI of SVGs. The TriActiv balloon-protected flush extraction system is another distal protection device combined with a suction mechanism, In the PRIDE trial, it was not inferior to the GuardWire and the FilterWire. However, a considerable number of patients with SVG disease intended for PCI have anatomic exclusions to currently available distal protection technology,[348] leaving room for further improvement. (*Recommendation for distal embolic protection devices for PCI in SVGs: I A*).

The positive results in SVG, however, were not corroborated in the setting of primary PCI of native vessels in STEMI. In the EMERALD trial, infarct size was reduced in 17% of the distal protection group and in 16% of the control PCI group.[349]

4.5.2. Proximal protection (suction, thrombectomy) devices

One limitation of distal application of occlusive balloons or filters to a lesion is the need to cross the lesion without scratching it and to look for a suitable 'landing zone' for the balloon or filter. Alternative devices for instant suction and/or proximal occlusion balloons are possibly more useful in this setting. The simplest technique would be to use the guiding catheter itself as a 'suction device'. The suction device AngioJet was investigated in a randomized study compared with Urokinase infusion in patients with angiographically evident thrombus in an SVG (VeGAS-2[350]) with no difference in the incidence of the primary composite endpoint of MACE. The AngioJet also failed to reduce infarct size in STEMI patients (AiMI). The X-SIZER is another suction device, which may be useful in patients with acute MI.[351,352] In the X-TRACT randomized study, patients with SVG or thrombus-containing native coronary arteries were prospectively allocated to stent implantation with vs. without prior thrombectomy with the X-SIZER device.[353] Periprocedural MI at 30 days occurred in 15.8% of patients assigned to the X-SIZER device compared with 16.6% of control patients (not significant). A subgroup analysis

indicated that thrombectomy with the X-SIZER may reduce the extent, but not the occurrence of myonecrosis. Early and late event-free survival, however, was not improved by routine thrombectomy with this device. Distal protection with a filter device might be useful in lesions with higher embolic potential.[354] (*Recommendation for distal and proximal embolic protection devices for PCI in lesions with a high thrombus load: IIb C*).

For the emergency management of coronary perforations, PTFE-covered stents ('graft stents') are recommended at level I C on the basis of expert consensus (*Table 15*).[355]

In summary, intracoronary brachytherapy proved to be the only evidence-based non-surgical treatment of in-stent restenosis. To avoid late vessel thrombosis, a prolonged intake of clopidogrel for 1 year after radiation therapy is necessary.

Rotablation is recommended for fibrotic or heavily calcified lesions that can be wired but not crossed by a balloon or adequately dilated before planned stenting. One must know how to manage the complications inherent to rotablation.

PCI of SVGs or primary PCI in ACS with a high thrombotic load is at elevated risk for coronary embolization. Two distal protection devices (GuardWire and FilterWire EX) have proved their safety and efficacy as an adjunctive device for PCI of SVG lesions.

Whether balloon occlusion and aspiration systems or filter-based catheters will be preferred in other clinical settings such as primary PCI for STEMI will require more randomized trials with a clinical primary endpoint. At present, no definite recommendations can be given regarding the use of embolic protection devices in the setting of STEMI.

4.6. Adjunctive diagnostic technology

4.6.1. Intravascular ultrasound

Whereas angiography depicts only a 2-dimensional silhouette of the lumen, intravascular ultrasound (IVUS) allows tomographic assessment of lumen area, plaque size, distribution, and composition. IVUS is a valuable adjunct to angiography, providing extended insights into the diagnosis and therapy, including stent implantation for CAD.[356–359] Although interventional cardiology has learnt a lot by IVUS, it has been difficult to translate this effect into a reduction of major adverse clinical endpoints during follow-up. The routine performance of IVUS during stent placement did not improve clinical outcome at 9 months.[360]

4.6.2. Fractional flow reserve

Although non-invasive stress imaging with its sensitivity of 76–88% and its specificity of 80–88% should be the gold standard before cardiac catheterization, many patients in the real world come to the catheterization laboratory without prior functional tests. If ever possible, an appropriate functional test should be done before the procedure. If contra-indications to non-invasive stress imaging exist or when exercise-induced ischaemia cannot be excluded in the perfusion bed of a coronary artery with 'intermediate' stenosis, the measurement of fractional flow reserve (FFR) is helpful. Furthermore, interventional cardiologists usually choose not to treat stenoses that do not appear haemodynamically significant. However, pathology studies and IVUS demonstrated that diffuse coronary lesions, particularly after plaque rupture, are complex, with distorted luminal shapes that are difficult to assess using a planar angiographic silhouette. Even experienced interventional cardiologists

Table 15 Recommendations for adjunctive PCI devices

Device	Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Brachytherapy	In-stent restenosis in native coronary arteries	I A	SCRIPPS-I,GAMMA-1,WRIST, LONG-WRIST, START, INHIBIT
Brachytherapy	In-stent restenosis in saphenous bypass grafts	I B	SVG-WRIST
Cutting balloon	In-stent restenosis in conjunction with brachytherapy to avoid geographical miss, slippage of balloons with risk of jeopardizing adjacent segments	IIa C	—
Rotablation	Fibrotic or heavily calcified lesions that cannot be crossed by a balloon or adequately dilated before planned stenting	I C	—
DCA	*De novo* ostial or bifurcational lesions in experienced hands	IIb C	—
Distal embolic protection	Saphenous vein grafts	I A	SAFER, FIRE
Distal and proximal protection devices	ACS with high thrombus load in native coronary arteries	IIb C	—
PTFE-covered stents	Emergency tool for coronary perforations	I C	—

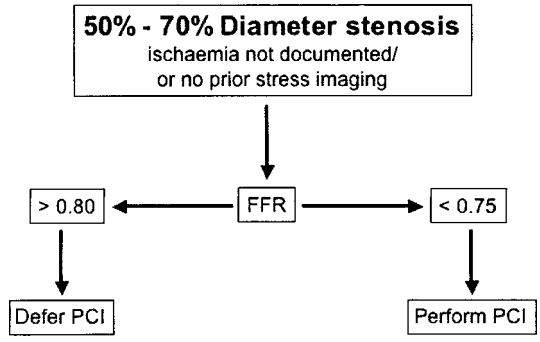

Figure 4 Decision-making for the management of angiographically intermediate coronary stenoses without documented myocardial ischaemia (absence of any localizing information, such as resting ECG changes, new wall motion abnormalities, or prior stress imaging). For FFR values between 0.75 and 0.80, a 'grey zone' exists.

cannot accurately predict the significance of most intermediate narrowings on the basis of visual assessment or QCA.[361]

An FFR < 0.75 is very specific and always represents inducible ischaemia (*Figure 4*). An FFR > 0.80 excludes ischaemia in 90%.[362] Within this window, 'false positive' and 'false negative' findings must be accepted (*Figure 4*). FFR thus appears to be the ideal method for interrogating intermediate coronary lesions if no prior tests or signs of myocardial ischaemia have been documented. Retrospective analyses suggested that deferral of angioplasty in patients with FFR > 0.75 is safe and results in an excellent clinical outcome.[363,364] The importance of demonstrating that a given 'to be dilated' stenosis truly impedes maximal flow to the myocardium downstream was underscored in the DEFER trial:[365] if FFR was <0.75, PCI was performed as planned (reference group); if FFR was ≥ 0.75, PCI was either deferred or performed. Event-free survival was similar between the deferral and PCI groups (92 vs. 89% at 12 months and 89 vs. 83% at 24 months). Thus, the measurement of FFR is a valuable tool to identify patients with borderline lesions in whom PCI is an appropriate treatment, including patients with angiographic 40–70% in-stent restenosis.[366]

The concept of 'plaque sealing',[367,368] i.e. stenting of mild, so-called 'non-significant' lesions cannot be recommended because the short-term MACE rates outweigh any hypothetical long-term benefit—at least with bare metal stents.[369–371] First results in patients treated with a sirolimus-eluting stent for mild *de novo* lesions (defined as a diameter stenosis $<50\%$) showed that no patient required target lesion revascularization at a mean follow-up of 400 days.[372]

5. Drug-eluting stents

Drug-eluting stents (DES) have been the focus of attention of PCI since the RAVEL study was first presented at the ESC Congress in September 2001.[373] A variety of different drugs released from various stent platforms with or without a polymer carrier was investigated. Numerous studies have assessed the effects of various anti-proliferative and anti-inflammatory substances, like sirolimus, paclitaxel and tacrolimus, everolimus, ABT-578, biolimus as well as QP2 and other drugs, like dexamethasone, 17-β-estradiol, batimastat, actinomycin-D, methotrexat, angiopeptin, tyrosinkinase inhibitors, vincristin, mitomycin, cyclosporin, and the C-myc antisense-Technology (Resten-NG, AVI-4126). Statins, carvedilol, abciximab, and trapidil were also suggested as drugs to be released from stents. The intracoronary application of many anti-proliferative and anti-inflammatory drugs via DES was abandoned despite initially encouraging experimental and clinical results, because the clinical results were either harmful (e.g. QP2 in the SCORE Study,[374,375] actinomycin-D in the ACTION Study[376]) or too weak (e.g. dexamethason in the STRIDE Study[377]; even high dose dexamethasone-loaded stents did not significantly reduce neointimal proliferation[378]). The results of these trials indicate that all anti-proliferative drugs will not uniformly show a drug class effect in the prevention of restenosis.

Primary endpoints of randomized DES studies were either angiographic (e.g. late lumen loss, LLL) or clinical (e.g. target vessel revascularization, TVR). For the patients, their clinical course is more important than their angiographic parameters. As the power of a randomized trial is only valid for its primary endpoint, we will focus on randomized DES trials with a clinical primary endpoint.[379] So far, only four controlled randomized studies with a clinical primary endpoint at an adequate time interval have been published (*Table 16*). Paclitaxel without a polymer carrier did not reach the primary endpoint in spite of a positive angiographic result in DELIVER-I.[380] In contrast, when released from a polymer carrier, Paclitaxel significantly improved clinical outcome in the TAXUS-IV[381] and TAXUS-VI[382] trials (*Table 16*). Thus, not all Paclitaxel-eluting stents are equal.[383,384] Sirolimus has been clinically tested only by being eluted from a polymer carrier, like in the SIRIUS trial[385] (*Table 16*). Although the dream of 'no restenosis'[386] is beyond realization, DES provide a fair single-digit number for angiographic and clinical restenosis at 9 months (*Table 16*). In 'real life' (RESEARCH registry[387]), the 1-year risk of clinically driven TVR for the Sirolimus-eluting stent was 3.7%. In a Swiss registry, MACE-free survival at 6–9 months was 95.6%.[388] In LAD lesions, sirolimus-eluting stent revascularization rates are comparable to historic single vessel bypass surgery revascularization rates at 1 year.[389] First results of a prospective, randomized comparison of Cypher vs. Taxus stents (TAXi trial[390]) confirmed that the high success rate obtained with both stents in the pivotal randomized trials could be replicated in routine clinical practice. This small trial in 202 patients was unable to show any advantage of one stent over the other.

5.1. Vessel size, long lesions, diabetes

Table 17 shows the effects of the Cypher stent in SIRIUS and of the Taxus stent in TAXUS-IV after subgroup analysis regarding the vessel size in three steps (terciles).

Table 16 Prospective, randomized controlled studies for drug-eluting stents with a clinical parameter as primary endpoint at an adequate time interval (9 months)

	DELIVER-I		TAXUS-IV		SIRIUS		TAXUS-VI	
Drug	Paclitaxel		Paclitaxel		Sirolimus		Paclitaxel	
Polymer carrier	No		Yes		Yes		Yes	
Inclusion criteria reference diameter (mm)	2.5–4.0		2.5–3.75		2.5–3.5		2.5–3.75	
Inclusion criteria lesion length (mm)	<25		10–28		15–30		18–40	
Randomized group	*Control*	*DES*	*Control*	*DES*	*Control*	*DES*	*Control*	*DES*
Patients	519	522	652	662	525	533	227	219
Reference diameter (mm)	2.77	2.85	2.75	2.75	2.81	2.78	2.77	2.81
Lesion length (mm)	11.1	11.7	13.4	13.4	14.4	14.4	20.3	20.9
RR (%) in-segment	22.4	16.7	26.6	7.9[a]	36.3	8.9[a]	35.7	12.4[a]
LLL (mm) in-stent	0.98	0.81[a]	0.92	0.39[a]	1.0	0.17[a]	0.99	0.39[a]
TLR (%)	11.3	8.1	11.3	3.0[a]	16.6	4.1[a]	18.9	6.8[a]
TVR (%)	–	–	12.0	4.7[a]	19.2	6.4[a]	19.4	9.1[a]
TVF (%)	14.5	11.9	14.4	7.6[a]	21.0	8.6[a]	22.0	16.0
Death (%)	1.0	1.0	1.1	1.4	0.6	0.9	0.9	0.0
Infarction (%)	1.0	1.2	3.7	3.5	3.2	2.8	1.3	1.4
MACE 9 months (%)	13.3	10.3	15.0	8.5[a]	18.9	7.1[a]	22.5	16.4
Primary endpoint reached?	No (TVF)		Yes (TVR)		Yes (TVF)		Yes (TVR)	

[a]$P < 0.05$ compared with the bare stent.
RR = restenosis rate, LLL = late lumen loss, TLR = target lesion revascularization, TVR = target vessel revascularization, TVF = target vessel failure.

Table 17 The effect of DES depending on mean size of the reference vessel

	SIRIUS			TAXUS-IV		
	Small ~2.3 mm	Medium ~2.8 mm	Large ~3.3 mm	Small ~2.2 mm	Medium ~2.7 mm	Large ~3.3 mm
Restenosis rate (RR)						
Control(%)	42.9	36.5	30.2	38.5	26.5	15.7
DES (%)	18.6[a]	6.3[a]	1.9[a]	10.2[a]	6.5[a]	7.1
Target lesion revascularization (TLR)						
Control (%)	20.6	18.3	12.0	15.6	10.3	7.5
DES (%)	7.3[a]	3.2[a]	1.8[a]	3.3[a]	3.1[a]	2.7[a]

[a]$P < 0.05$ compared with the bare stent.

Table 18 Percentage of patients with diabetes mellitus and the effects of DES depending on the kind of antidiabetic therapy

	SIRIUS		TAXUS-IV	
	Control	DES	Control	DES
Diabetic patients (%)	28.2	24.6	25.0	23.4
Oral antidiabetics	19.6	17.9	16.7	15.7
Insulin dependent (%)	8.4	7.1	8.3	7.7
Restenosis rate, RR (%)				
All diabetic patients	50.5	17.6[a]	34.5	6.4[a]
Oral antidiabetics	50.7	12.3[a]	29.7	5.8[a]
Insulin dependent	50.0	35.0	42.9	7.7[a]
Target lesion revascularization, TLR (%)				
All diabetic patients	22.9	7.2[a]	16.0	5.2[a]
Oral antidiabetics	23.8	4.4[a]	17.4	4.8[a]
Insulin dependent	20.8	13.9	13.0	5.9

[a]$P < 0.05$ compared with the bare stent.

In TAXUS-VI, TLR was significantly reduced in small vessels (<2.5 mm) from 29.7 to 5.0%.[382] A subgroup analysis of the RESEARCH registry in 112 lesions of 91 patients treated with 2.25-mm Cypher stents (reference vessel diameter = 1.88 ± 0.34 mm) reported a late loss of 0.07 ± 0.48 mm and a restenosis rate of 10.7%.[391]

Diabetes mellitus is another known risk factor for restenosis after stent implantation.[392] In an analysis of all patients with diabetes mellitus, RR and TLR could be significantly reduced in SIRIUS as well as in TAXUS-IV (*Table 18*).

Although the results of the SIRIUS subgroup analysis are promising, a trend towards a higher frequency of repeat intervention remains in diabetic patients compared with non-diabetic patients, particularly in the insulin-requiring patients.[393] In the diabetic patients with long lesions of TAXUS-VI, TLR was significantly reduced from 22.0 to 2.6%.[382]

5.2. Stent thrombosis of DES

Stent thrombosis has not been detected as a relevant problem in the randomized trials when administering clopidogrel in addition to ASA for differing periods of 2, (E-SIRIUS[394]), 3 (SIRIUS), and 6 months in the TAXUS series. The rate of stent thrombosis in DELIVER-I after 1 year was 0.4% in both groups; in SIRIUS after 9 months it was 0.4% in the DES group and 0.8% in the control group. In E-SIRIUS, the two cases of subacute stent thromboses (1.1%) with consecutive MI occurred in the Sirolimus group, whereas there was no case of subacute or late stent thrombosis in the control group. In TAXUS-IV, stent thrombosis occurred within 9 months in 0.6% of the DES group and in 0.8% of the control group. In the long run (and in over 50% of complex lesions) of TAXUS-VI, stent thrombosis at 300 days occurred in 1.3% of the control group and in 0.5% of the DES group.[382] Between day 31 and day 300 stent thrombosis occurred in neither group.[382]

On the other hand, complete healing of the DES may theoretically take up to 2 years. Registries are important to see whether the results of the controlled studies can be applied to everyday practice. The premature discontinuation of thienopyridines was strongly associated with the development of stent thrombosis.[395] (*Recommendation for 6–12 months clopidogrel administration after DES: I C*).

In patients in whom prolonged administration of clopidogrel is known to be unlikely (i.e. major extracardiac surgery planned soon[396]), DES should be used with caution. In these patients, bare stents are probably the safer choice.

5.3. Indications for DES

Fears of medicolegal repercussions for either using or failing to use DES are unfounded and unlikely to materialize.[397] DES should never be implanted solely to avoid potential litigation.[397]

There are two alternative approaches for making recommendations for the use of DES: one is based on cost-effectiveness calculations,[398] the other is purely recommending their use according to the inclusion/exclusion criteria of the pivotal randomized trials. According to the levels of evidence, only the Cypher and the Taxus stents can be recommended at a level I B, regarding the inclusion/exclusion criteria of the SIRIUS, TAXUS-IV, and TAXUS-VI studies (*Table 19*).

The UK NHS NICE Institute recommends the use of DES as follows:[399] 'The use of either a Cypher (sirolimus-eluting) or Taxus (paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic CAD, in whom the target artery is <3 mm in calibre (internal diameter) or the lesion is >15 mm. This guidance for the use of DES does not apply to people who have had an MI in the preceding 24 h, or for whom there is angiographic evidence of thrombus in the target artery.[399] Nevertheless, DES have been used in unstable angina and acute MI.[400]

All of the following applications, especially in situations with increased risk of restenosis,[401–403] require further evidence-based evaluation (present recommendation IIa C):

- small vessels
- chronic total occlusions
- bifurcational/ostial lesions
- bypass stenoses
- insulin-dependent diabetes mellitus
- multi-vessel disease
- unprotected left main stenoses
- in-stent restenoses

Although randomized trials have yet to be performed, direct stenting (i.e. without pre-dilatation) appears to be safe and effective with the Cypher and the Taxus stents.[404]

A convincing reduction of costs in medical care will also be achieved if DES considerably reduce the number of patients undergoing CABG surgery, especially patients with multi-vessel disease and/or diabetes mellitus.

In summary, only two DES have shown significantly positive effects in prospective, randomized studies with clinical primary endpoints at an appropriate time: the Cypher stent (Sirolimus) and the Taxus stent (Paclitaxel). Evidence-based recommendations for the use of DES must focus on the enrolment criteria of SIRIUS, TAXUS-IV, and TAXUS-VI. In these patients,

Table 19 Recommendations for the use of DES in *de novo* lesions of native coronary arteries

DES	Indication	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Cypher stent	*De novo* lesions in native vessels according to the inclusion criteria	I B	SIRIUS
Taxus stent	*De novo* lesions in native vessels according to the inclusion criteria	I B	TAXUS-IV
Taxus stent	*De novo* long lesions in native vessels according to the inclusion criteria	I B	TAXUS-VI

There are only three positive controlled, randomized, adequately powered trials with a primary clinical endpoint at an appropriate time interval. Main clinical inclusion criteria for SIRIUS, TAXUS-IV, and TAXUS-VI were similar: stable or unstable angina or documented ischaemia. The stenoses had to be in native vessels >50 <100%. In SIRIUS, reference diameter and lesion length for inclusion were 2.5–3.5 mm and 15–30 mm, respectively. The reference diameter in TAXUS-IV and TAXUS-VI was 2.5–3.75 mm. In TAXUS-IV, the lesion length was 10–28 mm and in TAXUS-VI 18–40 mm. The main common exclusion criteria were acute MI or status post MI with elevated CK/CK-MB, bifurcational or ostial lesions, unprotected left main, visible thrombus, severe tortuosity, and/or calcification.

target vessel revascularization (TVR) rates were single-digit numbers. Subgroup analyses regarding smaller vessels and patients with diabetes are encouraging. Although registry data for in-stent restenosis as well as for other lesions with high risk for in-stent restenosis (bifurcational or ostial lesions, chronic total occlusions, multi-vessel disease, bypass stenoses and unprotected left main stenoses) is promising, randomized trials must be conducted for achieving higher levels of evidence in these special subsets of patients. At present, we consider the prolonged (at least 6 months) administration of clopidogrel (in addition to ASA) as mandatory to avoid late stent thrombosis. Therefore, in patients undergoing or soon will be undergoing urgent major extracardiac surgery, DES should not be implanted. In these patients, bare stents are probably the safer choice. Physicians and patients must be made aware that clopidogrel should not be discontinued too early, even for minor procedures like dental care.

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