European Heart Journal (2005) **26**, 804–847
doi:10.1093/eurheartj/ehi138

EUROPEAN SOCIETY OF CARDIOLOGY®

ESC Guidelines

Guidelines for Percutaneous Coronary Interventions

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

Authors/Task Force Members: Sigmund Silber, Chairperson* (Germany), Per Albertsson (Sweden), Francisco F. Avilés (Spain), Paolo G. Camici (UK), Antonio Colombo (Italy), Christian Hamm (Germany), Erik Jørgensen (Denmark), Jean Marco (France), Jan-Erik Nordrehaug (Norway), Witold Ruzyllo (Poland), Philip Urban (Switzerland), Gregg W. Stone (USA), William Wijns (Belgium)

ESC Committee for Practice Guidelines (CPG): Silvia G. Priori (Chairperson) (Italy), Maria Angeles Alonso Garcia (Spain), Jean-Jacques Blanc (France), Andrzej Budaj (Poland), Martin Cowie (UK), Veronica Dean (France), Jaap Deckers (The Netherlands), Enrique Fernandez Burgos (Spain), John Lekakis (Greece), Bertil Lindahl (Sweden), Gianfranco Mazzotta (Italy), Keith McGregor (France), João Morais (Portugal), Ali Oto (Turkey), Otto A. Smiseth (Norway)

Document Reviewers: Jaap Deckers (CPG Review Coordinator) (The Netherlands), Jean-Pierre Bassand (France), Alexander Battler (Israel), Michel Bertrand (France), Amadeo Gibert Betriu (Spain), Dennis Cokkinos (Greece), Nicolas Danchin (France), Carlo Di Mario (Italy), Pim de Feyter (The Netherlands), Kim Fox (UK), Ciro Indolfi (Italy), Karl Karsch (UK), Manfred Niederberger (Austria), Philippe Gabriel Steg (France), Michal Tendera (Poland), Frans Van de Werf (Belgium), Freek W.A. Verheugt (The Netherlands), Petr Widimski (Czech Republic)

Online publish-ahead-of-print 15 March 2005

Table of Contents

Summary 2
Preamble 2
1. Introduction and definitions 3
1.1. Method of review 3
1.2. Definition of levels of recommendation 3
2. Indications for PCI 4
2.1. Indications for PCI in stable coronary artery disease 3
2.2. Indications for PCI in acute coronary syndromes without ST-segment elevation 6
2.3. Indications for PCI in ACS with ST-segment elevation 8
3. Adjunctive medications for PCI 15
3.1. Acetylsalicylic acid 16
3.2. Ticlopidine and clopidogrel 16
3.3. Unfractionated heparin 17
3.4. Low molecular weight heparins 18
3.5. Glycoprotein IIb/IIIa inhibitors 19
3.6. Direct thrombin inhibitors 22
4. Adjunctive devices for PCI 25
4.1. Intracoronary brachytherapy for in-stent restenosis 25
4.2. Cutting balloon 25
4.3. Rotablation 25
4.4. Directional coronary atherectomy 26
4.5. Embolic protection devices 26
4.6. Adjunctive diagnostic technology 27
5. Drug-eluting stents 28
5.1. Vessel size, long lesions, diabetes 28
5.2. Stent thrombosis of DES 29
5.3. Indications for DES 30
References 31

* Corresponding author. Chairperson: Prof. Sigmund Silber, MD, FACC, FESC, Kardiologische Praxis und Praxisklinik, Am Isarkanal 36, 81379 München, Germany. Tel: +49 89 742 15130; fax: +49 89 742 151 31.
E-mail address: sigmund@silber.com

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 $\geq$0.1 mV or transient (<30 min) ST-segment elevation $\geq$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	—

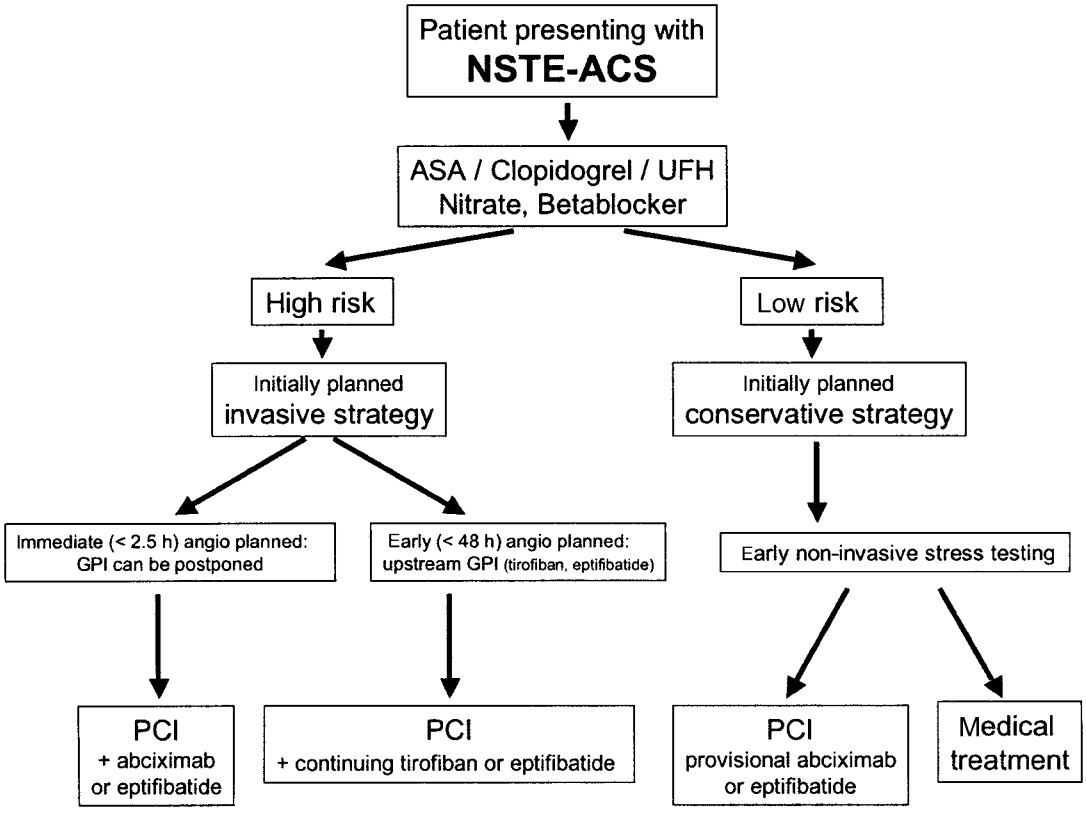

Figure 1 Flow-chart for planning coronary angiography and PCI, if appropriate, according to risk stratification in patients with NSTE-ACS (unstable angina or NSTEMI). GPI, Glycoprotein IIb/IIIa inhibitor. If for some reason the delay between diagnostic catheterization and planned PCI is up to 24 h, abciximab 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

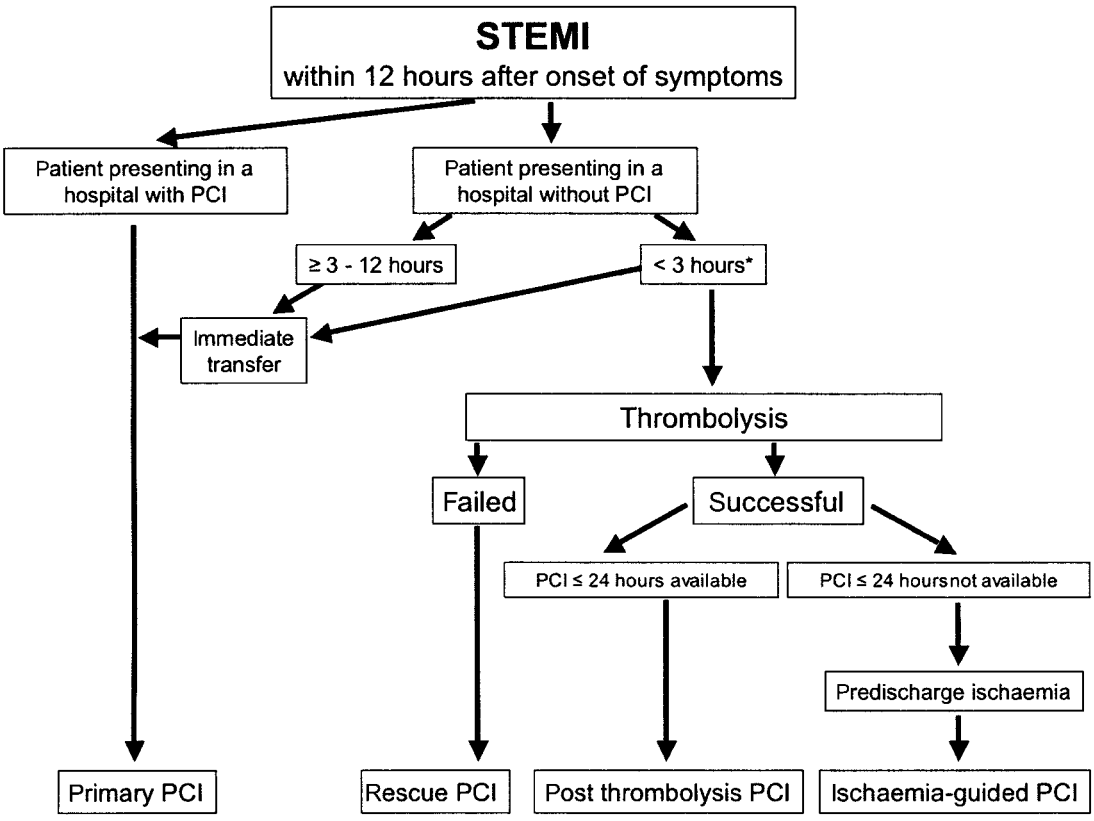

Figure 2 Within the first 3 h after onset of chest pain or other symptoms, thrombolysis is a viable alternative to primary PCI. *If thrombolysis is contra-indicated or the patient is at high risk, immediate transfer for primary PCI is strongly advised. The main rationale for possible preference of primary 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

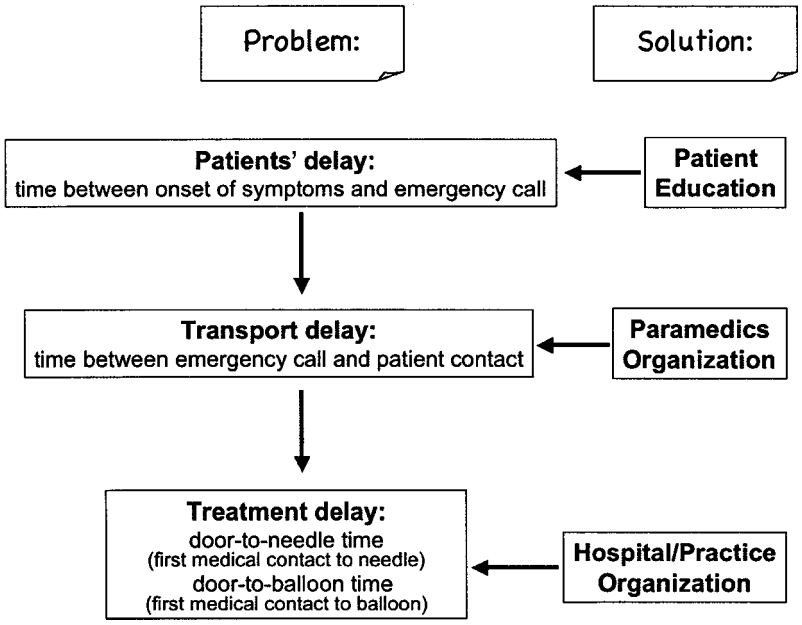

Figure 3 Sources of possible time delays between onset of symptoms and start of reperfusion therapy in patients with STEMI. Solutions to keep the sum of these delays ('total ischaemia time') as low as possible include improvements in the organization of ambulance services as well as optimization of organization 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	—

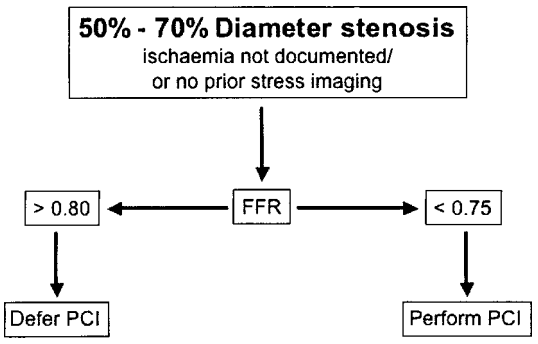

Figure 4 Decision-making for the management of angiographically intermediate coronary stenoses without documented myocardial ischaemia (absence of any localizing information, such as resting ECG changes, new wall motion abnormalities, or prior stress imaging). For FFR values between 0.75 and 0.80, a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

References

1. Priori SG, Klein W, Bassand JP. Medical Practice Guidelines. Separating science from economics. *Eur Heart J* 2003;**24**: 1962–1964.
2. Bassand JP. Improving the quality and dissemination of guidelines: the quest for the Holy Grail. *Eur Heart J* 2000;**21**:1289–1290.
3. Togni M, Balmer F, Pfiffner D, Maier W, Zeiher AM, Meier B. Percutaneous coronary interventions in Europe 1992–2001. *Eur Heart J* 2004;**25**:1208–1213.
4. Committee for Practice Guidelines (CPG). European Society of Cardiology: Recommendations for Task Force Creation and Report Production. A document for Task Force members and expert panels responsible for the creation and production of Guidelines and Expert Consensus Documents. http://www.escardio.org (2003).
5. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 2001;**37**:2215–2239.
6. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med* 1992;**326**:10–16.
7. Hartigan PM, Giacomini JC, Folland ED, Parisi AF. Two- to three-year follow-up of patients with single-vessel coronary artery disease randomized to PTCA or medical therapy (results of a VA cooperative study). Veterans Affairs Cooperative Studies Program ACME Investigators. Angioplasty Compared to Medicine. *Am J Cardiol* 1998;**82**:1445–1450.
8. Pepine CJ, Geller NL, Knatterud GL, Bourassa MG, Chaitman BR, Davies RF, Day P, Deanfield JE, Goldberg AD, McMahon RP. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study: design of a randomized clinical trial, baseline data and implications for a long-term outcome trial. *J Am Coll Cardiol* 1994;**24**:1–10.
9. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997;**95**:2037–2043.
10. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, Eisenberg D, Shurzinske L, McCormick LS. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;**341**:70–76.
11. Amoroso G, Van Boven AJ, Crijns HJ. Drug therapy or coronary angioplasty for the treatment of coronary artery disease: new insights. *Am Heart J* 2001;**141**:S22–S25.
12. The RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet* 1997;**350**:461–468.
13. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ* 2000;**321**:73–77.
14. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;**110**:1213–1218.
15. Claude J, Schindler C, Kuster GM, Schwenkglenks M, Szucs T, Buser P, Osswald S, Kaiser C, Grädel C, Estlinbaum W, Rickenbacher P, Pfisterer M. Cost-effectiveness of invasive versus medical management of elderly patients with chronic symptomatic coronary artery disease. Findings of the randomized trial of invasive versus medical therapy in elderly patients with chronic angina (TIME). *Eur Heart J* 2004;**25**:2195–2203.
16. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol* 2003;**41**:1293–1304.
17. Rubartelli P, Verna E, Niccoli L, Giachero C, Zimarino M, Bernardi G, Vassanelli C, Campolo L, Martuscelli E. Coronary stent implantation is superior to balloon angioplasty for chronic coronary occlusions: six-year clinical follow-up of the GISSOC trial. *J Am Coll Cardiol* 2003;**41**:1488–1492.
18. Rahel BM, Suttorp MJ, Laarman GJ, Kiemeneij F, Bal ET, Rensing BJ, Ernst SM, ten Berg JM, Kelder JC, Plokker HW, Primary stenting of occluded native coronary arteries: final results of the Primary Stenting of Occluded Native Coronary Arteries (PRISON) study. *Am Heart J* 2004;**147**:e22.
19. Sievert H, Rohde S, Utech A, Schulze R, Scherer D, Merle H, Ensslen R, Schräder R, Spies H, Fach A. Stent or angioplasty after recanalization of chronic coronary occlusions? (The SARECCO Trial). *Am J Cardiol* 1999;**84**:386–390.
20. Sirnes PA, Golf S, Myreng Y, Molstad P, Emanuelsson H, Albertsson P, Brekke M, Mangschau A, Endresen K, Kjekshus J. Stenting in Chronic Coronary Occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;**28**:1444–1451.
21. Höher M, Wohrle J, Grebe OC, Kochs M, Osterhues HH, Hombach V, Buchwald AB. A randomized trial of elective stenting after balloon recanalization of chronic total occlusions. *J Am Coll Cardiol* 1999;**34**:722–729.
22. Lotan C, Rozenman Y, Hendler A, Turgeman Y, Ayzenberg O, Beyar R, Krakover R, Rosenfeld T, Gotsman MS. Stents in total occlusion for restenosis prevention. The multicentre randomized STOP study. The Israeli Working Group for Interventional Cardiology. *Eur Heart J* 2000;**21**:1960–1966.
23. Buller CE, Dzavik V, Carere RG, Mancini GB, Barbeau G, Lazzam C, Anderson TJ, Knudtson ML, Marquis JF, Suzuki T, Cohen EA, Fox RS, Teo KK. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 1999;**100**:236–242.
24. Werner GS, Krack A, Schwarz G, Prochnau D, Betge S, Figulla HR. Prevention of lesion recurrence in chronic total coronary occlusions by Paclitaxel-Eluting stents. *J Am Coll Cardiol* 2004;**44**:2301–2306.
25. Hoye A, Tanabe K, Lemos P, Aoki J, Saia F, Arampatzis CA, Degertekin M, Hofma S, Sianos G, Mc Fadden EP, van der Giessen W, Smits PC, de Feyter P, van Domburg R, Serruys P. Significant reduction in restenosis after the use of Sirolimus-Eluting stents in the treatment of chronic total occlusions. *J Am Coll Cardiol* 2004;**43**:1954–1958.
26. Morrison DA, Sethi G, Sacks J, Grover F, Sedlis S, Esposito R, Ramanathan KB, Weiman D, Krucoff M, Duhaylongsod F, Raya T, Pett S, Vernon S, Birjiniuk V, Booth D, Robinson C, Talley JD, Antckli T, Murphy E, Floten H, Curcovic V, Lucke JC, Lewis D,

Barbiere C, Henderson W. A multicentre, randomized trial of percutaneous coronary intervention versus bypass surgery in high-risk unstable angina patients. The AWESOME (Veterans Affairs Cooperative Study #385, angina with extremely serious operative mortality evaluation) investigators from the Cooperative Studies Program of the Department of Veterans Affairs. Control Clin Trials 1999;**20**:601–619.
27. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, Esposito R. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol* 2002;**40**:1951–1954.
28. Sedlis SP, Ramanathan KB, Morrison DA, Sethi G, Sacks J, Henderson W. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). *Am J Cardiol* 2004;**94**:118–120.
29. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multi-vessel coronary artery disease and high-risk features. *Circulation* 2004;**109**: 2290–2295.
30. Hlatky MA, Boothroyd DB, Melsop KA, Brooks MM, Mark DB, Pitt B, Reeder GS, Rogers WJ, Ryan TJ, Whitlow PL, Wiens RD. Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multi-vessel coronary artery disease. *Circulation* 2004;**110**:1960–1966.
31. Ijsselmuiden AJ, Ezechiels J, Westendorp IC, Tijssen JG, Kiemeneij F, Slagboom T, van der Wieken R, Tangelder G, Serruys PW, Laarman G. Complete versus culprit vessel percutaneous coronary intervention in multi-vessel disease: a randomized comparison. *Am Heart J* 2004;**148**:467–474.
32. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multi-vessel disease. *N Engl J Med* 2001;**344**:1117–1124.
33. Legrand VM, Serruys PW, Unger F, van Hout BA, Vrolix MC, Fransen GM, Nielsen TT, Paulsen PK, Gomes RS, de Queiroz e Melo JM, Neves JP, Lindeboom W, Backx B. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multi-vessel disease. *Circulation* 2004;**109**:1114–1120.
34. Botman KJ, Pijls NH, Bech JW, Aarnoudse W, Peels K, van Straten B, Penn O, Michels HR, Bonnier H, Koolen JJ. Percutaneous coronary intervention or bypass surgery in multi-vessel disease? A tailored approach based on coronary pressure measurement. *Catheter Cardiovasc Interv* 2004;**63**:184–191.
35. Lopez JJ, Ho KK, Stoler RC, Caputo RP, Carrozza JP, Kuntz RE, Baim DS, Cohen DJ. Percutaneous treatment of protected and unprotected left main coronary stenoses with new devices: immediate angiographic results and intermediate-term follow-up. *J Am Coll Cardiol* 1997;**29**:345–352.
36. Kelley MP, Klugherz BD, Hashemi SM, Meneveau NF, Johnston JM, Matthai WH, Banka VS, Herrmann HC, Hirshfeld JW, Kimmel SE, Kolansky DM, Horwitz PA, Schiele F, Bassand JP, Wilensky RL. One-year clinical outcomes of protected and unprotected left main coronary artery stenting. *Eur Heart J* 2003;**24**:1554–1559.
37. Arampatzis CA, Lemos PA, Tanabe K, Hoye A, Degertekin M, Saia F, Lee CH, Ruiter A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feijter P, van Domburg R, Serruys PW. Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease. *Am J Cardiol* 2003;**92**:327–329.
38. de Lezo JS, Medina A, Pan M, Delgado A, Segura J, Pavlovic D, Melian F, Romero M, Burgos L, Hernandez E, Urena I, Herrador J. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. *Am Heart J* 2004;**148**:481–485.
39. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P *et al*. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;**331**:489–495.
40. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M *et al*. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994;**331**:496–501.
41. Erbel R, Haude M, Hopp HW, Franzen D, Rupprecht HJ, Heublein B, Fischer K, de Jaegere P, Serruys P, Rutsch W, Probst P. Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. Restenosis Stent Study Group. *N Engl J Med* 1998;**339**:1672–1678.
42. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA, A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;**336**:817–822.
43. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**: 673–681.
44. Betriu A, Masotti M, Serra A, Alonso J, Fernandez-Aviles F, Gimeno F, Colman T, Zueco J, Delcan JL, Garcia E, Calabuig J. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. *J Am Coll Cardiol* 1999;**34**:1498–1506.
45. Al Suwaidi J, Berger PB, Holmes DR Jr, Coronary artery stents. *JAMA* 2000;**284**:1828–1836.
46. Brophy JM, Belisle P, Joseph L, Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med* 2003;**138**: 777–786.
47. Nordmann AJ, Hengstler P, Leimenstoll BM, Harr T, Young J, Bucher HC. Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease. A meta-analysis of randomized controlled trials. *Eur Heart J* 2004;**25**:69–80.
48. Al Suwaidi J, Holmes DR Jr, Salam AM, Lennon R, Berger PB, Impact of coronary artery stents on mortality and nonfatal myocardial infarction: meta-analysis of randomized trials comparing a strategy of routine stenting with that of balloon angioplasty. *Am Heart J* 2004;**147**:815–822.
49. Moreno R, Fernandez C, Alfonso F, Hernandez R, Perez-Vizcayno MJ, Escaned J, Sabate M, Banuelos C, Angiolillo DJ, Azcona L, Macaya C. Coronary stenting versus balloon angioplasty in small vessels a meta-analysis from 11 randomized studies. *J Am Coll Cardiol* 2004;**43**:1964–1972.
50. Savage MP, Douglas JS Jr, Fischman DL, Pepine CJ, King SB III, Werner JA, Bailey SR, Overlie PA, Fenton SH, Brinker JA, Leon MB, Goldberg S. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 1997;**337**:740–747.
51. Hanekamp CE, Koolen JJ, Den Heijer P, Schalij MJ, Piek JJ, Bar FW, De Scheerder I, Bonnier HJ, Pijls NH. Randomized study to compare balloon angioplasty and elective stent implantation in venous bypass grafts: the Venestent study. *Catheter Cardiovasc Interv* 2003;**60**: 452–457.
52. Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, Bakhai A, Cohen DJ, Kuntz RE, Ho KK. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 2004;**110**:1226–1230.
53. Versaci F, Gaspardone A, Tomai F, Proietti I, Ghini AS, Altamura L, Ando G, Crea F, Gioffre PA, Chiariello L. A comparison of coronary artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery: five year clinical follow up. *Heart* 2004;**90**:672–675.
54. Mandadi VR, DeVoe MC, Ambrose JA, Prakash AM, Varshneya N, Gould RB, Nguyen TH, Geagea JP, Radojevic JA, Sehhat K, Barua RS. Predictors of troponin elevation after percutaneous coronary intervention. *Am J Cardiol* 2004;**93**:747–750.
55. Ricciardi MJ, Davidson CJ, Gubernikoff G, Beohar N, Eckman LJ, Parker MA, Bonow RO. Troponin I elevation and cardiac events after percutaneous coronary intervention. *Am Heart J* 2003; **145**:522–528.
56. Kini AS, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, Sharma SK. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. *Am J Cardiol* 2004;**93**:18–23.

57. Fuchs S, Kornowski R, Mehran R, Lansky AJ, Satler LF, Pichard AD, Kent KM, Clark CE, Stone GW, Leon MB. Prognostic value of cardiac troponin-I levels following catheter-based coronary interventions. *Am J Cardiol* 2000;**85**:1077–1082.
58. Wu AH, Boden WE, McKay RG. Long-term follow-up of patients with increased cardiac troponin concentrations following percutaneous coronary intervention. *Am J Cardiol* 2002;**89**:1300–1302.
59. Natarajan MK, Kreatsoulas C, Velianou JL, Mehta SR, Pericak D, Goodhart DM. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 2004;**93**:750–753.
60. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–1840.
61. Thambyrajah J, De Belder MA. Management of non ST-segment elevation acute coronary syndromes-continuing the search for the bad guys. *Eur Heart J* 2003;**24**:490–493.
62. Brener SJ, Ellis SG, Schneider J, Apperson-Hansen C, Topol EJ. Abciximab-facilitated percutaneous coronary intervention and long-term survival—a prospective single-centre registry. *Eur Heart J* 2003;**24**:630–638.
63. McKay RG, "Ischemia-guided" versus "early invasive" strategies in the management of acute coronary syndrome/non-ST-segment elevation myocardial infarction: the interventionalist's perspective. *J Am Coll Cardiol* 2003;**41**:96S–102S.
64. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
65. Garcia S, Canoniero M, Peter A, de Marchena E, Ferreira A. Correlation of TIMI risk score with angiographic severity and extent of coronary artery disease in patients with non-ST-elevation acute coronary syndromes. *Am J Cardiol* 2004;**93**:813–816.
66. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–2567.
67. Cannon CP. Evidence-based risk stratification to target therapies in acute coronary syndromes. *Circulation* 2002;**106**:1588–1591.
68. Mukherjee D, Gurm H, Tang WH, Roffi M, Wolski K, Moliterno DJ, Guetta V, Ardissinio D, Bode C, Steg G, Lincoff AM, Topol EJ. Outcome of acute myocardial infarction in patients with prior coronary artery bypass grafting treated with combination reduced fibrinolytic therapy and abciximab. *Am J Cardiol* 2002;**90**:1198–1203.
69. Wu AH, Parsons L, Every NR, Bates ER. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol* 2002;**40**:1389–1394.
70. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;**345**:1014–1021.
71. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002;**105**:1760–1763.
72. Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, Topol EJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA* 2003;**290**:2174–2181.
73. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J, Budaj A, Goldberg RJ, Klein W, Anderson FA Jr. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). *Circulation* 2004;**109**:494–499.
74. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;**335**:1342–1349.
75. Okamatsu K, Takano M, Sakai S, Ishibashi F, Uemura R, Takano T, Mizuno K. Elevated troponin T levels and lesion characteristics in non-ST-elevation acute coronary syndromes. *Circulation* 2004;**109**:465–470.
76. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999;**354**:1757–1762.
77. De Servi S, Cavallini C, Dellavalle A, Santoro GM, Bonizzoni E, Marzocchi A, Politi A, Pesaresi A, Mariani M, Chierchia S. Non-ST-elevation acute coronary syndrome in the elderly: treatment strategies and 30-day outcome. *Am Heart J* 2004;**147**:830–836.
78. Jernberg T, James S, Lindahl B, Johnston N, Stridsberg M, Venge P, Wallentin L. Natriuretic peptides in unstable coronary artery disease. *Eur Heart J* 2004;**25**:1486–1493.
79. Bazzino O, Fuselli JJ, Botto F, Perez De Arenaza D, Bahit C, Dadone J. Relative value of N-terminal probrain natriuretic peptide, TIMI risk score, ACC/AHA prognostic classification and other risk markers in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2004;**25**:859–866.
80. Gibson CM, Dumaine RL, Gelfand EV, Murphy SA, Morrow DA, Wiviott SD, Giugliano RP, Cannon CP, Antman EM, Braunwald E. Association of glomerular filtration rate on presentation with subsequent mortality in non-ST segment elevation acute coronary syndrome; observations in 13307 patients in five TIMI trials. *Eur Heart J* 2004;**25**:1998–2005.
81. Bach RG, Cannon CP, Weintraub WS, DiBattiste PM, Demopoulos LA, Anderson HV, DeLucca PT, Mahoney EM, Murphy SA, Braunwald E. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med* 2004;**141**:186–195.
82. Fox KA, Goodman SG, Anderson FA Jr, Granger CB, Moscucci M, Flather MD, Spencer F, Budaj A, Dabbous OH, Gore JM. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1414–1424.
83. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC Jr, Pollack CV Jr, Gibler WB, Ohman EM. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA* 2004;**292**:2096–2104.
84. TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994;**89**:1545–1556.
85. McCullough PA, O'Neill WW, Graham M, Stomel RJ, Rogers F, David S, Farhat A, Kazlauskaite R, Al-Zagoum M, Grines CL. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;**32**:596–605.
86. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;**338**:1785–1792.
87. Ottervanger JP, Armstrong P, Barnathan ES, Boersma E, Cooper JS, Ohman EM, James S, Wallentin L, Simoons ML. Association of revascularisation with low mortality in non-ST elevation acute coronary

syndrome, a report from GUSTO IV-ACS. *Eur Heart J* 2004;**25**:1494–1501.
88. Michalis LK, Stroumbis CS, Pappas K, Sourla E, Niokou D, Goudevenos JA, Siogas C, Sideris DA. Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery. Invasive versus conservative strategy (TRUCS study). *Eur Heart J* 2000;**21**:1954–1959.
89. Spacek R, Widimsky P, Straka Z, Jiresova E, Dvorak J, Polasek R, Karel I, Jirmar R, Lisa L, Budesinsky T, Malek F, Stanka P. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicentre randomized trial. The VINO Study. *Eur Heart J* 2002;**23**:230–238.
90. The FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999;**354**:708–715.
91. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–1887.
92. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002;**360**:743–751.
93. Clayton TC, Pocock SJ, Henderson RA, Poole-Wilson PA, Shaw TR, Knight R, Fox KA. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST elevation myocardial infarction? The impact of gender in the RITA 3 trial. *Eur Heart J* 2004;**25**:1641–1650.
94. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schömig A. Evaluation of prolonged anti-thrombotic pre-treatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;**290**: 1593–1599.
95. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28–66.
96. Anderson HV, Shaw RE, Brindis RG, Hewitt K, Krone RJ, Block PC, McKay CR, Weintraub WS. A contemporary overview of percutaneous coronary interventions. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *J Am Coll Cardiol* 2002;**39**:1096–1103.
97. Vakili BA, Kaplan R, Brown DL. Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York state. *Circulation* 2001;**104**:2171–2176.
98. Zijlstra F. Does it matter where you go with an acute myocardial infarction? *Eur Heart J* 2001;**22**:1764–1766.
99. Canto JG, Every NR, Magid DJ, Rogers WJ, Malmgren JA, Frederick PD, French WJ, Tiefenbrunn AJ, Misra VK, Kiefe CI, Barron HV. The volume of primary angioplasty procedures and survival after acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *N Engl J Med* 2000;**342**:1573–1580.
100. Thiemann DR, Coresh J, Oetgen WJ, Powe NR. The association between hospital volume and survival after acute myocardial infarction in elderly patients. *N Engl J Med* 1999;**340**:1640–1648.
101. Zahn R, Schiele R, Schneider S, Gitt AK, Wienbergen H, Seidl K, Bossaller C, Buttner HJ, Gottwik M, Altmann E, Rosahl W, Senges J. Decreasing hospital mortality between 1994 and 1998 in patients with acute myocardial infarction treated with primary angioplasty but not in patients treated with intravenous thrombolysis. Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Registry and the Myocardial Infarction Registry (MIR). *J Am Coll Cardiol* 2000;**36**:2064–2071.
102. Chen EW, Canto JG, Parsons LS, Peterson ED, Littrell KA, Every NR, Gibson CM, Hochman JS, Ohman EM, Cheeks M, Barron HV. Relation between hospital intra-aortic balloon counterpulsation volume and mortality in acute myocardial infarction complicated by cardiogenic shock. *Circulation* 2003;**108**:951–957.
103. Epstein AJ, Rathore SS, Volpp KG, Krumholz HM. Hospital percutaneous coronary intervention volume and patient mortality, 1998 to 2000: does the evidence support current procedure volume minimums? *J Am Coll Cardiol* 2004;**43**:1755–1762.
104. Magid DJ, Calonge BN, Rumsfeld JS, Canto JG, Frederick PD, Every NR, Barron HV. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* 2000;**284**: 3131–3138.
105. Corpus RA, House JA, Marso SP, Grantham JA, Huber KC Jr, Laster SB, Johnson WL, Daniels WC, Barth CW, Giorgi LV, Rutherford BD. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *Am Heart J* 2004;**148**:493–500.
106. Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, Roychoudhury C, Borzak S, Fox S, Franklin M, Freundl M, Kline-Rogers E, LaLonde T, Orza M, Parrish R, Satwicz M, Smith MJ, Sobotka P, Winston S, Riba AA, Eagle KA. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. *JAMA* 2002;**287**:1269–1276.
107. Henriques JP, Haasdijk AP, Zijlstra F. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. *J Am Coll Cardiol* 2003;**41**:2138–2142.
108. Sadeghi HM, Grines CL, Chandra HR, Mehran R, Fahy M, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Stuckey TD, Lansky AJ, O'Neill WW, Stone GW. Magnitude and impact of treatment delays on weeknights and weekends in patients undergoing primary angioplasty for acute myocardial infarction (the CADILLAC trial). *Am J Cardiol* 2004;**94**:637–640.
109. Rentrop P, Blanke H, Wiegand V, Karsch KR. Wiedereroffnung verschlossener Kranzgefässe im akuten Infarkt mit Hilfe von Kathetern. Transluminale Rekanalisation. *Dtsch Med Wochenschr* 1979;**104**:1401–1405.
110. Grüntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978;**1**:263.
111. Tamis-Holland JE, Palazzo A, Stebbins AL, Slater JN, Boland J, Ellis SG, Hochman JS. Benefits of direct angioplasty for women and men with acute myocardial infarction: results of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Angioplasty (GUSTO II-B) Angioplasty Substudy. *Am Heart J* 2004;**147**:133–139.
112. Goldenberg I, Matetzky S, Halkin A, Roth A, Di Segni E, Freimark D, Elian D, Agranat O, Har Zahav Y, Guetta V, Hod H. Primary angioplasty with routine stenting compared with thrombolytic therapy in elderly patients with acute myocardial infarction. *Am Heart J* 2003;**145**:862–867.
113. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
114. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 'T Hof AWJ, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**: 1413–1419.
115. Nunn CM, O'Neill WW, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Grines L, Browne KF, Vlietstra RE, Catlin T, Grines CL. Long-term outcome after primary angioplasty: report from the primary angioplasty in myocardial infarction (PAMI-I) trial. *J Am Coll Cardiol* 1999;**33**:640–646.
116. Grines CL, Serruys P, O'Neill WW. Fibrinolytic therapy: is it a treatment of the past? *Circulation* 2003;**107**:2538–2542.
117. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC *et al*. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;**328**:673–679.
118. The GUSTO IIb investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO

IIb) Angioplasty Substudy Investigators. *N Engl J Med* 1997;**336**: 1621–1628.
119. Aversano T, Aversano LT, Passamani E, Knatterud GL, Terrin ML, Williams DO, Forman SA. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 2002;**287**:1943–1951.
120. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J* 2000;**21**:823–831.
121. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, St'asek J, Formanek P. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J* 2003;**24**:94–104.
122. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;**349**:733–742.
123. Cragg DR, Friedman HZ, Bonema JD, Jaiyesimi IA, Ramos RG, Timmis GC, O'Neill WW, Schreiber TL. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med* 1991;**115**:173–177.
124. Brodie BR, Weintraub RA, Stuckey TD, LeBauer EJ, Katz JD, Kelly TA, Hansen CJ. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. *Am J Cardiol* 1991;**67**:7–12.
125. Zijlstra F, van't Hof AW, Liem AL, Hoorntje JC, Suryapranata H, de Boer MJ. Transferring patients for primary angioplasty: a retrospective analysis of 104 selected high risk patients with acute myocardial infarction. *Heart* 1997;**78**:333–336.
126. Vermeer F, Oude Ophuis AJ, vd Berg EJ, Brunninkhuis LG, Werter CJ, Boehmer AG, Lousberg AH, Dassen WR, Bar FW. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999;**82**:426–431.
127. Grines CL, Westerhausen DR Jr, Grines LL, Hanlon JT, Logemann TL, Niemela M, Weaver WD, Graham M, Boura J, O'Neill WW, Balestrini C. A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in patients with high-risk myocardial infarction: the Air Primary Angioplasty in Myocardial Infarction study. *J Am Coll Cardiol* 2002;**39**:1713–1719.
128. Schömig A, Ndrepepa G, Mehilli J, Schwaiger M, Schühlen H, Nekolla S, Pache J, Martinoff S, Bollwein H, Kastrati A. Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. *Circulation* 2003;**108**:1084–1088.
129. Zahn R, Schiele R, Gitt AK, Schneider S, Seidl K, Voigtlander T, Gottwik M, Altmann E, Gieseler U, Rosahl W, Wagner S, Senges J. Impact of prehospital delay on mortality in patients with acute myocardial infarction treated with primary angioplasty and intravenous thrombolysis. *Am Heart J* 2001;**142**:105–111.
130. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;**360**:825–829.
131. Danchin N, Blanchard D, Steg PG, Sauval P, Hanania G, Goldstein P, Cambou JP, Gueret P, Vaur L, Boutalbi Y, Genes N, Lablanche JM. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: results from the French Nationwide USIC 2000 Registry. *Circulation* 2004;**110**:1909–1915.
132. Zijlstra F, Patel A, Jones M, Grines CL, Ellis S, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, Ribichini F, Granger C, Akhras F, Weaver WD, Simes RJ, for the PCAT collaboration. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J* 2002;**23**:550–557.
133. Bertrand ME, McFadden EP. Late is perhaps not too late for primary PCI in acute myocardial infarction. *Eur Heart J* 2002;**23**:1146–1148.
134. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003;**108**: 1809–1814.
135. Zijlstra F. Angioplasty vs thrombolysis for acute myocardial infarction: a quantitative overview of the effects of interhospital transportation. *Eur Heart J* 2003;**24**:21–23.
136. Wharton TP, Grines LL, Turco MA, Johnston JD, Souther J, Lew DC, Shaikh AZ, Bilnoski W, Singhi SK, Atay AE, Sinclair N, Shaddinger DE, Barsamian M, Graham M, Boura J, Grines C. Primary angioplasty in acute myocardial infarction at hospitals with no surgery on-site (The PAMI-No SOS Study) versus transfer to surgical centres for primary angioplasty. *J Am Coll Cardiol* 2004;**43**:1943–1950.
137. Wennberg DE, Lucas FL, Siewers AE, Kellett MA, Malenka DJ. Outcomes of percutaneous coronary interventions performed at centres without and with onsite coronary artery bypass graft surgery. *JAMA* 2004;**292**:1961–1968.
138. Loubeyre C, Morice MC, Lefevre T, Piechaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol* 2002;**39**:15–21.
139. Suryapranata H, van't Hof AW, Hoorntje JC, de Boer MJ, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. *Circulation* 1998;**97**:2502–2505.
140. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, Brodie BR, Madonna O, Eijgelshoven M, Lansky AJ, O'Neill WW, Morice MC. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;**341**: 1949–1956.
141. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Carroll JD, Rutherford BD, Lansky AJ, for the CADILLAC investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**:957–966.
142. Herrmann HC, Moliterno DJ, Ohman EM, Stebbins AL, Bode C, Betriu A, Forycki F, Miklin JS, Bachinsky WB, Lincoff AM, Califf RM, Topol EJ. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) Trial. *J Am Coll Cardiol* 2000;**36**:1489–1496.
143. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, Moreyra E, Traboulsi M, Racine N, Riba AL, Thompson MA, Rohrbeck S, Lundergan CF. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. PACT investigators. Plasminogen-activator Angioplasty Compatibility Trial. *J Am Coll Cardiol* 1999;**34**: 1954–1962.
144. Kastrati A, Mehilli J, Schlotterbeck K, Dotzer F, Dirschinger J, Schmitt C, Nekolla SG, Seyfarth M, Martinoff S, Markwardt C, Clermont G, Gerbig HW, Leiss J, Schwaiger M, Schömig A. Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2004;**291**:947–954.
145. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001;**357**:1905–1914.
146. Ellis SG, Armstrong P, Betriu A, Brodie B, Herrmann H, Montalescot G, Neumann FJ, Smith JJ, Topol E. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. *Am Heart J* 2004;**147**:E16.
147. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansieri M, Choussat R, Pinton P, for the ADMIRAL investigators. Platelet glycoprotein

IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895–1903.
148. Van't Hof AW, Ernst N, De Boer MJ, De Winter R, Boersma E, Bunt T, Petronio S, Marcel Gosselink AT, Jap W, Hollak F, Hoorntje JC, Suryapranata H, Dambrink JH, Zijlstra F. Facilitation of primary coronary angioplasty by early start of a glycoprotein 2b/3a inhibitor: results of the ongoing tirofiban in myocardial infarction evaluation (On-TIME) trial. *Eur Heart J* 2004;**25**:837–846.
149. Lee DP, Herity NA, Hiatt BL, Fearon WF, Rezaee M, Carter AJ, Huston M, Schreiber D, DiBattiste PM, Yeung AC. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the TIrofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. *Circulation* 2003;**107**:1497–1501.
150. Gyöngyösi M, Domanovits H, Benzer W, Haugk M, Heinisch B, Sodeck G, Hodl R, Gaul G, Bonner G, Wojta J, Laggner A, Glogar D, Huber K. Use of abciximab prior to primary angioplasty in STEMI results in early recanalization of the infarct-related artery and improved myocardial tissue reperfusion—results of the Austrian multi-centre randomized ReoPro-BRIDGING Study. *Eur Heart J* 2004;**25**:2125–2133.
151. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;**292**:362–366.
152. Ellis SG, da Silva ER, Heyndrickx G, Talley JD, Cernigliaro C, Steg G, Spaulding C, Nobuyoshi M, Erbel R, Vassanelli C *et al*. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. *Circulation* 1994;**90**:2280–2284.
153. Ellis SG, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley JD. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. *Am Heart J* 2000;**139**:1046–1053.
154. Sutton AG, Campbell PG, Graham R, Price DJ, Gray JC, Grech ED, Hall JA, Harcombe AA, Wright RA, Smith RH, Murphy JJ, Shyam-Sundar A, Stewart MJ, Davies A, Linker NJ, de Belder MA. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. *J Am Coll Cardiol* 2004;**44**:287–296.
155. Grines CL, O'Neill WW. Rescue angioplasty: does the concept need to be rescued? *J Am Coll Cardiol* 2004;**44**:297–299.
156. Gershlick AH, Hughes S, Abrams K, Stevens S, Uren N, De Belder M, Davis J, Pitt M, Alamgir F, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins K, Henderson R, Oldroyd K, Stephens-Lloyd A, Wilcox RG. Rescue angioplasty following failed thrombolysis: the REACT Trial. 2005 (in press).
157. Schömig A, Ndrepepa G, Mehilli J, Dirschinger J, Nekolla SG, Schmitt C, Martinoff S, Seyfarth M, Schwaiger M, Kastrati A. A randomized trial of coronary stenting versus balloon angioplasty as a rescue intervention after failed thrombolysis in patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;**44**:2073–2079.
158. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;**341**:625–634.
159. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, LeJemtel TH, Cotter G. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2004;**44**:340–348.
160. Urban P, Stauffer JC, Bleed D, Khatchatrian N, Amann W, Bertel O, van den Brand M, Danchin N, Kaufmann U, Meier B, Machecourt J, Pfisterer M. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicentre Trial of Angioplasty for Shock-(S)MASH. *Eur Heart J* 1999;**20**:1030–1038.
161. Webb JG, Lowe AM, Sanborn TA, White HD, Sleeper LA, Carere RG, Buller CE, Wong SC, Boland J, Dzavik V, Porway M, Pate G, Bergman G, Hochman JS. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. *J Am Coll Cardiol* 2003;**42**:1380–1386.
162. Urban PM, Freedman RJ, Ohman EM, Stone GW, Christenson JT, Cohen M, Miller MF, Joseph DL, Bynum DZ, Ferguson JJ, III. In-hospital mortality associated with the use of intra-aortic balloon counterpulsation. *Am J Cardiol* 2004;**94**:181–185.
163. Jacobs AK, French JK, Col J, Sleeper LA, Slater JN, Carnendran L, Boland J, Jiang X, LeJemtel T, Hochman JS. Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK? *J Am Coll Cardiol* 2000;**36**:1091–1096.
164. Zeymer U, Vogt A, Zahn R, Weber MA, Tebbe U, Gottwik M, Bonzel T, Senges J, Neuhaus KL. Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI); Results of the primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK). *Eur Heart J* 2004;**25**:322–328.
165. Prasad A, Lennon RJ, Rihal CS, Berger PB, Holmes DR Jr. Outcomes of elderly patients with cardiogenic shock treated with early percutaneous revascularization. *Am Heart J* 2004;**147**:1066–1070.
166. Fang J, Alderman MH. Revascularization among patients with acute myocardial infarction complicated by cardiogenic shock and impact of American College of Cardiology/American Heart Association guidelines. *Am J Cardiol* 2004;**94**:1281–1285.
167. Zeymer U, Uebis R, Vogt A, Glunz HG, Vöhringer HF, Harmjanz D, Neuhaus KL. Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte. *Circulation* 2003;**108**:1324–1328.
168. Gupta M, Chang WC, Van de Werf F, Granger CB, Midodzi W, Barbash G, Pehrson K, Oto A, Toutouzas P, Jansky P, Armstrong PW. International differences in in-hospital revascularization and outcomes following acute myocardial infarction: a multilevel analysis of patients in ASSENT-2. *Eur Heart J* 2003;**24**:1640–1650.
169. Gibson CM, Karha J, Murphy SA, James D, Morrow DA, Cannon CP, Giugliano RP, Antman EM, Braunwald E. Early and long-term clinical outcomes associated with re-infarction following fibrinolytic administration in the Thrombolysis in Myocardial Infarction trials. *J Am Coll Cardiol* 2003;**42**:7–16.
170. Stenestrand U, Wallentin L. Early revascularisation and 1-year survival in 14-day survivors of acute myocardial infarction: a prospective cohort study. *Lancet* 2002;**359**:1805–1811.
171. Kaul P, Armstrong PW, Chang WC, Naylor CD, Granger CB, Lee KL, Peterson ED, Califf RM, Topol EJ, Mark DB. Long-term mortality of patients with acute myocardial infarction in the United States and Canada: comparison of patients enrolled in Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-I. *Circulation* 2004;**110**:1754–1760.
172. Scheller B, Hennen B, Hammer B, Walle J, Hofer C, Hilpert V, Winter H, Nickenig G, Bohm M. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 2003;**42**:634–641.
173. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, Lopez-Mesa J, Fernandez-Vazquez F, Calvo I, Martinez-Elbal L, San Roman JA, Ramos B. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;**364**:1045–1053.
174. Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, Maloney J, Mc Kibbin T, Quinn B, Beanlands RS, Glover C, Marquis JF, O'Brien ER, Williams WL, Higginson LA. Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI), 2005 (in press).
175. Thiele H, Engelmann L, Elsner K, Kappl MJ, Storch WH, Rahimi K, Hartmann A, Pfeiffer D, Kneissl GD, Schneider D, Möller T, Heberling HJ, Weise I, Schuler G. Comparison of Prehospital Fibrinolytic/Abciximab Therapy with Prehospital Initiated Facilitated Percutaneous Coronary Intervention in Acute Myocardial Infarction. 2005 (in press).
176. Verheugt FW. Lyse now, stent later: the grace of GRACIA. *Lancet* 2004;**364**:1014–1015.

177. Madsen JK, Grande P, Saunamaki K, Thayssen P, Kassis E, Eriksen U, Rasmussen K, Haunso S, Nielsen TT, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen U, Andersen LI. Danish multicentre randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. *Circulation* 1997;**96**: 748–755.
178. Sheehan FH, Braunwald E, Canner P, Dodge HT, Gore J, Van Natta P, Passamani ER, Williams DO, Zaret B. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) trial. *Circulation* 1987;**75**:817–829.
179. Yousef ZR, Redwood SR, Bucknall CA, Sulke AN, Marber MS. Late intervention after anterior myocardial infarction: effects on left ventricular size, function, quality of life, and exercise tolerance: results of the Open Artery Trial (TOAT Study). *J Am Coll Cardiol* 2002;**40**:869–876.
180. Steg PG, Thuaire C, Himbert D, Carrier D, Champagne S, Coisne D, Khalife K, Cazaux P, Logeart D, Slama M, Spaulding C, Cohen A, Tirouvanziam A, Montely J, Rodriguez R, Garbarz E, Wijns W, Durand-Zaleski I, Porcher R, L. B, Chevret S, Chastang C. DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multicentre trial of occluded artery angioplasty after acute myocardial infarction. *Eur Heart J* 2004;**25**:2187–2194.
181. Yousef ZR, Marber MS. The open artery hypothesis: potential mechanisms of action. *Prog Cardiovasc Dis* 2000;**42**:419–438.
182. De Luca G, van't Hof AW, de Boer MJ, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, Zijlstra F, Suryapranata H. Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur Heart J* 2004;**25**:1009–1013.
183. De Luca G, Suryapranata H, Zijlstra F, van't Hof AW, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003;**42**:991–997.
184. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004;**109**:1223–1225.
185. Gibson CM, Murphy SA, Kirtane AJ, Giugliano RP, Cannon CP, Antman EM, Braunwald E. Association of duration of symptoms at presentation with angiographic and clinical outcomes after fibrinolytic therapy in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;**44**:980–987.
186. Nallamothu BK, Antman EM, Bates ER. Primary percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: does the choice of fibrinolytic agent impact on the importance of time-to-treatment? *Am J Cardiol* 2004;**94**:772–774.
187. Ozdemir M, Cemri M, Yalcin R, Cengel A. Use of intracoronary adenosine for the management of slow-no-reflow phenomenon during percutaneous interventions. *Catheter Cardiovasc Interv* 2001;**54**:267–268.
188. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol* 2001;**37**:1335–1343.
189. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. *Catheter Cardiovasc Interv* 2004;**63**:171–176.
190. Barcin C, Denktas AE, Lennon RJ, Hammes L, Higano ST, Holmes DR Jr, Garratt KN, Lerman A. Comparison of combination therapy of adenosine and nitroprusside with adenosine alone in the treatment of angiographic no-reflow phenomenon. *Catheter Cardiovasc Interv* 2004;**61**:484–491.
191. Patrono C, Bachmann F, Baigent C, Bode C, De Catarina R, Charbonier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, Rodriguez LAG, Verheugt F, Vermylen J, Wallentin L. Expert Consensus Document on the Use of Antiplatelet Agents. The Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. *Eur Heart J* 2004;**25**:1–16.
192. The Anti-thrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
193. Savage MP, Goldberg S, Bove AA, Deutsch E, Vetrovec G, Macdonald RG, Bass T, Margolis JR, Whitworth HB, Taussig A. Effect of thromboxane A2 blockade on clinical outcome and restenosis after successful coronary angioplasty. Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART II). *Circulation* 1995; **92**:3194–3200.
194. The ISIS-2 Investigators. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; **2**:349–360.
195. Bhatt DL. Aspirin resistance: more than just a laboratory curiosity. *J Am Coll Cardiol* 2004;**43**:1127–1129.
196. Hall P, Nakamura S, Maiello L, Itoh A, Blengino S, Martini G, Ferraro M, Colombo A. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation* 1996;**93**:215–222.
197. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**:1084–1089.
198. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three anti-thrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;**339**:1665–1671.
199. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicentre comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation* 1998;**98**:1597–1603.
200. Urban P, Macaya C, Rupprecht HJ, Kiemeneij F, Emanuelsson H, Fontanelli A, Pieper M, Wesseling T, Sagnard L. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicentre aspirin and ticlopidine trial after intracoronary stenting (MATTIS). *Circulation* 1998;**98**:2126–2132.
201. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–629.
202. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;**104**:539–543.
203. Müller C, Büttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;**101**:590–593.
204. Calver AL, Blows LJ, Harmer S, Dawkins KD, Gray HH, Morgan JH, Simpson IA. Clopidogrel for prevention of major cardiac events after coronary stent implantation: 30-day and 6-month results in patients with smaller stents. *Am Heart J* 2000;**140**:483–491.
205. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, Maida R, Collins M, Kreps E, Moses JW. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation* 1999;**99**:2364–2366.
206. Berger PB. Clopidogrel instead of ticlopidine after coronary stent placement: is the switch justified? *Am Heart J* 2000;**140**:354–358.
207. Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, Dangas G, Taniuchi M, Lasala JM, Holmes DR, Ellis SG, Topol EJ. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol* 2002;**39**:9–14.
208. Berger PB, Bell MR, Rihal CS, Ting H, Barsness G, Garratt K, Bellot V, Mathew V, Melby S, Hammes L, Grill D, Holmes DR Jr. Clopidogrel

versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999;**34**:1891–1894.
209. Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999;**34**:1884–1890.
210. Vivekananthan DP, Bhatt DL, Chew DP, Zidar FJ, Chan AW, Moliterno DJ, Ellis SG, Topol EJ. Effect of clopidogrel pre-treatment on periprocedural rise in C-reactive protein after percutaneous coronary intervention. *Am J Cardiol* 2004;**94**:358–360.
211. Lepäntalo A, Virtanen KS, Heikkilä J, Wartiovaara U, Lassila R. Limited early antiplatelet effect of 300 mg clopidogrel in patients with aspirin therapy undergoing percutaneous coronary interventions. *Eur Heart J* 2004;**25**:476–483.
212. Steinhubl SR, Berger PB, Mann JT, III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–2420.
213. Chan AW, Moliterno DJ, Berger PB, Stone GW, DiBattiste PM, Yakubov SL, Sapp SK, Wolski K, Bhatt DL, Topol EJ. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcomes including one-year survival: results from the Do Tirofiban and ReoProGive Similar Efficacy Outcome Trial (TARGET). *J Am Coll Cardiol* 2003;**42**:1188–1195.
214. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schömig A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation* 2004;**110**:1916–1919.
215. Kastrati A, Mehilli J, Schühlen H, Dirschinger J, Dotzer F, ten Berg JM, Neumann FJ, Bollwein H, Volmer C, Gawaz M, Berger PB, Schömig A. A clinical trial of abciximab in elective percutaneous coronary intervention after pre-treatment with clopidogrel. *N Engl J Med* 2004;**350**:232–238.
216. Kandzari DE, berger PB, Kastrati A, Steinhubl S, Mehilli J, Dotzer F, ten Berg JM, Neumann FJ, Bollwein H, Dirschinger J, Schömig A, Influence of Treatment Duration With a 600-mg Dose of Clopidogrel Before Percutaneous Coronary Revascularization. *J Am Coll Cardiol* 2004;**44**:2133–2136.
217. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
218. Berger PB, Steinhubl S. Clinical implications of percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events (PCI-CURE) study: a US perspective. *Circulation* 2002;**106**:2284–2287.
219. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;**110**:1202–1208.
220. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;**108**:1682–1687.
221. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002;**106**:1893–1900.
222. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–533.
223. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DG, Guyer KE, Bates ER. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug—drug interaction. *Circulation* 2003;**107**:32–37.
224. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, Topol EJ. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003;**108**:921–924.
225. Müller I, Besta F, Schulz C, Massberg S, Schömig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost* 2003;**89**:783–787.
226. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, Novikov I, Pres H, Savion N, Varon D, Hod H. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;**109**:3171–3175.
227. Kaluski E, Krakover R, Cotter G, Hendler A, Zyssman I, Milovanov O, Blatt A, Zimmerman E, Goldstein E, Nahman V, Vered Z. Minimal heparinization in coronary angioplasty—how much heparin is really warranted? *Am J Cardiol* 2000;**85**:953–956.
228. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996;**276**:811–815.
229. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P *et al*. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;**319**:1105–1111.
230. Cohen M. The role of low-molecular-weight heparin in the management of acute coronary syndromes. *J Am Coll Cardiol* 2003; **41**:55S–61S.
231. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AG, van der Meer J, Olaisson E, Undeland S, Ludwig K. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;**96**:61–68.
232. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, Bayes De Luna A, Fox K, Lablanche JM, Radley D, Premmereur J, Braunwald E. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;**100**:1593–1601.
233. Antman EM, Cohen M, McCabe C, Goodman SG, Murphy SA, Braunwald E. Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE. *Eur Heart J* 2002;**23**:308–314.
234. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;**337**:447–452.
235. The FRAXIS Investigators. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAxiparine in Ischaemic Syndrome). *Eur Heart J* 1999; **20**:1553–1562.
236. The FRISC II Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease. Investigators. *Lancet* 1999; **354**:701–707.
237. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 2004;**292**:45–54.
238. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, DiBattiste PM, Palmisano J, Bilheimer DW, Snapinn SM, Ramsey KE, Gardner LH, Hasselblad V, Pfeffer MA, Lewis EF, Braunwald E,

Califf RM. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* 2004;**292**:55–64.
239. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-Segment elevation acute coronary syndromes: a systematic overview. *JAMA* 2004;**292**:89–96.
240. Schünemann HJ, Cook D, Grimshaw J, Liberati A, Heffner J, Tapson V, Guyatt G. Anti-thrombotic and thrombolytic therapy: from evidence to application: the Seventh ACCP Conference on Anti-thrombotic and Thrombolytic Therapy. *Chest* 2004;126:688S–696S.
241. Collet JP, Montalescot G, Golmard JL, Tanguy ML, Ankri A, Choussat R, Beygui F, Drobinski G, Vignolles N, Thomas D. Subcutaneous enoxaparin with early invasive strategy in patients with acute coronary syndromes. *Am Heart J* 2004;**147**:655–661.
242. De Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, Fox KA, Palmisano J, Ramsey KE, Bilheimer DW, Lewis EF, Pfeffer M, Califf RM, Braunwald E. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial. *Eur Heart J* 2004;**25**:1688–1694.
243. Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, de Jong E, Coyne K. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation* 2001;**104**:648–652.
244. Antman EM, Louwerenburg HW, Baars HF, Wesdorp JC, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F. Enoxaparin as adjunctive anti-thrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation* 2002;**105**:1642–1649.
245. Coussement PK, Bassand JP, Convens C, Vrolix M, Boland J, Grollier G, Michels R, Vahanian A, Vanderheyden M, Rupprecht HJ, Van de Werf F, A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The PENTALYSE study. *Eur Heart J* 2001;**22**:1716–1724.
246. Marso SP, Lincoff AM, Ellis SG, Bhatt DL, Tanguay JF, Kleiman NS, Hammoud T, Booth JE, Sapp SK, Topol EJ. Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of platelet IIb/IIIa inhibitor for stenting trial) diabetic substudy. *Circulation* 1999;**100**:2477–2484.
247. Mehilli J, Kastrati A, Schühlen H, Dibra A, Dotzer F, von Beckerath N, Bollwein H, Pache J, Dirschinger J, Berger PP, Schömig A. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004; **110**:3627–3635.
248. Kong DF, Hasselblad V, Harrington RA, White HD, Tcheng JE, Kandzari DE, Topol EJ, Califf RM. Meta-analysis of survival with platelet glycoprotein IIb/IIIa antagonists for percutaneous coronary interventions. *Am J Cardiol* 2003;**92**:651–655.
249. Wijpkema JS, Jessurun GA, Van Boven AJ, Versteeg DI, Hautvast RW, Tio RA. Clinical impact of abciximab on long-term outcome after complex coronary angioplasty. *Catheter Cardiovasc Interv* 2003; **60**:339–343.
250. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001;**357**:1915–1924.
251. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;**338**:1498–1505.
252. The PRISM-PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;**338**:1488–1497.
253. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998;**97**:2386–2395.
254. The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436–443.
255. The PARAGON-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation* 2002;**105**:316–321.
256. Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999;**340**:1623–1629.
257. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994; **330**:956–961.
258. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689–1696.
259. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
260. The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). The ERASER Investigators. *Circulation* 1999;**100**:799–806.
261. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;**356**:2037–2044.
262. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;**349**:1422–1428.
263. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997; **96**:1445–1453.
264. Dalby M, Montalescot G, Sollier CB, Vicaut E, Soulat T, Collet JP, Choussat R, Gallois V, Drobinski G, Drouet L, Thomas D. Eptifibatide provides additional platelet inhibition in non-ST-elevation myocardial infarction patients already treated with aspirin and clopidogrel. Results of the platelet activity extinction in non-Q-wave myocardial infarction with aspirin, clopidogrel, and eptifibatide (PEACE) study. *J Am Coll Cardiol* 2004;**43**:162–168.
265. Roe MT, Christenson RH, Ohman EM, Bahr R, Fesmire FM, Storrow A, Mollod M, Peacock WF, Rosenblatt JA, Yang H, Fraulo ES, Hoekstra JW, Gibler WB. A randomized, placebo-controlled trial of early eptifibatide for non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2003;**146**:993–998.
266. Moliterno DJ, Yakubov SJ, DiBattiste PM, Herrmann HC, Stone GW, Macaya C, Neumann FJ, Ardissino D, Bassand JP, Borzi L, Yeung AC, Harris KA, Demopoulos LA, Topol EJ. Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002;**360**:355–360.
267. Stone GW, Moliterno DJ, Bertrand M, Neumann FJ, Herrmann HC, Powers ER, Grines CL, Moses JW, Cohen DJ, Cohen EA, Cohen M, Wolski K, DiBattiste PM, Topol EJ. Impact of clinical syndrome acuity on the differential response to 2 glycoprotein IIb/IIIa inhibitors in patients undergoing coronary stenting: the TARGET Trial. *Circulation* 2002;**105**:2347–2354.

268. Danzi GB, Sesana M, Capuano C, Mauri L, Berra Centurini P, Baglini R. Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function. *Am J Cardiol* 2004;**94**:35–39.
269. Valgimigli M, Percoco G, Barbieri D, Ferrari F, Guardigli G, Parrinello G, Soukhomovskaia O, Ferrari R. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004;**44**:14–19.
270. Ernst NM, Suryapranata H, Miedema K, Slingerland RJ, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ, Zijlstra F, van't Hof AW. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;**44**:1187–1193.
271. Theroux P, Alexander J Jr, Dupuis J, Pesant Y, Gervais P, Grandmont D, Kouz S, Laramee P, Huynh T, Barr E, Sax FL. Upstream use of tirofiban in patients admitted for an acute coronary syndrome in hospitals with or without facilities for invasive management. PRISM-PLUS Investigators. *Am J Cardiol* 2001;**87**:375–380.
272. Greenbaum AB, Harrington RA, Hudson MP, MacAulay CM, Wilcox RG, Simoons ML, Berdan LG, Guerci A, Cokkinos DV, Kitt MM, Lincoff AM, Topol EJ, Califf RM, Ohman EM. Therapeutic value of eptifibatide at community hospitals transferring patients to tertiary referral centres early after admission for acute coronary syndromes. PURSUIT Investigators. *J Am Coll Cardiol* 2001;**37**:492–498.
273. Cannon CP, Turpie AG. Unstable angina and non-ST-elevation myocardial infarction: initial anti-thrombotic therapy and early invasive strategy. *Circulation* 2003;**107**:2640–2645.
274. Boden WE, McKay RG. Optimal treatment of acute coronary syndromes—an evolving strategy. *N Engl J Med* 2001;**344**:1939–1942.
275. Boden WE, "Routine invasive" versus "selective invasive" approaches to non-ST-segment elevation acute coronary syndromes management in the post-stent/platelet inhibition era. *J Am Coll Cardiol* 2003;**41**:113S–122S.
276. Gibson CM, Singh KP, Murphy SA, DiBattiste PM, Demopoulos LA, Cannon CP, Braunwald E. Association between duration of tirofiban therapy before percutaneous intervention and tissue level perfusion (a TACTICS-TIMI 18 substudy). *Am J Cardiol* 2004;**94**:492–494.
277. Lange RA, Hillis LD. Antiplatelet therapy for ischemic heart disease. *N Engl J Med* 2004;**350**:277–280.
278. Rebeiz AG, Dery JP, Tsiatis AA, O'Shea J C, Johnson BA, Hellkamp AS, Pieper KS, Gilchrist IC, Slater J, Muhlestein JB, Joseph D, Kitt MM, Tcheng JE. Optimal duration of eptifibatide infusion in percutaneous coronary intervention (An ESPRIT substudy). *Am J Cardiol* 2004; **94**:926–929.
279. Brener SJ, Barr LA, Burchenal JE, Katz S, George BS, Jones AA, Cohen ED, Gainey PC, White HJ, Cheek HB, Moses JW, Moliterno DJ, Effron MB, Topol EJ. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation* 1998;**98**:734–741.
280. Neumann FJ, Kastrati A, Schmitt C, Blasini R, Hadamitzky M, Mehilli J, Gawaz M, Schleef M, Seyfarth M, Dirschinger J, Schömig A. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 2000;**35**:915–921.
281. Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, Parodi G, Fernandez-Pereira C, Moschi G, Bartorelli A, Santoro GM, Bolognese L, Colombo A. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;**42**:1879–1885.
282. de Queiroz Fernandes Araújo JO, Veloso HH, De Paiva JMB, Filho MW, De Paola AAV. Efficacy and safety of abciximab on acute myocardial infarction treated with percutaneous coronary interventions: A meta-analysis of randomized, controlled trials. *Am Heart J* 2004;**148**:937–943.
283. Petronio AS, Musumeci G, Limbruno U, De Carlo M, Baglini R, Paterni G, Grazia Delle Donne M, Caravelli P, Nardi C, Mariani M. Abciximab improves 6-month clinical outcome after rescue coronary angioplasty. *Am Heart J* 2002;**143**:334–341.
284. Ndrepepa G, Kastrati A, Neumann FJ, Schmitt C, Mehilli J, Schömig A. Five-year outcome of patients with acute myocardial infarction enrolled in a randomised trial assessing the value of abciximab during coronary artery stenting. *Eur Heart J* 2004;**25**:1635–1640.
285. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol* 2003; **42**:1886–1889.
286. Kandzari DE, Hasselblad V, Tcheng JE, Stone GW, Califf RM, Kastrati A, Neumann FJ, Brener SJ, Montalescot G, Kong DF, Harrington RA. Improved clinical outcomes with abciximab therapy in acute myocardial infarction: a systematic overview of randomized clinical trials. *Am Heart J* 2004;**147**:457–462.
287. Lincoff AM. Direct thrombin inhibitors for non-ST-segment elevation acute coronary syndromes: what, when, and where? *Am Heart J* 2003;**146**:S23–S30.
288. Lincoff AM, Kleiman NS, Kottke-Marchant K, Maierson ES, Maresh K, Wolski KE, Topol EJ. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am Heart J* 2002;**143**:847–853.
289. Koster A, Spiess B, Chew DP, Krabatsch T, Tambeur L, DeAnda A, Hetzer R, Kuppe H, Smedira NG, Lincoff AM. Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting. *Am J Cardiol* 2004;**93**:356–359.
290. Bittl JA, Strony J, Brinker JA, Ahmed WH, Meckel CR, Chaitman BR, Maraganore J, Deutsch E, Adelman B. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N Engl J Med* 1995;**333**:764–769.
291. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**: 853–863.
292. Schussler JM, Cameron CS, Anwar A, Donsky MS, Johnson KB, Vallabhan RC, Wischmeyer JB. Effect of bivalirudin on length of stay in the recovery area after percutaneous coronary intervention compared with heparin alone, heparin + abciximab, or heparin + eptifibatide. *Am J Cardiol* 2004;**94**:1417–1419.
293. Mahaffey KW, Lewis BE, Wildermann NM, Berkowitz SD, Oliverio RM, Turco MA, Shalev Y, Ver Lee P, Traverse JH, Rodriguez AR, Ohman EM, Harrington RA, Califf RM. The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol* 2003;**15**:611–616.
294. Serruys PW, Herrman JP, Simon R, Rutsch W, Bode C, Laarman GJ, van Dijk R, van den Bos AA, Umans VA, Fox KA *et al*. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. Helvetica Investigators. *N Engl J Med* 1995;**333**:757–763.
295. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001;**142**:952–959.
296. Lincoff AM, Bittl JA, Kleiman NS, Sarembock IJ, Jackman JD, Mehta S, Tannenbaum MA, Niederman AL, Bachinsky WB, Tift-Mann J, III, Parker HG, Kereiakes DJ, Harrington RA, Feit F, Maierson ES, Chew DP, Topol EJ. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). *Am J Cardiol* 2004;**93**:1092–1096.
297. Lincoff AM, Kleiman NS, Kereiakes DJ, Feit F, Bittl JA, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004;**292**:696–703.
298. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of

a meta-analysis based on individual patients' data. *Lancet* 2002;**359**:294–302.
299. Eikelboom J, White H, Yusuf S. The evolving role of direct thrombin inhibitors in acute coronary syndromes. *J Am Coll Cardiol* 2003;**41**:70S–78S.
300. Bauters C, Banos JL, Van Belle E, Mc Fadden EP, Lablanche JM, Bertrand ME. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. *Circulation* 1998;**97**:318–321.
301. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999;**100**:1872–1878.
302. Abizaid A, Kornowski R, Mintz GS, Hong MK, Abizaid AS, Mehran R, Pichard AD, Kent KM, Satler LF, Wu H, Popma JJ, Leon MB. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol* 1998;**32**: 584–589.
303. Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, Wong SC, Leon MB. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995;**26**:720–724.
304. Kastrati A, Schömig A, Elezi S, Schühlen H, Dirschinger J, Hadamitzky M, Wehinger A, Hausleiter J, Walter H, Neumann FJ. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997;**30**:1428–1436.
305. Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, Wong SC, Fish D, Ellis S, Holmes DR, Kerieakes D, Kuntz RE. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001; **344**:250–256.
306. Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, Satler LF, Mehran R, Serruys PW, Lansky AJ, Fitzgerald P, Bhargava B, Kent KM, Pichard AD, Leon MB. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis (WRIST). *Circulation* 2000;**101**:2165–2171.
307. Waksman R, Cheneau E, Ajani AE, White RL, Pinnow E, Torguson R, Deible R, Satler LF, Pichard AD, Kent KM, Teirstein PS, Lindsay J. Intracoronary radiation therapy improves the clinical and angiographic outcomes of diffuse in-stent restenotic lesions: results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies. *Circulation* 2003;**107**:1744–1749.
308. Popma JJ, Suntharalingam M, Lansky AJ, Heuser RR, Speiser B, Teirstein PS, Massullo V, Bass T, Henderson R, Silber S, von Rottkay P, Bonan R, Ho KK, Osattin A, Kuntz RE. Randomized trial of 90Sr/ 90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation* 2002;**106**:1090–1096.
309. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet* 2002; **359**:551–557.
310. Waksman R, Ajani AE, White RL, Chan RC, Satler LF, Kent KM, Pichard AD, Pinnow EE, Bui AB, Ramee S, Teirstein P, Lindsay J. Intravascular gamma radiation for in-stent restenosis in saphenous-vein bypass grafts. *N Engl J Med* 2002;**346**:1194–1199.
311. Urban P, Serruys P, Baumgart D, Colombo A, Silber S, Eeckhout E, Gershlick A, Wegscheider K, Verhees L, Bonan R. A multicentre European registry of intraluminal coronary beta brachytherapy. *Eur Heart J* 2003;**24**:604–612.
312. Silber S, Popma J, Suntharalingam M, Lansky A, Heuser R, Speiser B, Teirstein P, Bass BG, O'Neill W, Lasala JM, Reisman M, Sharma SK, Kuntz R, Bonan R. Two-Year Clinical Follow-Up of 90Sr/90Y Beta Radiation Versus Placebo-Control for the Treatment of In-Stent Restenosis. *Am Heart J* 2005 (in press).
313. Teirstein PS, Massullo V, Jani S, Russo RJ, Cloutier DA, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Norman S, Tripuraneni P. Two-year follow-up after catheter-based radiotherapy to inhibit coronary restenosis. *Circulation* 1999;**99**:243–247.
314. Teirstein PS, Kuntz RE. New frontiers in interventional cardiology: intravascular radiation to prevent restenosis. *Circulation* 2001;**104**:2620–2626.
315. Waksman R, Ajani AE, White RL, Pinnow E, Mehran R, Bui AB, Deible R, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KM, Lindsay J, Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse in-stent restenosis. *Am J Cardiol* 2001;**88**:425–428.
316. Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 2000;**101**:360–365.
317. Grise MA, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Cloutier DA, Leon MB, Tripuraneni P, Teirstein PS. Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 2002;**105**:2737–2740.
318. Waksman R, Ajani AE, Pinnow E, Cheneau E, Leborgne L, Dieble R, Bui AB, Satler LF, Pichard AD, Kent KK, Lindsay J. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS. *Circulation* 2002;**106**:776–778.
319. Silber S, Baumgart D, Hehrlein C, Meinertz T, Mügge A, Rutsch W, vom Dahl J. The IST Registry. *ZKardiol* 2002;**91**:III/33.
320. Mauri L, Bonan R, Weiner BH, Legrand V, Bassand JP, Popma JJ, Niemyski P, Prpic R, Ho KK, Chauhan MS, Cutlip DE, Bertrand OF, Kuntz RE. Cutting balloon angioplasty for the prevention of restenosis: results of the Cutting Balloon Global Randomized Trial. *Am J Cardiol* 2002;**90**:1079–1083.
321. Albiero R, Silber S, Di Mario C, Cernigliaro C, Battaglia S, Reimers B, Frasheri A, Klauss V, Auge JM, Rubartelli P, Morice MC, Cremonesi A, Schofer J, Bortone A, Colombo A. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol* 2004;**43**:943–949.
322. Cohen BM, Weber VJ, Blum RR, Ruck BE, Cohen DE, Haik BJ, Coletti RH. Cocktail attenuation of rotational ablation flow effects (CARAFE) study: pilot. *Cathet Cardiovasc Diagn* 1996;(Suppl. 3): 69–72.
323. Dill T, Dietz U, Hamm CW, Kuchler R, Rupprecht HJ, Haude M, Cyran J, Ozbek C, Kuck KH, Berger J, Erbel R. A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesions (COBRA study). *Eur Heart J* 2000; **21**:1759–1766.
324. Whitlow PL, Bass TA, Kipperman RM, Sharaf BL, Ho KK, Cutlip DE, Zhang Y, Kuntz RE, Williams DO, Lasorda DM, Moses JW, Cowley MJ, Eccleston DS, Horrigan MC, Bersin RM, Ramee SR, Feldman T. Results of the study to determine rotablator and transluminal angioplasty strategy (STRATAS). *Am J Cardiol* 2001;**87**:699–705.
325. Safian RD, Feldman T, Muller DW, Mason D, Schreiber T, Haik B, Mooney M, O'Neill WW. Coronary angioplasty and Rotablator atherectomy trial (CARAT): immediate and late results of a prospective multicentre randomized trial. *Catheter Cardiovasc Interv* 2001;**53**:213–220.
326. vom Dahl J, Dietz U, Haager PK, Silber S, Niccoli L, Buettner HJ, Schiele F, Thomas M, Commeau P, Ramsdale DR, Garcia E, Hamm CW, Hoffmann R, Reineke T, Klues HG. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation* 2002;**105**:583–588.
327. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J* 2004;**147**:16–22.
328. Kobayashi Y, Teirstein P, Linnemeier T, Stone G, Leon M, Moses J. Rotational atherectomy (stentablation) in a lesion with stent underexpansion due to heavily calcified plaque. *Catheter Cardiovasc Interv* 2001;**52**:208–211.
329. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, Masden RR, Serruys PW, Leon MB, Williams DO *et al*. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. *N Engl J Med* 1993;**329**:221–227.
330. Holmes DR Jr, Topol EJ, Califf RM, Berdan LG, Leya F, Berger PB, Whitlow PL, Safian RD, Adelman AG, Kellett MA Jr *et al*. A multicentre, randomized trial of coronary angioplasty versus directional atherectomy for patients with saphenous vein bypass graft lesions. CAVEAT-II Investigators. *Circulation* 1995;**91**:1966–1974.

331. Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, Lansky AJ, Popma JJ, Kuntz RE. Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). *Circulation* 1998;**97**:322–331.
332. Cohen EA, Sykora K, Kimball BP, Bonan R, Ricci DR, Webb JG, Laramee L, Barbeau G, Traboulsi M, Corbett BN, Schwartz L, Adelman AG. Clinical outcomes of patients more than one year following randomization in the Canadian Coronary Atherectomy Trial (CCAT). *Can J Cardiol* 1997;**13**:825–830.
333. Simonton CA, Leon MB, Baim DS, Hinohara T, Kent KM, Bersin RM, Wilson BH, Mintz GS, Fitzgerald PJ, Yock PG, Popma JJ, Ho KK, Cutlip DE, Senerchia C, Kuntz RE. 'Optimal' directional coronary atherectomy: final results of the Optimal Atherectomy Restenosis Study (OARS). *Circulation* 1998;**97**:332–339.
334. Stankovic G, Colombo A, Bersin R, Popma J, Sharma S, Cannon LA, Gordon P, Nukta D, Braden G, Collins M. Comparison of directional coronary atherectomy and stenting versus stenting alone for the treatment of de novo and restenotic coronary artery narrowing. *Am J Cardiol* 2004;**93**:953–958.
335. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;**101**:570–580.
336. Hong MK, Mehran R, Dangas G, Mintz GS, Lansky AJ, Pichard AD, Kent KM, Satler LF, Stone GW, Leon MB. Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. *Circulation* 1999;**100**:2400–2405.
337. de Feyter PJ, van Suylen RJ, de Jaegere PP, Topol EJ, Serruys PW. Balloon angioplasty for the treatment of lesions in saphenous vein bypass grafts. *J Am Coll Cardiol* 1993;**21**:1539–1549.
338. Plokker HW, Meester BH, Serruys PW. The Dutch experience in percutaneous transluminal angioplasty of narrowed saphenous veins used for aortocoronary arterial bypass. *Am J Cardiol* 1991;**67**: 361–366.
339. Roffi M, Mukherjee D, Chew DP, Bhatt DL, Cho L, Robbins MA, Ziada KM, Brennan DM, Ellis SG, Topol EJ. Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aortocoronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation* 2002;**106**:3063–3067.
340. Schächinger V, Hamm CW, Münzel T, Haude M, Baldus S, Grube E, Bonzel T, Konorza T, Koster R, Arnold R, Haase J, Probst P, vom Dahl J, Neumann FJ, Mudra H, Hennen B, Thiele L, Zeiher AM. A randomized trial of polytetrafluoroethylene-membrane-covered stents compared with conventional stents in aortocoronary saphenous vein grafts. *J Am Coll Cardiol* 2003;**42**:1360–1369.
341. Stankovic G, Colombo A, Presbitero P, van den Branden F, Inglese L, Cernigliaro C, Niccoli L, Bartorelli AL, Rubartelli P, Reifart N, Heyndrickx GR, Saunamaki K, Morice MC, Sgura FA, Di Mario C. - Randomized evaluation of polytetrafluoroethylene-covered stent in saphenous vein grafts: the Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) Trial. *Circulation* 2003;**108**:37–42.
342. Resnic FS, Wainstein M, Lee MK, Behrendt D, Wainstein RV, Ohno-Machado L, Kirshenbaum JM, Rogers CD, Popma JJ, Piana R. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. *Am Heart J* 2003;**145**:42–46.
343. Grube E, Gerckens U, Yeung AC, Rowold S, Kirchhof N, Sedgewick J, Yadav JS, Stertzer S. Prevention of distal embolization during coronary angioplasty in saphenous vein grafts and native vessels using porous filter protection. *Circulation* 2001;**104**:2436–2441.
344. Beran G, Lang I, Schreiber W, Denk S, Stefenelli T, Syeda B, Maurer G, Glogar D, Siostrzonek P. Intracoronary thrombectomy with the X-sizer catheter system improves epicardial flow and accelerates ST-segment resolution in patients with acute coronary syndrome: a prospective, randomized, controlled study. *Circulation* 2002;**105**: 2355–2360.
345. Exaire JE, Brener SJ, Ellis CG, Yadav JS, Bhatt DL. GuardWire emboli protection device is associated with improved myocardial perfusion grade in saphenous vein graft intervention. *Am Heart J* 2004;**148**: 1003–1006.
346. Baim DS, Wahr D, George B, Leon MB, Greenberg J, Cutlip DE, Kaya U, Popma JJ, Ho KK, Kuntz RE. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 2002;**105**:1285–1290.
347. Stone GW, Rogers C, Hermiller J, Feldman R, Hall P, Haber R, Masud A, Cambier P, Caputo RP, Turco M, Kovach R, Brodie B, Herrmann HC, Kuntz RE, Popma JJ, Ramee S, Cox DA. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation* 2003; **108**:548–553.
348. Mathew V, Lennon RJ, Rihal CS, Bresnahan JF, Holmes DR Jr. Applicability of distal protection for aortocoronary vein graft interventions in clinical practice. *Catheter Cardiovasc Interv* 2004;**63**: 148–151.
349. Stone G, Webb J, Cox D, Brodie B, Qureshi MA, Dulas D, Kalynych A, Turco M, Schultheiss H, Rutherford BD, Krucoff M, Gibbons RJ, Lansky A, R. P, Mehran R, Jones AA. Primary Angioplasty in Acute Myocardial Infarction with Distal Protection of the Microcirculation: Principal Results from the prospective, randomized EMERALD Trial. 2005 (in press).
350. Kuntz RE, Baim DS, Cohen DJ, Popma JJ, Carrozza JP, Sharma S, McCormick DJ, Schmidt DA, Lansky AJ, Ho KK, Dandreo KJ, Setum CM, Ramee SR. A trial comparing rheolytic thrombectomy with intracoronary urokinase for coronary and vein graft thrombus (the Vein Graft AngioJet Study [VeGAS 2]). *Am J Cardiol* 2002;**89**: 326–330.
351. Kornowski R, Ayzenberg O, Halon DA, Kusniec F, Assali A. Preliminary experiences using X-sizer catheter for mechanical thrombectomy of thrombus-containing lesions during acute coronary syndromes. *Catheter Cardiovasc Interv* 2003;**58**:443–448.
352. von Korn H, Scheinert D, Bruck M, Bremer J, Flachskampf FA, Klinghammer L, Daniel WG, Ludwig J. Initial experience with the Endicor X-sizer thrombectomy device in patients with ST segment elevation myocardial infarction. *Z Kardiol* 2002;**91**:466–471.
353. Stone G, Cox DA, Babb J, Nukta D, Bilodeau L, Cannon L, Stuckey T, Hermiller J, Cohen EA, Low R, Bailey SR, Lansky A, Kuntz RE. Prospective, randomized evaluation of thrombectomy prior to percutaneous intervention in diseased saphenous vein grafts and thrombus-containing coronary arteries. *J Am Coll Cardiol* 2003;**42**:2007–2013.
354. Angelini A, Rubartelli P, Mistrorigo F, Della Barbera M, Abbadessa F, Vischi M, Thiene G, Chierchia S. Distal protection with a filter device during coronary stenting in patients with stable and unstable angina. *Circulation* 2004;**110**:515–521.
355. Fasseas P, Orford JL, Panetta CJ, Bell MR, Denktas AE, Lennon RJ, Holmes DR, Berger PB. Incidence, correlates, management, and clinical outcome of coronary perforation: analysis of 16,298 procedures. *Am Heart J* 2004;**147**:140–145.
356. Schiele F, Meneveau N, Vuillemenot A, Zhang DD, Gupta S, Mercier M, Danchin N, Bertrand B, Bassand JP. Impact of intravascular ultrasound guidance in stent deployment on 6-month restenosis rate: a multicentre, randomized study comparing two strategies—with and without intravascular ultrasound guidance. RESIST Study Group. REStenosis after Ivus guided STenting. *J Am Coll Cardiol* 1998;**32**:320–328.
357. Schiele F, Meneveau N, Gilard M, Boschat J, Commeau P, Ming LP, Sewoke P, Seronde MF, Mercier M, Gupta S, Bassand JP. Intravascular ultrasound-guided balloon angioplasty compared with stent: immediate and 6-month results of the multicentre, randomized Balloon Equivalent to Stent Study (BEST). *Circulation* 2003;**107**:545–551.
358. Fitzgerald PJ, Oshima A, Hayase M, Metz JA, Bailey SR, Baim DS, Cleman MW, Deutsch E, Diver DJ, Leon MB, Moses JW, Oesterle SN, Overlie PA, Pepine CJ, Safian RD, Shani J, Simonton CA, Smalling RW, Teirstein PS, Zidar JP, Yeung AC, Kuntz RE, Yock PG. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation* 2000;**102**:523–530.
359. Mudra H, di Mario C, de Jaegere P, Figulla HR, Macaya C, Zahn R, Wennerblom B, Rutsch W, Voudris V, Regar E, Henneke KH, Schachinger V, Zeiher A. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). *Circulation* 2001;**104**:1343–1349.
360. Orford JL, Denktas AE, Williams BA, Fasseas P, Willerson JT, Berger PB, Holmes DR Jr. Routine intravascular ultrasound scanning guidance of

coronary stenting is not associated with improved clinical outcomes. *Am Heart J* 2004;**148**:501–506.
361. Fischer JJ, Samady H, McPherson JA, Sarembock IJ, Powers ER, Gimple LW, Ragosta M. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 2002;**90**:210–215.
362. Pijls NH. Is it time to measure fractional flow reserve in all patients? *J Am Coll Cardiol* 2003;**41**:1122–1124.
363. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;**334**:1703–1708.
364. Bech GJ, De Bruyne B, Bonnier HJ, Bartunek J, Wijns W, Peels K, Heyndrickx GR, Koolen JJ, Pijls NH. Long-term follow-up after deferral of percutaneous transluminal coronary angioplasty of intermediate stenosis on the basis of coronary pressure measurement. *J Am Coll Cardiol* 1998;**31**:841–847.
365. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;**103**:2928–2934.
366. Lopez-Palop R, Pinar E, Lozano I, Saura D, Pico F, Valdes M. Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis. *Eur Heart J* 2004;**25**:2040–2047.
367. Meier B, Ramamurthy S. Plaque sealing by coronary angioplasty. *Cathet Cardiovasc Diagn* 1995;**36**:295–297.
368. Meier B. Plaque sealing by coronary angioplasty. *Heart* 2004; **90**:1395–1398.
369. Hamon M, Bauters C, McFadden EP, Lablanche JM, Bertrand ME. Six-month quantitative angiographic follow-up of $<$ 50% diameter stenoses dilated during multilesion percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1993;**71**:1226–1229.
370. Mercado N, Maier W, Boersma E, Bucher C, de Valk V, O'Neill WW, Gersh BJ, Meier B, Serruys PW, Wijns W. Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting. Implications for mechanical plaque sealing. *Eur Heart J* 2003;**24**:541–551.
371. Oberhoff M, Karsch KR. Who wants his plaque sealed? *Eur Heart J* 2003;**24**:494–495.
372. Hoye A, Lemos PA, Arampatzis CA, Saia F, Tanabe K, Degertekin M, Daemen J, Smits PC, McFadden E, Hofma SH, Sianos G, de Feyter P, Giessen WJ, van Domburg RT, Serruys PW. Effectiveness of sirolimus-Eluting stent implantation for coronary narrowings $<$ 50% in diameter. *Am J Cardiol* 2004;**94**:112–114.
373. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–1780.
374. Silber S, Grube E, Fitzgerald P. The Quanam QUADDS-QP2 stent. In: Serruys P, Kutryk M, eds. *Handbook of Coronary Stents*, 4th ed. Martin Dunitz Publishers Ltd, 2001:343–347.
375. Grube E, Lansky A, Hauptmann KE, Di Mario C, Di Sciascio G, Colombo A, Silber S, Stumpf J, Reifart N, Fajadet J, Marzocchi A, Schofer J, Dumas P, Hoffmann R, Guagliumi G, Pitney M, Russell ME. High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization one-year results from the SCORE randomized trial. *J Am Coll Cardiol* 2004;**44**:1368–1372.
376. Serruys PW, Ormiston JA, Sianos G, Sousa JE, Grube E, den Heijer P, de Feyter P, Buszman P, Schömig A, Marco J, Polonski L, Thuesen L, Zeiher AM, Bett JH, Suttorp MJ, Glogar HD, Pitney M, Wilkins GT, Whitbourn R, Veldhof S, Miquel K, Johnson R, Coleman L, Virmani R. Actinomycin-eluting stent for coronary revascularization A randomized feasibility and safety study: The ACTION trial. *J Am Coll Cardiol* 2004;**44**:1363–1367.
377. Liu X, Huang Y, Hanet C, Vandormael M, Legrand V, Dens J, Vandenbossche JL, Missault L, Vrints C, De Scheerder I. Study of antirestenosis with the BiodivYsio dexamethasone-eluting stent (STRIDE): A first-in-human multicentre pilot trial. *Catheter Cardiovasc Interv* 2003;**60**:172–178.
378. Hoffmann R, Langenberg R, Radke P, Franke A, Blindt R, Ortlepp J, Popma JJ, Weber C, Hanrath P. Evaluation of a high-dose dexamethasone-eluting stent. *Am J Cardiol* 2004;**94**:193–195.
379. Silber S. Which parameter should be chosen as primary endpoint for randomized drug-eluting stent studies? *J Interv Cardiol* 2004;**17**:375–385.
380. Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA, O'-Shaughnessy C, Applegate RA, Cannon LA, Mooney M, Farah A, Tannenbaum MA, Yakubov S, Kereiakes DJ, Wong SC, Kaplan B, Cristea E, Stone GW, Leon MB, Knopf WD, O'Neill WW. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. *Circulation* 2004;**109**:1948–1954.
381. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;**350**:221–231.
382. Dawkins KD, Grube E, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptmann K, Marco J, Wijns W, Popma J, Koglin J, Russel ME. Clinical efficacy of polymer based paclitaxel eluting stents in the treatment of complex, long coronary artery lesions from a multicentre, randomised trial: support for the use od drug eluting stents in contemporary clinical practice (TAXUS-VI), 2005 (in press).
383. Silber S. Paclitaxel-eluting stents: are they all equal? An analysis of six randomized controlled trials in de novo lesions of 3,319 patients. *J Interv Cardiol* 2003;**16**:485–490.
384. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;**364**:583–591.
385. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;**349**:1315–1323.
386. Teirstein PS. Living the dream of no restenosis. *Circulation* 2001;**104**:1996–1998.
387. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004;**109**:190–195.
388. Goy JJ, Urban P, Seydoux C, De Benedetti E, Stauffer JC. Use of sirolimus-eluting coronary stents in routine clinical practice. *Catheter Cardiovasc Interv* 2004;**62**:26–29.
389. Sawhney N, Moses JW, Leon MB, Kuntz RE, Popma JJ, Bachinsky W, Bass T, DeMaio S, Fry E, Holmes DR Jr, Teirstein PS. Treatment of left anterior descending coronary artery disease with sirolimus-eluting stents. *Circulation* 2004;**110**:374–379.
390. Goy JJ, Stauffer JC, Siegenthaler WE, Benoit A, Seydoux C. A Prospective Randomized Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology: The TAXi Trial. *J Am Coll Cardiol*, 2005 (in press).
391. Lemos PA, Arampatzis CA, Saia F, Hoye A, Degertekin M, Tanabe K, Lee CH, Cummins P, Smits PC, McFadden E, Sianos G, de Feyter P, van der Giessen WJ, van Domburg RT, Serruys PW. Treatment of very small vessels with 2.25-mm diameter sirolimus-eluting stents (from the RESEARCH registry). *Am J Cardiol* 2004;**93**:633–636.
392. West NE, Ruygrok PN, Disco CM, Webster MW, Lindeboom WK, O'Neill WW, Mercado NF, Serruys PW. Clinical and angiographic predictors of restenosis after stent deployment in diafbetic patients. *Circulation* 2004;**109**:867–873.
393. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Keim E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004;**109**:2273–2278.
394. Schofer J, Schlüter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G, and E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions

in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;**362**:1093–1099.
395. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP Jr. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004;**109**:1930–1932.
396. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, Lindsay J. Major noncardiac surgery following coronary stenting: When is it safe to operate? *Catheter Cardiovasc Interv* 2004; **63**:141–145.
397. Hodgson JM, Bottner RK, Klein LW, Walpole HT Jr, Cohen DJ, Cutlip DE, Fenninger RB, Firth BG, Greenberg D, Kalisky I, Meskan T, Powell W, Stone GW, Zito JP, Clark MA. Drug-eluting stent task force: Final report and recommendations of the working committees on cost-effectiveness/economics, access to care, and medicolegal issues. *Catheter Cardiovasc Interv* 2004;**62**:1–17.
398. Cohen DJ, Bakhai A, Shi C, Githiora L, Lavelle T, Berezin RH, Leon MB, Moses JW, Carrozza JP Jr, Zidar JP, Kuntz RE. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial. *Circulation* 2004; **110**:508–514.
399. NICE (National Institute for Clinical Excellence), Coronary artery stents (No 71), (replacing Drug-eluting stents No 4). Available at http://www.nice.org.uk, 2004.
400. Lemos PA, Saia F, Hofma SH, Daemen J, Ong AT, Arampatzis CA, Hoye A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**:704–708.
401. Tanabe K, Hoye A, Lemos PA, Aoki J, Arampatzis CA, Saia F, Lee CH, Degertekin M, Hofma SH, Sianos G, McFadden E, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings. *Am J Cardiol* 2004; **94**:115–118.
402. Arampatzis CA, Lemos PA, Hoye A, Saia F, Tanabe K, Van Der Giessen WJ, Smits PC, McFadden E, De Feyter P, Serruys PW. Elective sirolimus-eluting stent implantation for left main coronary artery disease: Six-month angiographic follow-up and 1-year clinical outcome. *Catheter Cardiovasc Interv* 2004;**62**:292–296.
403. Saia F, Lemos PA, Hoye A, Sianos G, Arampatzis CA, De Feyter PJ, Van Der Giessen WJ, Smits PC, Van Domburg RT, Serruys PW. Clinical outcomes for sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis. *Catheter Cardiovasc Interv* 2004;**62**:283–288.
404. Silber S, Hamburger J, Grube E, Pfisterer M, Belardi J, Webb J, Zmudka K, Nienaber C, Hauptmann K, Rutsch W, Dawkins K, Drzewiecki J, Koglin J, Colombo A. Direct Stenting with TAXUS Stents Seems to be as Safe and Effective as with Predilatation: a post hoc analysis of TAXUS II. *Herz* 2004;**29**:171–180.