ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

European Heart Journal (2005) 26, 804–847
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EUROPEAN SOCIETY OF CARDIOLOGY®

For the first time !

ESC Guidelines

Guidelines for Percutaneous Coronary Interventions

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

Percutaneous coronary interventions in Europe 1992–2001

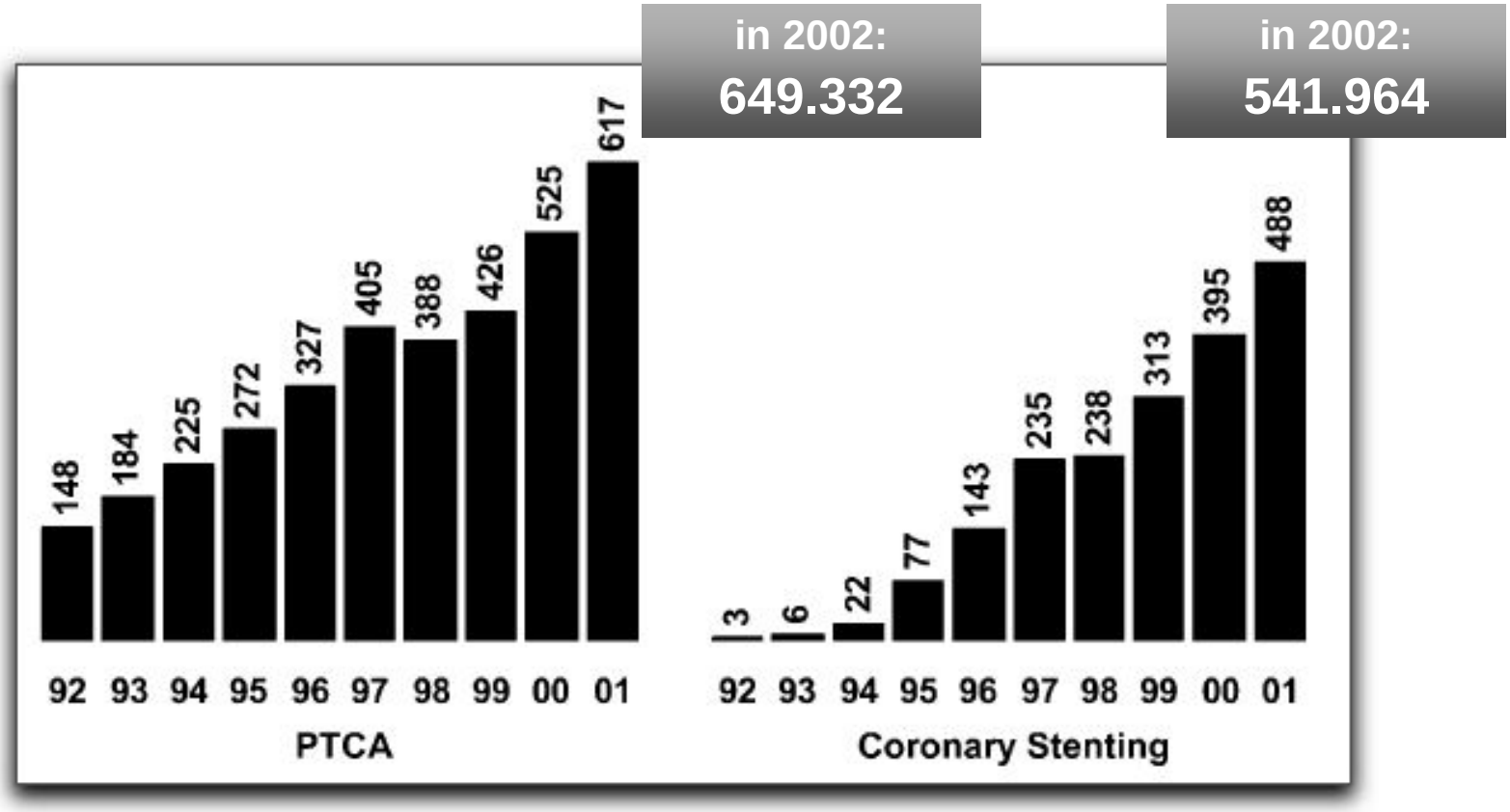


Fig. 1 Coronary angiograms, coronary angioplasty (PTCA), and coronary stenting from 1992 to 2001 in Europe in thousands of procedures.

European Heart Journal (2004) **25**, 1208–1213

Percutaneous coronary interventions in Europe 1992–2001

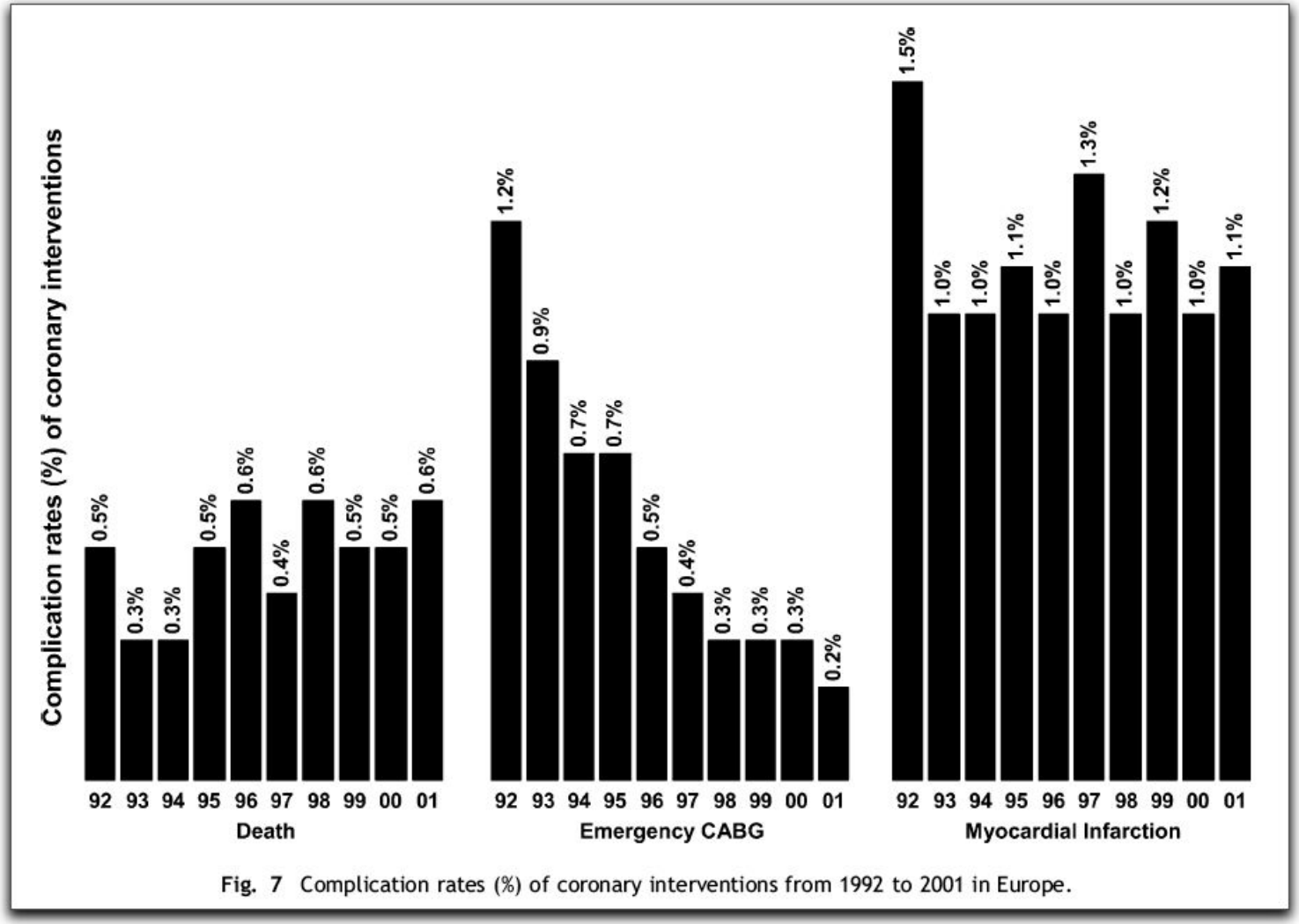


Fig. 7 Complication rates (%) of coronary interventions from 1992 to 2001 in Europe.

European Heart Journal (2004) **25**, 1208–1213

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)

Why do we need guidelines ?

1. Physicians are continuously flooded with studies

2. Guidelines should help to find the right way through this jungle of information

3. Experts should review existing data to provide clear recommendations based on evidence

4. Guidelines are increasingly used by health care providers and politicians to assess the „appropriate use“ and develop disease management programs

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

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

Committee for Practice Guidelines (CPG)

of the European Society of Cardiology

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

Table of Contents

EUROPEAN SOCIETY OF CARDIOLOGY

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

4.3 Evidence Gathering and Review

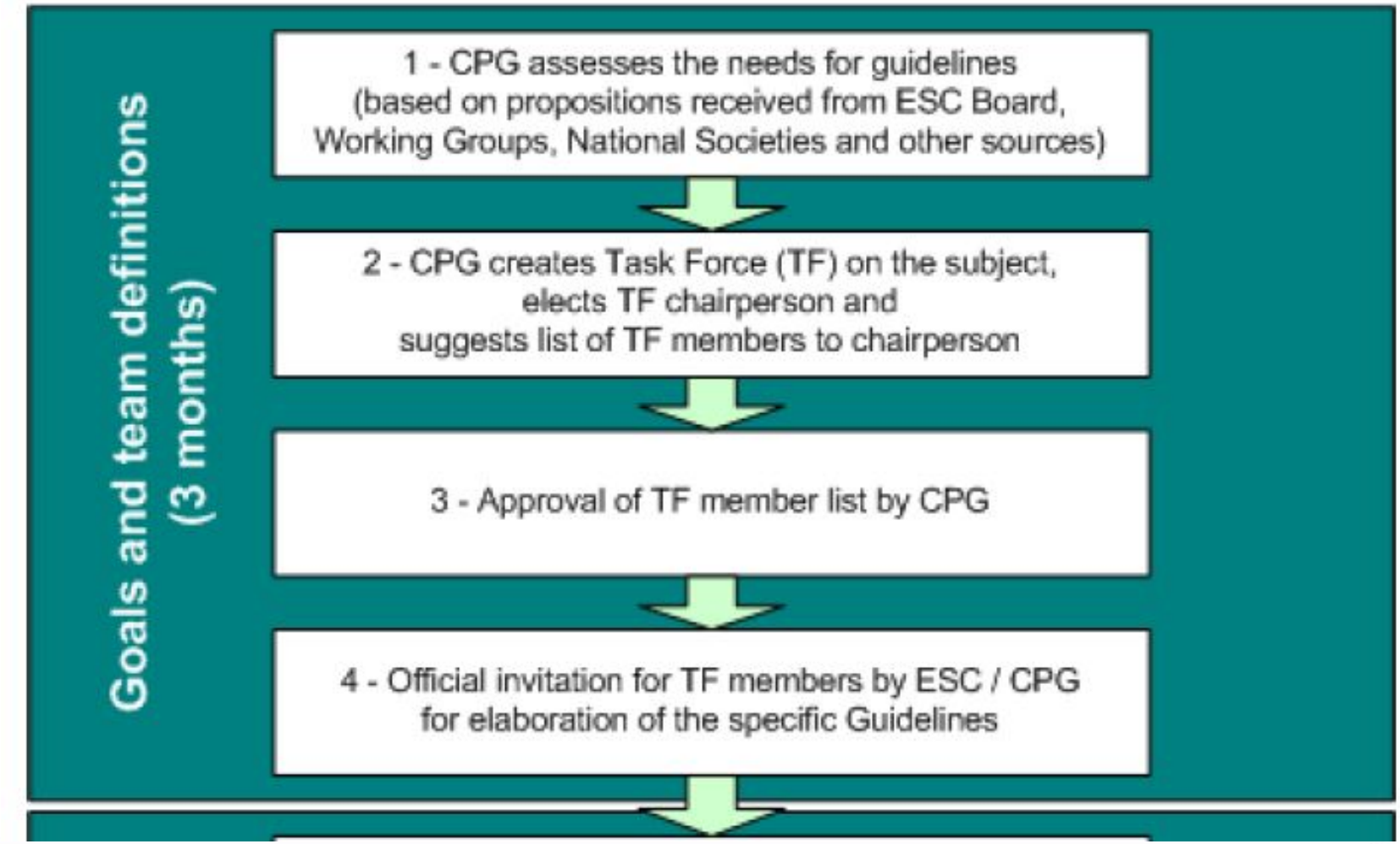
New tools are now available for literature searching which can make this process much easier, i.e. advanced PubMed, Medline, Embase, Cochrane, LocatorPlus, etc.

- A *formal literature review* must be performed. If deemed appropriate, a formal meta-analysis and evidence tables will be constructed by the Task Force. The processes used will be described in the completed document.
  - Only peer reviewed published literature will be considered.
  - The use of abstracts should be avoided except in very rare instances. Abstracts older than 2 years cannot be accepted. Quotation of the abstract must clearly indicate that it is an abstract and not a full paper.
  - Unpublished clinical trials cannot be quoted unless they have been formally presented at a major cardiology meeting and on condition that the authors of the trial have provided the writing group with a draft of the final document to be submitted for publication. Quotation of such trials must indicate at which cardiology meeting it has been presented.

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

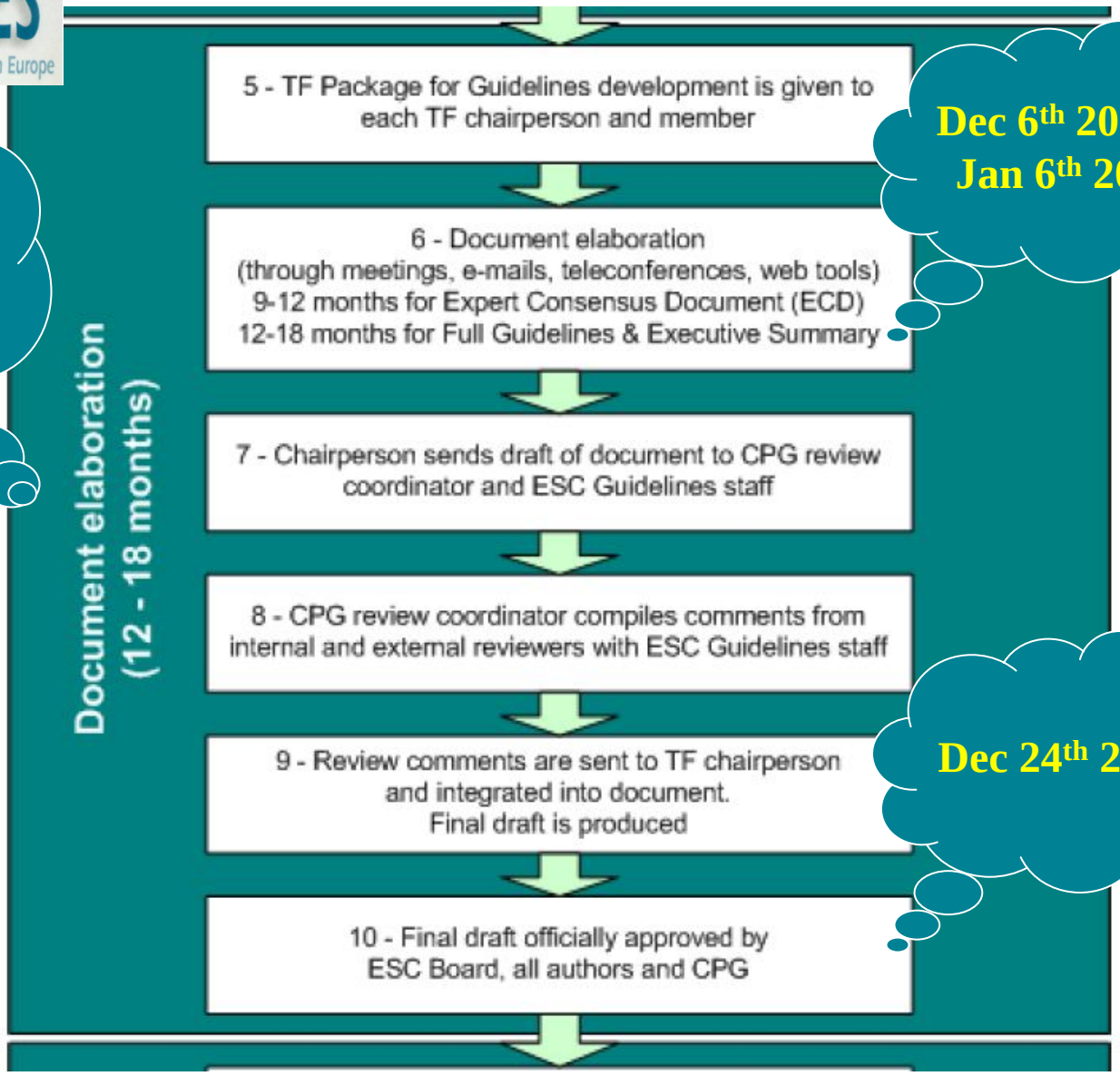
ESC Guidelines Production in 14 Steps



ESC GUIDELINES

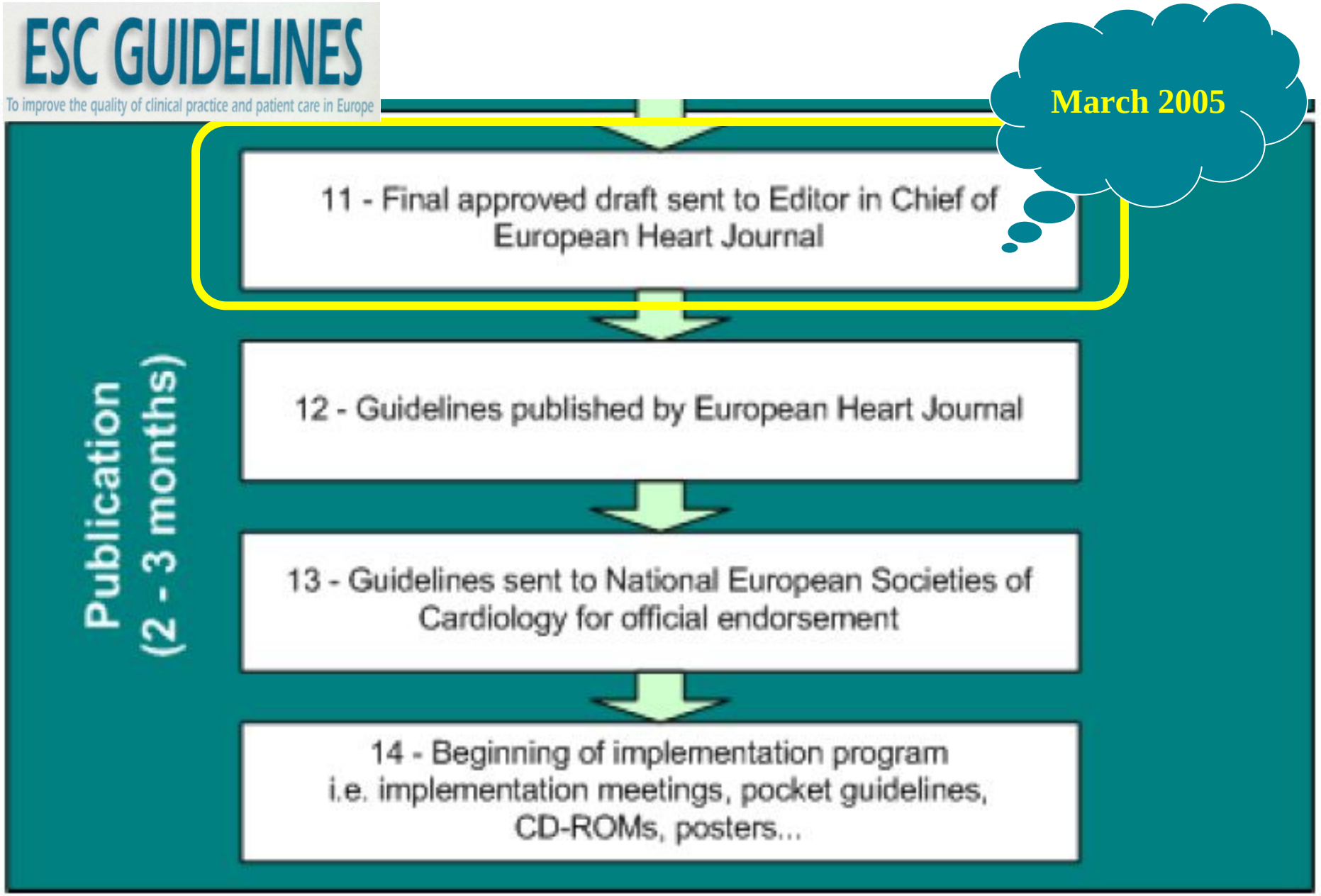
To improve the quality of clinical practice and patient care in Europe

For the PCI Guidelines



Dec 6th 2002 - Jan 6th 2004

Dec 24th 2004


ESC GUIDELINES
To improve the quality of clinical practice and patient care in Europe
March 2005
11 - Final approved draft sent to Editor in Chief of European Heart Journal
12 - Guidelines published by European Heart Journal
13 - Guidelines sent to National European Societies of Cardiology for official endorsement
14 - Beginning of implementation program i.e. implementation meetings, pocket guidelines, CD-ROMs, posters...
Publication (2 - 3 months)

Guidelines Classification for Evidence-Based Recommendations:

1. Classes of Recommendations : I, II, (III)
2. Levels of Evidence: A, B, C

Guidelines Classification for Evidence-Based Recommendations:

1. Classes of Recommendations :

Class I:
Evidence and/or general agreement that a given treatment is beneficial, useful and effective

Class II:
Conflicting evidence and/or divergence of opinions about the usefulness/efficacy of the treatment:

II a:
Weight of evidence/opinion is in favour of usefulness/efficacy

II b:
Usefulness/efficacy is less well established by evidence/opinion

Guidelines Classification for Evidence-Based Recommendations:

2. Levels of Evidence:

A:
Data derived from multiple randomised clinical trials or meta-analyses

B:
Data derived from a single randomised trial or multiple non-randomized studies ("registry trials") or a single metaanalysis

C:
Consensus of opinion of the experts and/or small studies

Problems of Evidence-Based Medicine Specific to PCI:

1. There is an overwhelming number of randomized trials making it rather easy for many treatments to achieve level of evidence A.
2. Our goal for treating patients with PCI is not to improve angiographic parameters (like restenosis rate or late lumen loss) or other surrogate parameters (like myocardial blush)...

   ...but to improve patients' outcome !
3. Many PCI trials have angiographic parameters or other surrogates as primary endpoints and outcome as a secondary endpoint.
4. Power calculations in randomized trials are performed for the primary endpoint...

   ...therefore, randomized studies, adequately powered with clinical outcome as a primary endpoint, should be preferred for the level of evidence.

Nine Different Levels of Recommendations:

Classes of Recommendations	Levels of Evidence		
	I A	I B	I C
	IIa A	IIa B	IIa C
	IIb A	IIb B	IIb C

What is not discussed:

1. Basic cathlab standards
2. Indications for stenting (bare stents)
3. Comparison of various bare stents
4. Operator and institutional PCI Volume
5. On-site cardiac surgical backup
6. Cost-effectiveness
7. Know "how to perform PCI"

Please note: Guidelines are not a text book !

ESC Guidelines on Percutaneous Coronary Interventions (PCI)

1. Challenge: finding consensus between 43 persons:
   - 13 members from the ESC-PCI Task Force (12 countries)
   - 13 reviewers from the ESC-CPG (Committee for Practice Guidelines)
   - 17 external reviewers
2. Potentially different points of view:
   - invasive vs. noninvasive cardiologists
   - invasive cardiologists performing PCI vs. invasive cardiologists performing only diagnostic angiography
   - hospitals with PCI facilities vs. hospitals without PCI
   - PCI hospitals with on-site cardiac surgery vs. without
   - possible inconsistencies with other recently published ESC guidelines
   - PCI in general is severely loaded with financial interests

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)

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Document R[illegible] Review Coordinator) (The Netherlands), Jean-Pierre Bassand (France), Alexander Ba[illegible] Bertrand (France), Amadeo Gibert Betriu (Spain), Dennis Cokkinos (Greece), Nicolas Danch[illegible]), 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)

Endorsed by 3 ESC Presidents

Guidelines for Percutaneous Coronary Interventions

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

Realistic Size:
30 printed text pages
& 404 references

Table of Contents

* 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

ESC GUIDELINES

To improve the quality of clinical practice and patient care in Europe

Summary:

Introduction and Definitions

1. For the first time, the ESC has created guidelines for PCI.
2. The criteria for levels of evidence (*A*, *B*, *C*) are stricter and more patient-oriented than previous definitions.
3. Based on evidence, the guidelines advise you what you *should* do and what you *could* do - but the final decision is still up to you.

Indications for PCI in Stable CAD

General Indications for PCI in stable CAD

PCI versus medical therapy :

- PCI gives earlier and more complete relief of angina than medical therapy and is associated with a better exercise tolerance and/or less ischaemia during exercise testing.
- In patients with no or mild symptoms, however, the scenario is different and unlikely to be improved by PCI.

Indications for PCI in Stable CAD

General Indications for PCI in stable CAD

PCI versus coronary artery bypass graft (CABG) surgery:

- Based on trials involving eight year follow-up, there is no significant difference in mortality between PCI and CABG surgery.
- 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 is no longer present in more recent trials with stents.
- 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.
- Stenting halved the risk difference for repeat revascularisation.
- Both PCI and CABG surgery provided good symptom relief.

Indications for PCI in Stable CAD

Indications for PCI in special subsets of stable patients

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.

PCI in high surgical risk patients:

Patients with severely depressed left ventricular function seem to benefit from revascularisation by PCI, in particular when there is evidence for residual viability of the dysfunctional myocardium.

Multi-vessel coronary artery disease and/or diabetes mellitus:

CABG surgery was associated with better survival than PCI after adjustment for patient risk profile. The presence of an unprotected left main coronary artery (LM) stenosis identifies an anatomic subset still requiring bypass surgery for revascularisation. Stenting for unprotected LM disease should only be considered in the absence of other revascularization options.

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 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 hours following balloon treatment is not uncommon, the treated lesion shows greater acute and sub-acute 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.

Recommendations of PCI Indications in Stable CAD:

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.

Summary - PCI in Stable CAD (1)

PCI can be considered a valuable initial mode of revascularisation in all patients with stable CAD and 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.

Summary - PCI in Stable CAD (2)

The decision to recommend PCI or CABG surgery will be guided by:

- technical improvements in cardiology or surgery
- local expertise
- patients' preference.

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.

Indications for PCI in Acute Coronary Syndromes without ST-Segment Elevation (NSTE-ACS)

Risk stratification in NSTE-ACS:

The importance of stratifying patients with unstable angina (UA) or NSTEMI in high risk versus 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. Patients at high risk for rapid progression to myocardial infarction or death that should undergo coronary angiography within 48 hours are:

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

Indications for PCI in Acute Coronary Syndromes without ST-Segment Elevation (NSTE-ACS)

Risk stratification in NSTE-ACS:

Furthermore, the following markers of severe underlying disease might also be helpful for risk assessment in NSTE-ACS:

- Age > 65 - 70 years
- History of known CAD, previous MI, prior PCI, or CABG surgery
- 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 3:

Part 1

The three randomized, controlled trials comparing initially conservative (catheterization as needed) versus initially invasive (routine catheterization with revascularization as needed) strategies in patients with NSTE-ACS. All 3 studies reached their primary endpoint ([a]p< 0.05).

	FRISC II
Enrolment period	1996–1998
Number of patients	2457
Patients' characterization (inclusion criteria)	UA/NSTEMI
Anticoagulation	Initially open label (UFH or LMWH dalteparin) up to 72 h, later randomization into four groups
GP IIb/IIIa usage (%) based on PCI cases only (early conservative/ early invasive)	Abciximab 10/10
Strategies	Early conservative (selectively invasive) vs. routine invasive: (PCI <7 days of the start of open treatment)
Catheterizations performed (%) (conservative/invasive at 4 or 6 months)	47/98
PCI performed (%) (conservative/invasive at 4 or 6 months)	37/77
Stent usage (%) (conservative/invasive at 4 or 6 months)	70/61
Any revascularization (%) (conservative/invasive at 4 or 6 months)	37/77
Primary endpoint defined	Death/MI
At time	6 months
Result of primary endpoint (%) (conservative/invasive)	12.1/9.4[a]
Primary endpoint reached	Yes

Table 3:

Part 2

The three randomized, controlled trials comparing initially conservative (catheterization as needed) versus initially invasive (routine catheterization with revascularization as needed) strategies in patients with NSTE-ACS. All 3 studies reached their primary endpoint ([a]p< 0.05).

	TACTICS-TIMI 18
Enrolment period	1997–1999
Number of patients	2220
Patients' characterization (inclusion criteria)	UA/NSTEMI
Anticoagulation	All UFH
GP IIb/IIIa usage (%) based on PCI cases only (early conservative/ early invasive)	Tirofiban 59/94
Strategies	Early conservative (selectively invasive) vs. early routine invasive (<4–48 h after randomization and revascularization when appropriate)
Catheterizations performed (%) (conservative/invasive at 4 or 6 months)	61/98
PCI performed (%) (conservative/invasive at 4 or 6 months)	29/42
Stent usage (%) (conservative/invasive at 4 or 6 months)	86/83
Any revascularization (%) (conservative/invasive at 4 or 6 months)	45/64
Primary endpoint defined	Death/nonfatal MI/ rehospitalization for ACS
At time	6 months
Result of primary endpoint (%) (conservative/invasive)	19.4/15.9[a]
Primary endpoint reached	Yes

Table 3:

Part 3

The three randomized, controlled trials comparing initially conservative (catheterization as needed) versus initially invasive (routine catheterization with revascularization as needed) strategies in patients with NSTE-ACS. All 3 studies reached their primary endpoint ([a]p< 0.05).

	RITA 3
Enrolment period	1997–2001
Number of patients	1810
Patients' characterization (inclusion criteria)	UA/NSTEMI
Anticoagulation	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)	Any 25
Strategies	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)	16/96
PCI performed (%) (conservative/invasive at 4 or 6 months)	7/33
Stent usage (%) (conservative/invasive at 4 or 6 months)	90/88
Any revascularization (%) (conservative/invasive at 4 or 6 months)	10/44
Primary endpoint defined	Death/MI/refractory angina
At time	4 months
Result of primary endpoint (%) (conservative/invasive)	14.5/9.6[a]
Primary endpoint reached	Yes

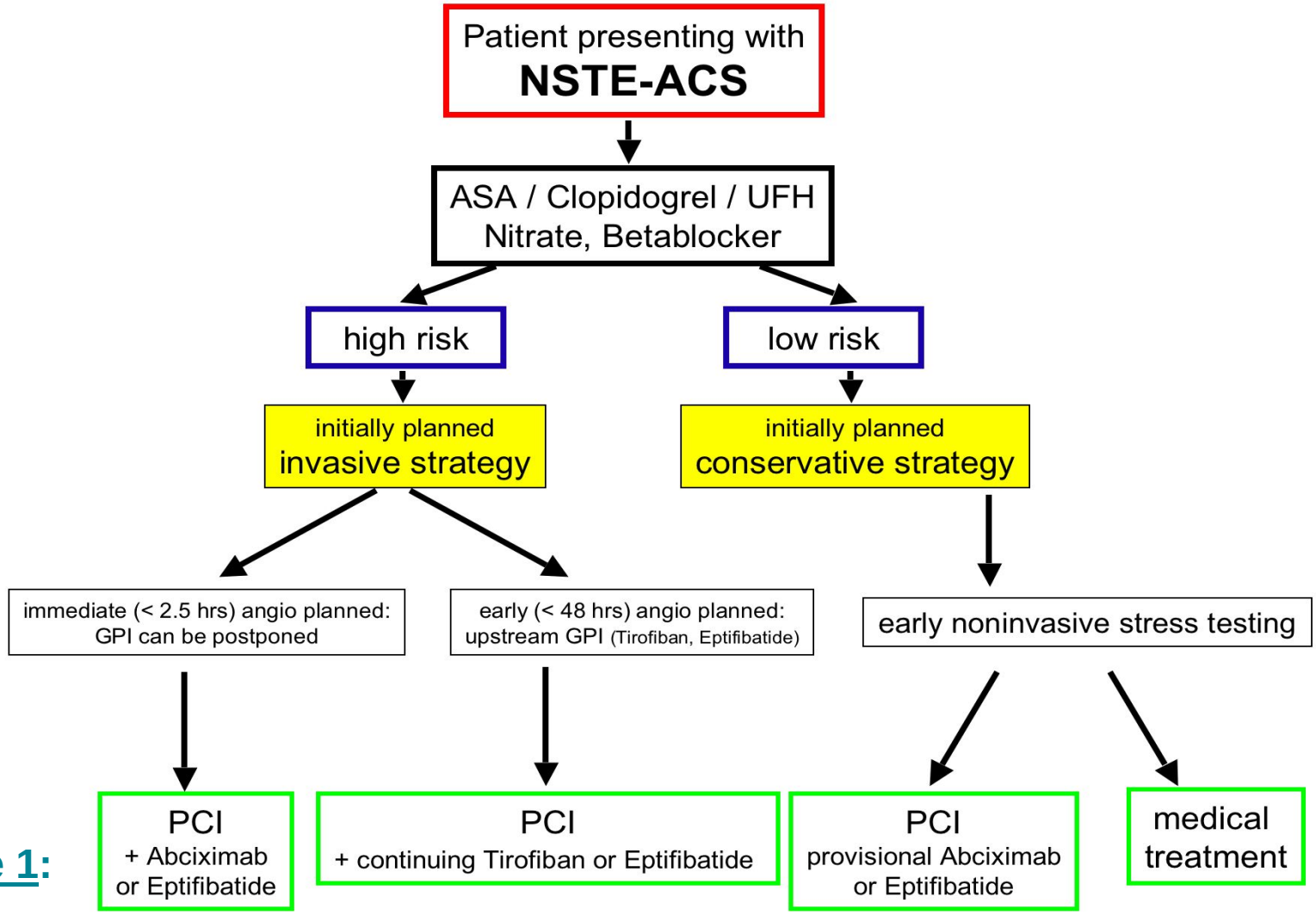


Figure 1:

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 catheterisation and planned PCI is up to 24 hours, 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.

Indications for PCI in Acute Coronary Syndromes without ST-Segment Elevation (NSTE-ACS)

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	–

Summary - PCI in NSTE-ACS

- 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 hours) 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 based on the predictability of the result and its immediate safety.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

- PCI for STEMI requires an experienced team of interventional cardiologists working together with skilled support staff.
- Only hospitals with an established interventional programme should use PCI for STEMI instead of intravenous thrombolysis.
- Most of the trials comparing thrombolysis versus primary PCI were carried out in high volume centres, by experienced operators, with short response times. Therefore, the results do not necessarily apply in other settings.
- Large variations between individual institutions have been documented.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

- 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..
- 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.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

Primary PCI:

Primary PCI is defined as intervention in the culprit vessel within 12 hours after the onset of chest pain or other symptoms, without prior (full or concomitant) thrombolytic or other clot dissolving therapy.

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 and also during long-term follow-up.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

Primary PCI:

There is no doubt that patients presenting within 12 hours after onset of chest pain or other symptoms in hospitals without PCI facilities and having contra-indications to thrombolysis should be immediately transferred to another hospital for coronary angiography and, if applicable, primary PCI, because PCI might be the only chance for quickly opening the coronary artery. Absolute contraindications to thrombolysis are the following conditions:

- Aortic dissection
- Status post haemorrhagic stroke
- Recent major trauma/surgery
- GI bleeding within the last month
- Known bleeding disorder

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation

Primary PCI: (STE-ACS, STEMI)

- Patients with a contraindication to thrombolysis are known to have a higher morbidity and mortality than those who are eligible.
- 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 logistical constraints and transport delays.
- Within the first 3 hours after onset of chest pain, thrombolysis is a viable alternative. Therefore, within the first 3 hours after onset of chest pain, both reperfusion strategies seem equally effective in reducing infarct size and mortality.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

- The major reason one could possibly prefer primary PCI over thrombolysis even within the first 3 hours after onset of chest pain is stroke prevention.
- In patients presenting 3 to 12 hours after onset of symptoms, myocardial salvage is significantly superior for primary PCI as compared to thrombolysis.
- It has been demonstrated that with increasing time to presentation, Major Adverse Cardiac Event (MACE) rates increase after thrombolysis but appear to remain relatively stable after PCI.

Table 5:

Part 1

Clinical outcome in patients transferred for primary PCI compared to thrombolysis initiated in-hospital. Times are listed as mean values ± standard deviation (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant ([a]p< 0.05); and only one trial reached the primary endpoint. (n/a: not applicable).

	Limburg
Enrolment period	1995–1997
Number of patients	224
Inclusion criteria	STEMI presenting within <6 h
Number of patients (thrombolysis/PCI)	75/75
Time from onset of symptoms to admission or randomization (min)	125 ± 80 130 (no SD)
Thrombolytic drug	Alteplase (t-PA)
Stent usage (%)	21
Distance for transfer of patients to primary PCI	25–50 km
Transport time of patients transferred to primary PCI (min)	20 (maximum 30)
Mean delay from emergency room or randomization to PCI (min)	85 ± 25
Mean delay from emergency room or randomization to start of thrombolysis (min)	10
Primary endpoint defined	Death and recurrent MI (secondary endpoint)
At time	42 days
Result of primary endpoint (thrombolysis/PCI, %)	16/8
Primary endpoint reached	N/A (pilot study)

Table 5:

Part 2

Clinical outcome in patients transferred for primary PCI compared to thrombolysis initiated in-hospital. Times are listed as mean values ± standard deviation (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant ([a]p< 0.05); and only one trial reached the primary endpoint. (n/a: not applicable).

	PRAGUE-1
Enrolment period	1997–1999
Number of patients	300
Inclusion criteria	STEMI presenting within <6 h (including new LBBB)
Number of patients (thrombolysis/PCI)	99/101
Time from onset of symptoms to admission or randomization (min)	110 (122) 120 (135)
Thrombolytic drug	Streptokinase
Stent usage (%)	79
Distance for transfer of patients to primary PCI	5–74 km
Transport time of patients transferred to primary PCI (min)	35
Mean delay from emergency room or randomization to PCI (min)	95
Mean delay from emergency room or randomization to start of thrombolysis (min)	22
Primary endpoint defined	Death (any cause)/ re-infarction/stroke
At time	30 days
Result of primary endpoint (thrombolysis/PCI, %)	23/8[a]
Primary endpoint reached	N/A (no power

Table 5:

Part 3

Clinical outcome in patients transferred for primary PCI compared to thrombolysis initiated in-hospital. Times are listed as mean values ± standard deviation (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant ([a]p< 0.05); and only one trial reached the primary endpoint. (n/a: not applicable).

	PRAGUE-2
Enrolment period	1999–2002
Number of patients	850
Inclusion criteria	STEMI presenting within <12 h
Number of patients (thrombolysis/PCI)	421/429
Time from onset of symptoms to admission or randomization (min)	173 ± 119 183 ± 162
Thrombolytic drug	Streptokinase
Stent usage (%)	63
Distance for transfer of patients to primary PCI	5–120 km
Transport time of patients transferred to primary PCI (min)	48 ± 20
Mean delay from emergency room or randomization to PCI (min)	94 (20 ± 9 + 48 ± 20 + 26 ± 11)
Mean delay from emergency room or randomization to start of thrombolysis (min)	12 ± 10
Primary endpoint defined	Death (any cause)
At time	30 days
Result of primary endpoint (thrombolysis/PCI, %)	10.0/6.8
Primary endpoint reached	N/A (prematurely

Table 5:

Part 4

Clinical outcome in patients transferred for primary PCI compared to thrombolysis initiated in-hospital. Times are listed as mean values ± standard deviation (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant ([a]p< 0.05); and only one trial reached the primary endpoint. (n/a: not applicable).

	Air-PAMI
Enrolment period	2000–2001
Number of patients	138
Inclusion criteria	High risk STEMI presenting within <12 h (including new LBBB)
Number of patients (thrombolysis/PCI)	66/71
Time from onset of symptoms to admission or randomization (min)	N/A
Thrombolytic drug	Streptokinase (32%) or alteplase/reteplase (68%)
Stent usage (%)	34
Distance for transfer of patients to primary PCI	51 ± 58 km; Air: 92 ± 80 km; Ground: 42 ± 45 km
Transport time of patients transferred to primary PCI (min)	33 ± 29
Mean delay from emergency room or randomization to PCI (min)	174 ± 80
Mean delay from emergency room or randomization to start of thrombolysis (min)	63 ± 39
Primary endpoint defined	Death/non-fatal re-infarction/disabling stroke
At time	30 days
Result of primary endpoint (thrombolysis/PCI, %)	13.6/8.4
Primary endpoint reached	N/A (prematurely

Table 5:

Part 5

Clinical outcome in patients transferred for primary PCI compared to thrombolysis initiated in-hospital. Times are listed as mean values ± standard deviation (Limburg, PRAGUE-1 and -2, Air-PAMI) or median and interquartile ranges (DANAMI-2). Only 2 of these 5 trials were statistically significant ([a]p< 0.05); and only one trial reached the primary endpoint. (n/a: not applicable).

	DANAMI-2
Enrolment period	1997–2001
Number of patients	1572
Inclusion criteria	STEMI presenting within <12 h
Number of patients (thrombolysis/PCI)	782/790
Time from onset of symptoms to admission or randomization (min)	105–107 (54–202)
Thrombolytic drug	Alteplase (t-PA)
Stent usage (%)	93
Distance for transfer of patients to primary PCI	50 (3–150) km
Transport time of patients transferred to primary PCI (min)	32 (20–45)
Mean delay from emergency room or randomization to PCI (min)	Referral hospital: 90 (74–108) PCI centres: 63 (49–77)
Mean delay from emergency room or randomization to start of thrombolysis (min)	Referral hospital: 20 (15–30) PCI centres: 20 (13–30)
Primary endpoint defined	Death/clinical evidence of re-infarction/disabling stroke
At time	30 days
Result of primary endpoint (thrombolysis/PCI, %)	13.7/8.0[a]
Primary endpoint reached	Yes

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

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 to 60 min after starting the administration.

Facilitated PCI:

...is defined as planned intervention within 12 hours after onset of chest pain or symptoms, soon after clot dissolving medication to bridge the delay between first medical contact and primary PCI. At the moment, there is no evidence for the recommendation of thrombolysis facilitated primary PCI and no evidence-based recommendation for GP IIb/IIIa inhibitor-facilitated primary PCI to improve patient outcomes.

Emergency PCI in cardiogenic shock:

In cardiogenic shock, emergency PCI may be life saving and should be considered at an early stage. If neither PCI nor surgery is available or can only be provided after a long delay, thrombolytic therapy should be given. In recent years, an increase in revascularisation of patients with AMI complicated for cardiogenic shock was observed, probably due to more frequent admission of eligible patients to hospitals capable of this service (Table 7).

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

Routine angiography early post thrombolysis:

After successful thrombolysis, the use of routine coronary angiography within 24 hours and PCI, if applicable, is recommended even in asymptomatic patients without demonstrable ischaemia to improve patients' outcome. This recommendation is based on the results of randomised clinical trials (Table 6). These trials 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 (Table 7 and Figure 2).

Ischaemia-driven PCI after thrombolysis:

If a PCI centre is not available within 24 hours, patients who have received successful thrombolysis with evidence of spontaneous or inducible ischaemia before discharge should be referred to coronary angiography and revascularised accordingly - independent of "maximal" medical therapy.

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

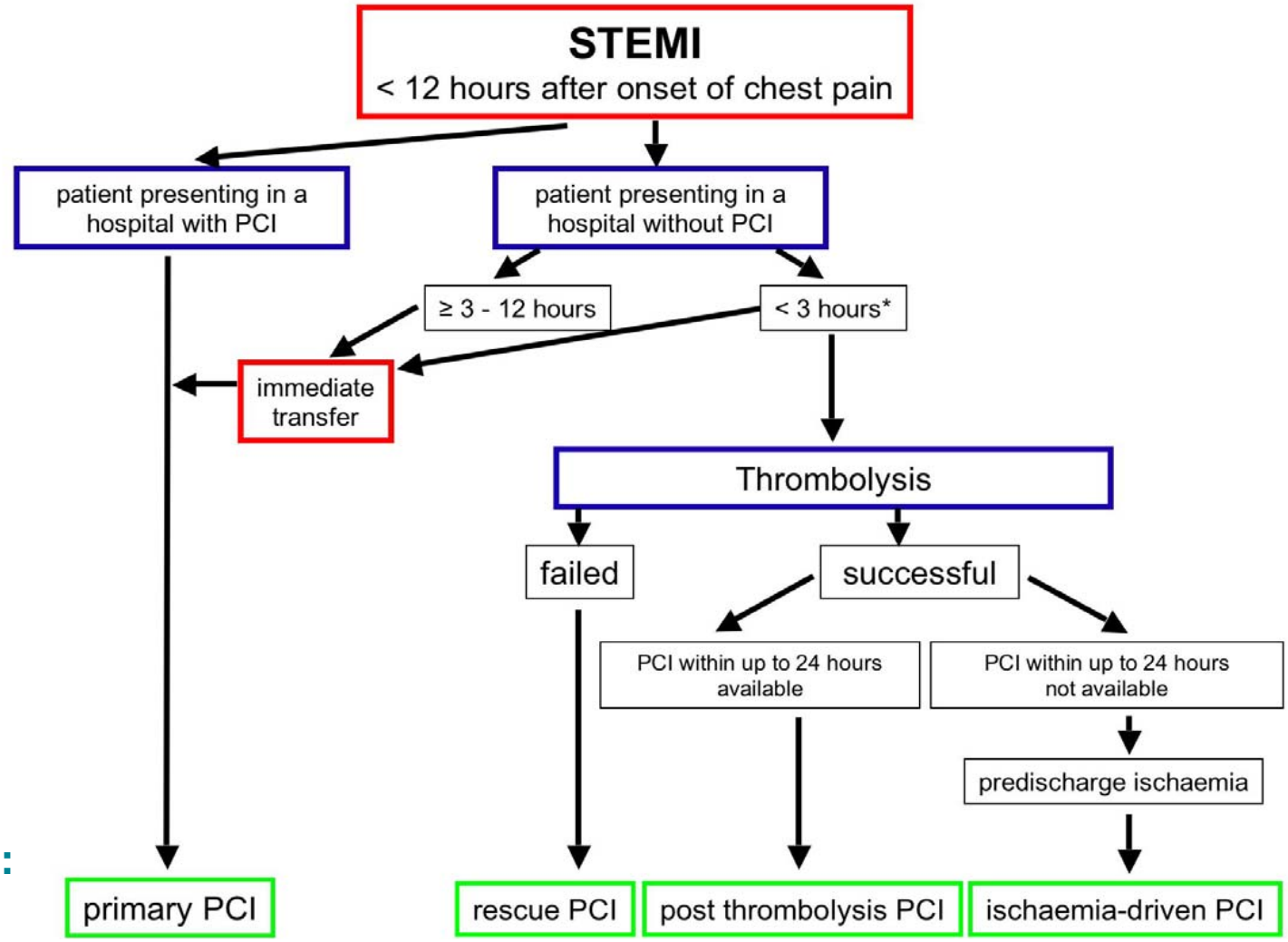


Figure 2:

Within the first 3 hours after onset of chest pain or other symptoms, thrombolysis is a viable alternative to primary PCI. *If thrombolysis is contraindicated or at high risk, immediate transfer for primary PCI is strongly advised. The major rationale for possible preference of primary PCI over thrombolysis within the first 3 hours is stroke prevention. The major rationale for preference of primary PCI over thrombolysis within 3 to 12 hours 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 hours and PCI, if applicable, should be considered.

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

PCI for patients not having received reperfusion within the first 12 hours:

- Patients often seek medical attention too late and either do not receive reperfusion therapy or reperfusion therapy fails to successfully recanalise the artery.
- Late reperfusion therapy is defined as thrombolysis or PCI starting > 12 hours after onset of symptoms

Indications for PCI in Acute Coronary Syndromes with ST-Segment Elevation (STE-ACS, STEMI)

- 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.
- PCI in these patients is supported by the “open artery hypothesis”.
- Although this seems appealing, there is currently no agreement on treatment recommendations for this group of patients.

Minimisation of Time Delays:

- For all forms of PCI there is unanimous agreement that every effort must be made to minimise any delays between onset of chest pain/other symptoms and the initiation of a safe and effective reperfusion strategy in patients with STEMI.
- Shortening the total ischaemic time is pivotal, not only for thrombolytic therapy but also for primary PCI.
- Minimising presentation and treatment delays significantly improves clinical outcome, whereas prolonged symptom-to-treatment times are associated with impaired myocardial perfusion independent of epicardial flow.

Minimisation of Time Delays:

- The effort starts with patient education and includes improvements in organisation of ambulance services as well as optimising procedures within the hospital or private practice.
- All efforts should be made to keep the average time between first medical contact and primary PCI below 90 minutes, including door to balloon time.
- Skipping the emergency room and directly transferring STEMI patients to the cath lab additionally reduces door-to-balloon times.
- Patients with longer delays should also be treated by primary PCI even when presenting more than 3 hours after onset of symptoms.
- Only when a substantial delay (e.g. > 2-3 hours) in initiating primary PCI is likely, reperfusion therapy with second or third generation fibrinolytic agents should be considered.

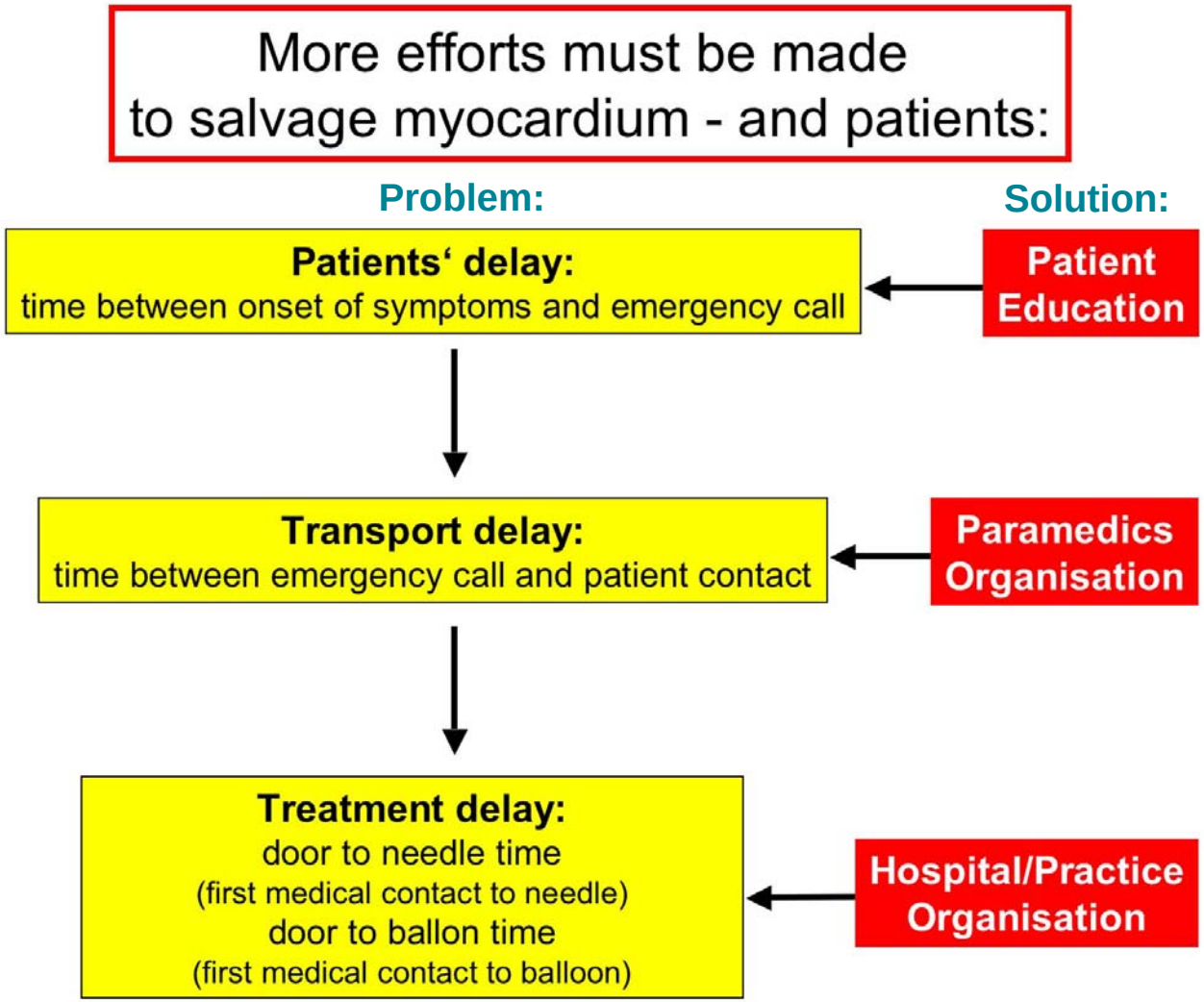


Figure 3:

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 organisation of ambulance services as well as organisational optimisations within the hospitals or private practices. Most importantly, patients have to be better educated to minimise the time delay between onset of symptoms and the emergency call.

Summary - PCI in STEMI (1)

- 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.
- In cardiogenic shock, emergency PCI for complete revascularization may be life-saving and should be considered at an early stage.

Summary - PCI in STEMI (2)

- Compared with thrombolysis, randomised 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 randomisation and start of treatment.
- The superiority of primary PCI over thrombolysis seems to be especially clinically relevant for the time interval between 3 and 12 hours after onset of chest pain or other symptoms, based on 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.

Summary - PCI in STEMI (3)

- Within the first 3 hours 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 hours 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 hours of chest pain to prevent stroke and in patients presenting 3 - 12 hours after the onset of chest pain to salvage myocardium and also prevent stroke.
- At the moment, there is no evidence to recommend facilitated PCI.

Summary - PCI in STEMI (4)

- Rescue PCI is recommended, if thrombolysis fails within 45-60 minutes after starting the administration.
- After successful thrombolysis, the use of routine coronary angiography within 24 hours and PCI, if applicable, is recommended even in asymptomatic patients without demonstrable ischaemia to improve patients' outcome.

Adjunctive Medications for PCI: (1)

Acetylsalicylic Acid (ASA), Ticlopidine and Clopidogrel

- 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 life-long.
- 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 75mg/d over 9-12 months is beneficial.

Adjunctive Medications for PCI : (2)

Acetylsalicylic Acid (ASA), Ticlopidine and Clopidogrel

- 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, preferably with a loading dose of 600 mg.
- After drug-eluting stents clopidogrel should be administered in addition to ASA for for 6-12 months to avoid late vessel thrombosis.

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

Adjunctive Medications for PCI: (3)

Unfractionated Heparin (UFH) and Low Molecular Weight Heparins (LMWHs)

- UFH is given as an i.v. bolus under activated clotting time (ACT) guidance.
- Due to 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.

Adjunctive Medications for PCI: (4)

Unfractionated Heparin (UFH) and Low Molecular Weight Heparins (LMWHs)

- UFH is preferred in high risk NSTE-ACS patients with planned invasive strategy and in lower risk patients with planned conservative strategy.
- If in a high risk NSTE-ACS patient 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.

Adjunctive Medications for PCI : (5)

Glycoprotein IIb/IIIa Inhibitors (GPI) *in stable CAD:*

- Given the overall low risk of PCI in stable CAD patients, the potential of GPI 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 GPI for PCI in stable angina should be considered on a case by case basis.
- Whenever there is a higher than average risk of acute thrombotic complications (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 patients with stable CAD.

Adjunctive Medications for PCI: (6)

Glycoprotein IIb/IIIa Inhibitors (GPI) in NSTE-ACS:

- With respect to PCI, the studies investigating the usefulness of GPI in NSTE-ACS can be divided into those discouraging an invasive strategy and into those in which PCI was planned per protocol.
- Overall, most of these studies do not reflect contemporary PCI techniques.

Adjunctive Medications for PCI: (7)

Glycoprotein IIb/IIIa Inhibitors (GPI) in NSTE-ACS:

- GPI 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 catheterisation is not planned or available within 2.5 hours), tirofiban and eptifibatide show benefit.
- If cardiac catheterisation is likely to be performed within 2.5 hours, GP IIb/IIIa inhibitors could possibly be postponed and abciximab or eptifibatide initiated in the catheterisation laboratory.
- If, for some reason, the delay between diagnostic catheterisation and planned PCI is up to 24 hours, abciximab can also be administered.

Table 9:

Part 1

Prospective randomized trials investigating the usefulness of abciximab in patients with NSTE-ACS, when PCI was not planned in all patients. PCI was left at the discretion of the physicians, discouraged or not scheduled ([a] p<0.05).

	GUSTO-IV ACS
Drug	Abciximab
Enrolment period	1998–2000
Number of patients	7800
Patients characterization	No persistent ST-elevation ACS
Drug administration related to PCI	Not scheduled
Heparin with drug	Yes (UFH or LMWH)
PCI	Discouraged, performed in 1.6% within 48 h, in 19% within 30 days
Stent usage (including non-urgent)	N/A
Primary endpoint defined	Death/MI
At time	30 days
Result of primary endpoint (placebo/drug, %)	(Placebo/drug for 24 h/drug for 48 h) 8.0/8.2/ 9.1
Primary endpoint reached	No

Table 9:

Part 2

Prospective randomized trials investigating the usefulness of tirofiban in patients with NSTE-ACS, when PCI was not planned in all patients. PCI was left at the discretion of the physicians, discouraged or not scheduled ([a] $p<0.05$).

	PRISM	PRISM-PLUS
Drug	Tirofiban	Tirofiban
Enrolment period	1994–1996	1994–1996
Number of patients	3232	1915
Patients characterization	Unstable angina	Unstable angina and non-Q-wave MI
Drug administration related to PCI	N/A	At least 48 h before PCI (upstream)
Heparin with drug	No	No/Yes
PCI	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%
Stent usage (including non-urgent)	N/A	N/A
Primary endpoint defined	Death/MI/ re-intervention	Death/MI/ re-intervention
At time	48 h	7 days
Result of primary endpoint (placebo/drug, %)	5.6/3.8[a]	Hep/tirof/hep + tirof 16.9 (17.9)/17.1/11.6 (12.9)[a]
Primary endpoint reached	Yes (tirofiban alone)	Yes (tirofiban + heparin)

Table 9:

Part 3

Prospective randomized trials investigating the usefulness of lamifiban in patients with NSTE-ACS, when PCI was not planned in all patients. PCI was left at the discretion of the physicians, discouraged or not scheduled ([a] $p<0.05$).

	PARAGON-A	PARAGON-B
Drug	Lamifiban	Lamifiban
Enrolment period	1995–1996	1998–1999
Number of patients	2282	5225
Patients characterization	Unstable angina and non-Q-wave MI	No persistent (<30 min) ST-elevation ACS
Drug administration related to PCI	At least 3–5 days in stable patients	Average 3 days before PCI
Heparin with drug	No/Yes (in low and high dose)	Yes (UFH or LMWH)
PCI	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	76%
Primary endpoint defined	Death (any cause)/MI	Death/MI/severe recurrent ischaemia
At time	30 days	30 days
Result of primary endpoint (placebo/drug, %)	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	No

Table 10:

Part 1

Prospective randomized PCI-trials investigating the usefulness of abciximab in patients with stable angina and/or NSTE-ACS. Although PCI was planned in all patients, these trials do not reflect contemporary PCI ([a]p<0.05).

	CAPTURE	EPIC	EPILOG
Drug	Abciximab	Abciximab	Abciximab
Enrolment period	1993–1995	Before 1994	1995
Number of patients	1265	2099	2792
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
Drug administration related to PCI	18–24 h before PCI	At least 10 min before PCI	10–60 min before PCI
Stent usage (placebo/drug, %)	7.4/7.8	0.6–1.7 (stenting discouraged)	N/A (planned stenting was exclusion
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
At time	30 days	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]
Primary endpoint reached	Yes	Yes	Yes

Table 10:

Part 2

Prospective randomized PCI-trials investigating the usefulness of abciximab in patients with stable angina and/or NSTE-ACS. Although PCI was planned in all patients, these trials do not reflect contemporary PCI ([a]p<0.05).

	EPISTENT	ERASER	ISAR-REACT
Drug	Abciximab	Abciximab	Abciximab
Enrolment period	1996–1997	1996–1997	2002–2003
Number of patients	2399	225	2159
Patients' characterization	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,
Drug administration related to PCI	Up to 60 min before PCI	Immediately before PCI	Immediately before PCI
Stent usage (placebo/drug, %)	Stenting in 67% (stenting was randomized to placebo or drug).	Planned in all patients	91%
Primary endpoint defined	Death/MI/ urgent unplanned revascularization	Percent in-stent volume obstruction (IVUS)	Death/MI/ urgent TVR
At time	30 days	6 months	30 days
Result of primary endpoint (placebo/drug, %)	Stent + placebo/ stent + drug/ balloon + drug: 10.8/5.3[a] /6.9[a]	Placebo/12 h infusion/ 24 hr infusion 25.1/ 27.04/29.15	4.0/4.2
Primary endpoint reached	Yes	No	No

Table 10:

Part 3

Prospective randomized PCI-trials investigating the usefulness of eptifibatide in patients with stable angina and/or NSTE-ACS. Although PCI was planned in all patients, these trials do not reflect contemporary PCI ([a]p<0.05).

	ESPRIT	IMPACT-II
Drug	Eptifibatide	Eptifibatide
Enrolment period	1999–2000	1993–1994
Number of patients	2064	4010
Patients' characterization	Stable CAD: 49%; UA/NQMI: 46%; STEMI: 5%	Elective, urgent, or emergency PCI
Drug administration related to PCI	Immediately before PCI	10–60 min before PCI
Stent usage (placebo/drug, %)	Planned in all patients	3.6/4.5 (stenting was permitted only if required to treat an abrupt closure event)
Primary endpoint defined	Death/MI/ urgent TVR/ bailout GP IIb/IIIa	Death/MI/urgent unplanned revascularization/ bailout stenting
At time	48 h	30 days
Result of primary endpoint (placebo/drug, %)	10.5/6.6[a]	Placebo/bolus + lower dose infusion/bolus+ higher dose infusion 11.4/9.2/9.9
Primary endpoint reached	Yes	No

Table 10:

Part 4

Prospective randomized PCI-trials investigating the usefulness of tirofiban in patients with stable angina and/or NSTE-ACS. Although PCI was planned in all patients, these trials do not reflect contemporary PCI ([a]p<0.05).

	RESTORE
Drug	Tirofiban
Enrolment period	1995
Number of patients	2212
Patients' characterization	UA or acute MI, (68% UA, primary PCI for AMI in 6%)
Drug administration related to PCI	At beginning of PCI
Stent usage (placebo/drug, %)	N/A (stenting discouraged)
Primary endpoint defined	Death (any cause)/ MI/ re-intervention/bailout stenting
At time	30 days
Result of primary endpoint (placebo/drug, %)	12.2/10.3
Primary endpoint reached	No

Adjunctive Medications for PCI (8):

Glycoprotein IIb/IIIa Inhibitors (GPI) STEMI:

- Compared with NSTE-ACS, tirofiban and eptifibatide are less well investigated in patients with STEMI. Abciximab has been evaluated in 5 randomized, controlled trials in association with primary PCI.
- In STEMI, stenting plus abciximab seems to be a more evidence-based reperfusion strategy.

	RAPPORT	ISAR-2	CADILLAC
Enrolment period	1995–1997	1997–1998	1997–1999
Number of patients	483	401	2082
Patients' characterization	STEMI <12 h	STEMI <48 h (including cardiogenic shock)	STEMI <12 h
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
Primary endpoint defined	Death (any cause)/ re-infarction/any TVR	Late lumen loss	Death (any cause)/re-infarction/ ischaemia-driven TVR/disabling stroke
At time	6 months	6 months	6 months
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
Primary endpoint reached	No	No	Yes (balloon only), No (stenting)
Death, re-infarction, TVR (%) (control/abciximab)	11.3/5.8[a]	10.5/5.0[a]	6.8/4.5[a]
Death, re-infarction (%) (control/abciximab)	5.8/4.6	6.0/2.6	3.2/2.7
Death (%) (control/abciximab)	2.1/2.5	4.5/2.0	2.35/1.9

Table 11: Part 1

Prospective randomized trials investigating the usefulness of abciximab in patients with planned PCI for STEMI, ([a]p<0.05).

	ADMIRAL	ACE	Pooled
Enrolment period	1997–1998	2001–2002	
Number of patients	300	400	
Patients' characterization	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	Planned in all patients	Planned in all patients	
Primary endpoint defined	Death /MI/urgent TVR	Death (any cause)/ re-infarction/TVR/ stroke	
At time	30 days	30 days	
Result of primary endpoint (placebo/drug, %)	14.6/6.0[a]	10.5/4.5[a]	
Primary endpoint reached	Yes	Yes	
Death, re-infarction, TVR (%) (control/abciximab)	14.6/6.0[a]	10.5/4.5[a]	8.8/4.8[a]
Death, re-infarction (%) (control/abciximab)	7.9/4.7	8.55/4.0	4.8/3.2[a]
Death (%) (control/abciximab)	6.6/3.4	4.0/3.5	3.1/2.3

Table 11: Part 2

Prospective randomized trials investigating the usefulness of abciximab in patients with planned PCI for STEMI, ([a]p<0.05). The pooled analysis for the clinical outcome relates to 30 days.

Adjunctive Medications for PCI (9):

Direct Thrombin Inhibitors:

- Bivalirudin is recommended as a replacement for UFH (or LMWHs), because of significantly less bleeding compared with UFH alone or UFH+ GP IIb/IIIa inhibitors.
- In NSTE-ACS, long-term clinical outcome with bivalirudin and provisional GP IIb/IIIa blockade is comparable with that of heparin plus planned GP IIb/IIIa inhibition during contemporary PCI.
- Bivalirudin is unanimously recommended for PCI as a replacement for UFH (and LMWHs) in patients with heparin-induced thrombocytopenia (HIT).

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	–

Summary - Adjunctive Medications for PCI (1)

Stable CAD

- 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.

Summary - Adjunctive Medications for PCI (2)

NSTE-ACS

- 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 catheterisation is not planned or available within 2.5 hours), tirofiban and eptifibatide show benefit.
- If cardiac catheterisation is likely to be performed within 2.5 hours, GP IIb/IIIa inhibitors could possibly be postponed and abciximab or eptifibatide initiated in the catheterisation laboratory.
- If for some reason the delay between diagnostic catheterisation and planned PCI is up to 24 hours, abciximab can also be administered.

Summary - Adjunctive Medications for PCI (3)

STEMI

- In patients with STEMI, the GP IIb/IIIa inhibitors tirofiban and eptifibatide are less well investigated.
- 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.

Adjunctive Devices for PCI (1):

Intracoronary Brachytherapy:

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 one year after radiation therapy is necessary. The future of intracoronary brachytherapy, however, is uncertain.

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] $P < 0.05$.

Adjunctive Devices for PCI: (2)

Rotablation:

- 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.

Adjunctive Devices for PCI: (3)

Embolic Protection Devices:

- PCI of saphenous vein grafts (SVG) or primary PCI in ACS with a high thrombotic load is at elevated risk for coronary embolisation.
- Two distal protection devices (GuardWire and FilterWire EX) have proven 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, requires more randomised trials with a clinical primary endpoint.
- At the present time, no definite recommendations can be given regarding the use of embolic protection devices in the setting of STEMI.

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	—

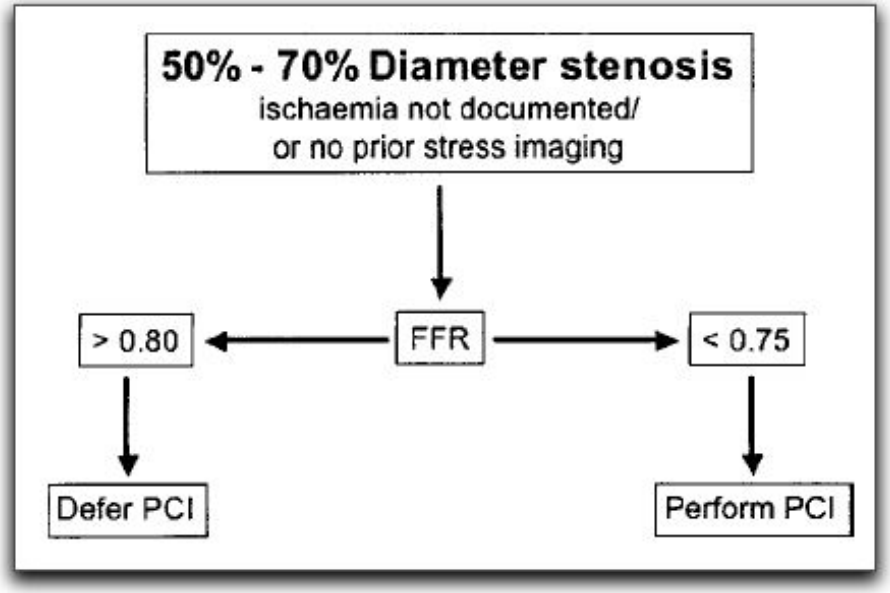
Adjunctive Diagnostic Technology for PCI:

Fractional Flow Reserve (FFR):

Although non-invasive stress imaging with its sensitivity of 76% - 88% and its specificity of 80% - 88% should be the gold standard before cardiac catheterisation, many patients in the real world come to the catheterisation laboratory without prior functional tests. If ever possible, an appropriate functional test should be done before the procedure. If contraindications 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 FFR is helpful.

Figure 4:

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



Drug-eluting Stents: background

- Primary endpoints of randomised DES studies were either angiographic (e.g. late lumen loss, LLL) or clinical (e.g. target vessel revascularisation, TVR).
- For the patients, their clinical course is more important than their angiographic parameters.
- Since the power of a randomised trial is only valid for its primary endpoint, we will focus on randomised DES trials with a clinical primary endpoint.
- Only four controlled randomised studies with a clinical primary endpoint at an adequate time interval have been published.
- Paclitaxel without a polymer carrier did not reach the primary endpoint in spite of a positive angiographic results in DELIVER-I.
- In contrast, when released from a polymer carrier, Paclitaxel significantly improved clinical outcome in the TAXUS-IV and TAXUS-VI trials.
- Thus, not all Paclitaxel-eluting stents are equal.

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.

Drug-eluting Stents - Vessel Size:

This table shows the positive 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 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.

Drug-eluting Stents - Diabetes mellitus:

In an analysis of all patients with diabetes mellitus, restenosis rate (RR) and target lesion revascularization (TLR) could be significantly reduced in SIRIUS as well as in TAXUS-IV.

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.

Drug-eluting Stents - Stent Thrombosis: (1)

- Stent thrombosis has not been detected as a relevant problem in the randomised trials when administering clopidogrel in addition to ASA for differing periods of 2 months, (E-SIRIUS), 3 months (SIRIUS) and 6 months in the TAXUS-series.
- The rate of stent thrombosis in DELIVER-I after one 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 2 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 nine months in 0.6% of the DES group and in 0.8% of the control group.

Drug-eluting Stents - Stent Thrombosis: (2)

- In the long run (and in over 50% 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. Between day 31 and day 300 stent thrombosis occurred in neither group.
- On the other hand, complete healing of the DES may theoretically take up to two 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.
- The prolonged (6 - 12 months) clopidogrel administration after drug-eluting stents (in addition to ASA) is recommended.

Drug-eluting Stents - Indications:

Evidence-based recommendations for the use of drug-eluting stents must focus on the enrolment criteria of SIRIUS, TAXUS-IV and TAXUS-VI. In these patients, target vessel revascularisation rates were single-digit numbers. The moderate release stent used in TAXUS-VI is currently not available.

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.

Drug-eluting Stents - Indications:

All of the following applications, especially in situations with increased risk of restenosis, must wait for further evidence-based recommendations and are thus presently only at evidence level II a 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

Drug-eluting Stents - Summary: (1)

- Only two drug-eluting stents have shown significantly positive effects in prospective, randomised 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 drug-eluting stents must focus on the enrolment criteria of SIRIUS, TAXUS-IV and TAXUS-VI.
- In these patients, TVR rates were single-digit numbers.
- Subgroup analyses regarding smaller vessels and patients with diabetes are encouraging.

Drug-eluting Stents - Summary: (2)

- 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, randomised trials, must be conducted for achieving higher levels of evidence in these special subsets of patients.
- In patients undergoing urgent or soon major extracardiac surgery, drug-eluting stents should rather 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.