# Coronary Artery Stenting

# 13

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**Key Points**

- Percutaneous coronary intervention (PCI) has been proven to be safe and effective in the treatment of coronary artery disease.
- PCI improves survival and prevents recurrent infarction in patients with acute MI.
- An early invasive strategy for ACS that includes PCI reduces major adverse coronary events.
- PCI in stable angina should be used as an adjunct to optimal medical therapy for symptom relief and ischemia reduction.
- PCI may be equivalent to CABG as the revascularization treatment of choice for selected patients with multivessel disease.
- Emerging evidence suggests the benefits of revascularization may be driven by ischemic burden and not symptom severity.
- In-stent restenosis (ISR) is the Achilles heel of PCI's efficacy and has been markedly reduced by drug-eluting stents (DES) and the introduction of novel antiplatelet therapies.
- Stent thrombosis is a rare but serious complication of PCI and is reduced by optimization of stent placement and adherence to dual antiplatelet therapy.

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## 13.1 Introduction

When Andreas Gruentzig performed the first percutaneous coronary angioplasty on an awake patient in 1977 (Zurich, Switzerland), he created the nascent field of interventional cardiology and ushered in a new era of coronary revascularization. Percutaneous coronary transluminal angioplasty (PTCA) was positioned to serve as an alternative and complement to coronary artery bypass grafting (CABG) and optimal medical therapy. As in many medical fields, the advancement of percutaneous coronary interventions (PCI) has been punctuated by innovations and pitfalls.

The refinement of PTCA for the treatment of ischemic coronary artery disease during the 1980s and 1990s led to a procedural success rate of >90%; however, while dilatation of the vessel wall led to improved clinical outcomes and augmented myocardial perfusion, PTCA also resulted in endothelial denudation, plaque modification, elastic recoil, and negative remodeling. The clinical correlates of controlled vessel injury were acute/subacute vessel closure (often requiring emergent CABG) and clinical restenosis (~30%). Laser angioplasty and directional or rotational atherectomy failed to improve on PTCA alone.

The concept of metal scaffolds that could prop open dilated arteries was conceived as early as 1912 by Nobel Laureate Alexis Carrel. The first human coronary stent was implanted after PTCA by Ulrich Sigwart in Lausanne, Switzerland (1986). Juan Palmaz and Richard Schatz, also pioneers in early stent design and implantation, worked with the concept that these scaffolds could help prevent abrupt/threatened vessel closure and restenosis. BENESTENT and STRESS, two pivotal trials published in 1994, demonstrated the improved clinical efficacy and significantly better restenosis rates as compared to PTCA [1, 2]. These data established bare-metal stents (BMS) as the gold standard for PCI.

The major initial concern with BMS was an unacceptably high rate of acute and subacute stent thrombosis. The optimization of a dual antithrombotic regimen consisting of aspirin



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and a thienopyridine (clopidogrel or ticlopidine) helped reduce BMS thrombosis rates to <1%. The Achilles heel of BMS has proven to be in-stent restenosis – neointimal formation driven by smooth muscle cell proliferation. Restenosis rates of approximately 15% (further increased in patients with comorbidities such as diabetes mellitus and renal insufficiency) led to repeat revascularization and, less often, acute coronary syndromes.

Drug-eluting stents (DES) were developed to reduce neointimal hyperplasia, thereby improving the efficacy while maintaining or improving the safety of PCI. First-generation DES contained sirolimus or paclitaxel, drugs that inhibit smooth muscle proliferation and migration through different mechanisms. These drugs are embedded into a polymer that is mounted onto a bare-metal scaffold. Multiple randomized trials showed that DES markedly reduced target lesion revascularization (TLR), target vessel revascularization (TVR), and major adverse coronary events (MACE). First-generation DES restenosis rates were 7–8% at 1 year. Over the past several years, registry data and meta-analyses have pointed to an increased rate of stent thrombosis, particularly very late stent thrombosis (>1 year) with DES as compared to BMS. Controversy has arisen as to how this may affect stent safety, in particular death and myocardial infarction. In 2008, the FDA approved second-generation DES that utilize everolimus and zotarolimus as antiproliferative agents. These compounds have been incorporated into stents with new polymers and bare-metal platforms in a concerted effort to improve the safety and efficacy of PCI. Most recently, third-generation DES have been approved by the FDA. This class comprises everolimus-eluting metallic stents with an absorbable coating polymer and completely bioresorbable scaffolds that are gradually reabsorbed by the body and completely disappear in 18–24 months.

This chapter will review the state of PCI in the DES era, including indications, controversies, adjunctive pharmacology, and the role of intravascular imaging.

## 13.2 Stent Technique

First-generation BMS, such as the Palmaz–Schatz and Gianturco–Roubin stents, have given way to second- and third-generation stents that exhibit superior conformability, flexibility, tracking, and positioning with a wider variety of diameters and lengths. This has resulted in higher procedural success for a wider variety and complexity of coronary lesion subsets including small vessels (<2.75 mm in diameter), diffuse disease, long lesions, bifurcation lesions, and chronic total occlusions.

Essentially all coronary stents are delivered and then deployed on balloons using guiding catheters and coronary guidewires. Femoral artery catheterization is most common, and brachial artery technique is rare, while radial artery technique has grown in the past few years as it is associated with significantly fewer bleeding and vascular complications. Although direct stenting may be performed in straightforward lesions, most coronary stenoses are pre-dilated with PTCA. High-pressure non-compliant balloons or rotational atherectomy may be used for plaque modification in "non-dilatable" (heavily calcified, diffusely diseased) lesions. Balloon inflation after stent deployment may be used to increase lumen diameter. Stent expansion, vessel apposition, and residual lumen stenosis are the most important factors in stent efficacy. These factors correlate directly with restenosis and thrombosis. The current *ACC/AHA guidelines on percutaneous coronary interventions* recommend a residual stenosis of <10% with an optimal goal of as close to 0% as possible with a final TIMI flow grade 3 [3].

Existing data have demonstrated a discrepancy between the trained eye of the interventionalist and quantitative coronary angiography in determining pre- and post-stent percentage of coronary stenosis. Intravascular ultrasound (IVUS) is a simple catheter-based imaging technique that may be used for diagnostic and interventional purposes. IVUS images cross sections of the arterial wall and can determine minimal lumen area, plaque burden, lesion length, plaque morphology, stent expansion, and stent apposition. In addition, IVUS may be used to diagnose complications of stenting such as coronary artery dissection and stent fracture. The benefit of routine IVUS guidance for stent placement remains controversial. A recent meta-analysis comprising over 11,000 IVUS-guided and 13,000 angiography-guided PCI suggested that IVUS-guided PCI was associated with significantly lower rates of target vessel revascularization and stent thrombosis and myocardial infarction [4]. Nevertheless, IVUS is not indicated in all PCI procedures. According to current AHA/ACC clinical guidelines, IVUS may be considered for guidance on coronary stent implantation particularly in case of left main coronary artery stenting [3]. Another useful technique for the evaluation of coronary lesions is the coronary pressure wire-derived fractional flow reserve (FFR). FFR is a simple and safe way to determine the functional severity of a lesion or efficacy of stent deployment. It measures the coronary artery pressure distal to a given lesion relative to aortic pressure at maximal hyperemia (achieved with intracoronary or intravenous adenosine). Abnormal FFR is a significant predictor of adverse coronary events. Multiple studies support the deferral of intervention in non hemodynamically significant lesions as measured by FFR (>0.80) or IVUS (>4.0 $cm^2$ for proximal epicardial vessels and > 6.0 $cm^2$ for the left main artery) [5–9]. Data from the FAME trial suggest that FFR-guided PCI in multivessel coronary artery disease may be superior to angiographically guided interventions with respect to hard clinical outcomes

such as death, MI, and repeat revascularization [10]. However, the subsequent FAME 2 trial received controversial reviews. All patients with any coronary artery disease with angiographic evidence of severe stenosis were evaluated with FFR. In case of positive FFR <0.80, patients were randomized to optimal medical therapy or PCI. Despite being interrupted early for excess of the primary composite endpoint in the optimal medical therapy (OMT) arm, the difference was driven solely by urgent revascularization in 49 (11%) patients in the OMT group compared to 7 (1.6%) in the PCI-treated arm. It could be argued, however, that the remaining 89% of the patients with positive FFR assigned to the OMT did not require any urgent intervention despite the positive FFR [11]. Therefore, some concerns still remain on the routine use of FFR. Nonetheless, FFR has found a role in the AHA/ACC guidelines as a reasonable tool to assess and guide PCI in angiographic intermediate coronary lesions (50–70% diameter stenosis) [3].

## 13.3 PCI in ACS

Unstable angina and biomarker-positive non-ST-segment elevation MI represent a continuum on the spectrum of acute coronary syndromes. Both conservative and invasive treatment strategies have been developed for the treatment of ACS. Based on the clinical presentation, the baseline characteristics, and the estimated TIMI and GRACE risk scores, patients can be assigned to either (1) conservative strategy/ischemia-driven revascularization or (2) invasive strategy. The conservative strategy employs intensive medical therapy utilizing antithrombotic, antiplatelet, and anti-ischemic agents over a period of several days. If the patient responds, pharmacologic therapy is often followed by stress testing with myocardial perfusion imaging. Either a positive stress test or persistent/recurrent angina is followed by cardiac catheterization with revascularization.

An invasive strategy involves early intensive therapy within 24 h or a delayed invasive therapy 25–72 h following admission with prompt cardiac catheterization and revascularization if indicated. The early invasive strategy involves targeting the culprit lesion, often with PCI, in hopes of limiting myocardial damage and improving overall prognosis [12]. A flowchart of the treatment strategies according to the AHA/ACC guidelines can be found in Fig. 13.1.

Multiple randomized trials have compared conservative versus early invasive strategies in the treatment of ACS patients. The preponderance of the evidence supports early intervention. In FRISC II, TACTICS-TIMI 18, and RITA 3, an early invasive strategy during ACS was associated with a sustained reduction in death and MI, primarily driven by the latter endpoint [13–15]. An early invasive strategy was also associated with a reduction in angina and hospital readmissions. In the TIMACS trial, for instance, there was no difference in the primary endpoint of death, myocardial infarction, and stroke between early (<24 h) and delayed (>36 h) invasive strategy. However, the early invasive therapy was associated with a significant reduction in the secondary composite endpoint of death, myocardial infarction, or refractory ischemia compared to delayed intervention in high-risk patients [16]. Data from meta-analyses have been consistent with these trials [17, 18]. The ICTUS trial was one of the few studies that failed to show a benefit of an early invasive strategy toward the composite endpoint of death, MI, or rehospitalization for anginal symptoms at 1–3- and 5-year follow-up [19]. However, when data from the 5-year follow-up of the FRISC II, TIA-3, and ICTUS were combined, a routine invasive strategy significantly reduced long-term rates of cardiovascular death or MI, with the largest benefit in higher-risk patients [20]. Subgroup analyses indicate that patients who may derive the most benefit from an early invasive strategy are those with positive troponin, new ST depression, LVEF <40%, prior PCI within 6 months or CABG, new heart failure or worsening mitral regurgitation, and high TIMI or GRACE risk scores [12].

The *ACC/AHA guidelines* recommend that ACS patients who are hemodynamically unstable or have refractory angina and malignant ventricular arrhythmias or have very high TIMI and GRACE risk scores undergo immediate catheterization and revascularization. Low-risk patients (i.e., TIMI risk score ≤2) may undergo a conservative strategy, called ischemia-guided strategy, at the discretion of the caring physician (Table 13.1) [12]. Attention should be paid to intermediate risk (TIMI risk 3–4) females who may have increased bleeding complication with an invasive strategy [13].

PCI is clearly indicated in ACS for the treatment of one vessel CAD; however, the majority of ACS patients will have multivessel disease. Multivessel stenting and complete revascularization are often preferred to culprit lesion PCI. There is a wealth of data indicating complete revascularization is superior to incomplete revascularization regardless of the clinical setting [13, 21]. Multivessel stenting is often staged to prevent the use of a large amount of contrast dye or radiation in one setting. However, recently published results from the SMILE trial showed that complete 1-stage coronary revascularization is superior to multistage PCI in terms of major adverse cardiovascular events driven by target vessel revascularization and cerebrovascular events [22]. There are scant and conflicting data as to whether PCI or CABG is preferable when both are viable options and most decisions are made on a case by case basis (patients' wishes, concomitant valvular disease, coronary anatomy, comorbidities). Some objective data can be derived from the SYNTAX trial that randomized an all-comer population with three-vessel disease or left main

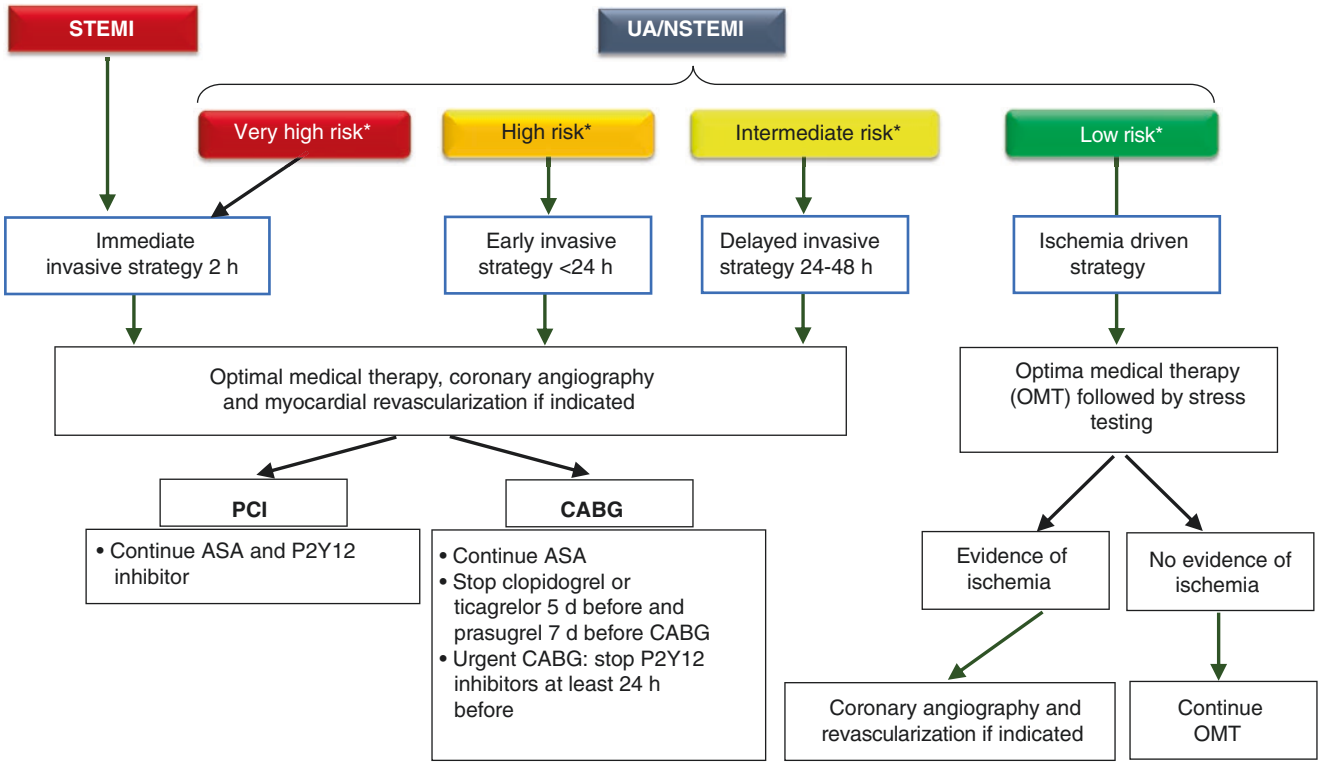


**Fig. 13.1** Treatment strategies for acute coronary syndromes. *For risk stratification, please refer to Table 13.1

**Table 13.1** Indications for early invasive and conservative strategies in the treatment of ACS [12]

| Preferred strategy | Patient characteristics |
|---|---|
| Immediate invasive (within 2 h) | Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy |
| | Refractory angina |
| | Signs or symptoms of heart failure or new or worsening mitral regurgitation |
| | Hemodynamic instability |
| | Sustained ventricular tachycardia or ventricular fibrillation |
| | High-risk score (e.g., TIMI, GRACE) |
| Ischemia-guided strategy | Low-risk score (e.g., TIMI 0 or 1, GRACE <109) |
| | Low-risk troponin-negative females |
| | Patient or physician preference in absence of high-risk features |
| Early-invasive (within 24 h) | None of the above, but GRACE risk score >140 |
| | Temporal change in troponin |
| | New or presumably new ST-segment depression |
| Delayed invasive (25–72 h) | None of the above but diabetes mellitus |
| | Renal insufficiency (eGFR < 60 ml/min/1.73 $mm^2$) |
| | Reduced left ventricular systolic function |
| | PCI within 6 months |
| | Prior CABG |
| | GRACE risk score 109–140; TIMI score ≥2 |

disease to PCI with paclitaxel-eluting stents or CABG. At 1 year, CABG, as compared with PCI, led to lower rates of major adverse cardiac or cerebrovascular events in this population [23]. To provide guidance on the best treatment strategy after coronary angiography, clinical practice guidelines recommend the use of the SYNTAX score. This score is based solely on anatomic criteria of CAD and significantly predicts the risk of 1-year major adverse cardiovascular and cerebrovascular events [24]. Nevertheless, patients' clinical characteristics and patients' wishes should also be considered in the evaluation. When PCI is preferred, drug-eluting stents appear to be safe in ACS and reduce restenosis and the need for repeat revascularization [19]. In particular, second-generation DES might help close the gap with CABG toward long-term outcomes. While the SYNTAX trial was led with paclitaxel-eluting stent (first-generation DES), observational data from the New York registry showed that in contemporary clinical practice, second-generation DES (everolimus-eluting stents) are associated with similar risk of death compared to CABG. Although PCI-treated patients had a higher risk of repeat revascularization and of myocardial infarction, when revascularization was incomplete, they had a lower risk of stroke [25].

## 13.4 Acute ST-Segment Elevation Myocardial Infarction (STEMI)

Primary PCI with stenting of the culprit lesion is the revascularization therapy of choice in acute MI with time to reperfusion resulting in incremental benefit. Multiple randomized trials have demonstrated the clinical benefit of primary stenting as opposed to thrombolysis [26]. The largest of these trials were DANAMI-2 and PRAGUE-2. DANAMI-2 randomized 1572 AMI patients to primary PCI versus thrombolysis with alteplase [27]. Patients had to have a symptom duration <12 h and be transferred to a PCI center within 3 h of randomization. Primary PCI was associated with a significant reduction in death, MI, or stroke at 30 days. PRAGUE-2 randomized 850 AMI patients with a duration of symptoms <12 h to primary PCI versus thrombolysis with streptokinase [28]. Primary PCI was associated with a trend toward reduced mortality at 30 days and a significant reduction in all-cause mortality, recurrent MI, stroke, or repeat revascularization at 5 years. Several randomized trials have demonstrated a significant decrease in repeat revascularization in primary PCI with no increase in stent thrombosis for DES as compared to BMS. Meta-analyses have shown similar results [29, 30]. HORIZONS-AMI randomized 3600 AMI patients to receive BMS versus paclitaxel-eluting stents [31]. DES were associated with a significant reduction in target lesion revascularization and no difference in the rate of stent thrombosis. A recent meta-analysis comprising trials with second-generation DES found a significantly lower incidence of cardiovascular events, myocardial infarction, target vessel revascularization, and stent thrombosis with second-generation DES compared to BMS [32].

The *ACC/AHA guidelines* recommend primary PCI as the preferred method of revascularization for patients within 12 h of symptom onset [33]. The guidelines also suggest that the preponderance of the evidence favors primary PCI in patients who present within 12–24 h of symptom onset and who have persistent angina, cardiogenic shock, malignant arrhythmias, or severe CHF. Primary PCI should only be performed on the culprit vessel. Intervention on other lesions is contraindicated in the AHA/ACC guidelines on the management of patients with STEMI unless a patient presents in cardiogenic shock. However, since the publication of the guidelines, two main trials, PRAMI and CvLPRIT, have been published which support the use of complete revascularization during primary PCI or at least during index hospitalization vs a culprit-only approach [34, 35]. Both studies showed that immediate complete revascularization was associated with a reduction in cardiovascular outcomes. Results from recent meta-analysis confirmed that immediate or staged complete revascularization results in a significant reduction in major adverse cardiovascular events, cardiovascular mortality, and repeat revascularization without significant harm compared to the culprit-only approach [36, 37]. This data is consistent with what observed in NSTEMI patients and might lead to a re-evaluation of the official indication for the treatment of multivessel disease during primary PCI in the next guidelines.

Finally, PCI following failure of thrombolysis (rescue PCI) has demonstrated clinical benefit. Facilitated PCI with full-dose thrombolytics is contraindicated, and the same is true for repeat thrombolysis [38]. The most recent *ACC/AHA guidelines* recommend PCI as adjunctive therapy to fibrinolysis for patients with cardiogenic shock, recurrent MI, or significant post-infarct ischemia [39]. Adjunctive PCI may be reasonable in patients who develop malignant ventricular arrhythmias, CHF, have an ejection fraction <40%, or have a critical stenosis in an infarct-related artery >24 h after AMI.

## 13.5 Stable CAD

### 13.5.1 Role and Limitations of Medical Therapy

The goals of therapy in stable CAD are to ameliorate symptoms and improve quality of life, delay/prevent/reverse progression of atherosclerotic coronary disease, and prevent hard clinical endpoints such as death and myocardial infarction. All of these objectives can be accomplished with aggressive risk factor modification and secondary prevention with a medical regimen that includes aspirin, P2Y12 inhibitor, beta-blockers, ACE inhibitors/ARBs, statins, nitrates, calcium channel blockers, and aldosterone antagonists. Revascularization with PCI or CABG is indicated in selected groups of patients, such as those whose angina is refractory to medical therapy, those who cannot tolerate medical therapy, and those in whom the evidence supports a survival benefit with revascularization (left main disease, three-vessel disease with decreased LV function).

A number of clinical trials have compared medical therapy to percutaneous and/or surgical revascularization; however, up until recently, these trials have had significant limitations. In most trials, patients had focal coronary disease and preserved LV function, limiting generalizability. Studies comparing PCI and CABG are dated and mostly

used vein grafts for surgical revascularization as opposed to the accepted current standard of arterial conduit (i.e., internal mammary artery) to bypass the left anterior descending (LAD) vessel, the intermediated branch or marginal branches. Even when the mammary artery is used, in several studies it is often a single conduit to the LAD which does not reflect the complexity of most of the patients treated with CABG in contemporary practice. Recently the STICH trial tested the efficacy and safety of surgical revascularization in patients with stable CAD and heart failure. This study did not find a significant reduction of all-cause mortality and cardiovascular death in patients treated with CABG compared to medical therapy only [40].

A number of trials compared PCI to "optimal" medical therapy, including RITA-2 and MASS II [41, 42] (Table 13.2). These studies demonstrated a symptomatic improvement in favor of PCI or CABG but no difference in death or myocardial infarction. ACIP was a small study in patients with silent ischemia which demonstrated favorable clinical outcomes with revascularization; however, all of these trials were performed before the drug-eluting stent era and before the advent of the current concept of optimal medical therapy.

The COURAGE trial compared medical therapy to PCI with BMS. COURAGE randomized 2287 patients with stable CAD to optimal medical therapy (OMT) or OMT plus PCI with bare-metal stenting [43]. All subjects were required to have objective evidence of ischemia and angiographic evidence of significant CAD (stenosis ≥70%). The vast majority of patients (87%) were symptomatic and had Canadian Cardiovascular Society (CCS) class II or III angina (58%). High-risk patients (LM disease ≥50%, EF <30%, high-risk stress test, CCS class IV angina) and those with unsuitable coronary anatomy for PCI were excluded from the trial.

At a mean follow-up of 4.6 years, there was no significant difference in all-cause mortality or nonfatal MI. There was also no significant difference in hospitalization for ACS. PCI was associated with decreased angina and improved quality of life up to 3 years; however, the results in the OMT group caught up thereafter. PCI was also associated with the ability to pare down a patient's antianginal pharmacologic regimen (calcium channel blockers, nitrates). Overall, the quality of life benefit in the PCI group was associated with more severe baseline ischemia.

The COURAGE nuclear substudy addressed whether a patient's quantitative ischemic burden during stress testing affected prognosis based upon treatment randomization [44]. Three hundred and fourteen patients within the COURAGE study population received baseline myocardial perfusion scans before and then 6–18 months following randomization. PCI was associated with a significant reduction in ischemic myocardium as compared to OMT alone. Those patients with moderate to severe ischemia at baseline received the greatest benefit from PCI. Patients with ≥5% ischemia reduction had significantly lower unadjusted (but not adjusted) rates of death and myocardial infarction. This subgroup analysis suggests that the extent and severity of ischemic burden in patients with CAD should influence an initial strategy of OMT versus OMT plus PCI. Of note, almost one-third of patients in the OMT arm of COURAGE eventually crossed over to have PCI, and the results were analyzed on an intention-to-treat basis.

It should be noted, though, that most of the listed trials utilized bare-metal stents and antithrombotic regimens that would be considered substandard as compared with current *ACC/AHA guidelines*. Nevertheless, recent meta-analysis has confirmed the results of the COURAGE trial displaying that PCI for stable coronary artery disease does not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization compared to medical therapy. However, PCI seemed to provide a greater angina relief compared with medical therapy alone [45, 46].

### 13.5.2 Multivessel Disease

Revascularization in multivessel coronary disease has traditionally fallen under the purview of CABG; however, with refinements and advancements of PCI, there have been multiple efforts to compare the percutaneous strategy to the surgical gold standard. In the mid-1990s, studies such as BARI, RITA, and CABRI compared CABG versus PTCA in multivessel disease [47–50]. The ARTS I and SOS trials compared CABG to PCI with bare-metal stents [51–54]. These trials concluded that the hard clinical endpoints of death and myocardial infarction were similar between the two treatment strategies; however, PCI was associated with a significant increase in repeat revascularization which was ameliorated by the introduction of bare-metal stents.

The ARTS II registry was conducted in the DES/GP IIB/IIIA era and compared 607 patients treated with sirolimus-eluting stents for multivessel disease with the ARTS I PCI and CABG populations [55]. At 1 year of follow-up, major adverse cardiovascular and cerebral events were similar between the ARTS II registry and ARTS I CABG populations; however, PCI with DES was associated with a statistically significant increase in repeat revascularization (8.4% versus 4.1%) but with much narrower gap than the one observed between bare-metal stents and CABG in ARTS- I trial.

Most recently, the SYNTAX trial made an ambitious attempt to compare PCI versus CABG in moderate- to high-risk patients with multivessel disease [23]. Eighteen hundred patients with three-vessel or left main disease were randomized 1:1 to either CABG or PCI with paclitaxel-eluting stents (PES). Anatomy was suitable for either means of revascular-

**Table 13.2** Patient characteristics **(a)** and results **(b)** of randomized trials comparing PCI versus medical therapy for the treatment of stable angina [61]

| | AVERT | RITA-2 | TIME | MASS II | SWISSI II | COURAGE | Fame 2 |
|---|---|---|---|---|---|---|---|
| (a) Patient characteristics | | | | | | | |
| Patients, no. | 341 | 1018 | 301 | 611 | 201 | 2287 | 888 |
| Women, no. (%) | 53(16) | 183(18) | 131(44) | 187(31) | 25(12) | 338(15) | 194(21) |
| Mean age, year | 59 | 58 | 80 | 60 | 55 | 62 | 63 |
| Angina, Canadian class | Nearly all 0 to II | 53% II, III, or IV | 100% II, III, or IV | 81% II or III | None (silent ischemia) | 58% II or III | 81% I, II, or III; 6.9 IV |
| Prior MI no. (%) | 136(40) | 471(46) | 141(47) | 269(44) | 201(100) (first in preceding 3 months) | 836(38) | 329(37) |
| Diabetes, no. (%) | 51(15) | 90(9) | 68(23) | 177(29) | 23(11) | 766(34) | 240(27) |
| Mean LVEF, % | 61 | 54 | 53 | 67 | 57 | 62 | <50 in 139 (16) |
| LVEF exclusion, % | <40 | None | "Predominant CHF" | 40 | None | 30; 35 if 3-vessel disease | <30 |
| Ischemia by treadmill test | Excluded | Not required | Not required | Required | Required | Required | |
| Fractional flow reserve (FFR) | N/A | N/A | N/A | N/A | N/A | N/A | Yes, 0.80 cutoff |
| Vessels diseased %[a] | | | | | | | |
| 1 | 57 | 60 | 14 | Excluded | 1- or 2-vessel disease required | 35 | 58 |
| 2 | 43 | 33 | 19 | 42 | See above | 39 | 34 |
| 3 | Excluded | 7 | 60 | 58 | Excluded | 25 | 8 |
| Previous CABG or PCI | Excluded if PCI in the last 6 months or if history of CABG | Excluded | 18% PCI<br>20% MT | Excluded | Not reported | 16% PCI<br>11% MT | 18% PCI<br>17% MT |
| (b) Results | | | | | | | |
| Primary endpoint | Ischemic event: cardiac death, cardiac resuscitation, nonfatal MI, stroke, CABG, PCI, or angina with hospitalization | Death, nonfatal MI | Freedom from MACI[b] | Death, nonfatal MI, or refractory angina requiring revascularization | Survival free of MACEs; cardiac death, nonfatal MI, or symptom-driven revascularization | Death, nonfatal MI | MACE: all-cause death, nonfatal MI, urgent revascularization |

(continued)

**Table 13.2** (continued)

| | AVERT | RITA-2 | TIME | MASS II | SWISSI II | COURAGE | Fame 2 |
|---|---|---|---|---|---|---|---|
| Results (most recent follow-up published) | PCI 21%<br>MT 13%<br>*P* = 0.048 | PCI 14.5%<br>MT 12.3%<br>*P* = 0.21 | Freedom from MACE<br>INV 39%<br>MT 20%<br>*P* < 0.001; no difference in mortality or other quality-of-life measures at 4 years | PCI 32.7%<br>MT 36%<br>CABG 21.2%<br>*P* = 0.003; pairwise comparison: no difference between PCI and MT | Adjusted HR (favoring PCI 0.33; 95% CI. 0.20–0.55; *P* < 0.001 [using person-years]) | PCI 19.0%<br>MT 18.5%<br>*P* = 0.62 and no difference in angina at 5 years | PCI 4.3%<br>MT 12.7%<br>HR = 0.32[0.19–0.53]<br>p < 0.001 |
| Main result for primary endpoint | Longer time to and fewer ischemic events with MT + high-dose statin | No advantage of PCI over MT | Revascularization improves freedom from MACEs for the elderly no effect on mortality | If revascularization is needed, favor CABG | Patients with silent ischemia after MIT may benefit from PCI | No advantage of PCI over MT | FFR-guided PCI reduces MACE driven by urgent revascularization compared to MT |

*AVERT* Atorvastatin Versus Revascularization Treatment, *CABG* coronary artery bypass grafting, *CHF* congestive heart failure, *COURAGE* Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation, *LVEF* left ventricular ejection fraction, *MASS II* Medicine, Angioplasty, or Surgery Study, *MI* myocardial infarction, *MT* medical therapy, *PCI* percutaneous coronary intervention, *RITA-2* Second Randomized Intervention Treatment of Angina, *SWISSI II* Swiss Interventional Study on Silent Ischemia Trial II, *TIME* Trial of Invasive Versus Medical Therapy in the Elderly, *CI* confidence interval, *HR* hazard ratio, *INV* interventional arm, including percutaneous coronary intervention (PCI) and CABG, *MACE* major adverse cardiac event, *MASS II* Medicine Angioplasty, or Surgery Study, *MI* myocardial infarction, *MT* medical therapy; *RITA-2* Second Randomized Intervention Treatment of Angina, *SWISSI II* Swiss Interventional Study on Silent Ischemia Trial, *TIME* Trial of Invasive Versus Medical Therapy in the Elderly, *FAME 2* Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2

[a]In the TIME trial, the percentage of vessels diseased pertains only to individuals in PCI group; MT group not assessed

[b]Initial primary outcome was improvement in measures of quality of life, including relief of angina and lower rates of MACEs (death, nonfatal MI, or hospitalization for angina or acute coronary syndrome a: 6 month). Freedom from MACEs was reported in the 1-year follow-up

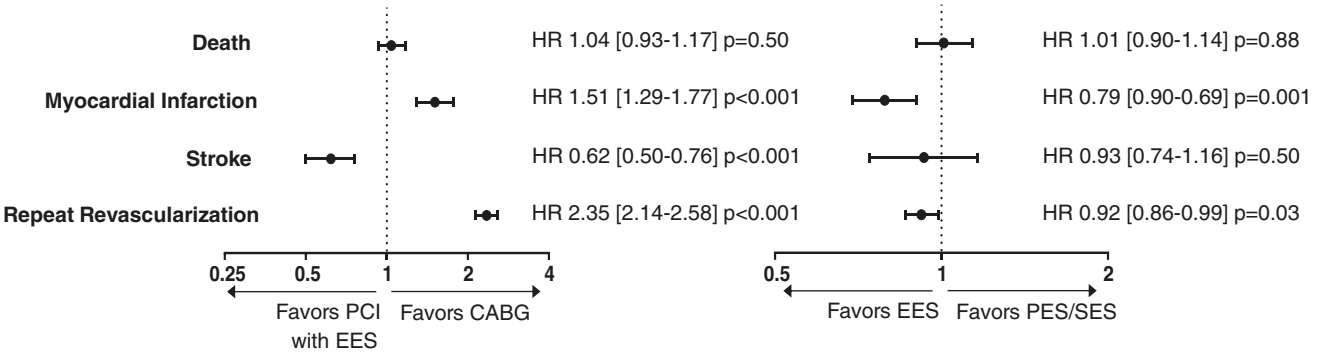


**Fig. 13.2** Treatment strategies for stable patients with multivessel coronary disease. Comparison between PCI with everolimus eluting stents (EES) and CABG in the left panel and between PCI with econd (EES) and first generation stents (PES=paclitaxel eluting stents, SES=sirolimus eluting stents) in the right panel using registry data (25).

**Table 13.3** Results of the SYNTAX trial (Kaplan–Meier Curves) [44]

| | 12-month follow-up | | |
|---|---|---|---|
| Outcome | PCI with 1st-gen DES (%) | CABG (%) | *p* value |
| Death, stroke, or MI | 7.6 | 7.7 | 0.98 |
| Death | 4.4 | 3.5 | 0.37 |
| Stroke | 0.6 | 2.2 | 0.003 |
| MI | 4.8 | 3.3 | 0.11 |
| Repeat revascularization | 13.5 | 5.9 | <0.001 |

ization. At 12-month follow-up, PCI was associated with a statistically significant increase in death, MI, stroke, or repeat revascularization (17.8% versus 12.4%) (Table 13.3). The difference was driven by repeat revascularization (13.5% versus 5.9%), whereas there was no difference in death or MI and there was actually a statistically significant decrease in stroke in the PCI population (Table 13.3). There were similar rates of stent thrombosis and symptomatic graft occlusion. These results are consistent with those of the PTCA and BMS eras. Notably, there was a significant narrowing between PCI and CABG with respect to the rates of repeat revascularization as compared with BARI and RITA II. The left main SYNTAX substudy, the largest set of patients with left main disease randomized to CABG versus PCI to date, showed excellent results with PCI with no difference in death/MI, more repeat procedures, and lower risk of stroke than CABG. Observational registry data have shown that the gap between CABG and PCI for long-term clinical benefit in patients with multivessel disease is further reduced by the use of second-generation DES. PCI still has a higher rate of repeat revascularization and myocardial infarction compared to CABG, but the difference disappears in case of complete revascularization during index PCI. Importantly compared to CABG, PCI was associated with a lower rate of stroke (Fig. 13.2) [25].

The SYNTAX score, a tool for angiographic risk stratification based upon disease burden and complexity, correlated highly with outcomes and may be used to guide a decision for surgical versus percutaneous revascularization. In the final analysis, the physician and patient must balance the surgical risk (including stroke) of CABG versus the risk of repeat revascularization with PCI when making a decision regarding revascularization for multivessel and high-risk CAD.

### 13.5.3 Diabetic Patients

There has been particular interest in the optimal method of revascularization in diabetic patients. In the BARI trial, which compared CABG to PTCA, CABG was associated with significantly increased survival (58% versus 46% at 10 years) [56]. The survival benefit was most marked in insulin-requiring patients and observed only to those who received an internal mammary graft. The diabetic patients in the study had more severe and diffuse disease than the rest of the study population, a potential confounder especially since the chosen method of percutaneous revascularization was with PTCA. The CARDIA trial randomized diabetic patients with multivessel disease to either PCI (with BMS and later on sirolimus-eluting stents) or CABG. At 1 year the study failed to prove the non-inferiority of PCI compared to CABG.

The BARI-2D trial studied stable diabetic patients with few symptoms or silent ischemia. The investigators concluded the following: (1) an initial medical stabilization therapy with reservation of a revascularization procedure can be undertaken safely and was utilized in about half of the patients studied; (2) as the ischemic risk and coronary heart disease burden increases, complete revascularization may offer significant clinical benefit even in survival; and (3) insulin-sensitizing therapy offers improved metabolic and lipid profiles to an insulin-providing therapy, and this may translate into a clinical benefit in combination with revascularization in the higher-risk patients [57]. This study

included routine coronary angiography in all patients as a method to define risk and did not directly compare stenting with CABG. Furthermore, both bare-metal and drug-eluting stent types were used in PCI procedures. Results indicated (1) no major difference between types of diabetic management, (2) not much difference in death or MI between revascularization and optimal therapy in the low-risk cohort, and (3) advantage with surgery over optimal medical therapy in the higher-risk cohort.

Finally, the FREEDOM trial was specifically designed to discern the optimal means of revascularization for higher-risk (greater than that studied in BARI-2D) diabetic patients with multivessel CAD. FREEDOM has randomized 1901 patients with type I or type II diabetes and multivessel disease with angina or ischemia to CABG versus DES. The primary endpoint was death, MI, or stroke at 3 years [58]. The study concluded that CABG is superior to PCI in that it significantly reduced rates of death and myocardial infarction, at the expense of a higher rate of stroke.

## 13.6 Ischemic Burden and Revascularization

Multiple lines of investigation in the cardiac imaging literature have correlated the quantitative ischemic burden in CAD patients with adverse cardiac outcomes. Invasive studies using fractional flow reserve (FFR) and intravascular ultrasound have demonstrated that certain cutoffs for hemodynamic flow reserve or lumen cross-sectional area are associated with, and predictive for, future cardiac death and MI. The COURAGE nuclear study, a hypothesis generating subgroup analysis, demonstrated that ischemic burden correlated with the degree of anginal relief following PCI [44]. A mounting body of evidence supports targeting quantitative ischemic burden rather than symptoms with medical therapy and revascularization in an effort to reduce death, MI, and stroke. Among the most recent studies in this series are the FAME trials.

FAME was a multicenter trial that randomized 1005 patients with stable CAD to angiographically versus FFR-guided PCI with DES [10]. The former group underwent revascularization of all angiographically significant lesions. The latter group underwent revascularization of angiographically significant lesions only if the FFR was ≤0.8 (deemed hemodynamically significant). FFR-driven revascularization was associated with a significant reduction in the primary endpoint of death, MI, or repeat revascularization at 1 year. FAME 2 addresses the primary targeting of ischemic burden and outcomes with revascularization and medical therapy.

This trial showed that FFR-guided PCI plus the best available medical therapy decreased the need for urgent revascularization compared to medical therapy alone. Conversely in patient with negative FFR, the clinical outcomes were similar to the medical therapy only patients [11] (Table 13.4).

**Table 13.4** Results from the FAME II trial (Kaplan–Meier Curves) [5]

| | Positive FFR <0.8 | | Negative FFR >0.8 |
|---|---|---|---|
| Outcome | PCI plus medical therapy, n (%) | Medical therapy alone, n (%) | FAME II registry medical therapy alone, n (%) |
| Death, MI, or urgent revascularization, *n* (%) | 19 (4.3) | 56 (12.7) | 5 (3.0) |
| Death, *n* (%) | 1 (0.2) | 3 (0.7) | 0 (0) |
| MI, *n* (%) | 15 (3.4) | 14 (3.2) | 3 (1.8) |
| Urgent revascularization, *n* (%) | 7 (1.6) | 49 (11.1) | 4 (2.4) |

### 13.6.1 Recommendations and Guidelines

The latest joint update of the *ACC/AHA guidelines for the management of stable CAD* was published in 2014 [59, 60].

PCI has been deemed appropriate for patients with asymptomatic ischemia and/or CCS class I/II angina who (1) have significant lesion(s) in one to two coronary arteries that subtend a moderate to large area of viable myocardium on noninvasive testing and have a high likelihood of procedural success, (2) restenosis after PCI with a large area of viable myocardium at-risk or high-risk features on noninvasive testing, and (3) left main disease in a patient who is not eligible for CABG.

PCI for stable CAD and unprotected left main disease has a class IIa indication for patients with both a low risk of PCI procedural complications, a high likelihood of good long-term outcome (e.g., a low SYNTAX score of ≤22, ostial or trunk left main CAD), and an increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%) or IIb in case of low to intermediate risk of PCI-related complications. In case of three-vessel disease and/or two-vessel disease, the indication for PCI is class IIb. In patients with single-vessel disease without proximal LAD involvement, the current guidelines give a class III indication for PCI, and medical therapy should be preferred [60].

The focused update in 2014 stresses the importance of a Heart Team approach to revascularization in patients with diabetes mellitus and complex multivessel CAD. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD) [60].

However, PCI in multivessel disease may be considered particularly in patients with multifocal disease and preserved left ventricular ejection fractions, younger patients who may require multiple reoperations during the course of their lives,

and older patients with multiple comorbidities that make the morbidity/mortality of CABG unacceptably high. Finally, all decisions regarding revascularization should take into account the educated opinions of the cardiologist and referring physicians as well as the particular concerns of the individual patient.

Most recently the ACC, AHA, and numerous other professional organizations have published a consensus document regarding the appropriate criteria for percutaneous and/or surgical revascularization of patients in 180 different clinical scenarios [61]. Following this publication, we assisted to a reduction of the non-acute PCI procedures and a reduction of PCIs classified as inappropriate according to current guidelines [62]. A more extensive discussion of these criteria and scenarios is beyond the scope of this chapter.

## 13.7 Post-Stent Care

Patients who have undergone uncomplicated PCI may be discharged the day after their procedure. The duration of dual antiplatelet therapy varies depending upon the type of stent placed. The current *ACC/AHA guidelines* recommend treatment with aspirin and a thienopyridine for at least 1 month following placement of BMS and at least 1 year following DES [12, 33]. Dual antiplatelet therapy may be extended for patients with complex/high-risk lesions and/or major comorbidities. Result from the recently published DAPT trial showed that prolonged DAPT up to 30 months after DES was associated with a significant reduction in the risk of stent thrombosis and major cardiovascular and cerebrovascular events at the expense of an increased risk of bleeding complications [63]. Similarly the PEGASUS TIMI 54 trial tested the use of DAPT with ticagrelor for 36 months compared to aspirin alone and found a reduction of ischemic events with an excess of bleeding events [64]. Therefore, routine use of prolonged DAPT is not indicated in all patients. However, subgroups of patients with high ischemic risk such as diabetic patients might benefit from this treatment strategy [65]. Regardless of the strategy chosen, a patient's cardiologist should be consulted if there is an indication to suspend dual antiplatelet therapy, for instance, prior to surgery or other circumstances. The importance of the pattern and reason of DAPT cessation has been highlighted by the results of the PARIS observational registry [66]. This study prospectively collected data from an all-comer PCI population in 15 sites in the USA and Europe mostly treated with DES. Antiplatelet therapy was based on aspirin and clopidogrel since data collection preceded the coming of novel P2Y12 inhibitors, prasugrel, and ticagrelor. Patients were followed up for 2 years during which information on compliance to DAPT cessation mode and outcomes were collected. DAPT cessation was classified as follows: physician-recommended discontinuation, brief interruption (for surgery), or disruption due to non-compliance or bleeding events. PARIS revealed that in the real-world setting, cardiovascular adverse events depended on the reason and type of cessation. DAPT disruption seemed associated with the highest risk of clinical outcomes. The risk of events attenuated over time [66].

Prasugrel and ticagrelor have emerged as an alternative to clopidogrel, with higher antiplatelet efficacy (greater inhibition of the P2Y12 receptor), albeit with more bleeding complications. For this reason, prasugrel is contraindicated in patients with low body weight, prior stroke (or transient ischemic attack), or age over 75 years [67]. Prasugrel should not be used in patients where the coronary anatomy is unknown. Ticagrelor is quickly active after administration and has a short half-life. It has been proven to be safe and effective compared to clopidogrel and can be used upstream before coronary angiography. According to recent guidelines, both prasugrel and ticagrelor are indicated as maintenance drug with aspirin for 1 year after stenting and can be particularly useful in patients with clopidogrel hyporesponsiveness due to generic polymorphism [12].

### 13.7.1 Estimation of Patient's Clinical Risk

Determining the ischemic and bleeding risk of patients after PCI is essential for tailoring the treatment strategy and reducing the rate of DAPT cessation and adverse outcomes. The ACUITY risk score was developed using 2 ACS patient populations from the ACUITY and the HORIZONS-AMI trials [68]. It is based on six baseline measurements (female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, non-ST-segment elevation MI, or ST-segment elevation MI) and one treatment-related variable (use of heparin + glycoprotein IIb/IIIa) (Table 13.5). This score accurately identifies patients at increased risk for non-CABG-related bleeding and subsequent 1-year mortality. The same ACS populations were also used to develop a risk model specific for stent thrombosis (ST). The variables present in this ST score are listed in Table 13.5. Besides baseline clinical characteristics, angiographic characteristics such as the presence of ulcerated lesions and TIMI flow were also taken into account. The rates of ST at 1 year in low-, intermediate-, and high-risk categories were 1.36%, 3.06%, and 9.18%, respectively, in the development cohort and 1.65%, 2.77%, and 6.45% in the validation cohort, proving a very good predictive value of this score [69].

Most recently two new scores have been developed using the contemporary PCI population of the PARIS registry comprising both stable and ACS patients [70]. The PARIS bleeding risk score partially overlaps with the ACUITY score and the PARIS coronary thromboembolic risk score

**Table 13.5** Recently published scores for the evaluation of bleeding and thromboembolic risk in patients undergoing PCI (68–70)

| PARIS score | | | | DAPT score | |
|---|---|---|---|---|---|
| Bleeding risk score | | Thromboembolic risk score | | | |
| Low 0–3; intermediate 4–7; high ≥8 | | Low 0–2; intermediate 3–4; high ≥5 | | Low risk <2; high risk ≥2 | |
| Parameter | Score | Parameter | Score | Parameter | Score |
| Age, years | | Diabetes mellitus | | Age ≥ 75 | **−2** |
| <50 | **0** | None | **0** | Age 65–75 years | **−1** |
| 50–59 | **+1** | Non-insulin-dependent | **+1** | Age < 65 years | **0** |
| 60–69 | **+2** | Insulin-dependent | **+3** | Current cigarette smoker | **1** |
| 70–79 | **+3** | Acute coronary syndrome | | Diabetes mellitus | **1** |
| ≥80 | **+4** | No | **0** | MI at presentation | **1** |
| BMI, kg/m$^2$ | | Yes, Tn-negative | **+1** | Prior PCI or prior MI | **1** |
| <25 | **+2** | Yes, Tn-positive | **+2** | Stent diameter < 3 mm | **1** |
| 25–34.9 | **0** | Prior PCI | **+2** | Paclitaxel-eluting stent | **1** |
| ≥35 | **+2** | Prior CABG | **+2** | CHF or LVEF <30% | **2** |
| Current smoking | **+2** | Current smoking | **+1** | Saphenous vein graft | **2** |
| CrCl < 60 ml/min | **+2** | CrCl <60 ml/min | **+2** | | |
| Presence of anemia | **+3** | | | | |
| Triple therapy on discharge | **+2** | | | | |

| ACUITY bleeding risk score | | | | | | | |
|---|---|---|---|---|---|---|---|
| Low risk <15; high risk ≥15 | | | | | | | |
| Parameter | Score | | | | | | |
| Gender | Male | | | Female | | | |
| | **0** | | | **+8** | | | |
| Age (years) | <50 | 50–59 | 60–69 | | 70–79 | ≥80 | |
| | **0** | **+3** | **+6** | | **+9** | **+12** | |
| Serum creatinine (mg/dl) | <1.0 | 1.0- | 1.2- | 1.4- | 1.6- | 1.8- | ≥2.0 |
| | **0** | **+2** | **+3** | **+5** | **+6** | **+8** | **+10** |
| White blood cell count (giga/L) | <10 | 10- | 12- | 14- | 16- | 18- | ≥20 |
| | **0** | **+2** | **+3** | **+5** | **+6** | **+8** | **+10** |
| Anemia | No | | | Yes | | | |
| | **0** | | | **+6** | | | |
| Presentation | STEMI | NSTEMI – raised biomarkers | | | NSTEMI – normal biomarkers | | |
| | **+6** | **+2** | | | **0** | | |
| Antithrombotic medication | Heparin plus GPI | | | Bivalirudin monotherapy | | | |
| | **0** | | | **−5** | | | |

| Stent thrombosis risk score | | | |
|---|---|---|---|
| Low 1–6; intermediate 7–9; high ≥10 | | | |
| Parameter | Score | | |
| Type of ACS | NSTEMI w/o ST changes: +1 | NSTEMI with ST changes: +2 | STEMI +4 |
| Current smoking | Yes +1 | No +0 | |
| Insulin-treated DM | Yes +2 | No +0 | |
| History of PCI | Yes +1 | No +0 | |
| Baseline platelet count, K/μL | <250: +0 | 250–400: +1 | >400: +2 |
| Absence pre-PCI heparin | Yes +1 | No +0 | |
| Aneurysm or ulceration | Yes +2 | No +0 | |
| Baseline TIMI flow grade 0/1 | Yes +1 | No +0 | |
| Final TIMI flow grade < 3 | Yes +1 | No +0 | |
| Number of vessels treated | 1: +0 | 2: +1 | 3: +2 |

*BMI* body mass index, *CrCl* creatinine clearance, *Tn* troponin, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *MI* myocardial infarction, *CHF* cardiac heart failure, *LVEF* left ventricular ejection fraction, *GPI* glycoprotein IIb/IIIa inhibitors

(Table 13.5). Both scores have been tested in the ADAPT DES population and have shown excellent predictive value for 2-year events.

Finally, the DAPT score provides a tool to determine the benefit of prolonging DAPT beyond 1 year after index PCI [71]. The DAPT score takes into consideration variables predictive of both ischemic and bleeding events and combines them in one elegant model (Table 13.5). Similar to the PARIS score, DAPT was developed in a mixed PCI population with 37% stable CAD patients. At 2 years after index PCI, the DAPT score effectively predicts the overall benefit of prolonged DAPT compared to DAPT cessation at 1 year.

### 13.7.2 Restenosis

Intracoronary stent restenosis has been the Achilles heel of PCI with respect to efficacy. Studies in the 1990s showed that PTCA alone was associated with a 30–40% rate of angiographic restenosis. First-generation stents, such as the Palmaz–Schatz stents, were associated with a 20–30% rate of restenosis. The advent of second-generation bare-metal stent platforms, better post-dilatation techniques, and a standardized antithrombotic regimen dramatically reduced the rates of clinical restenosis to 12–14% at 1 year. After 1 year, restenosis rates dropped precipitously, and recurrent angina and/or ischemia was more likely due to a de novo lesion. The mechanism underlying restenosis appears to be an inflammatory/wound healing response to the stent, smooth muscle cell proliferation and migration, and neointimal growth within the stent.

Drug-eluting stents brought great promise in combating restenosis. Paclitaxel and sirolimus are both drugs that inhibit vascular smooth muscle cell proliferation/migration and, therefore, were expected to reduce neointimal formation within the stent. First-generation DES reduced the rate of clinical restenosis to 6–7% at 1-year follow-up (target lesion revascularization). Second-generation DES, such as those containing everolimus or zotarolimus, have been shown to significantly reduce stent thrombosis compared to first-generation DES [72, 73]. Second-generation DES also reduced the composite endpoint of myocardial infarction, stent thrombosis, and revascularization in both randomized trials and observational studies [74, 75]. Most recently, the bioresorbable scaffolds eluting everolimus might resolve the problem of early, late, and very late stent restenosis: the presence of everolimus reduces inflammation, early/late stent restenosis and favors endothelialization. Since the polymer completely dissolves in 18–24 months, the risk of very late stent restenosis is virtually erased. In addition, the full disappearance of the stent ensures that the vessel wall and endothelium can return to their physiological function and allows for the implantation of a graft in case CABG is required in the future [76].

Restenosis may be focal or diffuse (intrastent, proliferative, occlusive), and the pattern of restenosis correlates with prognosis [77]. Independent procedural predictors include stent length, multiple stents, small vessel size, ostial lesions, prior restenosis at the stent site, post-procedural plaque burden, final minimal lumen diameter <3 mm, stent malapposition, and stent underexpansion. The latter two variables can be optimized by IVUS guidance. Independent clinical predictors include diabetes, renal insufficiency, hypertension, increased BMI, and multivessel disease.

Most cases of clinical restenosis present with new onset angina rather than an acute coronary syndrome or acute MI [78]. Treatment for in-stent restenosis includes DES place-

**Table 13.6** Temporal categorization of stent thrombosis [83]

| | |
|---|---|
| Acute stent thrombosis | 0–24 h after stent implantation |
| Subacute stent thrombosis | >24 h to 30 days after stent implantation |
| Late stent thrombosis | >30 days to 1 year after stent implantation |
| Very late stent thrombosis | >1 year after stent implantation |

**Table 13.7** ARC definitions of stent thrombosis (82)

| |
|---|
| **Definite stent thrombosis** |
| Angiographic confirmation of stent thrombosis |
| Presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and the presence of at least one of the following criteria within a 48 h time window: |
| 1. Acute onset of ischemic symptoms at rest |
| 2. New ischemic ECG changes that suggest acute ischemia |
| 3. Typical rise and fall in cardiac biomarkers (refer to the definition of spontaneous MI) |
| 4. Nonocclusive thrombus: |
| Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream |
| 5. Occlusive thrombus |
| TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch) |
| Pathological confirmation of stent thrombosis |
| Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy |
| **Probable stent thrombosis** |
| Any unexplained death within the first 30 days after intracoronary stenting |
| Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause |
| **Possible stent thrombosis** |
| Any unexplained death >30 days after intracoronary stenting |

ment or PTCA alone, often with IVUS guidance. Multiple randomized trials have confirmed the efficacy of treating BMS restenosis with DES [79, 80]. Small observational studies suggest the efficacy of bioresorbable scaffold as well in this setting [81]. CABG is only considered with multiple restenoses or in high-risk clinical cases.

### 13.7.3 Stent Thrombosis

Stent thrombosis is the Achilles heel of PCI with respect to safety. Stent thrombosis is a rare but often severe complication of PCI that may be fatal. Stent thrombosis often presents as an acute MI. Thrombosis may be classified temporally as acute (≤24 h), subacute (1–30 days), late (1 month–1 year), and very late (>1 year) (Table 13.6) [82]. Each case can be classified according to the consensus ARC definition as definite, probable, or possible (Table 13.7) [83]. Risk factors may be broadly characterized into patient, procedure, stent, or lesion related and are thought to stem from one of the three mechanisms: (1) hypoperfusion, (2) lack of subendothelialization of the stent surface, and (3) increased thrombogenicity. Specific risk factors include impaired LV function, emergent stent placement, increased stent length, stent underexpansion, residual plaque burden, small vessel caliber, residual thrombus or dissection, and medical non-compliance.

Dual antiplatelet therapy with aspirin and a thienopyridine, especially novel potent P2Y12 inhibitors, markedly reduces the incidence of acute, subacute, and late stent thrombosis and may have an impact on very late stent thrombosis [84]. A subanalysis of the PLATO trial has showed that ticagrelor significantly reduces the incidence of stent thrombosis in ACS patients compared with clopidogrel [85]. Some studies have shown that the addition of cilostazol to dual antiplatelet therapy may reduce the incidence of stent thrombosis in selected high-risk clinical scenarios [86].

Most (80%) stent thrombosis after placement of BMS occurs during the first 2 weeks; subacute stent thrombosis is less common, late stent thrombosis is rare, and very late stent thrombosis is almost never described. Notably, sensitivity over this very rare event was not present during BMS trials, and this may have led to underreporting. Meta-analyses of randomized trials have shown DES incurs approximately a 0.6% rate of stent thrombosis at 30 days and 0.75% at 1 year [82]. Very late stent thrombosis may occur at an annual rate of 0.6–0.9% after 1 year. Real-world registries show slightly higher rates of stent thrombosis. Very late stent thrombosis may occur several years following PCI at a very low rate. Ongoing studies are further characterizing the time course of this adverse event.

There is an increased risk of very late stent thrombosis with DES as compared to BMS of approximately 0.5–0.6% per year [87]. However, virtually every pooled analysis shows there is no difference in death or MI during this period of time. Individual risk/benefit analyses should be performed in every case to determine candidacy for BMS versus DES. If a patient has a history of non-compliance with medication, or will be unable to receive DAPT for at least 6 months due to planned surgery of high bleeding risk, strong consideration should be given to placement of a BMS rather than DES. Due to the extremely small incidence of stent thrombosis, any prospective study evaluating this phenomenon would require several thousand patients and long-term follow-up making feasibility extremely difficult.

Newer stent platforms, polymers, and drug formulations seek to maximize stent efficacy by abrogating restenosis while also maximizing safety through better prevention of stent thrombosis.

## 13.8 Case Studies

### 13.8.1 Case Study 1

An active 57-year-old male with a history of type 2 diabetes on oral medication, hypertension, and hypercholesterolemia presents to his primary care physician complaining of exertional chest pain after walking ten blocks. He is referred for an exercise stress test with a myocardial perfusion scan. The patient completes 8 min of Bruce protocol, achieving 87% of maximal predicted heart rate. He experiences the same exertional chest pain. There are no EKG changes. The myocardial perfusion scan reveals a moderate-sized area of anterior ischemia (moderate intensity). The patient is referred for cardiac catheterization, which reveals a 70% mid-LAD stenosis. What is the next step in management?

This case represents the plight of a typical patient who would fall within the realm of the COURAGE trial. It is the responsibility of the patient's cardiologist to explain that the LAD stenosis does not present an imminent risk for acute MI or acute coronary syndrome. The main goals of therapy should be symptomatic improvement, secondary prevention, and risk factor reduction. First, the cardiologist must ensure that the patient is receiving optimal medical therapy. PCI would not reduce the patient's risk of death or MI but would reduce the patient's angina and improve quality of life as compared to medical therapy in the short and intermediate terms. The risks of restenosis and stent thrombosis with PCI, as well as the requirement for dual antiplatelet therapy, must be discussed. The decision for adding PCI to optimal medical therapy must be jointly made between the patient, primary care physician, and cardiologist.

### 13.8.2 Case Study 2

A 66-year-old female with a history of hypertension and hypercholesterolemia presents to her primary care physician complaining of exertional chest pain and dyspnea. The patient has no other medical problems. She is referred to a cardiologist who sends her for an exercise nuclear stress test. The patient performs 7 min of Bruce protocol, achieving 90% of maximal predicted heart rate for her age. She experiences chest pain but no EKG changes. Myocardial perfusion scanning reveals moderate-sized, moderate intensity anterior and inferior defects. Cardiac catheterization reveals a 90% proximal LAD lesion, a 70% lesion of the first obtuse marginal artery, and an 80% mid-RCA lesion. All lesions are focal. Left ventriculography reveals an ejection fraction of 55% with no regional wall motion abnormalities. The patient is reluctant to undergo coronary bypass surgery but is not confident that multiple stents will be the best treatment. She desires the safest and most effective therapy. How should her cardiologist counsel her?

This patient has multivessel coronary disease with a normal ejection fraction. She is otherwise relatively healthy and has focal coronary disease that would be anatomically amenable to both CABG and PCI. A recommendation for this patient should take into account the data from numerous randomized trials in the literature comparing CABG with PCI in multivessel disease. The SYNTAX trial is of particular significance. A conversation with the patient would clarify that the extent and severity of her coronary disease would be amenable to both CABG and PCI. Given that she is relatively healthy, is not diabetic, and has normal LV function, either treatment modality would provide her with symptomatic improvement. With PCI, she would expect an increased likelihood of requiring repeat revascularization. Based on the lesion description, the SYNTAX score would be expected to be low and the repeat procedure rate after PCI not high. She would need to weigh the short-term morbidity of cardiac surgery (including a finite stoke risk) against that associated with subsequent hospitalization(s) for repeat PCI and the requirement of dual antiplatelet therapy for at least 1 year with DES. The patient's treatment plan should be individualized based upon her own thoughts and concerns regarding her health. She should have consultations with both an experienced interventional cardiologist and a cardiac surgeon. The ultimate plan should be a joint decision between the patient, her primary care physician, and clinical cardiologist – the physicians who know her the best. Typically, such conversations might have preceded the catheterization procedure based on noninvasive studies, and if an option of PCI was favored, this could have been performed at the same time as angiography.

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