



# Factors influencing the outcomes of percutaneous coronary intervention in the stent era

In the three decades following the performance of the first angioplasty by Andreas Gruentzig in 1977, the volume of percutaneous coronary interventions (PCIs) has exponentially increased. Our knowledge of the factors which influence PCI outcomes drove development of new techniques and technology, resulting in improved outcomes for patients. For example, the advent and advances in stents have significantly reduced acute procedural complications, and the incidence of restenosis and repeat revascularization procedures. In addition, developments in pharmacology have influenced ischemic complications and bleeding rates. Randomized controlled trials and registries have contributed to the wealth of data currently available and form the basis for the development of PCI guidelines. In general, factors that influence PCI outcomes include two broad categories: patient related encompassing clinical and anatomical and procedure related. A review of procedural and late PCI outcomes is presented, including identification of the main factors that have been associated with risk.

**KEYWORDS:** complications • coronary intervention • outcomes • restenosis • stents  
• stent thrombosis

Since percutaneous coronary intervention (PCI) was first performed over 30 years ago tremendous progress has been made with regards to making the procedure safer and more effective, while at the same time expanding the indications and patient populations treated. Although this article will focus on the factors influencing PCI outcomes in contemporary practice, in the era of stents and aggressive pharmacology, an understanding of the progress in the field thus far is warranted. Several large studies have documented temporal trends in the characteristics of patients treated with PCI and the in-hospital outcomes of the procedure. The National Heart, Lung and Blood Institute-sponsored 1985–1986 percutaneous transluminal coronary angioplasty and 1997–2006 Dynamic Registries, the Northern New England Registry and the Mayo Clinic PCI Registry have examined outcomes for over 68,000 consecutive PCI procedures over time [1–3]. All of these studies demonstrated an increase in the complexity of patients treated over time including older age, increased comorbidity and increasing treatment of acute coronary syndromes (ACSs). However, with the routine use of stents supplanting percutaneous transluminal coronary angioplasty, procedural success has significantly increased from 78–82 to 94–95%. Rates of major complications over the same time period have decreased including: emergent coronary artery bypass grafting (CABG) 3.7–5 down to 0.4%, and mortality from 3 to 0.7–1.8% [1,3].

## PCI outcomes

A successful PCI can be defined angiographically, procedurally or clinically. A summary of PCI outcome definitions, complications and late outcomes is presented in Box 1. There has been intense interest in the incidence and risk factors for bleeding complications including relationship to procedural access site and stent thrombosis. These specific complications are highly associated with myocardial infarction (MI) and mortality. The goal of understanding these outcomes is to make PCI safer. In addition, the late clinical outcome of target-vessel revascularization is an indicator of the efficacy of PCI with stents and the patient and lesion subsets that would benefit from further developments in stent technology. A comprehensive discussion of the factors associated with all PCI-related outcomes is beyond the scope of this article, but several important outcomes will be covered.

## Periprocedural bleeding

Patients undergoing PCI have a significant risk of hemorrhagic complications that can occur at the access site or remotely. Avoidance of bleeding complications is very important since periprocedural bleeding is now recognized to be significantly associated with subsequent mortality. Bleeding events may directly result in mortality or result in changes to medications that increase ischemic risk. In the REPLACE-2 trial of elective or urgent PCI, major hemorrhage occurred

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**Box 1. Summary of percutaneous coronary intervention definitions and outcomes.****Definitions of percutaneous coronary intervention success**

- Angiographic: residual minimum diameter stenosis of <10% (with an optimal goal of 0%) for lesions treated with stents
- Procedural: angiographic success without associated in-hospital major clinical complications
- Clinical: procedural success and relief of signs and/or symptoms of myocardial ischemia
- Long term: benefits persist beyond 9 months

**In-hospital major clinical complications**

- Death
- Myocardial infarction
- Stroke
- Emergency coronary artery bypass grafting

**Additional complications**

- Coronary dissection, perforation and no reflow
- Vascular/access site complication
- Bleeding
- Stent thrombosis
- Contrast-induced nephropathy

**Late clinical outcomes**

- Death
- Myocardial infarction
- Restenosis
- Target-lesion and -vessel revascularization

in 3.2% of patients and was independently associated with a 2.7-fold increase in 1-year mortality [4]. In the larger ACUITY study (n = 13,819) of ACS patients, major bleeding resulted in higher rates of 30 day mortality, ischemia and stent thrombosis. Absolute rates of bleeding were nearly double in patients receiving glycoprotein (GP) IIb/IIIa inhibitors with heparin or bivalirudin compared with bivalirudin alone that had a 3.0% major bleeding rate. At 30 days, the odds ratio (OR) for mortality in patients with major bleeding was 7.55 (95% CI: 4.68–12.18;  $p < 0.0001$ ) [5]. These studies and other have identified numerous independent risk factors for bleeding which are summarized in Box 2 [6]. The most commonly noted factors include advanced age, female gender, low BMI, chronic kidney disease and intensity of antiplatelet therapy. Since the majority of patient variables cannot be modified at the time of PCI, an appreciation for patients at risk of bleeding can assist in procedure-related decisions including the access site and anticoagulation strategy.

In the most recent PCI guidelines, evaluation of bleeding risk before PCI received a Class I recommendation [7]. To assist physicians in assessing the risk of bleeding after PCI, risk scores have been developed. For periprocedural bleeding in elective and urgent PCI, a risk score was derived using seven variables (age >55 years, female gender, estimated glomerular filtration rate <60 ml/min/1.73 m<sup>2</sup>, pre-existing anemia, low-molecular-weight heparin within 48 h pre-PCI, use of GP IIb/IIIa inhibitors

and intra-aortic balloon pump use). The risk of major bleeding in patients without any risk factors was 1% compared with those with several factors in whom the risk was greater than 5% [8]. These types of risk score are helpful due the variability of bleeding risk that has been demonstrated in PCI patients. In ACS patients, major bleeding rates varied from 1 to 40% depending on the number of independent risk factors for bleeding with the only modifiable predictor being the treatment-related variable of heparin plus a GP IIb/IIIa compared with bivalirudin alone [9]. The overall approach to PCI should be based on a balance of ischemic and bleeding risks for the individual patient.

Similar to trends in major in-hospital clinical outcomes, the rate of major bleeding in unselected PCI patients has decreased over time. From 2005 to 2009 bleeding rates were examined for elective and ACS patients including ST-elevation MI (STEMI) in over 1.7 million patients in the CathPCI Registry. In all clinical scenarios, elective PCI, unstable angina/non-STEMI and STEMI, an approximate 20% reduction in post-PCI bleeding was observed. Half of the reduction in bleeding was attributed to changes in anticoagulation strategies, with an increase in bivalirudin use and decrease in GP IIb/IIIa inhibitors. During the period of this study, radial approach was quite low at <3% [10].

**■ Access-site complications**

The catheterization access site is responsible for 50–60% of bleeding events in PCI patients. The

femoral artery is the most common access site for PCI in the USA. Femoral vascular complications include access-site bleeding, hematoma, retroperitoneal hematoma, pseudoaneurysm, arteriovenous fistula and arterial dissection and/or thrombosis. The incidence of complications ranges from 2 to 6% and has decreased over time in both men and women, but female sex is still associated with a twofold risk [11,12]. Other independent risk factors for vascular complications include sheath size, intensity and duration of anticoagulation with heparin and procedure time [13]. In femoral access cases, when femoral angiography shows suitable anatomy, closure devices are often used to shorten the time-to-ambulation and have a Class IIa recommendation for this purpose. It should be recognized, however, that vascular closure devices do not reduce vascular complications (Class III indication for routine use of a vascular closure device for the purpose of reducing vascular complications) [7,14].

#### ■ Radial access

Compared with femoral access, radial access reduces complications. A meta-analysis of randomized trials showed that radial access reduced major bleeding by 73% compared with femoral access (0.05 vs 2.3%, OR: 0.27 [95% CI: 0.16–0.45];  $p < 0.001$ ). Additionally, there was a trend for a reduction in the composite of death, MI or stroke (2.5 vs 3.8%, OR: 0.71 [95% CI: 0.49–1.01];  $p = 0.058$ ) as well as death (1.2 vs 1.8%, OR: 0.74 [95% CI: 0.42–1.30];  $p = 0.29$ ) [15]. The more contemporary RIVAL trial randomized 7021 patients undergoing coronary angiography or intervention to a radial or femoral approach. There was a lower rate of local vascular complications with the use of radial access. In patients treated at high volume radial centers and in those with STEMI, there was a lower risk of the primary composite end point of death, MI, stroke or non-CABG-related major bleeding at 30 days [16]. The benefit of radial compared with femoral access was confirmed in ST-segment elevation ACS patients in the multicenter, randomized, RIFLE-STEACS study. The primary end point, a 30-day composite of cardiac death, stroke, MI, target-lesion revascularization and bleeding, occurred in 13.6% of patients assigned to radial compared with 21.0% of femoral access patients ( $p = 0.003$ ). Individual end points of bleeding and mortality were also significantly lower with radial access [17]. An analysis of nearly 600,000 PCI procedures in the National Cardiovascular Data Registry showed that the radial approach had a

58% lower risk of bleeding than femoral. The reduction in bleeding complications with the radial approach was more pronounced among patients <75 years old, women and patients undergoing PCI for an ACS [18]. Use of radial access to decrease access-site complications carries a Class IIa recommendation in the PCI guidelines [7].

#### Stent thrombosis

Stent thrombosis was recognized as a serious complication in the bare-metal stent (BMS) era; however, the use of high-pressure stent deployment and dual antiplatelet therapy with aspirin and a thienopyridine decreased the incidence to an acceptable level of less than 0.5% at 30 days [19]. With the rapid adoption of drug-eluting stents (DES) after approval in the USA, reports of stent thrombosis at later time points, even after 1 year, raised concerns about this new technology that has led to intense investigation into the factors associated with its occurrence in both BMS and DES. Although the incidence is low, approximately 1% at 30 days, and 0.2–0.6% per year thereafter, this complication results in a high rate of MI, repeat revascularization and death. Therefore, an understanding of the risk factors for stent thrombosis is of paramount importance [20–24]. As with other complications,

#### Box 2. Factors associated with bleeding and/or access-site complications in percutaneous coronary intervention patients.

##### Patient-related

- Older age
- Lower BMI
- Female sex
- Peripheral arterial disease
- Chronic kidney disease
- Anemia
- Diabetes
- Hypertension
- Acute coronary syndrome
- Positive cardiac biomarkers
- ST-segment elevation
- Cardiogenic shock

##### Procedure-related

- Emergent indication
- Larger sheath size
- Femoral access versus radial
- Periprocedural glycoprotein IIb/IIIa inhibitors
- Failure to dose adjust anticoagulant agents when required
- Post-thrombolytic therapy
- Intra-aortic balloon pump use
- Longer procedure duration
- Increased time to sheath removal
- Need for femoral venous sheath
- Lack of use of fluoroscopy-guided access

identification of patients at risk for stent thrombosis can assist in the developed preventative strategies.

Standard definitions have been developed in order to compare stent thrombosis rates across trials and observational studies. Early stent thrombosis occurs within 30 days, late is from 30 days to 1 year and very late stent thrombosis is beyond 1 year. Definite stent thrombosis is confirmed by pathology or angiography in the appropriate clinical setting. Probable stent thrombosis is unexplained death within 30 days of stent placement or an MI in the territory of the stent at any time. Most studies report definite or the composite of definite and probable. Possible stent thrombosis is unexplained death beyond 30 days of the stent.

Risk factors for stent thrombosis can be categorized into patient related, including clinical and anatomical, or procedure related, which encompasses stent characteristics (Box 3). There are several potential mechanisms for stent thrombosis including reduced coronary flow and inadequate suppression of thrombin and platelet aggregation during critical time periods, such as during stent deployment and the period of stent re-endothelialization. At later time points, delays in complete neointimal coverage or a functional endothelium can contribute to risk [25]. Large clinical studies, autopsy reports and intracoronary imaging findings have contributed to our knowledge in this area.

#### ■ Patient-related factors for stent thrombosis

Cessation of antiplatelet therapy before the recommended duration, which has varied from 3 to 12 months, is the strongest risk factor for stent thrombosis. One of the original studies that brought this to attention showed a 90-fold increase in stent thrombosis in patients that prematurely discontinued antiplatelet therapy [20]. Several other studies have confirmed the importance of compliance to dual antiplatelet therapy. In the Dutch Stent Thrombosis Registry, premature discontinuation of clopidogrel was the most predictive factors for stent thrombosis therapy (OR: 36.5) [23]. In a study of 10,778 patients treated with DES, patients that discontinued antiplatelet therapy had a late stent thrombosis rate of 1.76% and very late stent thrombosis rate of 2.1% compared with 0.1 and 0.14% of compliant patients [26]. These studies highlight the importance of ensuring that patients can comply with prolonged dual antiplatelet therapy prior to placement of a DES.

Presence of an ACS at the time of stenting is another well-described risk factor for stent thrombosis. The plaque characteristics and thrombotic milieu in ACS are contributing mechanisms. Compared with patients with stable angina, the rates of stent thrombosis for ACS are three- to nine-fold higher, both in BMS and DES, with the highest risk group being STEMI patients [27,28]. In ACS patients the use of more potent oral antiplatelet therapies than clopidogrel, including prasugrel or ticagrelor, reduces the risk of stent thrombosis about 50%. This is due to several factors including a greater level of platelet inhibition and less interindividual variability in response and the lack of influence of genetic polymorphisms known to influence clopidogrel metabolism [29–32].

Numerous other clinical factors have been associated with an increased risk of stent thrombosis, including but not limited to diabetes, chronic kidney disease and hypersensitivity to DES [20,33]. These factors result in inflammation, delayed healing and endothelial dysfunction. In addition, several anatomic- or lesion-related variables have been identified, such as low ejection fraction and bifurcation lesion. A more comprehensive list patient-related variables shown to be associated with stent thrombosis in one or more studies is provided in Box 3 [34–36].

#### ■ Procedure-related factors for stent thrombosis

The majority of procedure-related factors increase the risk of stent thrombosis through an influence on coronary flow or delay in healing. Intravascular ultrasound (IVUS) identified inadequate postprocedure lumen dimensions, dissection, thrombus or tissue prolapse to be associated [37]. Incomplete stent apposition, either at the time of deployment or acquired, and overlapping stents have also been observed in patients with stent thrombosis [34,38]. Intravascular optical coherence tomography, which has approximately tenfold greater resolution than IVUS, can also be instructional in assessing risk for stent thrombosis as it has a higher sensitivity to detect stent strut malapposition, plaque protrusion and stent-edge dissection [39]. Autopsy studies have identified stenting across branch ostia, disruption of adjacent vulnerable plaques and extensive plaque prolapse as possible precipitants of stent thrombosis [40]. Use of IVUS, therefore, should be considered in patients with complex anatomy to optimize stent deployment and assess for contributors to the risk for stent thrombosis [41]. The PCI guidelines give a Class IIb recommendation

for the use of IVUS to determine the mechanism of stent thrombosis [7].

The influence of stent type on stent thrombosis risk has been controversial. After extensive analysis of randomized trials and observational studies of BMS compared with DES, it is accepted that the rates of stent thrombosis are similar except for very late stent thrombosis, which is higher with DES [42–44]. In 2012, a network meta-analysis including 49 randomized trials compared either one DES to a BMS or to another DES. This meta-analysis suggests that, compared with BMS, paclitaxel-eluting stents (PES) and zotalrolimus-eluting stents (ZES) have comparable rates of definite early stent thrombosis, but the rates with everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) may be lower. Cumulative rates of stent thrombosis at 2 years showed no difference in DES versus BMS with the exception of EES, which had a significantly lower rate. However, since few studies directly compared newer generation DES, such as EES and ZES with BMS, not all types of DES have been directly compared, and other changes such as BMS design and practice changes over time cannot be assessed, these findings should be considered exploratory [45]. Much less data is available for the newer DES, particularly the Resolute® (Medtronic, MN, USA) ZES. In a registry study that included 12,339 patients who received SES, PES or EES, the cumulative incidence rate of definite stent thrombosis over 4 years was lower with EES compared with PES or SES (adjusted hazard ratios: 0.33, 95% CI: 0.23–0.48 and 0.41, 95% CI: 0.27–0.62, respectively). The difference was primarily driven by a lower incidence of very late stent thrombosis with EES [46]. The above studies suggest that the newer DES may have a more favorable late safety profile.

### Periprocedural MI

The definition of periprocedural MI has evolved over time. According to the universal definition of MI, PCI-related MI is considered a type 4 MI and is defined as an increase of biomarker greater than threefold the 99th percentile upper reference level (in patients with normal baseline levels) or a new rise of greater than 20% in serum biomarkers over and beyond the last nadir [47]. The incidence is 15–30% depending on the definition used and patient population studied [48,49]. The clinical significance of periprocedural MI has also been argued and many studies have found no independent association between periprocedural MI and outcomes. A meta-analysis

### Box 3. Factors associated with early, late and very late stent thrombosis.

#### Patient-related

- Clinical
  - Premature discontinuation of antiplatelet therapy
  - Acute coronary syndrome as indication for percutaneous coronary intervention
  - Diabetes mellitus
  - Chronic kidney disease
  - Cocaine use
  - Prior brachytherapy
  - Smoking
  - Malignancy
  - High on-treatment platelet reactivity
  - Potency of oral antiplatelet therapy
  - Genetic polymorphisms for clopidogrel metabolism
  - Prior history of stent thrombosis
- Anatomic
  - Proximal left anterior descending location
  - Bifurcation lesion
  - Lesion length
  - Plaque burden
  - Small vessels
  - Low ejection fraction
  - Abnormal postprocedure flow
  - Multivessel disease
  - Saphenous vein graft disease
  - Plaque with necrotic core

#### Procedure-related

- Technique/device
  - Incomplete stent expansion
  - Residual thrombus or dissection post-stenting
  - Inflow or outflow obstruction
  - Periprocedural anticoagulation
  - Lack of aspirin at the time of percutaneous coronary intervention
  - Inadequate stent expansion/sizing
  - Stent overlap
  - Bifurcation side branch stenting
  - Incomplete stent apposition
- Stent type

of 20 studies including over 15,000 patients, however, suggested an association between troponin elevation and mortality during follow-up (OR: 1.35; 95% CI: 1.13–1.60) [50]. Increased mortality in patients with troponin elevation after PCI was also observed in the Evaluation of Drug Eluting Stents and Ischemic Events Evaluation Registry and was related to the degree of elevation with the hazard of mortality increased from 1.02 at a threefold to 1.67 at a 20-fold elevation [51].

Procedural myonecrosis can be caused by a number of mechanisms, including macrovascular and microvascular obstruction and

the thrombotic and neurohormonal milieu. Angiographically evident causes of epicardial obstruction include side-branch occlusion, plaque or thrombus embolization, dissection or spasm. Additional factors for procedural biomarker elevation identified by IVUS include *de novo* lesions, atheroablative technique, plaque burden at the lesion and reference segments and stent overexpansion [52,53]. Angiographic no-reflow is a sign of microvascular damage. In one study of elective and emergent PCI, the incidence was 2%, but rates were as high as 11.5% for STEMI patients. Additional risk factors for no reflow are PCI of saphenous vein grafts and use of stent or atherectomy devices compared with balloon angioplasty [54]. The above and additional patient and procedure-related factors that have been associated with periprocedural MI are presented in Box 4.

Adequate antiplatelet therapy at the time of PCI is important for preventing thrombotic complications. Patients undergoing elective PCI demonstrated to have aspirin resistance had a

significantly higher rate of periprocedural MI despite pretreatment with clopidogrel. After adjustment, aspirin resistance (OR: 2.9) and bifurcation lesions (OR: 2.8) remained independently associated with biomarker elevation after PCI [55]. High platelet reactivity after clopidogrel as defined by a point of care assay is also an independent predictor of periprocedural MI [56].

Factors associated with a decreased risk of pre- and periprocedural MI are pretreatment with clopidogrel and statins, respectively [57]. A meta-analysis of six randomized trials demonstrated a 50% lower risk of periprocedural MI in the statin pretreatment group compared with controls [58]. In the PCI guidelines, administration of a high-dose statin before PCI to reduce the risk of periprocedural MI received a Class IIa recommendation for patients naive and on chronic therapy [7].

### Mortality risk in the stent era

Mortality for patients undergoing PCI has decreased over time [1,3]. The ability to predict the risk of in-hospital mortality following PCI in contemporary practice is important for comparing outcomes and appropriately informing patients. Risk models delineate the factors associated with the outcome of interest. Using data from 588,398 PCI procedures in the National Cardiovascular Data Registry, patient-related variables associated with in-hospital mortality were examined. Mortality was highly related to the clinical circumstances of PCI, 0.65% in elective cases compared with 4.81% in STEMI. Unadjusted in-hospital mortality was higher in patients over 70 years of age, women and those with diabetes mellitus. Female sex, however, was not independently associated with mortality after adjustment for differences in comorbidities. The strongest clinical predictors of mortality were cardiogenic shock, renal function and age. Clinical factors were more prognostic than angiographic variables; however, lesion location in the left main or proximal left anterior descending artery were predictive. Additional factors independently associated with in-hospital mortality are presented in Box 5 and include diabetes, peripheral vascular disease and PCI for stent thrombosis [59].

### In-stent restenosis & target-vessel revascularization

Stents were developed to improve upon the results of balloon angioplasty, to decrease acute complications and increase durability of PCI. BMS reduced the incidence of restenosis to

#### Box 4. Factors associated with periprocedural myocardial infarction.

##### Patient-related factors

- Clinical
  - Age
  - Acute coronary syndrome
  - Diabetes mellitus
  - Chronic kidney disease
  - Elevated C-reactive protein
  - Aspirin resistance
  - High on treatment platelet reactivity
  - Potency of antiplatelet therapy
  - Lack of statin pretreatment
  - Prior coronary bypass surgery
- Anatomic
  - Multivessel disease
  - Calcification
  - Thrombus
  - Plaque extent
  - Bifurcations
  - Positive vascular remodeling
  - Saphenous vein graft disease

##### Procedure-related factors

- Technique/device
  - Use of atherectomy
  - Dissection
  - No reflow
  - Spasm
  - Stent use vs balloon angioplasty
  - Stent oversizing
  - Side-branch occlusion
  - Side-branch stenting

20–30% and of target-lesion revascularization to 15%, about half that of balloon angioplasty [60,61]. Restenosis is due to vessel injury and subsequent neointimal hyperplasia and is defined angiographically as a greater than 50% luminal narrowing. The clinical significance of restenosis is better measured by rates of target-lesion or -vessel revascularization. To inhibit neointimal hyperplasia and reduce restenosis risk, DES were developed. DES elute an antirestenotic drug from a polymer applied to a BMS platform. In the USA, four types of DES have been approved: SES, PES, ZES and EES. DES are very effective and, compared with BMS, reduce restenosis by 40–60% depending on patient and lesion complexity [43,62].

DES restenosis occurs in 4–10% of patients by 1 year and is lowest in randomized trials of *do novo* lesions and higher in unselected patients in routine practice or in subsets considered to be off-label from the initial indications studied [63]. DES reduce restenosis compared with BMS in all patient and lesion subsets. In BMS, several factors predicted the need for target-lesion revascularization, including smaller pretreatment minimum lumen diameter, smaller final minimum lumen diameter, longer stent length, diabetes mellitus, unstable angina and hypertension [64]. Risk factors for restenosis and target-lesion revascularization in the DES are similar. In patients with DES, angiographic follow-up multivariate predictors of restenosis included: in-stent restenosis, ostial lesion location, diabetes mellitus, stented length >36 mm, reference vessel diameter <2.17 mm, and vessel other than left anterior descending coronary artery [65]. Predictors of target-lesion revascularization in other studies include: age <60, prior PCI, unprotected left main PCI, saphenous vein graft PCI, minimum stent diameter ≤2.5 mm, total stent length ≥40 mm, complex lesions (B2/C) [66,67]. Multivariable analysis showed that vessel size, final diameter stenosis and DES type (SES adjusted OR of 0.60 compared with PES) were the strongest predictors of restenosis [68]. As with the PCI outcomes discussed above, factors associated with restenosis and target-lesion or -vessel revascularization can be grouped according to whether they are patient or procedure related (Box 6). Additional factors determined by angiography or IVUS include stent under expansion (minimum stent area <5.0 mm<sup>2</sup>), stent gaps, stent overlap, edge stenosis or dissection [69,70]. A recent randomized study demonstrated that patients that have PCI at sites without surgical back-up have higher rates of target-vessel revascularization. The exact

#### Box 5. Factors independently associated with in-hospital mortality in percutaneous coronary intervention patients.

##### Clinical

- Older age
- ST-segment elevation myocardial infarction
- Cardiogenic shock
- Percutaneous coronary intervention status (emergent or salvage)
- Lower renal function
- Class IV heart failure
- Chronic lung disease
- Peripheral vascular disease
- History of congestive heart failure
- Lower ejection fraction
- Insulin-dependent diabetes
- Noninsulin depended diabetes
- Intra-aortic balloon pump
- Cerebrovascular disease
- Known vascular disease
- Lower BMI
- No prior percutaneous coronary intervention

##### Angiographic

- Lesion location left main
- Lesion location proximal vessel
- Society for Cardiovascular Angiography and Interventions lesion class >1

mechanism for this is unclear but may relate to operators being less aggressive with stent deployment in the absence of surgical back-up [71]. Procedural variables that reduce the risk of restenosis or repeat revascularization include an IVUS cross-sectional stent area of greater than 9 mm<sup>2</sup> and the use of fractional flow reserve to guide multivessel PCI [72].

#### ■ Complex anatomy

Improvements in technology and operator skill have made the percutaneous treatment of complex anatomy such as left main, multivessel disease and chronic total occlusions more common. While acute outcomes for multivessel PCI with DES are favorable, restenosis remains an issue. In the SYNERGY™ (Boston Scientific, MA, USA) between PCI with the SYNTAX trial, the rate of repeat revascularization was higher in PCI compared with CABG (13.5 vs 5.9%;  $p < 0.001$ ) [73]. To assist in the decision of whether a patient is better suited for PCI or CABG the anatomic SYNTAX score can be calculated [101]. Higher SYNTAX scores indicate more complex coronary disease. Patients with low (≤22) or intermediate (23–32) scores have similar outcomes with PCI or CABG and treatment decision can be individualized, whereas those with a high score (≥33) should, in general, have surgical revascularization. Determining the lesions causing ischemic in multivessel disease is also important. The use of fractional flow reserve, an index of the

physiological significance of a coronary stenosis, is superior to angiography in guiding multivessel PCI. In the FAME trial, patients randomized to fractional flow reserve compared with angiography guided PCI received fewer stents and had a lower 1-year rate of death, nonfatal MI and repeat revascularization with similar rates of angina [72].

Several other lesion subsets remain procedurally challenging in the current era. In the treatment of chronic total occlusions, several novel devices and techniques have been developed to improve upon acute procedural success. In experienced hands, dedicated chronic total occlusion wires and microcatheters can be used in antegrade, retrograde and subintimal approaches to achieve success [74]. Improving guiding support and device delivery with the mother-in-child catheter technique has also allowed more complex PCI, particularly via radial access, where small guiding catheters are required [75].

#### ■ Stent type

There have been several studies comparing one DES to a second DES. Based on available data,

SES and EES have lower rates of target-lesion revascularization than PES. The Resolute ZES has similar efficacy as EES [76]. The data are limited, however, with respect to differences in specific patient and lesion subsets. For example, in patients with diabetes mellitus no differences in target-vessel revascularization have been observed according to DES type.

Based on the above findings, several potential mechanisms for restenosis have been described. Failure to inhibit neointimal hyperplasia may result from resistance to the antirestenotic drug or a hypersensitivity reaction to the polymer. Issues with stent deployment and integrity include underexpansion, nonuniform expansion, fracture, polymer disruption, barotrauma outside the stented segment and incomplete lesion coverage. The PCI guidelines give a Class IIa recommendation for the use of IVUS to determine the mechanism of stent restenosis [7].

#### Conclusion & future perspective

Currently available DES are composed of a metallic stent platform, a durable polymer and an antirestenotic drug. While DES have improved outcomes for patients, they have several limitations. The drug-polymer combination delays vessel healing, including endothelialization and function and can cause a hypersensitivity reaction, therefore, increasing risk of stent thrombosis. The metallic component prevents positive vascular remodeling, can limit side-branch access or targets for surgical revascularization and interferes with noninvasive coronary imaging such as computed tomography angiography. Novel technologies under development that should be available over the next few years including DES with bioabsorbable polymers and completely bioresorbable vascular scaffolds. The SYNERGY stent, an EES with a bioabsorbable polymer is in human trials and initial data are promising, with low rates of restenosis and no stent thrombosis events reported [77]. The ABSORB™ (Abbott Vascular, IL, USA) stent consists of a bioresorbable backbone of poly-L-lactide coated with a biodegradable polymer that controls the release of everolimus. The device has been termed a scaffold rather than a stent since it is not permanent. The vascular scaffold degrades over several years and is replaced by a proteoglycan matrix. The most recent iteration studied has stable scaffold area over time and sufficient inhibition of neointimal hyperplasia. A randomized trial is planned comparing the ABSORB scaffold and the Xience® (Abbott Vascular) EES [78]. These devices may

#### Box 6. Factors associated with drug-eluting stent restenosis & target-lesion revascularization.

##### Patient-related

- Clinical
  - Age
  - Acute coronary syndrome
  - Diabetes mellitus
  - Chronic kidney disease
  - Prior coronary bypass surgery
- Anatomic
  - Multivessel disease
  - In-stent restenosis
  - Ostial lesion
  - Unprotected left main
  - Bifurcation
  - Saphenous vein graft
  - Small vessels <2.5 mm
  - Long lesion length

##### Procedure-related

- Technique/device
  - Drug-eluting stent type
  - Small final minimal lumen diameter
  - Stent underexpansion
  - Stent gaps
  - Longer stent length
  - Stent overlap
  - Edge stenosis or dissection
  - No on-site cardiac surgery
  - Lack of use of fraction flow reserve



reduce the risk of stent thrombosis and the need for prolonged dual-antiplatelet therapy, which in turn would lower risk of bleeding. Benefits on vascular function are also expected.

In addition to advances in technology, heightened attention to the appropriateness of PCI and the use of outcomes as reimbursement and quality measures will further generate interest in understanding the factors that influence procedural safety and efficacy. Similar to risk models developed for mortality, prediction models for complications such as bleeding and periprocedural MI and for outcomes such as restenosis will be an

important way to individualize care and assure similar outcomes across institutions.

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### Executive summary

#### Percutaneous coronary intervention outcomes

- Over the past three decades, our understanding of the patient and procedure-related factors that influence percutaneous coronary intervention (PCI) outcomes have advanced the field of interventional cardiology.
- Advances in techniques, equipment, pharmacotherapy and patient management have reduced the risk of bleeding, vascular complications, and myocardial infarction (MI) and improved the durability of PCI by reducing restenosis.
- Although the risk factors for various outcomes differ, several clinical variables consistently predict increased risk including advanced age, acute coronary syndromes, diabetes mellitus and chronic kidney disease.
- Operators should be aware of high-risk variables and guideline recommendations that allow the safe performance of PCI in patients with cardiovascular disease.

#### Periprocedural bleeding

- PCI related bleeding, which may be due to an access or nonaccess site source, is significantly associated with mortality.
- The use of bivalirudin and radial access reduce periprocedural bleeding.

#### Stent thrombosis

- Stent thrombosis is uncommon but results in devastating consequences including MI and death.
- Dual antiplatelet therapy and optimal stent deployment are critical for reducing the risk of stent thrombosis.

#### Periprocedural MI

- Procedural myonecrosis can be caused by a number of mechanisms.
- Pretreatment with antiplatelet therapy and statins can reduce the risk of periprocedural MI.

#### Mortality risk in the stent era

- Models can be used to predict the risk of in-hospital mortality following PCI in contemporary practice.

#### In-stent restenosis & target-vessel revascularization

- Drug-eluting stents reduce restenosis compared with bare-metal stents in all patient and lesion subsets.
- Several anatomic and clinical factors increase the risk of restenosis in drug-eluting stent-treated patients.

#### Future perspective

- Drug-eluting stents with bioabsorbable polymers and completely bioresorbable vascular scaffolds are under development and may improve upon the safety of PCI.
- Individualizing care with risk models may reduce complications and improve outcomes.

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