Myocardial revascularization began in 1968 with the development of surgical bypass of the coronary arteries by Rene Favaloro [1]. The use of percutaneous coronary intervention (PCI) was first introduced by Grüntzig et al. in 1977 by percutaneous transluminal coronary angioplasty (PTCA) [2]. However, in the first 50 patients who underwent PTCA, the complication rate was high, with a primary success rate of only 64%, and emergency coronary artery bypass grafting (CABG) was needed in 14% of patients [2]. As operators became more experienced with PTCA, the success rate improved, although complications remained. PTCA was frequently complicated by vessel closure during the procedure, as well as angiographic restenosis with an occurrence rate of 30–40% [3]. The need for improved catheter-based interventions for coronary artery disease led to an evaluation of other potential techniques, including directional atherectomy, rotational atherectomy and excimer laser angioplasty [4]. In 1987, Schatz et al. introduced the first successful coronary stent, the Palmaz-Schatz bare-metal stent (BMS), to be implanted in humans [5,6]. Two randomized clinical trials were published in 1994 comparing coronary stent implantation with PTCA; the BENESTENT study and STRESS study established that intracoronary stents significantly reduced the incidence of angiographic restenosis and repeat revascularization compared with PTCA [7,8]. The benefits of stent implantation occur by allowing the stent to act as a scaffold to tack up intimal and medial dissections and provide radial support to oppose elastic recoil [9]. Since that time, percutaneous coronary coronary artery stenting has become the preferred method of percutaneous revascularization, with approximately 600,000 procedures performed each year in the USA [10]. Although coronary stenting has been proven to have improved outcomes compared with PTCA, periprocedural complications remain. Improvements in interventional technique, stent technology and antiplatelet therapy have reduced the incidence of these complications; however, further progress still needs to be made.

Complications
Complications after PCI occur, although fortunately the risk of major complications during most interventions remains low. The degree of complications range from minor events (i.e., minor bleeding or mild periprocedural biomarker elevation) to major events (i.e., major bleeding, vascular-access complications requiring surgical repair, renal failure or stent thrombosis (ST) resulting in myocardial infarction or death). Most complications after PCI occur in the periprocedural period related to the procedure itself, with fewer events occurring in the longer-term follow-up period. A review of recent National Cardiovascular Data Registry data reports a 4.53% risk of any periprocedural adverse event in patients undergoing PCI for indications other than ST-elevation myocardial infarction (STEMI) [11]. The overall in-hospital mortality rate varied by individual factors ranging from 0.65%, in elective PCI, to 4.81%, in patients with STEMI, with an overall rate of
1.27% [12]. Long-term complications after PCI are largely related to recurrent ischemia from progression of atherosclerotic coronary artery disease or restenosis at the site of revascularization. The following sections will review the acute and chronic complications of PCI and strategies to prevent such events (Box 1).

**Acute complications**

**Acute stent-related coronary perforation**

Coronary artery perforation (CAP) is a potentially life-threatening complication, occurring in 0.1–0.84% of patients undergoing stent placement [13,14]. CAP occurs more commonly during complex coronary interventions where coronary atheroablution is utilized, although it does occur during stent implantation, with an incidence of 0.05–0.15%, when angioplasty and/or stent placement are utilized [13,15]. The etiology of CAP during stent placement can occur from guidewire-related perforations, specifically stiffer, hydrophilic wires, oversized stent implantation with a balloon–artery ratio of >1:1, or high-pressure balloon dilatation [13,16–18]. The Ellis classification scheme is the most widely used system, with CAP classified into three types: type I, extraluminal crater without extravasation; type II, pericardial or myocardial blushing; and type III, perforation ≥1 mm diameter with contrast streaming or cavity spilling [19]. Complications from CAP include periprocedural myocardial infarction, cardiac tamponade and death with incidence increasing for severity of perforation [13–15]. Management of patients with CAP ranges from close inpatient observation to emergency CABG. All patients with identified CAP should have heparin reversed with protamine infusion, preventing such events.

**Stent thrombosis**

ST is a rare, but dreaded, complication of PCI and often presents as death or nonfatal acute myocardial infarction [22]. ST is defined by the time interval from PCI to occurrence by using acute (<24 h), early (0–30 days), late (31 days to 1 year) and very late (>1 year), with the majority of events occurring early in both drug-eluting stents (DES) and BMS [23]. The results of a 2006 meta-analysis of 19 randomized controlled trials found 1-year ST incidences of 0.87% for BMS and 0.99% for first-generation DES (p = nonsignificant) [24]. Beyond 1 year (very late), ST is more commonly associated with DES placement and is rarely seen after BMS. Stone et al. demonstrated equivalent 4-year ST rates between BMS and first-generation DES paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES); however, there was a statistically significant difference in ST after 1 year, with only two events occurring in patients with BMS [25]. In addition, the Swedish Coronary Angiography and Angioplasty Registry reported a 1.18-times higher 3-year mortality rate in patients receiving first-generation DES, which was driven by events occurring 6 months after implantation [26]. These results brought into question the safety of DES, particularly in off-label use. Subsequent studies with longer-term follow-up showed no difference in cardiovascular death, myocardial infarction or ST between BMS and first-generation DES [27,28]. A large meta-analysis, including both randomized controlled trials and observational data, found that first-generation DES had equivalent rates of
mortality and myocardial infarction compared with BMS, and in the observational studies, a significant reduction in these outcomes was seen [29]. The development of second-generation DES has led to reduced rates of ST (Table 1). A 2012 meta-analysis of 11 trials and 16,000 patients showed the use of everolimus-eluting stents (EES) compared with first-generation DES, resulted in a 0.6% absolute risk reduction in ST, with lower risk occurring at all time intervals [30]. Similarly, zotarolimus-eluting stent (ZES) placement demonstrated a significantly lower incidence of ST compared with first-generation DES placement [31]. When comparing EES with second-generation DES, EES was found to have a lower rate of ST compared with ZES (0.3 vs 1.2%; p = 0.01), as well as other DES [30,32,33].

Intracoronary balloon angioplasty and stenting results in vascular injury, with resultant exposure of thrombogenic factors of the subintima and subsequent endothelial inflammation, platelet activation and long-term neointimal proliferation. Early, late and very-late ST result from different mechanisms. This inflammatory response at time of PCI, as well as the inherent thrombogenicity of the foreign stent itself, is responsible for the development of ST in the early and late time period. The pathophysiology of very-late ST seen with DES has histopathologic features with cellular thrombus infiltrate and elevated intracoronary inflammatory markers distinct from early DES ST, BMS ST and native coronary thrombosis (Figure 1) [34]. Very-late DES ST has been attributed to abnormal vascular responses to DES, including incomplete endothelialization, hypersensitivity reaction to the stent platform or antiproliferative medication coating and aneurysm formation. Predictors for developing ST have been identified after BMS and DES placement (Figures 2 & 3). The main predictor of early and late ST is the premature discontinuation of thienopyridine therapy (odds ratio [OR]: 36.5) [35]. Other clinical factors, such as acute or chronic kidney disease, depressed left-ventricular systolic function, diabetes mellitus, malignancy and cocaine use have been independently associated with increased rates of ST [35–39]. Procedural risk factors in ST include number and length of stents placed, stent undersizing, vessel dissection, stent fracture, stenting of vein grafts and complexity of stenosis [35,40–48].

Periprocedural biomarker elevation
Periprocedural cardiac biomarker elevation is a common complication, with varying significance depending on clinical context occurring in up to 44% of PCIs [44,45]. Major complications of myocardial infarction associated with PCIs include abrupt vessel closure, dissection, jailing of side-branch vessel and distal embolization with no reflow. Routine monitoring of periprocedural cardiac markers has been a common practice; however, the development of highly sensitive cardiac biomarkers and evolving definitions of periprocedural myocardial infarction has made interpretation difficult.

The adverse outcomes associated with periprocedural biomarker elevation are well known. Several earlier studies, including a meta-analysis of 23,230 patients, have shown a statistically significant increased mortality rate in patients with elevated creatine kinase-MB greater than three-times the upper limit of normal [45–50]. Subsequent studies have not been as conclusive. The ACUITY trial evaluated 7773 patients with non-STEMI who underwent PCI. The results suggested that the development of a spontaneous myocardial infarction unrelated to the procedure was associated with subsequent mortality, and periprocedural biomarker elevation did not have an independent association [51]. Several additional studies showed consistent results with ACUITY.

Table 1. Drug-eluting stent characteristics and complication rates at 12-month follow-up.

<table>
<thead>
<tr>
<th>Drug elution</th>
<th>Trade name</th>
<th>Manufacturer (location)</th>
<th>Platform</th>
<th>Strut thickness</th>
<th>ST (%)</th>
<th>TLR (%)</th>
<th>MACE (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>TAXUS™ Express™</td>
<td>Boston Scientific (MA, USA)</td>
<td>Stainless steel</td>
<td>132</td>
<td>0.7</td>
<td>5.5</td>
<td>12.3</td>
<td>[130]</td>
</tr>
<tr>
<td></td>
<td>TAXUS Liberté™</td>
<td>Boston Scientific</td>
<td>Stainless steel</td>
<td>97</td>
<td>0.9</td>
<td>6.1</td>
<td>12.5</td>
<td>[130]</td>
</tr>
<tr>
<td></td>
<td>TAXUS ION™</td>
<td>Boston Scientific</td>
<td>Platinum–chrome</td>
<td>81</td>
<td>0.4</td>
<td>3.8</td>
<td>7.4</td>
<td>[133]</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>CYPHER®</td>
<td>Cordis Corporation (FL, USA)</td>
<td>Stainless steel</td>
<td>140</td>
<td>0.4</td>
<td>4.9</td>
<td>8.3</td>
<td>[64]</td>
</tr>
<tr>
<td>Everolimus</td>
<td>XIENCE®</td>
<td>Boston Scientific and Abbott Vascular (CA, USA)</td>
<td>Cobalt–chrome</td>
<td>81</td>
<td>0.3</td>
<td>2.5</td>
<td>4.2</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>PROMUS™ Element™</td>
<td>Boston Scientific</td>
<td>Platinum–chrome</td>
<td>81</td>
<td>0.4</td>
<td>1.9</td>
<td>5</td>
<td>[132]</td>
</tr>
<tr>
<td>Zotorolimus</td>
<td>Endeavor®</td>
<td>Medtronic (MN, USA)</td>
<td>Cobalt–chrome</td>
<td>91</td>
<td>0.8</td>
<td>4.5</td>
<td>6.5</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Resolute</td>
<td>Medtronic</td>
<td>Cobalt–chrome</td>
<td>91</td>
<td>0.1</td>
<td>2.8</td>
<td>4.7</td>
<td>[133]</td>
</tr>
</tbody>
</table>

MACE: Major adverse cardiac event; ST: Stent thrombosis; TLR: Target-lesion revascularization.
revealing that poor outcomes were related to patient comorbidities, preprocedure biomarker elevation and procedure complexity, not post-procedure biomarker levels [51–54]. Conversely, a meta-analysis of 20 studies evaluating troponin elevation after PCI found a significant association with increased mortality (OR: 1.35; 95% CI: 1.13–1.60) [55]. The disparities in the data may be attributed to the varying definitions of periprocedural myocardial infarction, heterogeneous patient populations and differences in duration of follow-up. The discrepancy in the data has led to controversy surrounding the significance of biomarker elevation post-PCI, especially in mild biomarker elevation in the absence of clinical symptoms of myocardial ischemia, and the development of highly sensitive troponin assays has increased this incidence [56,57]. In an attempt to provide a clear consensus, the ‘universal definition’ of PCI-related myocardial infarction (type 4a) was recently published. A type 4a myocardial infarction in patients with normal baseline troponin level is defined as a rise in troponin greater than five-times 99th percentile upper limit of normal occurring within 48 h of the intervention, with one of the following: evidence of prolonged ischemia (>20 min) as demonstrated by prolonged chest pain; ischemic ST changes or new pathological Q waves; evidence of a flow-limiting complication by angiography; or evidence of new loss of myocardial viability or new regional wall-motion abnormality as seen by imaging [58]. If preprocedure troponin is elevated, but stable or falling, a >20% increase in addition to one of the above clinical criteria is required for a diagnosis type 4a myocardial infarction [58]. In the current American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions guideline for PCI, it is recommended that patients who have symptoms of myocardial infarction during or after PCI, or asymptomatic patients with evidence of angiographic complications, have either creatine kinase-MB and/or troponin measured (class I, level of evidence C) [59]. It may be reasonable for all patients after PCI to have routine measurement of cardiac biomarkers (class IIb, level of evidence: C) [59]. While there are conflicting results on the independent association of cardiac biomarker elevation post-PCI with mortality, more standardized data are needed to determine the significance of periprocedural enzyme elevation.

**Chronic complications**

**In-stent restenosis**

In-stent restenosis (ISR) is defined angiographically as >50% diameter stenosis on repeat angiography or clinically as anginal symptoms requiring target-lesion revascularization. The clinical presentation of ISR, unlike ST, typically involves stable angina, although up to 25% of patients can present with an acute coronary syndrome (ACS) [60,61]. The onset of symptoms occurs months after stent implantation and is further delayed if DES is deployed [62]. The development of intracoronary stenting has greatly reduced the rate of target-lesion restenosis compared with PTCA. The introduction of DES resulted in a significant decrease in the incidence of ISR compared with BMS. The incidence of ISR at 6 months was significantly less after BMS compared with PTCA (22 vs 32%; p = 0.02) [7]. ISR rates with first-generation DES were further reduced compared with BMS, as shown in randomized controlled trials, and were shown to have ISR rates of <6% at 9-month follow-up [63,64]. Second-generation DES provided improvement in stent platform and medications, resulting in further reduction in ISR rates. Randomized trial data have shown superiority of EES compared with PES for rates of target-lesion revascularization (TLR; 2.5 vs 4.6%; p = 0.001; Figure 4) [65].
Minimizing complications following stent implantation: outcomes & follow-up

The mechanism for ISR is similar for both BMS and DES. As described above, PCI results in vascular trauma with subsequent inflammatory and healing response. Excessive response to vascular injury by neointimal hyperplasia and vascular remodeling over weeks to months after intervention are primarily responsible for ISR [66]. The mechanisms for the abnormal response to vascular injury can be attributed to biological, mechanical and technical factors. Biological factors common to both DES and BMS is a hypersensitivity response to the metal alloy of the stent itself. BMS and first-generation DES stent-platform materials were mostly stainless steel; it has been suggested that nickel and molybdenum released from the stainless-steel stent served as an allergic trigger for ISR [67]. A second-generation DES stent platform is cobalt chromium, which appears to have less hyperproliferative effects. Unique to DES, the antiproliferative drug itself or stent polymer coating can result in hypersensitivity reactions. Also, resistance to the chemotherapeutic agent of the DES can result in excessive neointimal hyperplasia without the desired antirestenotic effects. Delayed restenosis after DES implantation occurring after 1 year has been reported, resulting in smaller absolute difference in luminal diameter and TLR compared with BMS, resulting in a ‘catch up’ phenomenon. While both first- and second-generation DES are associated with delayed restenosis, first-generation DES have a higher late TLR rate than second generation DES, with continued risk up to 5 years postimplantation [68,69].

Mechanical factors of ISR include stent underexpansion and stent fracture. Kang et al. found that 42% of patients with ISR after DES had evidence of stent underexpansion [70]. Stent underexpansion at the time of PCI can be difficult to detect with angiography alone, and the use of intravascular ultrasound can be useful in the diagnosis. Stent strut fracture results in complete or partial stent separation, and thus decreases mechanical support and local drug delivery. The extent of stent fracture can range from single-strut fracture (grade I) to complete transection (grade V) [71]. Vessel tortuosity, longer stents, right coronary artery location, stent overlap and use of SES have all been associated with an increased risk of stent fracture [72,73]. Technical factors contributing to ISR include barotrauma outside of the

<table>
<thead>
<tr>
<th>Risk factors for acute stent thrombosis</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel stop &lt;30 days</td>
<td>36.53</td>
<td>7.98–167.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Undersizing</td>
<td>13.39</td>
<td>5.27–34.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel stop 180–365 days</td>
<td>5.87</td>
<td>1.74–19.80</td>
<td>0.0043</td>
</tr>
<tr>
<td>Clopidogrel stop 30–180 days</td>
<td>4.63</td>
<td>1.40–15.35</td>
<td>0.0122</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4.50</td>
<td>2.14–9.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD ≥50% proximal of culprit</td>
<td>4.40</td>
<td>2.71–7.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI flow post-PCI &lt;3</td>
<td>3.77</td>
<td>2.09–6.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dissection</td>
<td>2.88</td>
<td>1.67–5.00</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bifurcation stenting</td>
<td>2.27</td>
<td>1.48–3.47</td>
<td>0.0002</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>2.27</td>
<td>1.43–3.60</td>
<td>0.0005</td>
</tr>
<tr>
<td>PAD</td>
<td>2.13</td>
<td>1.01–4.51</td>
<td>0.0482</td>
</tr>
<tr>
<td>CAD ≥50% distal of culprit</td>
<td>1.98</td>
<td>1.32–2.95</td>
<td>0.0009</td>
</tr>
<tr>
<td>No ASA</td>
<td>1.88</td>
<td>1.01–3.88</td>
<td>0.0487</td>
</tr>
<tr>
<td>Any DES</td>
<td>1.66</td>
<td>1.21–2.94</td>
<td>0.0052</td>
</tr>
<tr>
<td>DM</td>
<td>1.98</td>
<td>1.02–2.70</td>
<td>0.0432</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.80</td>
<td>0.68–0.94</td>
<td>0.0072</td>
</tr>
</tbody>
</table>

Figure 2. Independent risk factors for stent thrombosis. A comparison of the total group of patients with stent thrombosis with all matched-control subjects, represented by HR and 95% CI. The dotted line represents a HR of 1. Error bars represent 95% CI. The arrow is a graphical representation that the CI goes beyond the shown graph.

ASA: Acetyl salicylic acid; CAD: Coronary artery disease; DES: Drug-eluting stent; DM: Diabetes mellitus; HR: Hazard ratio; LVEF: Left-ventricular ejection fraction; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

Reproduced with permission from [35].
Minimizing complications

- **Stent choice**

There are currently five types of stents available in the USA: BMS with either stainless steel or cobalt chromium alloy stent platforms, SES, PES, EES and ZES. As reviewed above, randomized controlled data have shown DES, specifically second-generation DES, to be superior to BMS, with a reduced rate of in-stent restenosis, ST and need for repeat TLR [76–78]. The antiproliferative drug elution with DES results in delayed endothelialization of the stent and thus requires longer duration of dual antiplatelet therapy (DAPT; 12 months) and leads to an increased risk of bleeding in some patients. DES should be the preferred stent choice, especially in patients that are at an increased risk of ISR or have a large area of myocardium at risk if stent complications occur [Box 2]. BMS is the preferred stent choice in patients that are unable to comply with DAPT, have planned upcoming surgical procedures in the next 12 months or are considered to be a high risk for bleeding complications that may result in early discontinuation of DAPT.

- **Intraprocedural pharmacotherapy**

The use of antithrombotic therapy during PCI to reduce the incidence of thrombus formation is mandatory. More aggressive anticoagulation regimens have been implemented since the onset of PCI, resulting in a reduction in early ST, myocardial infarction and death, although at a cost of increased bleeding and vascular complications. The development of radial access for coronary intervention provides decreased vascular and bleeding complications compared with femoral access, allowing for improved outcomes despite aggressive anticoagulation [83]. Antithrombotic therapy is centered on the inhibition of platelet activation and the coagulation cascade. Multiple antithrombotic regimens have been employed with varying results.

stented segment, discontinuous serial stent coverage and suboptimal stent placement [64,74,75]. Moses et al. showed, in a subgroup analyses of patients randomized to receive SES, that the portions of the vessel that were exposed to balloon injury and were not covered by the SES were the primary sites for ISR [64]. Stent gap, like stent fracture, results in interruption of drug deposition in the vessel wall and an increased risk of ISR [74]. Underestimating the length of the diseased vessel, or misplacement of the stent during PCI resulting in the diseased artery not being covered by the stent, has been associated with increased risk of target-vessel revascularization and myocardial infarction at 1-year follow-up [75]. Predictors of developing ISR include patient, lesion and procedural characteristics, and are similar between BMS and DES [76–78]. Of the patient characteristics, diabetes mellitus is the strongest clinical predictor of ISR; however, the rate of ISR is lower with DES compared with BMS in diabetic patients, there remains to be an increased incidence compared with nondiabetics [78,79]. Lesion length, diameter, vessel size and complexity have all been associated with increased rates of ISR [76–78,80]. Procedural predictors, such as stent length and strut platform thickness have been shown to increase the incidence of ISR. The ISAR-STEREO-2 trial showed a significant reduction in angiographic restenosis at 6 months and target-vessel revascularization at 1 year in patients receiving BMS with thin (50 µM) versus thick (140 µM) struts [81]. With newer DES platforms with thinner stent struts, longitudinal stent deformation as a result of decreased longitudinal integrity can occur with resultant predisposition to ISR, as well as ST [82]. Patients undergoing stenting of multiple lesions and utilization of longer stent length have an increased risk for the development of ISR [76–78,80].
Antiplatelet pharmacologic therapy targets cyclooxygenase inhibition, ADP P2Y12 receptor blockade and, in certain patients, GP IIb/IIIa inhibition. Aspirin has been shown to reduce the frequency of ischemic complications after PCI [84]. The minimum dose of aspirin to prevent complications is unclear; however, it is recommended that all patients undergoing PCI receive 325 mg of aspirin prior to the intervention [59]. The current available ADP P2Y12 receptor blockers include clopidogrel, prasugrel, ticagrelor and ticlopidine, with clopidogrel being the most widely used and well studied of the group.

Ticlopidine was the earliest developed ADP P2Y12 inhibitor, and was shown to reduce major adverse cardiovascular events, as well as subacute ST compared with warfarin plus aspirin [85,86]. Due to multiple adverse side effects associated with the usage of ticlopidine, and the development of newer antiplatelet agents, ticlopidine is

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**Figure 4. Time-to-event curves for everolimus-eluting stents versus paclitaxel-eluting stents.**

(A) Target-lesion failure (1-year hazard ratio [HR]: 0.70, 95% CI: 0.46–0.82; p < 0.009 and 2-year HR: 0.62, 95% CI: 0.55–0.83; p < 0.003), (B) death or myocardial infarction (1-year HR: 0.70 (95% CI: 0.48–1.01; p < 0.05 and 2-year HR: 0.76, 95% CI: 0.56–1.02; p < 0.007), (C) ischemia-driven TLR (1-year HR: 0.54, 95% CI: 0.38–0.78; p < 0.007 and 2-year HR: 0.66, 95% CI: 0.50–0.88; p < 0.004) and (D) definite or probable stent thrombosis (1-year HR: 0.27, 95% CI: 0.11–0.67; p < 0.003 and 2-year HR: 0.36, 95% CI: 0.17–0.79; p < 0.008).

EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent; TLR: Target-lesion revascularization.

Reproduced with permission from [135].
In the USA, Clopidogrel has proven to be beneficial in secondary prevention of myocardial infarction, stroke, and vascular death in patients with ACS [87]. Clopidogrel is a prodrug requiring activation in the liver, with onset of action between 4 and 6 h. Several studies have evaluated the optimal loading dose for clopidogrel with PCI to have adequate anticoagulation at the time of procedure. A loading dose of 600 mg of clopidogrel provides greater platelet inhibition compared with 300 mg dose; however, there is no additional benefit for doses greater than 600 mg [88]. A meta-analysis of over 25,000 patients in seven studies undergoing PCI showed that a 600 mg loading dose of clopidogrel resulted in improved cardiovascular outcomes without an increase in bleeding complications, compared with a 300 mg loading dose [89]. Since clopidogrel is a prodrug requiring hepatic activation through the CYP2C19 enzyme, patients with decreased CYP2C19 function poorly metabolize the drug, resulting in higher cardiovascular events after PCI compared with normal [90]. Clopidogrel resistance testing is commercially available, although it has only had modest ability to predict clinical outcomes [90,91]. The efficacy of prasugrel compared with clopidogrel was evaluated in the TRITON-TIMI 38 trial, a randomized trial of 13,608 patients with ACS undergoing PCI [92]. Prasugrel usage resulted in a significant reduction in cardiovascular death, nonfatal myocardial infarction or nonfatal stroke compared with clopidogrel (9.9 vs 12.1%, hazard ratio [HR]: 0.81; 95% CI: 0.73–0.90), as well as a reduction in ST (1.1 vs 2.4%); however, it was associated with an increased rate of major bleeding (2.4 vs 1.8%, HR: 1.32; 95% CI: 1.03–1.68) [92]. Ticagrelor, a reversible ADP P2Y12 inhibitor that does not require conversion to an active metabolite, was compared with clopidogrel in patients with ACS in the PLATO trial [93]. Ticagrelor resulted in a reduction in the primary end point of cardiovascular death, myocardial infarction or stroke (9.8 vs 11.7%, HR: 0.84; 95% CI: 0.77–0.92), though again a higher rate of major bleeding not related to CABG was seen [93].

GP IIb/IIIa inhibitors, abciximab and the small molecule inhibitors epifibatide and tirofiban, have been shown to improve outcomes in clinical trials of patients undergoing PCI. Earlier trials, conducted before the routine use of DAPT with ADP P2Y12 inhibition during PCI, demonstrated a reduction in ischemic events, mainly driven by a decrease in periprocedural cardiac biomarker elevation, with the use of GP IIb/IIIa agents. However, they were associated with an increased bleeding risk [94,95]. Trial data in the modern era of PCI with routine DAPT have been less clear. The ISAR-REACT trial of 2159 patients undergoing elective PCI, after receiving 600 mg clopidogrel loading, randomized patients to abciximab plus heparin versus heparin alone [96]. Results showed no difference in outcomes of death, myocardial infarction or urgent target-vessel revascularization (p = 0.82), and thus decreased enthusiasm for the routine use of GP IIb/IIIa inhibitors in patients undergoing PCI. However, the ISAR-REACT 2 trial, evaluating the use of abciximab in patients with high-risk ACS undergoing PCI receiving clopidogrel 600 mg loading, revealed a significant reduction in the primary end point of death, myocardial infarction or target-vessel revascularization at 30 days (8.9 vs 11.9%, relative risk: 0.75; 95% CI: 0.58–0.97), specifically in patients with elevated troponin, without a significantly increased bleeding risk [97]. Similar results were seen in high-risk patients undergoing PCI receiving epifibatide in the ESPRIT trial, suggesting that GP IIb/IIIa inhibition should be reserved for patients at the highest risk [98].

Parenteral anticoagulation therapy during intervention is centered on the use of heparin, enoxaparin or bivalirudin. Unfractionated heparin (UFH) has historically been the most commonly used anticoagulant for PCI and has become the standard by which other anticoagulants are measured by. The degree of anticoagulation with UFH is determined by the activated clotting time, with analysis showing that higher degrees of anticoagulation (activated clotting time of >325 s) increase risk of bleeding without additional reduction in thrombotic events [99]. When GP IIb/IIIa
inhibitors are used, a lower dose of heparin with target activated clotting time of 200–250 s has been shown to decrease major bleeding, without an increase in ischemic events [100]. UFH has several limitations, including a narrow therapeutic window and risk of heparin-induced thrombocytopenia, resulting in the subsequent development of newer antithrombotic agents.

Low-molecular weight heparin has been evaluated for use during PCI, with enoxaparin being the most widely studied therapeutic agent. The SYNERGY trial randomized 10,027 patients with ACS undergoing PCI to subcutaneous enoxaparin versus UFH [101]. There was no significant difference in all-cause mortality, nonfatal myocardial infarction or procedural complications at 30-day follow-up. There was an increase in bleeding complications in patients receiving enoxaparin, although significance varied owing to different bleeding definitions. The use of intravenous (iv.) enoxaparin has also been evaluated in randomized clinical trials. The STEEPLE trial evaluated over 3500 patients undergoing PCI receiving either 0.5 mg/kg iv. enoxaparin, 0.75 mg/kg iv. enoxaparin or UFH. Patients receiving 0.5 mg/kg iv. enoxaparin had a reduced rate of bleeding (5.9 vs 8.5%, 95% CI: -4.7 to -0.6; p = 0.01); however, the trial was not large enough to evaluate the prevention of ischemic complications [99]. A subsequent meta-analysis comparing iv. low-molecular weight heparin with UFH found that iv. low-molecular weight heparin resulted in a significant reduction in major bleeding (OR: 0.57; 95% CI: 0.40–0.82) with no significant difference in death, myocardial infarction or target-vessel revascularization [102].

Fondaparinux, a synthetically derived pentasaccharide, is an indirect factor Xa inhibitor that has been evaluated for the use in patients undergoing PCI. The OASIS-5 trial randomized over 20,000 patients with ACS to fondaparinux or enoxaparin [103]. Patients who underwent coronary intervention had similar ischemic outcomes (5.8 vs 5.7%, HR: 0.91; 95% CI: 0.9–1.13), and patients receiving fondaparinux had decreased major bleeding complications (2.4 vs 5.1%, HR: 0.46; p < 0.00001). However, patients undergoing PCI had a higher rate of catheter-related thrombosis (1.3 vs 0.5%; p = 0.001). Similar increased incidence of catheter-related thrombosis was again noted in the OASIS 6 trial [103]. Current guidelines state fondaparinux should not be used as the sole antithrombotic therapy in patients undergoing PCI [99].

More recently, the direct thrombin inhibitors bivalirudin and argatroban have been evaluated for use in patients undergoing PCI. The REPLACE-2 trial randomized over 6000 stable or low-risk ACS patients undergoing PCI to bivalirudin, with provisional GP IIb/IIIa inhibition versus UFH plus GP IIb/IIIa inhibition. Bivalirudin was found to be noninferior to UFH plus GP IIb/IIIa inhibition with regard to 30-day mortality, myocardial infarction, urgent target- vessel revascularization or major bleeding, and was associated with a significant reduction in bleeding complications (2.4 vs 4.1%; p < 0.001) [104]. Subsequently, the ACUITY trial evaluated the use of bivalirudin in patients with ACS [105]. Patients were randomized to one of three antithrombotic regimens: UFH or enoxaparin plus GP IIb/IIIa inhibitor; bivalirudin plus GP IIb/IIIa inhibitor; or bivalirudin alone. Bivalirudin alone was noninferior to the other two regimens, with regard to the composite ischemic end point, but resulted in significantly reduced major bleeding (3.0 vs 5.7%; Figure 5) [105]. The role of bivalirudin in STEMI was evaluated in the HORIZONS-AMI study, which randomized 3602 patients with STEMI undergoing PCI to receive UFH plus GP IIb/IIIa inhibition or bivalirudin [106]. Bivalirudin was associated with a lower rate of bleeding (4.9 vs 8.3%; p < 0.001), as well as significantly lower 30-day rates of death from a cardiovascular cause (1.6 vs 2.9%, relative risk: 0.62, 95% CI: 0.40–0.95; p = 0.03) and all-cause mortality (2.1 vs 3.1%, relative risk: 0.66, 95% CI: 0.44–1.00; p = 0.047) [106]. There was no significant difference in rates of reinfarction, target-vessel revascularization and stroke. Interestingly, the bivalirudin arm was associated with an increase in acute ST (<24 h); however, as above, it still resulted in a decreased 30-day rate of cardiovascular death.

### DAPT post-PCI

The optimal duration of DAPT with aspirin and ADP P2Y12 inhibition after PCI is uncertain, with current guidelines largely based on observational data and expert opinion. The challenge of determining the optimal length of DAPT is balancing the benefit of thrombosis prevention with the risk of increased bleeding and excess cost. Current guidelines recommend DAPT for at least 12 months after PCI, with DES or BMS in the case of an ACS [99]. In patients receiving BMS for non-ACS indications, 1 month of DAPT is recommended and ideally 12 months if there are no contraindications to continuing usage [99]. Recent data have suggested that DAPT for longer durations has not improved outcomes. Park et al. randomized 2701 patients treated with DES either to discontinue clopidogrel after 12 months or to continue it past 12 months [107]. The results...
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HR: 0.83 (95% CI: 0.71–0.97); p = 0.022

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HR: 0.61 (95% CI: 0.48–0.78); p = 0.0001

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HR: 1.00 (95% CI: 0.82–1.21); p = 0.098

Figure 5. Time-to-event curves for patients in bivalirudin and control groups up to 1 year. (A) NACE major bleeding or composite MACE. (B) Major bleeding (not related to coronary artery bypass surgery) and (C) MACE (death, reinfarction, target-vessel revascularisation for ischemia or stroke).

HR: Hazard ratio; MACE: Major adverse cardiovascular event; NACE: Net adverse clinical events.

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Minimizing complications following stent implantation: outcomes & follow-up

revealed a nonsignificant difference in reducing the rate of myocardial infarction or cardiovascular death (HR: 1.65; 95% CI: 0.80–3.36), although few patients reached the primary end point [107]. The PRODIGY trial was a randomized clinical trial evaluating the effect of DAPT for 6 months versus 24 months in patients with ACS or stable angina who underwent PCI with BMS or DES [108]. Results showed that overall risk of all-cause mortality, nonfatal myocardial infarction or stroke at 2 years follow-up were similar (HR: 0.98; 95% CI: 0.74–1.29). Patients were also randomized to one of three different DES (PES, EES or ZES) or BMS, without change in outcomes in any of the stent types. Patients who received DES did not see a difference in ST between the 6 and 24 months of DAPT (0.42 vs 0.56%; p > 0.99). There was a significant reduction in major bleeding events in the patients receiving 6-month DAPT compared with those with 24 months of therapy (HR: 0.38; 95% CI: 0.15–0.97) [108]. Additional similar randomized trials have shown similar results, with no significant differences in adverse cardiovascular events with shorter durations of DAPT, although they were limited by sample size and duration of follow-up [109,110]. A meta-analysis of four randomized trials evaluated the clinical outcomes of the duration of DAPT after PCI [111]. The median DAPT duration was 16.8 months for the extended DAPT group versus 6.2 months for the control group. In the 8158 patients analyzed, there was no reduction in the primary end point of all-cause death (OR: 1.15; 95% CI: 0.85–1.54) or in secondary end points of myocardial infarction (OR: 0.95; 95% CI: 0.66–1.36) or ST (OR: 0.88; 95% CI: 0.43–1.81) [111].

Given the limitations of the current data, additional trials are required to determine the optimal duration of DAPT after PCI. Until further studies are completed, patients undergoing PCI with DES or BMS for ACS should continue DAPT for at least 12 months and possibly longer depending on individual risk of ST and risk of major bleeding complications. Patients undergoing BMS for non-ACS indications should have 1 month minimum of DAPT, and preferably 12 months if there are no contraindications. In patients with an indication for oral anticoagulation and DAPT, there is an increased risk of bleeding complications. Patients requiring ‘triple therapy’ should be maintained on low-dose aspirin and have goal international normalized ratio in the lower therapeutic range (2.0–2.5) to reduce bleeding risk. Recent randomized data suggest that the omission of aspirin in patients on triple therapy results in decreased bleeding complications, without an increase in thrombotic events; however, further studies are needed [112].

Clinical follow-up

Stress testing

Noninvasive stress testing, with or without an imaging modality of nuclear imaging, echocardiography or MRI after PCI is frequently utilized, although the data for improved outcomes with the practice are lacking. An analysis of a national health insurance claims database with 21,046 patients status post-PCI found that 61% underwent stress testing within 2 years of intervention, and only 5% of these patients required revascularization [113]. The routine use of stress testing in asymptomatic patients after PCI has not been shown to improve outcomes [114,115]. The 2011 Appropriate Use Criteria for Echocardiography by the American College of Cardiology Foundation Appropriate Use Criteria Task Force/American Society of Echocardiography state that stress echocardiography less than 2 years following PCI in asymptomatic individuals is inappropriate; however, the appropriateness after 2 or more years is uncertain [116]. The American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions guidelines for PCI suggest that routine periodic stress testing of asymptomatic patients after PCI without clinical indications should not be performed (class III recommendation, level of evidence C), but it is reasonable to perform treadmill exercise testing in this patient population prior to enrolling in a formal cardiac rehabilitation program [59]. Based on the current data, there is no indication for routine stress testing in asymptomatic patients after PCI. If clinical symptoms develop, a stress-imaging modality should be used to increase sensitivity for detecting restenosis.

Secondary prevention

Secondary prevention measures for patients with coronary artery disease are essential to management after PCI in order to reduce adverse outcomes and the need for revascularization, and to improve quality of life. Aggressive lipid management should be utilized with lifestyle modification and statin therapy. The target goal of LDL cholesterol is a 30% reduction in baseline LDL, and a level of <100 mg/dl with a more aggressive treatment goal of <70 mg/dl in high-risk individuals [117–119]. Once the LDL goal is achieved, patients with triglyceride levels >200 mg/dl should have statins increased to lower non-HDL cholesterol to <130 mg/dl [120]. Blood pressure control with lifestyle modification and pharmacotherapy should
With the aging population in the USA, the prevalence of coronary artery disease will only continue to rise, as will the number of individuals undergoing PCI. While technique and technology have advanced greatly over the past decades, there remains room for improvement to reduce complications and improve outcomes. Stent technology continues to progress, with the most promising new development being biodegradable stents. In the short term, the benefit of PCI is to provide vessel stability and prevent restenosis after intervention. Once the time period in which restenosis occurs has passed, the remaining stent platform remains a nidus for complications. The prospect of implanting biodegradable stents was established in the ABSORB trial [124]. A stent composed of bioabsorbable poly-L-lactic acid, with a polymer coating of everolimus containing poly-D,L-lactide, was utilized in 30 patients with de novo coronary lesions resulting in only one non-STEMI and no cases of cardiac death or ST at 4-year follow-up [125]. A second iteration of this stent was created to improve the radial strength and reduce early and late recoil, and a randomized clinical trial (ABSORB II) comparing this bioresorbable stent with a standard EES is currently in progress [126]. Other new stent technology includes dual-therapy stenting, which combines the antiproliferative therapy of conventional DES with proendothelialization effects. The prohealing effects are achieved by eluting anti-human CD34 antibodies that enhance endothelialization by attracting endothelial progenitor cells. Clinical trials of dual-therapy stents are underway, and early results reveal rapid strut endothelialization [127,128]. Bioabsorbable polymer DES and polymer-free DES are under development, on the basis that removing the polymer will result in decreased ST while still providing drug delivery to reduce ISR. These new developments have promise to reduce complications and improve outcomes.
ISR, ST and bleeding risk, by allowing for the early withdrawal of DAPT without increased complications.

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No writing assistance was utilized in the production of this manuscript.

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* of interest
** of considerable interest
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**Meta-analysis of 11 randomized trials comparing 2-year rates of definite stent thrombosis between everolimus-eluting stents and other drug-eluting stents.


* Review of a large Dutch registry to identify clinical- and procedural-related factors related to stent thrombosis.


Minimizing complications following stent implantation: outcomes & follow-up

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66 Multicenter randomized trial comparing outcomes in over 3600 patients receiving everolimus- or paclitaxel-eluting stents.
91 Meta-analysis of over 25,000 patients demonstrating reduced rates of major cardiovascular events in patients undergoing percutaneous coronary intervention receiving 600 mg clopidogrel compared with 300 mg clopidogrel.


**Randomized, multicenter trial demonstrating confined benefit of abciximab to patients with non-ST-segment elevation acute coronary syndrome with elevated troponin undergoing percutaneous coronary intervention in patients who received a clopidogrel loading dose.**


116 American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Echocardiography; American Heart Association; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Critical Care Medicine; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; Douglas PS, Garcia MJ, Haines DE et al. ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCMR 2011 appropriate use criteria for echocardiography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography.


