

# Stroke After Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention: Incidence, Pathogenesis, and Outcomes

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Stroke is a devastating complication of both coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention (PCI). In a recent survey of 3112 cardiac patients by Sun and colleagues, death or prolonged hospitalization and long-term disability due to stroke was identified as the main concerns of patients undergoing invasive procedures.<sup>1</sup> Better understanding of the prevalence of stroke and its acute and long-term sequelae by both physicians and patients may have important implications for the choice of a particular revascularization strategy.

Surgical revascularization carries a higher procedural risk of stroke than PCI.<sup>2</sup> However, CABG may offer better long-term survival in certain subsets of patients. Advancements in

surgical techniques, medical therapy optimization, and neurologic risk stratification as well as in stent technology and pharmacological treatment continue to improve outcomes, so comparisons are often generally outdated soon after guideline recommendations are made. This speed adds to the challenges that patients, who are likely to prefer a less invasive approach, and physicians need to deal with in their decision process.

In this review, we summarize the current evidence on the incidence, pathogenesis, and outcomes of stroke after CABG and PCI. Moreover, we provide strategies on how to reduce the risk of stroke with both types of revascularization and relevant potentially preventative measures for use in daily practice.

## Search Methods

Because this article is an expert review and not a systematic review, no systematic search was performed and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were not followed.

In November 2018 a comprehensive search was performed to identify studies examining risk factors, incidence, pathogenesis, and outcomes of periprocedural stroke in the setting of CABG and PCI; studies evaluating strategies aimed at minimizing neurological risk in both settings were also included. The following databases were searched from inception to the present: Ovid Medline, Ovid Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Methodology Register).

Search keywords included *stroke* in combination with *CABG*, *myocardial revascularization*, *coronary artery bypass*, *PCI*, and *percutaneous coronary interventions*. Relevant abstracts were reviewed, and the “related articles” function was used for all included papers. References for all selected studies were crosschecked. The writing groups selected the most relevant papers according to both methodological and

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clinical considerations. Observational series were considered only in the absence of data from randomized controlled trials (RCTs).

## Risk Factors and Incidence of Periprocedural Stroke

### Coronary Artery Bypass Grafting

According to the Society of Thoracic Surgeons CABG Adult Cardiac Surgery Database (STS ACSD), the incidence of stroke after CABG is 1.3%, with a decrease from 1.6% to 1.2% between 2000 and 2009.<sup>3</sup> The most important risk factors for stroke are age, dialysis dependency, severe chronic lung disease, emergency surgery, and atherosclerotic burden in the coronary artery and other vascular beds.<sup>4,5</sup> Based on large single-center studies and the most recent data from the STS ACSD, the perioperative mortality for patients who had a stroke after CABG is close to 20%.<sup>6,7</sup>

### Percutaneous Coronary Intervention

In observational PCI series, the risk of stroke, both ischemic and hemorrhagic, ranges between 0.2% and 0.5% (Table 1).<sup>8–12</sup> The incidence of ischemic stroke is generally 3-fold higher compared with hemorrhagic stroke.<sup>8</sup> The rates of ischemic stroke appear to have slightly increased in recent years, most likely because of the increasing complexity of the patients. Conversely, hemorrhagic stroke rates have decreased, probably as a consequence of reduced use of thrombolytics and stricter monitoring of anticoagulation.<sup>8</sup>

Independent predictors of periprocedural stroke include older age, history of prior stroke, acute coronary syndrome (ACS), and use of an intra-aortic balloon pump (IABP; Table 1).<sup>8–11</sup> It has been estimated that the risk of periprocedural ischemic stroke increases by  $\approx 35\%$  for each additional point in the CHA<sub>2</sub>DS<sub>2</sub>-VASC score.<sup>13</sup>

### CABG Versus PCI

An individual patient data meta-analysis of 11 trials of 11 518 patients randomized to CABG versus PCI reported a significantly higher rate of stroke at 5-year follow-up after CABG (3.2% in the CABG arm versus 2.6% in the PCI arm; hazard ratio [HR]: 1.23; 95% CI, 1.03–1.39). The differential in stroke rate was driven by a reduced risk of stroke with PCI (0.4%) versus CABG (1.1%) in the 30-day postprocedural period (HR: 1.67; 95% CI, 1.47–1.80) but a similar risk of stroke between 31 days and 5 years (HR: 0.95; 95% CI, 0.62–1.20; Figure 1). Of note, the greater risk of stroke after CABG was most evident in patients with a heavy atherosclerotic burden and diabetes mellitus.<sup>14</sup>

In an 11-year statewide analysis from New Jersey comparing different revascularization strategies, on-pump CABG had a higher risk of stroke compared with off-pump CABG (odds ratio [OR]: 1.36; 95% CI, 1.18–1.56), although off-pump CABG still had a higher risk of stroke than PCI with drug-eluting stents (OR: 1.36; 95% CI, 1.26–1.45).<sup>10</sup>

Regardless of the specific setting (CABG or PCI), it should be noted that when a neurologist is directly involved in the determination, diagnostic accuracy for stroke (and thus its incidence) can be higher compared with patients who are assessed by other clinicians (ie, nonneurologists, who are more likely to miss subtle strokes).<sup>15–18</sup>

## Timing and Pathogenesis of Periprocedural Stroke

### Coronary Artery Bypass Grafting

An analysis of stroke after 45 432 CABG procedures reported that the risk of stroke peaked at postoperative day 2 (0.6% cumulative incidence) and stabilized to a constant hazard after the first postoperative week (0.8% cumulative incidence) up to 30 days.<sup>7</sup> In the above-mentioned individual patient-data meta-analysis, the risk of stroke remained constant after 30 days up to 5-year follow-up.<sup>14</sup> Because the risk of stroke after CABG evolves during follow-up, it is important to assess the etiology in 3 distinct time periods (Table 2): (1) intraoperative, (2) early postoperative (first 7 days), and (3) late (beyond 7 days) phases.<sup>19–22</sup>

#### *Intraoperative stroke*

Thromboembolism and hypoperfusion are the main etiologies of stroke during the procedure or in the immediate postoperative period, with studies reporting that  $\approx 60\%$  are thromboembolic and 40% are due to hypoperfusion; hemorrhagic strokes are uncommon.<sup>23–25</sup>

Thromboembolism may arise from aortic, cardiac, or cardiopulmonary bypass sources. Manipulation of the aorta occurs during cannulation, cross-clamping, and proximal anastomosis of a conduit. Atherosclerosis of the ascending aorta is documented in  $>50\%$  of patients undergoing CABG, and surgical manipulation can cause dislodgement of atheroma or calcium.<sup>26,27</sup> Studies examining intra-aortic embolic filters demonstrate that particulate emboli are frequent during CABG, especially at the time of placement or removal of the aortic cross-clamp.<sup>28,29</sup> Doppler detection of microembolic signals is higher at the start of cardiopulmonary bypass, and at the time of aortic clamping and unclamping.<sup>30</sup>

Bilateral watershed strokes are found significantly more often after cardiac surgery than in the general population. One

**Table 1.** Incidence and Predictors of Periprocedural Stroke in Large (N>10 000) Unselected Series of PCI

Study	Year	Patients (N)	Incidence of Stroke	Mortality Rates	Predictors
Aggarwal et al <sup>11</sup>	2004–2007	706 782	Periprocedural: 0.22%	In-hospital: 30% (any stroke) vs 1% (no stroke)	Known CVD, older age, ACS, IABP use
Werner et al <sup>9</sup>	2005–2008	46 888	Periprocedural: 0.4%	In-hospital: 19.2% (any stroke) vs 1.3% (no stroke)	Hemodynamic instability, older age, history of stroke, congestive heart failure, graft PCI, renal failure
Kwok et al <sup>8</sup>	2007–2012	426 046	Periprocedural: 0.13%	30-d: 16% (ischemic stroke/TIA) vs 48% (hemorrhagic stroke) vs 2% (no stroke)	Ischemic: older age, male gender, prior stroke, prior VHD, IABP use, thrombus aspiration, ACS Hemorrhagic: age, VHD, ACS, warfarin use, thrombolysis
Moreyra et al <sup>10</sup>	2002–2012	115 942	Periprocedural: 0.48%	NR	NR

ACS indicates acute coronary syndrome; CVD, cerebrovascular disease; IABP, intra-aortic balloon pump; NR, not reported; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; VHD, valvular heart disease.

study evaluated 98 patients with postoperative stroke and found that bilateral watershed strokes were diagnosed in 48% of magnetic resonance imaging and 22% of computed tomography (CT) scans.<sup>31</sup> A decrease in mean arterial pressure of  $\geq 10$  mm Hg was an important predictor of watershed strokes (OR: 4.06; 95% CI, 1.03–15.98). Although hypoperfusion has been implicated in postoperative neurological dysfunction, elevated mean arterial pressure may also be associated with postoperative delirium and stroke.<sup>32</sup> Patients with severe carotid artery disease have a higher risk of stroke when hypoperfusion occurs during surgery, but it is still largely accepted that CABG is safe in most patients with carotid artery disease; the role of systematic preoperative carotid screening is still debated.<sup>33</sup>

### Early postoperative stroke

The majority of strokes related to CABG occur during the first 7 postoperative days and are related to arrhythmias and hemodynamic instability. Postoperative atrial fibrillation (POAF) occurs in up to 30% of CABG patients before hospital discharge and is a significant predictor of stroke.<sup>34–36</sup> One study reported that stroke was preceded by POAF in about a third of patients, with a mean time of 21 hours.<sup>36</sup> Other thromboembolic causes of stroke are less common during this period, although theoretically, intraoperative aortic manipulation (cannulation, cross-clamping sites, and proximal anastomoses) may still generate embolic clots that result in a delayed neurological event. Of note, residual effects of anesthesia may delay the recognition of intraoperative strokes during the early postoperative period.

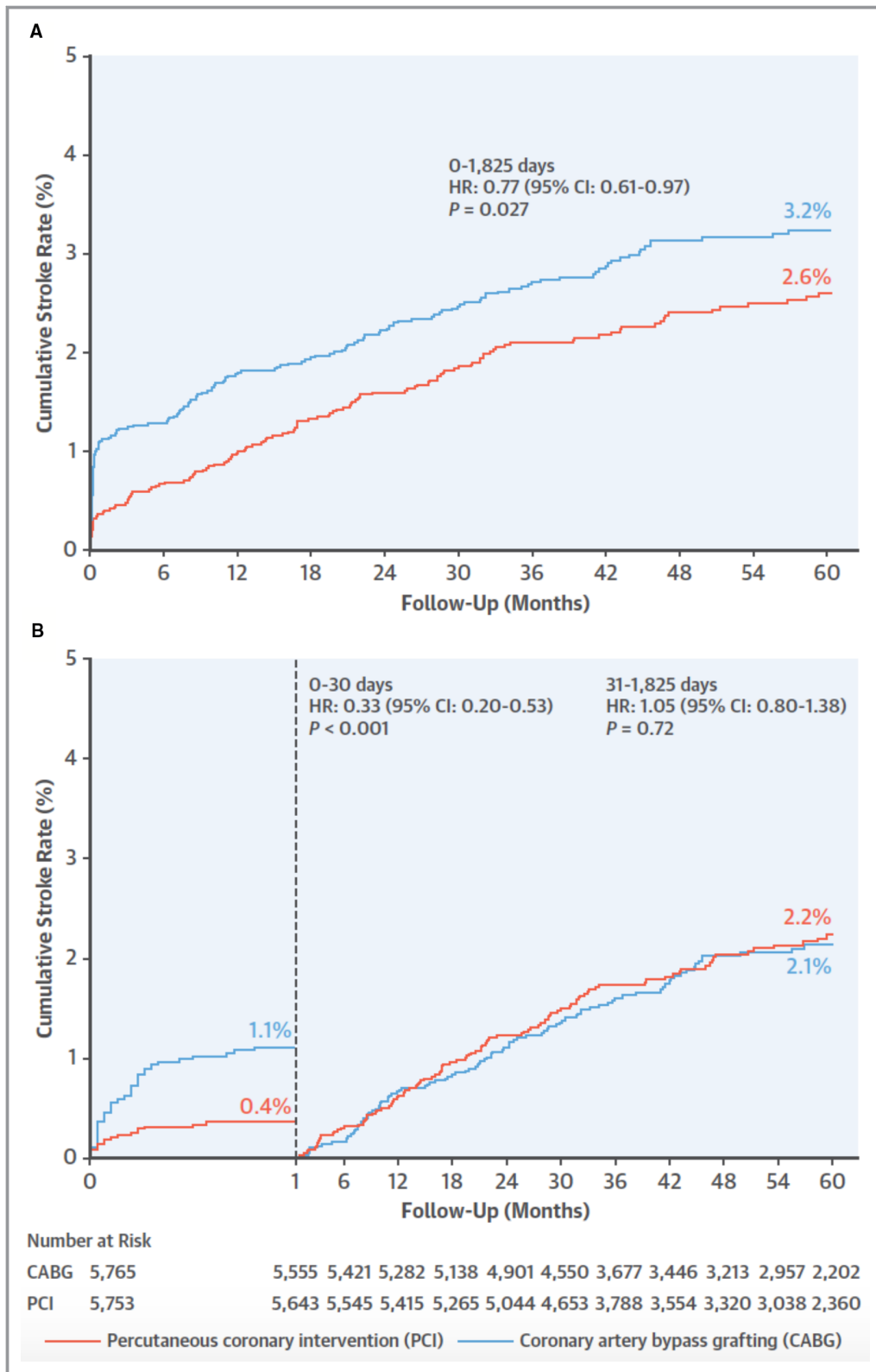
Low cardiac output syndrome is an important predictor of stroke through hypoperfusion.<sup>37,38</sup> One study of 11 825 patients found that low cardiac output syndrome and the need for prolonged use of inotropes increased the risk of stroke with ORs of 3 and 5, respectively.<sup>38</sup> Another factor that may be related to stroke is postoperative bleeding, associated with hypoperfusion by hypovolemia and often anemia.

### Late stroke

Late stroke is largely predicted by the overall atherosclerotic risk profile of patients, with risk increased in older patients, patients who have previously had a stroke, or those with hypertension, hypercholesterolemia, diabetes mellitus, or peripheral vascular disease.<sup>39,40</sup> POAF after CABG is an important contributor to the risk of stroke during long-term follow-up.<sup>41</sup> A meta-analysis reported that the risk of stroke in patients with POAF remained significantly higher during a median follow-up of 2 years compared with patients without POAF.<sup>42</sup> Nevertheless, the long-term risk of stroke associated with new-onset POAF appears to be smaller than the risk associated with nonvalvular atrial fibrillation.

### Percutaneous Coronary Intervention

In the first weeks after PCI, there is an early peak in the risk of stroke, followed by a gradual decline. In a nationwide PCI registry from Norway, the relative risk of stroke was highest during the first 48 hours (relative risk: 17.5; 95% CI, 4.2–72.8) and then decreased gradually, with a relative risk of 2.0 (95% CI, 1.2–3.3) at 4 to 8 weeks after PCI.<sup>43</sup>



**Figure 1.** Comparison of CABG and PCI for stroke during 5-year follow-up (A) and in landmark analyses of stroke at and beyond 30 days (B). HRs are for PCI vs CABG. Reprinted from Head et al<sup>14</sup> with permission. Copyright ©2018, Elsevier. CABG indicates coronary artery bypass grafting; HR, hazard ratio; PCI, percutaneous coronary intervention.

**Table 2.** Stroke Etiology in the Intraoperative, Early Postoperative (First 7 Days), and Late (>7 Days) Phases After CABG

Timing	CABG
Intraoperative	1. Thromboembolic: (a) macroembolism from atherosclerotic aorta; (b) cardiac etiology; (c) air embolism 2. Cerebral hypoperfusion: (a) low mean arterial pressure; (b) carotid stenosis; (c) cerebral atherosclerosis
Early postoperative	1. Atrial fibrillation: (a) new-onset postoperative; (b) preexisting chronic 2. Low cardiac output syndrome 3. Bleeding
Late	1. Thromboembolic: (a) atherosclerotic risk profile; (b) atrial fibrillation 2. Repeat revascularization procedures

CABG indicates coronary artery bypass grafting.

The possible mechanisms of periprocedural stroke after PCI are summarized in Figure 2. In a retrospective study of 35 patients with radiologically confirmed ischemic stroke occurring after PCI, the majority of strokes (91%) were embolic, typically at the level of the middle cerebral artery territory.<sup>44</sup> Dislodgement of atherosclerotic debris or other material from the aorta may occur from manipulation of wires and catheters during the cannulation of the coronary ostia. Intuitively, this theoretical risk is enhanced in the context of tortuous anatomies.

In a meta-analysis of 3 RCTs comparing manual thrombectomy and PCI alone in ST-segment-elevation myocardial infarction, stroke or transient ischemic attack occurred more frequently in patients randomized to thrombus aspiration, although the difference was not statistically significant.<sup>45</sup> The increased risk of stroke with manual thrombectomy is probably related to embolization of debris or fragments of thrombus.<sup>46</sup>

The risk of embolization is greater when larger devices, such as an IABP, are used. In a meta-analysis of 33 studies involving 18 889 patients, the risk of stroke was significantly increased when an IABP was used (OR: 1.71; 95% CI, 1.04–2.82).<sup>47</sup> Of note, in a relatively small trial of hemodynamic support for complex PCI with the Impella 2.5 (Abiomed) or IABP, the incidence of stroke or transient ischemic attack at 30 days was lower in patients supported by Impella 2.5 ( $P=0.04$ ).<sup>48</sup> The mechanism of cerebrovascular events with these support devices is not fully elucidated and may be attributed to confounders in light of the increased risk profile of these patients.

Additional causes of periprocedural stroke include air embolism, hypo- or hypertension, arrhythmias, and arterial dissection.<sup>49,50</sup> Aggressive antiplatelet or anticoagulant treatment regimens may increase the risk of hemorrhagic stroke.<sup>8</sup> Finally, atrial fibrillation is an important contributor to the risk of stroke even after PCI,<sup>51</sup> although it is much less common than after CABG.<sup>41</sup>

The risk of ischemic and hemorrhagic stroke continues to increase steadily during follow-up related to nonprocedural

factors but does not exceed the risk observed in patients with stable coronary artery disease who did not undergo PCI.<sup>52</sup>

### CABG Versus PCI

In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, stroke was more common after CABG than after PCI; however, a third of the periprocedural strokes occurred before the index procedure, presumably related to the discontinuation of dual-antiplatelet therapy (DAPT) in patients randomized to surgical revascularization.<sup>39</sup>

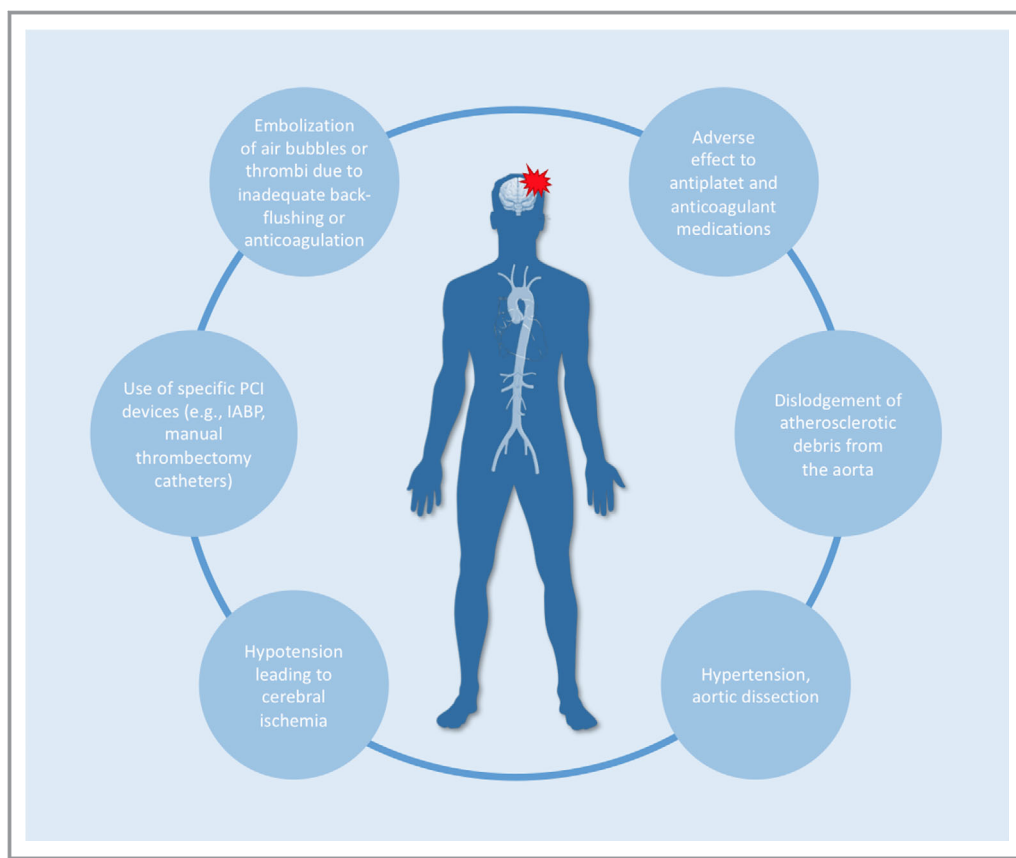
In their patient-level meta-analysis of RCTs comparing CABG and PCI, Head and colleagues confirmed that the highest rate of stroke occurred within the first 7 to 10 days after CABG. After the initial intra- and early postoperative periods, stroke rates after CABG and PCI were similar (2.2% versus 2.1%), and the risk of stroke remained low during 5-year follow-up.<sup>14</sup>

In a post hoc analysis of the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, patients with known cerebrovascular disease had had higher rates of stroke at 30 days (2.2% versus 0.8%;  $P=0.05$ ) and 3 years (6.4% versus 2.2%;  $P=0.0003$ ) compared with patients without cerebrovascular disease, independent of treatment modality.<sup>53</sup>

### Effect of Periprocedural Stroke on Short- and Long-Term Survival and Quality of Life

#### Coronary Artery Bypass Grafting

In a large single-institution study of >45 000 patients with a mean follow-up of 11 years, patients who experienced a perioperative stroke had 37% 10-year survival compared with 68% of patients who did not have stroke ( $P<0.001$  even after adjustment).<sup>7</sup> Among 5971 patients undergoing cardiac surgery at Johns Hopkins Hospital (3974 CABG), stroke was diagnosed in 214 (3.6%). Survival of stroke patients was 67%



**Figure 2.** Mechanism of stroke during and immediately after PCI. IABP indicates intra-aortic balloon pump; PCI, percutaneous coronary intervention.

at 1 year and 47% at 5 years, and long-term disability was moderate to severe in 69%. Of note, stroke patients who carried the diagnosis of previous stroke were much less likely to be discharged directly home (22.2% versus 50.3%), and patients who demonstrated acute watershed infarction on brain imaging were half as likely to be discharged directly home (22.2% versus 51.4%) than those without watershed infarction.<sup>54</sup>

### Percutaneous Coronary Intervention

Both periprocedural ischemic and hemorrhagic strokes have high mortality (Table 1).<sup>8–11</sup> In the National Cardiovascular Data Registry, in-hospital mortality was 30% for patients who developed a stroke compared with 1% for those without stroke.<sup>11</sup> In the PCI registry of the Euro Heart Survey Program, overall in-hospital mortality was 19.2% for patients who developed stroke compared with 1.3% for those without stroke.<sup>9</sup> In the British Cardiovascular Intervention Society (BCIS) database, ischemic stroke was independently associated with 30-day mortality (OR: 4.92; 95% CI, 3.06–7.92) and an even greater impact on prognosis was observed with hemorrhagic stroke (OR: 13.87; 95% CI, 6.37–30.21).<sup>8</sup> More

than half of patients who have a PCI-related stroke are left with a neurological deficit, and a quarter need skilled home assistance.<sup>55</sup> In the above-mentioned individual patient-data pooled analysis of 11 RCTs, PCI patients who experienced a stroke had significantly higher 5-year mortality compared with those without a stroke (45.7% versus 11.1%,  $P < 0.001$ ).<sup>14</sup>

The prognostic impact of periprocedural stroke on early mortality may also depend on the clinical presentation. An analysis of 560 439 PCI patients from the BCIS database documented an adjusted OR of 37.9 for 30-day mortality after elective PCI (unadjusted crude rate: 13% versus 0.3%) and an adjusted OR of 5.0 for PCI in the context of an ACS (unadjusted crude rate: 27% versus 3%).<sup>56</sup>

### CABG Versus PCI

Beyond periprocedural mortality, stroke after either CABG or PCI carries a 4-fold increase in all-cause mortality at 5 years.<sup>14</sup> In the SYNTAX trial, although no significant difference was noted between CABG (3.7%) and PCI (2.4%) in the cumulative incidence of stroke at 5 years, the majority of patients who had a stroke either died (10% of patients with stroke after CABG; 16% after PCI) or had long-term residual

impairment (68% of patients with stroke after CABG; 47% after PCI).<sup>39</sup>

At 5 years, patients enrolled in the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial who experienced a stroke within 30 days of the procedure had significantly higher mortality versus those without a stroke, after both PCI (45.7% versus 11.1%) and CABG (41.5% versus 8.9%).<sup>57</sup> An 11-year statewide analysis from New Jersey reported that for both CABG and PCI, the occurrence of postprocedural stroke was associated with increased 30-day and 1-year mortality.<sup>10</sup>

## Strategies to Minimize the Neurological Risk in CABG and PCI

### Coronary Artery Bypass Grafting

Possible measures to reduce emboli include intra-operative epiaortic scanning, preoperative CT scanning, and the use of single cross-clamp techniques,<sup>26,27</sup> although the level of evidence supporting these approaches is low.<sup>33,58</sup> Several investigations have proven the superior sensitivity of epiaortic scanning over both transesophageal echocardiography and surgical palpation for accurate assessment of ascending aortic atherosclerosis<sup>59</sup>; accordingly, international guidelines recommend epiaortic ultrasound before aortic manipulation “to identify atheromatous plaques and select the optimal surgical strategy” (class of recommendation IIa, level of evidence C).<sup>33</sup> Zingone and colleagues assessed the impact of epiaortic scanning on the incidence of perioperative stroke in 2172 patients undergoing cardiac surgery. In the CABG cohort, perioperative stroke rates were 3.4%, 0.5%, and 1.7% in the no-scan, selective-scan (high-risk patients only), and regular-scan groups, respectively ( $P=0.002$ ), with no substantial change following risk adjustment.<sup>60</sup>

As opposite to epiaortic scanning, pre-operative CT offers the advantage of identifying high-risk patients and allowing discussion of alternate strategies before sternotomy is performed. CT scan was used by Lee and coworkers to preoperatively assess 114 cardiac surgery patients at high risk for stroke; significant calcifications in the ascending aorta were found in 20 of these, leading to alteration of surgical strategy in 19 cases. Of note, the authors reported stroke rates of 3.04% and 0.73% in the pre- and post-CT period, respectively ( $P=0.05$ ).<sup>61</sup>

A recent multicenter RCT enrolled 383 patients undergoing surgical aortic valve replacement to evaluate the potential neuroprotective role of 2 cannulation systems designed to capture aortic microemboli (Embol-X embolic protection device [Edwards Life Science] and CardioGard cannula). Rate

of freedom from cerebral infarction at 7 days was 32.0% versus 33.3% for suction-based extraction versus control (ie, standard aortic cannula), respectively (between-group difference:  $-1.3\%$ ; 95% CI,  $-13.8\%$  to  $11.2\%$ ) and 25.6% versus 32.4% for intra-aortic filtration versus control, respectively (between-group difference:  $-6.9\%$ ; 95% CI,  $-17.9\%$  to  $4.2\%$ ); no significant differences in mortality or clinical stroke were shown.<sup>62</sup>

Off-pump surgery reduces the amount of aortic manipulation by avoiding cannulation and cross-clamping. However, RCTs have not demonstrated a difference in the risk of procedure-related stroke after on- versus off-pump CABG; in a small randomized trial, early brain magnetic resonance imaging showed no significant differences in acute cerebral infarctions between on- and off-pump CABG.<sup>63</sup> Conversely, a meta-analysis (consisting of mostly observational studies) found that on-pump CABG was associated with an increased incidence of stroke in comparison to off-pump CABG.<sup>64</sup> In addition, a review of a national administrative database associated off-pump surgery with a significant reduction in stroke rates compared with on-pump surgery in patients aged  $\geq 80$  years, those with peripheral vascular disease, and those with aortic atherosclerosis.<sup>65</sup> The lack of difference in stroke rate between off- and on-pump techniques in RCTs has been attributed to aortic manipulation required for the use of lateral side clamps for proximal anastomoses during off-pump CABG.

Anaortic CABG is a technique aimed at avoiding any degree of aortic manipulation during surgery by using complex in situ graft configurations and off-pump techniques.<sup>66</sup> A recent network meta-analysis compared different degrees of aortic manipulation from on-pump CABG with single or multiple aortic clamps and found that anaortic CABG versus traditional on-pump CABG significantly reduced stroke risk (OR: 0.22; 95% CI, 0.14–0.33).<sup>67</sup> Similar results were reported in a large single-center study of  $>13\,000$  patients.<sup>68</sup> This technique, however, is technically challenging and there is a learning curve, so superspecialization in complex CABG is being advocated by some.<sup>66,69</sup> It should also be noted that complex CABG techniques, expected to decrease stroke incidence (eg, off-pump CABG, anaortic CABG), might act as confounders for surgeons who are more skilled or who have a wider variety of techniques in their armamentarium.

Continuous monitoring of cerebral perfusion may allow optimization of cerebral perfusion pressure and reduce the incidence of watershed infarction.<sup>70</sup>

Regarding salvage strategies for stroke following CABG, given the contraindication to systemic fibrinolysis because of the high risk of hemorrhage, currently available alternative techniques entail intra-arterial fibrinolysis and mechanical thrombectomy, with the latter associated with higher recanalization rates (63.2% versus 83.6% for intra-arterial fibrinolysis versus mechanical thrombectomy, respectively;  $P<0.01$ ).<sup>71</sup> Of

note, an important factor in mechanical thrombectomy is timing; the procedure should be performed in the first 6 hours after the onset of symptoms. A number of devices are available, including retrieval stents that are deployed within the thrombus, incorporating and then removing it; memory-shaped nitinol wires that are advanced in the thrombus to engage and remove it; and aspiration devices designed to aspirate the thrombus from larger vessels.<sup>72</sup>

DAPT after CABG does not appear to reduce the risk of recurrent stroke. A recent analysis of CABG patients in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial found the rate of stroke to be similar at 5 years in patients who were discharged on DAPT versus aspirin only (HR: 0.85; 95% CI, 0.36–1.99),<sup>73</sup> and a meta-analysis confirmed this finding.<sup>74</sup> Ongoing randomized trials will shed more light on the relative risks and benefits of prolonged DAPT after CABG. In patients with POAF, guidelines recommend anticoagulation with unfractionated or low-molecular-weight heparin if POAF persists 12 to 48 hours and anticoagulation therapy for at least 4 weeks if POAF persists at discharge.<sup>75</sup>

Of note, in contemporary RCTs, the use of optimal medical therapy is lower after CABG than after PCI and correlates with a composite of adverse follow-up clinical outcomes including death, myocardial infarction, and stroke.<sup>76</sup>

## Percutaneous Coronary Intervention

In a meta-analysis of 22 843 patients, compared with femoral access, radial access reduced mortality, major adverse ischemic events, and major bleeding across the spectrum of patients with coronary artery disease. Nevertheless, no differences were noted in rates of stroke between radial and femoral approaches.<sup>77</sup> However, recent results of a large prospective Japanese registry of 17 966 patients undergoing PCI showed that, compared with transfemoral procedures, transradial interventions were associated with reduced risk of periprocedural stroke. This finding was confirmed using both multivariable logistic regression (OR: 0.33; 95% CI, 0.16–0.71;  $P=0.004$ ) and propensity score matching (0.1% versus 0.4%;  $P=0.01$ ) analysis.<sup>78</sup> In another meta-analysis of 6450 patients from 12 trials, no significant differences in stroke rates were noted between right and left radial accesses.<sup>79</sup> However, operator experience with catheter manipulation along the aortic wall, which can lead to embolization, may play a role in stroke risk, and the use of a transradial approach must be considered as a surrogate for operator experience.

Effective anticoagulation is key to avoid thrombus formation during PCI. Current guidelines recommend a 70- to 100-U/kg intravenous bolus of unfractionated heparin when no glycoprotein IIb/IIIa inhibitor is planned and a 50- to 70-U/kg intravenous bolus with glycoprotein IIb/IIIa

inhibitors.<sup>33</sup> Full-dose unfractionated heparin should be also administered to patients with non-ST-segment-elevation ACS undergoing cardiac catheterization after a conservative treatment phase if they were treated with fondaparinux because of the increased risk of catheter thrombosis compared with heparin.<sup>80</sup> Alternatively, bivalirudin may be used for procedural anticoagulation. Because of the high rates of catheter thrombosis, fondaparinux is contraindicated in patients with ST-segment-elevation myocardial infarction undergoing primary PCI.<sup>81,82</sup> No differences in stroke were reported in trials and meta-analyses of bivalirudin versus heparin.<sup>83–86</sup>

The combination of aspirin and P2Y<sub>12</sub> inhibitors is the standard of care after PCI. Although trials of DAPT have generally been powered to assess the impact on a combined ischemic end point (cardiovascular death, myocardial infarction, and stroke) and not for stroke alone, by acting on the platelet-mediated process of thrombus formation DAPT may also affect cerebrovascular ischemic event rates.<sup>87,88</sup> DAPT with aspirin and clopidogrel is the standard of care for PCI in patients with stable coronary artery disease, whereas the combination of aspirin with clopidogrel, prasugrel, or ticagrelor is the recommended standard of care for PCI in patients with ACS.<sup>89</sup> However, the use of prasugrel or ticagrelor has not been shown to reduce the risk of stroke compared with clopidogrel in pivotal regulatory trials of PCI in ACS.<sup>90–92</sup> Importantly, prasugrel may increase the risk of fatal and intracranial bleeding in patients with prior stroke or transient ischemic attack, representing an absolute contraindication for its use.<sup>90</sup>

Special considerations apply to patients with ST-segment-elevation myocardial infarction, where there is a decrease in the incidence of stroke after primary PCI compared with rescue or facilitated PCI after thrombolysis. In the TOTAL (Thrombectomy with PCI vs. PCI Alone in patients with STEMI) trial, the risk of stroke after thrombus aspiration during primary PCI was increased, and current guidelines contraindicate the routine use of thrombus aspiration.<sup>33,81</sup> The routine use of IABP, including use in patients with acute myocardial infarction complicated by cardiogenic shock, is also not recommended.<sup>33,93</sup> Limited data exist on cerebral embolic protective devices for both PCI and CABG to prevent the risk of stroke.

## Practical Implications

Stroke carries high short- and long-term mortality and significantly adversely affects quality of life after both CABG and PCI. In an era in which practice guidelines endorse fully informing patients of the available treatment options and actively including them in the decision-making process, defining the risk of stroke, both acute and long term, and its clinical implications is of paramount importance. CABG carries higher perioperative risk of stroke but provides greater long-term freedom from recurrent ischemic coronary events



and better survival, especially in the patients with most severe disease.<sup>2</sup> Percutaneous revascularization is feasible in many patients and is associated with relatively low stroke rates, but this benefit needs to be weighed against the higher rates of long-term mortality and myocardial infarction, particularly in some categories of patients with diabetes mellitus and/or extensive multivessel disease. Indeed, better understanding the size of an injury deriving from a stroke with the 2 available revascularization approaches and the significance of silent brain lesions or neurocognitive changes that may occur would inform the decision-making process. However, data on these measures (eg, serial brain imaging) are lacking.

A number of measures can be considered to reduce neurological risk in patients undergoing revascularization. For surgery, pre- and intraoperative screening of the ascending aorta and optimization of cerebral perfusion pressure based on continuous monitoring are important measures to minimize stroke risk. The use of the anaortic technique has the potential to minimize stroke risk during CABG. Given its technical complexity, specific training is required, ideally in the context of a new CABG subspecialty. Other technical advancements (eg, embolic protection) warrant investigation to reduce the perioperative risk of stroke in patients undergoing CABG.

For PCI, the reduction in mortality and bleeding—with some data also showing a reduction in periprocedural stroke—associated with radial access potentially makes this approach the vascular access of choice. Regardless of vascular access, operator experience and competency play key roles in minimizing catheter-induced trauma to the aortic wall and cerebral embolization. Other important measures include optimal anticoagulation and avoidance of air embolism with adequate flushing and connections to the manifold. Routine use of manual thrombectomy in ST-segment–elevation myocardial infarction should be avoided; if required, adequate catheter engagement should be maintained to avoid embolization of thrombotic material. Finally, IABP and hemodynamic support devices in general should be used with caution, particularly in patients with diffuse atherosclerotic aortic disease.

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