JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 4, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.01.134

EDITORIAL COMMENT

Coronary Revascularization and Stroke*

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The SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial (1) was designed to determine whether treatment of complex coronary artery disease with percutaneous coronary intervention (PCI) with a drug-eluting stent was noninferior to treatment with coronary bypass surgery (CABG). The overall outcome analysis demonstrated that the rate of major adverse cardiac or cerebrovascular events was significantly higher in the PCI group (17.8%) compared with the CABG group (12.4%) ($p = 0.002$). However, the rate of stroke was significantly

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higher in the CABG group, reported as (2.2%) compared with the PCI group (0.6%) ($p = 0.003$) in the original SYNTAX paper. The study by Mack et al. (2) in this issue of *JACC: Cardiovascular Interventions*, focused specifically on stroke, reports a stroke difference of 1% (CABG) versus 0.2% (PCI) at 0 to 30 days by intent-to-treat ($p = 0.037$), and 3 of the 9 strokes in the CABG group occurred pre-operatively, so a statistically meaningful difference in an as-treated analysis is doubtful. Nonetheless, an increased rate of stroke with CABG has been observed in the majority of other comparative studies (3), acknowledging, as with SYNTAX, that none were powered to assess an event as infrequent as stroke. The increase in the rate of early, perioperative stroke does not detract from the overall superiority of CABG for prevention of the combined endpoints of these studies, but any increase in stroke risk causes considerable concern because of the impact of stroke on quality of life. The current paper analyzes the possible causes of the increased incidence of stroke in patients treated with CABG in attempt to find methods for prevention of stroke in the future (2).

The overall incidence of stroke after 4 years of follow-up was 33 in the CABG arm with 2 patients sustaining 2 strokes, and was 20 in the PCI arm with 1 patient sustaining 2 strokes ($p = 0.06$). As noted in the previous text, 9 of the 33 strokes occurred within 30 days of the procedure in the CABG arm compared with 2 of 20 in the PCI arm. Stroke after cardiac surgery has traditionally been assessed from 0 to 30 days, on the assumption that early events, whether attributed to intraoperative technique, patient factors, or atrial fibrillation (4), have some likely causal relationship to the procedure. In this paper (2), the subsequent rate of stroke in the 2 groups after 30 days, which reflects the natural history of stroke in these patients with severe vascular disease, was similar: 24 of 33 in the CABG arm and 18 of 20 in the PCI arm.

The fact that 3 of the strokes in the CABG arm occurred prior to surgery suggests that discontinuation of antithrombotic therapy may play a role in the increased incidence of stroke, particularly in patients on anticoagulation for stroke prevention from atrial fibrillation. It is not documented whether these 3 strokes occurred in patients with atrial fibrillation. However, patients treated with PCI are maintained on dual antiplatelet therapy with aspirin and thienopyridines during the procedure. Patients treated with CABG are either not maintained on antithrombotic therapy or are treated with aspirin alone during the perioperative period because of the risk of bleeding (4). This may lead to a greater susceptibility to cerebral embolic events before, during, and after the procedure. The authors considered this explanation for the 3 preoperative strokes, and concluded that only 1 of the 3 occurred at a time (1 day pre-operatively) when discontinuation of antithrombotic agents was a likely factor. Dual antiplatelet therapy would not play a role in the long-term outcome for stroke in these patients. There was no difference in stroke incidence between the PCI arm and the CABG arm in long-term follow-up after the perioperative period, and combined therapy with aspirin and clopidogrel has not been shown to be more effective than either clopidogrel or aspirin alone in the prevention of recurrent stroke with a significant and unacceptable increase of intracranial hemorrhage (5,6).

Other etiologies that have been implicated for stroke during CABG include coexisting significant carotid artery stenosis, embolic events from plaque due to manipulation of the aorta, and systemic hypotension producing watershed infarction (4). In the SYNTAX trial, the prevalence of significant carotid stenosis was equal in the PCI (8.1%) and CABG (8.4%) arms (1) and did not influence the frequency of stroke, although the number of events was too low to be definitive (2). Carotid surgery before or during CABG has also not been shown to be beneficial in reducing the rate of stroke and may increase the number of adverse events (4). Off-pump coronary bypass surgery has the theoretical advantage of avoiding emboli from aortic cannulation and other pump-related factors, but there was no influence of off-pump surgery on stroke incidence in the current study

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 6, NO. 4, 2013
APRIL 2013:355–6

(3) or as reported in a recent review (4). The common risk factors for stroke including increased age, hypertension, poor left ventricular function (left ventricular ejection fraction) and angina were associated with an increased risk of stroke in the current study, but the increased risk was equivalent for both treatment arms. New onset of atrial fibrillation was actually a greater predictor of stroke in the PCI arm than the CABG arm. Diabetes was not associated with an increase in the incidence of stroke. The recently completed FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial comparing drug-eluting stents to coronary bypass surgery in diabetic patients with multivessel coronary artery occlusive disease demonstrated a similar significant increase in stroke with coronary bypass surgery compared with percutaneous stenting. An analysis of the etiology of stroke in these patients has not yet been performed (7).

The SYNTAX study was not specifically designed to determine the etiology of stroke in patients treated with CABG or PCI. It is imperative to establish the causes of the increased risk of stroke during CABG and develop strategies to prevent these strokes, because the overall outcome for prevention of cardiovascular disease is so significant. A prospective study may be warranted to analyze risk factors and define stroke subtype with methodology employed in trials of acute stroke management and prevention of recurrent stroke (8,9).

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Key Words: coronary artery bypass graft ■ coronary revascularization ■ diabetes mellitus ■ drug-eluting stents ■ multivessel coronary artery disease ■ percutaneous coronary intervention.