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Factors Associated with Increased Rates of Post-procedural Stroke or Death following Carotid Artery Stent Placement: a Systematic Review.

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Abstract

Background and Purpose—We provide an assessment of clinical, angiographic, and procedure related risk factors associated with stroke and/or death in patients undergoing carotid artery stent placement which will assist in patient stratification and identification of high-stent risk patients.

Methods—A comprehensive search of Medline from January 1st 1996 to December 31st 2011 was performed with key words “carotid artery stenosis”, “ carotid artery stenting”, “carotid artery stent placement”, “death” , ” mortality”, “stroke”, “outcome”, “clinical predictors”, “angiographic predictors”, was performed in various combinations. We independently abstracted data and assessed the quality of the studies. This analysis led to the selection of 71 articles for review.

Results—Clinical factors including age≥80 years, symptomatic status, procedure within 2 weeks of symptoms, chronic renal failure, diabetes mellitus, and hemispheric TIA were associated with stroke (ischemic or hemorrhagic) and death within 1 month after carotid artery stent placement. Angiographic factors including left carotid artery intervention, stenosis > 90%, ulcerated and calcified plaques, lesion length > 10mm, thrombus at the site, ostial involvement, predilation without EPD, ICA-CCA angulation > 60%, aortic arch type III, and aortic arch calcification were also associated with 1 month stroke and/or death. Intra-procedural platelet GP IIb/IIIa inhibitors, protamine use, multiple stents, predilatation prior to stent placement were associated with stroke (ischemic or hemorrhagic) and death after carotid artery stent placement. Intra-procedural use of embolic protection devices and stent design (open versus closed cell design) did not demonstrate a consistent relationship with 1 month stroke and/or death. Procedural statin use, and operator and center experience of more than 50 procedures per year were protective for 1 month stroke and/or death.

Conclusions—Our review identified risk factors for stroke, death, and MI within 1 month in patients undergoing carotid artery stent placement. Such information will result in better patient selection for carotid artery stent placement particularly in those who are also candidates for carotid endarterectomy.

Keywords

carotidartery stenosis; carotid artery stent placement; clinical predictors; angiographic predictors; stroke

Introduction

Extracranial stenosis of internal carotid artery is an important cause for transient ischemic attacks and ischemic strokes of retinal or cerebral origin. Carotid revascularization is an effective intervention to prevent recurrent stroke or death in both symptomatic and asymptomatic patients with carotid artery stenosis [1]. Currently available treatments include carotid endarterectomy (CEA), carotid artery stent placement (CAS) and medical therapy. An estimated 151,000 CEAs are performed every year, providing some data regarding the burden of carotid stenosis in United States. CAS has emerged as an alternative and less invasive treatment for high surgical risk patients and currently 9,000 CAS are performed in the United States annually [2].

After the results of carotid revascularization endarterectomy versus stenting trial (CREST) [3], a large proportion of patients with carotid artery stenosis can be candidates for either CAS or CEA. Better identification of high surgical risk and high stent risk patients is neces-

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sary to provide the best treatment option to each patient. Factors characterizing patients at high surgical risk for complications following CEA has been extensively described [4]; however, a comprehensive review of such factors in patients undergoing CAS is not available. We performed a systematic review of clinical, anatomic, and procedure-related factors associated with a higher rate of periprocedural stroke and/or death which is required to identify the high stent risk patients.

Methods

A literature search was conducted during 10–16 February 2012. The database searched: PubMed. The search included search terms: "carotid artery stenosis." "carotid artery stenting," "carotid artery stent placement," "death," "mortality," "stroke," "outcome," "clinical predictors," and "angiographic predictors." The time period selected for the search was limited to 1 January 1996 to 31 December 2011. A total of 978 articles were identified. Initially the articles were scrutinized for eligibility and included if the sample population composed of patients undergoing carotid artery stent placement with reported stroke and/or death rate. The first search resulted in 118 articles for which abstracts and/or full articles were obtained for content and eligibility. All articles were reviewed by one investigator (MAK) and 47 articles were excluded owing to small sample size, inconclusive results, observational design, and analysis with CEA cases. Finally 71 articles were selected for inclusion in this review. The schematic (Figure 1) describes the process of study identification.

Results

Clinical Factors

Age—Older age was identified as an independent risk factor for 30-day stroke and death in multiple studies. Multiple studies have shown that patient aged more than 80 years undergoing CAS have significantly higher 30-day stroke rates. Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE) registry revealed a higher 30-day stroke rate of 7.2% in patients aged >80 years compared with 4.0% in patients aged <80 years [5]. CAPTURE 2 showed similar results of 30-day stroke rate of 3.8% in patients aged >80 years as compared with 2.4% in patients aged <80 years [6]. Stent-protected angioplasty versus carotid endarterectomy in symptomatic patients (SPACE) study found that patients older than 68 years were at a higher risk of 30-day stroke and/or death undergoing CAS [7]. Single center studies from various sites have been consistent with these results [8–11]. Recently published CREST study also showed that patients >70 years of age are at higher risk of 4-year stroke compared with patients <70 years undergoing CAS [3].

The SPACE investigators suggested that this difference in rates of stroke and/or death was because of embolisms related to manipulation in the presence of aortic arch atherosclerosis in older patients; however, the contralateral stroke rate was not high in older patients which question's this hypothesis [7]. CAPTURE 2 trial found that patients aged >80 compared with patients aged <80 years had higher frequency of calcified carotid lesions (26.9% versus 21.8%) and Type III aortic arch (defined as the arch vessels arise proximal or caudal to the lesser curvature of the arch or off the ascending aorta) (19.8% versus 10.1%) which may have accounted for the higher rate of stroke and/or death with CAS in older patients [6].

Although most prospective studies have demonstrated a higher rate of stroke and death among patients aged >80 years and perhaps a reduced benefit compared with CEA in prevent ipsilateral stroke following treatment, the data does not support complete exclusion of older patients from undergoing CAS. The rate of postprocedural stroke, myocardial infarction (MI), and death in patients >70 years was higher with both CEA and CAS in an analysis of Nationwide Inpatient Sample presumably owing to higher rate of MI cause by CEA being performed in high surgical patients in general population [12]. The SAPPHIRE study demonstrated lower rates of stroke and/or death at 1 month and at 1–3 years with CAS compared with CEA in high surgical risk patients consisted of 66 patients aged >80 years [13]. A recent analysis of the Medicare population which is predominantly limited to high surgical risk patients also showed no difference in 1-year stroke and death rates between patient below and above 80 years of age [14]. The data supports the value of CAS in high surgical risk patients aged >80 years in current practice; however, greater caution is required in performing CAS in average risk patients aged >80 years.

Gender—CAPTURE registry did not observe any significant difference in 30-day stroke and/or death rates between women and men undergoing CAS although there was a trend toward higher rates in women (5.6% in women and 4.3% in men) [5]. SPACE study also did not observe any significant difference in 30-day stroke and/or death rates between women (8.2%) and men (6.4%) undergoing CAS [7]. A nationwide registry showed no significant difference in rate of periprocedural stroke rates between women (2.7%) and men

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(2.0%) undergoing CAS [15]. However, CREST investigators in a subgroup analysis recently reported that women had trend toward a higher 4-year stroke rate (5.5%) compared with men (3.3%) although these results were not statistically significant [16]. This slight higher stroke rate trend can be explained by the smaller lumen size diameter of carotid artery in women [17].

Chronic Renal Failure—Single center studies have shown that patients with chronic renal insufficiency defined by serum creatinine of 1.3 or greater had higher 30-day stroke rates (11.1%) compared with patients having normal renal function (0.6%) undergoing CAS [18,19]. However, both CAPTURE registry (8.2% patients with renal failure defined by history) and CAPTURE 2 trial (3.2% with renal failure defined by history) failed to show any impact of chronic renal failure on 30-day stroke rate in patients undergoing CAS [5,6]. Similarly SAPPHIRE trial (6.0% patients with renal failure defined by history in CAS arm) did not identify any impact of presence of chronic renal failure on 30-day stroke rate in patients undergoing CAS [13]. This reason underlying the difference in results is unclear but studies with greater sample size of patients have adequate power to test the hypothesis. Another reason could be the definition of chronic renal failure used in studies.

Diabetes mellitus—A single center study found that patients with diabetes mellitus undergoing CAS especially if they were older than 75 years had a higher 30-day stroke and/or death rates (6.3%) compared with nondiabetics (3.2%) [20]. However, both CAPTURE and CAPTURE 2 trials did not find any difference in the rate of stroke and/or death in patients with diabetics mellitus compared with nondiabetic patients in those undergoing CAS [5,6]. It is not clear that this difference in results is due to severity of disease itself because the severity of disease was not characterized in all the studies.

Cardiac disease—The data has been consistent in demonstrating that the 30-day stroke, MI, or death is not increased in patients with cardiac disease defined as proven coronary artery disease, symptomatic unstable angina, recent MI, congestive heart failure, or those anticipating a coronary artery bypass in CAPTURE and CAPTURE 2 trials. CAPTURE and CAPTURE 2 trials separately evaluated the effect of history of coronary artery disease and history of recent MI or unstable angina and were unable to find impact on 30-day stroke and/or death at in patients undergoing CAS [5,6]. CAPTURE 2 trial also did not find an increase in risk of stroke, MI, and/or death in patients with CAD requiring CABG within 30 days of CAS [6]. CAPTURE 2 trial also did not find any increase in the rate of stroke and/or death in patients with history of cardiac arrhythmias or atrial fibrillation or CHF undergoing CAS [6]. Single center studies have shown similar results although the definition of cardiac disease was unclear in some of these studies and sample size was small [8,9,18].

Cardiovascular risk factors—Single center studies, CAPTURE, and CAPTURE2 did not identify any increase in risk of 30-day stroke and/or death associated with pre-existing hypertension [5,6], hyperlipidemia [5,6,11], chronic obstructive pulmonary disease [5,6,9,11,18], peripheral artery disease [5,6,9,11], or cigarette smoking [5,6] in patients undergoing CAS. High C-reactive protein levels were associated with 30-day strokes in patients undergoing CAS in one study [48]. These high levels of CRP could be a marker of unstable plaque and on-going inflammation but this notion is unclear.

Symptomatic versus asymptomatic status—Multiple trials have shown that patients with symptomatic status have higher 30-day stroke rates compared with asymptomatic patients when undergoing CAS. The finding is similar to that described in patients undergoing CEA in previous studies [4] but the magnitude of difference may be more pronounced in CAS-treated patients. SAPPHIRE which comprised of 30% symptomatic patients in the CAS arm found a cumulative incidence of stroke, death and/or MI of 16.8% in symptomatic patients compared with 9.9% in asymptomatic patients at 1 year [13]. The time interval between index ischemic symptom symptoms and CAS was not analyzed in this trial [13]. SPACE trial enrolled only symptomatic patients and CAS was performed with 180 days of ischemic symptoms [21]. This trial found a 30-day stroke and/or death rate of 6.8% in the symptomatic patients undergoing CAS [21]. Similarly EVA-3S also enrolled only symptomatic patients and CAS was performed within 120 days of ischemic symptoms [22]. The study found a 30-day stroke and/or death 9.6% in these symptomatic patients undergoing CAS [22]. The CREST trial [23] composed of 53% symptomatic patients and CAS was performed within 180 days of ischemic symptoms [23]. ICSS trial enrolled only symptomatic patients and CAS was performed within 12 months of ischemic symptoms [24]. The study reported a 120-day stroke and/or death rate of 8.5% in these symptomatic patients undergoing CAS [24]. A pooled analysis of 2104 patients derived from four major Cordis-sponsored studies (SAPPHIRE, CASES, CNC, and ADVANCE) of which 24.2% patients were symptomatic found that asymptomatic patients had a 30-day

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stroke and/or death rate of 3.8% compared with 5.3% in symptomatic patients [25]. This pooled analysis also showed that symptomatic patients had higher stroke rates (8.8%) when CAS was performed within 14 days of index ischemic symptoms onset compared with lower stroke rates (5.9%) when performed within 180 days [25]. A review of CAS trials by Qureshi *et al* found that 30-day stroke rates in symptomatic patients was 8.3% compared with a lower rate of 6.0% in asymptomatic patients [26]. Multiple single center studies have shown similar results that CAS performed in patients with symptomatic carotid artery stenosis is associated with higher stroke rates compared with patients with asymptomatic carotid artery stenosis [27–30]. These higher rates are not only limited to the immediate postprocedure period but also seen during the long term [31,32]. It is to be noted that trials that included only symptomatic patients had higher rates of stroke and/or death in patients undergoing CAS compared with trials that include both symptomatic and asymptomatic patients. Patients with ischemic symptoms referable to the carotid artery also have higher rates of ipsilateral stroke with medical treatment compared with asymptomatic patients [81,82]. The higher vulnerability to recurrent ischemic events with or without CAS or CEA is due to plaque characteristics (fissure, intramural microthrombi, inflammation) and higher embolic load [40,53,83–84]. Similarly, the vulnerability to recurrent ischemic symptoms appeared to the highest in the first 2 weeks after index ischemic event with medical treatment alone [4]. Therefore, the finding of a higher rate of 1 month stroke and/or death with CAS in symptomatic patients is not unexpected. The critical question remains whether the magnitude of difference between symptomatic and asymptomatic patients undergoing CAS is similar to that observed in patients undergoing CEA. The results of EVA 3S and ICSS would support the concept of a more prominent magnitude of difference between symptomatic and asymptomatic patients undergoing CAS. However, CREST reported a lower 4-year stroke and/or death rate of 4.5% in asymptomatic patients compared with stroke and/or death rate of 8.0% in symptomatic patients although these differences did not achieve statistical significance [23]. The magnitude of difference in 1-month stroke and/or death between symptomatic and asymptomatic patients was 4% for patients undergoing CAS and 3.7% for those undergoing CEA [23]. Therefore, the evidence in not conclusive enough to selectively prefer CEA for symptomatic patients.

Pre- and periprocedural statin medication use— Pre- and postprocedural use of statin medications is associated with lower periprocedural stroke and/or death among patients undergoing CEA [33]. These effects appear to be independent of the lipid lowering mechanism and are attribute to anti-inflammatory effects which lead to plaque stabilization [34,35]. The protective effects of statins are more pronounced in symptomatic patients compared with asymptomatic patients [36]. A retrospective study found that use of statins in patients undergoing CAS was associated with a lower rate of 30-day stroke/MI/death rate of 4% compared with 15% rate in patients not using statins [37].

Timing of procedure—There may be a higher vulnerability for periprocedural ischemic events immediately after the index ischemic event. A pooled analysis of four major Cordis-sponsored studies (SAPPHIRE, CASES, CNC, and ADVANCE) that included a total of 2104 patients found that symptomatic patients had higher 30-day stroke rates of 8.8% when CAS was performed within 14 days of index ischemic event compared with lower rates of 5.9% when performed between beyond 14 days of symptoms onset [25].

Periprocedural hemodynamic instability—Peri- and postprocedural hypotension has been associated with higher periprocedural stroke rates in some studies [45–47] but in not in all studies [5,6]. It is unclear that events such as hypotension and bradycardia directly cause ischemic events or are merely representative of a difficult carotid lesions requiring extensive manipulation around the carotid sinus.

Institutional Factors

Center experience—CAPTURE [5] and pooled analysis of four major Cordis-sponsored studies [25] did not find significant difference in rates of 30-day stroke and/or death associated with center experience. Experienced centers were defined as those who enrolled more than 25 CAS-treated patients in CAPTURE [5] and more than 20 patients in the pooled analysis of Cordis-sponsored studies [25]. However, CAPTURE 2 trial found that high volume centers (>70 CAS performed annually) had lower rates of <3% 30-day stroke and/or death rates compared with low volume centers with a rate of >3% 30-day stroke [38]. Pro-CAS data also showed that experienced centers (>50 CAS annually) had lower periprocedural stroke rates [27]. An analysis of the Medicare data also reveals that 30-day death are lower in patients undergoing CAS at high volume centers (2.5% versus 1.4%) defined as more than 24 CAS procedures performed annually [39].

Operator experience and training background— A prospective registry from an Italian institution showed

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that operator experience of less than 50 procedures was associated with higher 30-day stroke rate associated with CAS [40]. Other studies have also found operator experience to be predictive of periprocedural stroke rate in CAS [41,42]. Verzini *et al* also found peri- and postprocedural stroke rate decrease with higher number of CAS procedures stabilizing at <2% after 195 CAS procedures performed by a single operator [41]. Medicare data analysis also revealed that 30-day stroke rates were lower after operators had performed 12 CAS procedures [39]. The stroke and mortality rates did not differ between vascular surgeons and nonvascular surgeon (interventional cardiologist and interventional neuroradiologist) in one study [43]. However, the recently published data from CREST trial found that interventional cardiologist (3.9%) and neuroradiologists (1.6%) had lower periprocedural stroke rate compared with vascular surgeons (7.7%) and interventional radiologists (6.6%) [44].

Angiographic Factors

Left versus right ICA lesion treatment—A pooled analysis of 34,398 patients revealed that CAS performed for left ICA stenosis was associated with higher 30-day stroke and/or death rates 7.5% versus 6.0% in patients with CAS for the right carotid artery stenosis [49]. This higher rate was due to difficult access from aorta to the left common carotid artery and under-recognized strokes in the noneloquent right hemisphere. The results of other studies have not been found a differential rate of 30-day stroke and/or death [5,6]. Bilateral carotid disease with simultaneous procedures on both sides is also a predictor of higher 1-year stroke rate in patients undergoing CAS (8% versus 1% p = 0.01) [70]. Possible explanations are that bilateral carotid disease is a surrogate marker of widespread cerebrovascular disease and lower vascular reserve for tolerating ischemia. It should be noted that several studies have not found an increased risk of 1-month stroke and/or death with CAS including those with contralateral occlusion [5,6,8,9].

Severity of stenosis—A single center study found that CAS performed in lesions with angiographic severity >90% stenosis were associated with higher 30-day stroke rate of 14.9% compared with lower rate of 3.5% in patients with lesion severity <90% stenosis [8]. The study did not distinguish asymptomatic patients from those who were symptomatic. Numerous studies have found no difference in the mean severity of stenosis [5,6], and proportion of strata defined by severity of stenosis [50%–69% versus 70%–99%] [5,6] or those by presence or absence of string sign [5,6] in patients who develop ischemic stroke with those who do not in patients undergoing CAS.

Lesion characteristics—Lesion characteristics, angiographic (ulceration, irregularity, calcification), and pathological (in-situ thrombosis, fissures), have been correlated with periprocedural ischemic stroke in patients undergoing CEA and ischemic events in followup period [50,51]. Symptomatic plaques have higher baseline microembolic events as detected by transcranial Doppler studies [52,53]. A higher proportion of symptomatic patients have microembolic events (34.2%) compared with only 3.5% in asymptomatic patients [53]. This high microemboli burden was strongly associated with plaque ulceration and lumen thrombus on pathological evaluation [52]. A single institution prospective registry also showed that presence of lesion ulceration determined by angiography was associated with higher 30-day stroke rates of 7.9% after CAS compared with the lower stroke rates of 2.0% in patients with no plaque ulceration [40]. Angiographic ulceration is thought to represent unstable plaques having thinner or even an ulcerated fibrous cap with a high number of inflammatory cells such as macrophages and T lymphocytes compared with plaques which are not ulcerated [51].

A single center study found that presence of lesion calcification was associated with higher 30-day stroke rate of 6.5% compared with a lower stroke rate of 2.3% in patients without lesion calcification [40]. Echolucent plaques (as characterized by carotid Doppler ultrasound) are associated with increased number of solid emboli which subsequently translate into periprocedural ipsilateral ischemic strokes and new ipsilateral diffusion-weighted MRI lesions [54]. In one study, presence of such echolucent plaques was associated with higher 30-day stroke rates of 7.1% compared with a lower rate of 1.5% among patients with nonecholucent plaques undergoing CAS [55]. Echolucent plaques have been shown to have high lipid and hemorrhage content on histological assessment [56] providing an explanation of higher stroke rates in these patients. Angiographically visible thrombus at the site of stenosis has been shown as a predictor of periprocedural strokes in patients undergoing CAS [25].

Target lesion length—Target lesion length was found to be associated with higher risk of 30-day stroke particularly in octogenarians in CAPTURE 2 trial [6]. Multiple studies found lesion length to be predictive of higher 30-day stroke rates following CAS [8,11,40]. The exact threshold beyond which lesion length is associated with higher stroke rate varies between 10 and 15 mm in studies. The 30-day stroke rate of 11.4% (versus 3.8%) [8], 17% (versus 2.1%) [11], and 5.6% (versus 2.6%) [40] in lesions longer than either 10 mm or 15 mm dem-

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onstrates a consistent relationship. Long lesions have a higher atherosclerotic burden attached with them which leads to a higher risk of dislodgement of embolic particles during balloon angioplasty and stent placement. Long lesions also require multiple stents which may increase the thrombotic foreign body reaction.

ICA ostial involvement and CCA-ICA angulation —Ostial involvement where the maximal point of stenosis was located at the internal carotid artery ostium was associated with a higher stroke rate in multiple studies [11,19,40]. Sayeed *et al* found a 30-day stroke rate of 7.1% in patients with ostial lesions as compared with 1.8% in patient's without any ostial involvement undergoing CAS [11]. Setacci *et al* also found a higher 30-day stroke rate of 8.8% in patients with ostial lesions as compared with lower stroke rate of 2.5% in patients without ostial lesions [40] The higher stroke event rate associated with CAS in lesions involving the ostium is multifactorial. One explanation is that ostial lesions are more difficult to initially engage by catheter manipulation resulting in higher rate of embolic particles. Another explanation is based on the location of baroreceptors within the carotid wall ostia that predisposes to hemodynamic instability (hypotension, bradycardia, transient asystole, or a combination) owing to carotid sinus stimulation by angioplasty and stent placement [57]. Such hemodynamic vulnerability may increase the odds of stroke associated with the procedure. EVA-3S study showed that ICA-CCA angulation of >60% was associated with higher 30-day stroke rates compared with those with lesser angulation (37.5% versus 7.2%) [49]. Single center studies also found a higher 30-day stroke rate in patients with severe ICA-CCA >60% angulation (5.2% versus 13.6%) [71,72]. Severe angulation is seen in octogenarians (74% compared with nonoctogenarians 50%) [73]. Greater ICA-CCA angulation results in greater catheter manipulation and stent distortion with subsequent increase in endothelial injury, dissections, and thrombosis.

Aortic arch anatomy and calcification—Aortic arch types is defined as: arch vessels arising from the top of the arch (Class I), between the parallel planes delineated by the outer and inner curves of the arch (Class II), and caudal to the inner surface of the arch or of the ascending aorta (Class III). The type III aortic arch is more common in octogenarians 82% versus 56% in nonoctogenarians [73]. Aortic arch Class III was associated with higher 30-day stroke rates of 17.2% versus 8.1% in patients with Classes I and II aortic arch in the EVA-3S trial [49]. Aortic arch calcification was significantly higher in patients aged â‰¥59% versus 30% compared with those aged <80 years [73]. Studies have shown that aortic arch calcification is associated with higher 30-day strokes in patients undergoing CAS [71–74]. Aortic arch atherosclerosis as identified by transesophageal echocardiography has been shown to be associated with a higher number of DWI lesions 78% versus 15% in patients with no arch atherosclerosis at 30-days in patients undergoing CAS [75]. The risk of late microembolic events after CAS (6 months after the procedure) as detected by transcranial Doppler is higher with any aortic arch calcification (62.5% versus 23.8%) [76]. These complicated aortic arch plaques are found to be higher in patients suffering from coronary artery disease (54.6% versus 21.7%) and dyslipidemia (54.6% versus 26.1%) [76].

Final residual stenosis—A pooled analysis of four major Cordis-sponsored studies (SAPPHIRE, CASES, CNC, and ADVANCE) involving 2104 patients found that severity of final residual stenosis of more than 30% was a predictor of 30-day strokes in patients undergoing CAS [25] The severity of residual stenosis (OR 1.091; 95% CI 1.05–1.13) and number of stents deployed (OR 5.2; 95% CI 1.49–1.85) are also strong predictors of in-stent restenosis [83,84].

Procedural Factors

Intraprocedural platelet GP IIb/IIIa inhibitors—Multiple studies have found a higher periprocedural stroke rate in patients treated with intraprocedural platelet GPIIb/IIIa inhibitors compared with those who are not treated with such agents: 7.4% versus 2.7% [58]; and 10.2% versus 5.7% [59]. Qureshi *et al* reported a lower periprocedural ischemic stroke rate of 3% in platelet GP IIb/IIIa inhibitor-treated patients compared with 12% rate in those who underwent CAS without such inhibitors but this benefit was offset by higher rates of intracranial hemorrhage rate [59]. A comparative analysis showed that EPD use alone had lower 30-day stroke rates (0%) compared with GPIIb/IIIa (5.1%) alone [85]. There is a selection bias in patients who receive platelet GP IIb/IIIa inhibitor because they are considered at high risk for ischemic events associated with the procedure.

Periprocedural medication use—A pooled analysis of four major Cordis-sponsored studies (SAPPHIRE, CASES, CNC, and ADVANCE) involving 2,104 patients found that vasopressors or protamine use during or after the procedure was associated with a higher rate of ischemic stroke within 1 month in patients undergoing CAS (OR 1.96 CI 1.00–3.84 p = 0.05) [25]. Pro-CAS trial found that high doses of IV heparin (>5,000 IU) were associated with higher periprocedural stroke

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rate (4.5% versus 2.9% p = 0.0019) [27]. It is not clear that what magnitude of this higher rate was related to more complex procedures which necessitate high-intensity anticoagulation or medication themselves [27]. Chaturvedi and Yadav in their review also note that patients who received heparin and GP IIb/IIIa inhibitors during CAS had higher stroke rates [79].

Stent design (open versus closed cell design)— Carotid stents of different design and configuration are available. Depending on the density of struts, stents can be classified into stents with a closed-cell or an open-cell configuration. Usually if free-cell area is more than 7 mm the stent is considered of open-cell configuration. A multicenter study from Europe of 3,179 patients found that a free-cell area of more than 7.5 mm is associated with higher 30-day stroke rates (1.3% versus 3.4%) suggesting that closed cell design stents may be associated with lower rates of ischemic events [60]. However, the data from the Society of Vascular Surgery registry did not find any significant difference in outcomes after CAS using open or closed stent cell designs [61]. A recent randomized controlled trial randomized 40 patients to CAS treatment either by closed cell design or open-cell design stents found no significant difference in embolization events detected by DWI-MRI and TCD [62]. An ex vivo study showed that polyurethane membrane covered stent result in lower embolic events [63]. They also can reduce the risk of late embolization especially after the removal of embolic protection devices (EPDs) [64]. However, subsequently a randomized trial was prematurely discontinued due to higher rate of restenosis (38% versus 0%) in patients treated with covered stents [80].

Multiple stents—CAPTURE study showed that use of multiple carotid stents was associated with a higher 30-day stroke rate of 9.7% compared with a lower stroke rate of 4.5% in patients requiring only one stent placement [5]. Use of multiple stents probably is a surrogate marker of lesion length, which is associated with higher rate of ischemic events. It is also possible that increasing number of stents is associated with greater platelet activation.

Predilatation prior to stent placement—Operators at times perform angioplasty initially before placing the stent. In some difficult lesions this predilation is performed prior to the distal placement of an EPD. CAPTURE study found that predilatation without EPD was associated with higher 30-day stroke rates of 15.4% compared with a lower stroke rates of 4.3% in patients without predilatation with an EPD [5]. Pro-CAS registry data also showed that predilatation led to higher periprocedural stroke rate of 4.1% versus 3.0% [27]. Predilalation probably is a surrogate marker of lesion severity but it is unclear from current data.

Intraprocedural use of EPDs—EPDs have been used to reduce the embolic events associated with CAS. They have been successful in reducing the number of embolic particles detected by TCD [65] and lower 30-day stroke rates (1.7% with EPD use versus 4.1% without EPD use) in a multicenter study [66]. However, EPD are not able to completely eliminate the emboli detected by TCD [67,68]. EVA-3S study also showed that use of EPD was associated with lower 30-day stroke rate [49]. EPD use is associated with technical difficulties in traversing the lesion at the time of CAS leading to additional risk of embolization during device manipulation. EPD time within artery was associated with a higher 30-day rate of stroke and/or, death especially in patients aged 80 years or greater OR 1.04 (95% CI 1.01, 1.07 p = 0.0089) [6]. Recently published results of ICSS show that CAS using EPD was associated with a significantly higher number of new diffusion weighted-MRI lesions compared with CAS without EPD at 1 month (73% versus 34% p = 0.019) [69]. Another randomized trial comparing CAS with (n = 44) and without EPDs (n = 35) was found no significant different in 30-day stroke rates (11.1% versus 11.1%) [86]. However, this trial observed a trend toward higher number of DWI lesions in patients undergoing CAS with EPDs (72%) compared with the CAS group without EPD use at 1 month (44%) [86].

Level of Evidence

Table 1 provides the level of evidence for the predictors of outcomes identified in our systematic review. The level of evidence is defined by the American Academy of Neurology guidelines [87].

Conclusion

Our review identified multiple risk factors for stroke, death, and MI within 1 month in patients undergoing carotid artery stent placement. Such information will result in better patient selection for carotid artery stent placement particularly in those who are also candidates for carotid endarterectomy.

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