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PERIPHERAL

Proximal Versus Distal Embolic Protection for Carotid Artery Stenting

A National Cardiovascular Data Registry Analysis

Jay Giri, MD, MPH,* Sahil A. Parikh, MD,† Kevin F. Kennedy, MS,‡ Ido Weinberg, MD,§ Cameron Donaldson, MD,§ Beau M. Hawkins, MD,‖ Daniel J. McCormick, DO,* Benjamin Jackson, MD,¶ Ehrin J. Armstrong, MD, MSc,# Preethi Ramchand, MD,** Christopher J. White, MD,†† Michael R. Jaff, DO,§ Kenneth Rosenfield, MD,§ Robert W. Yeh, MD, MSc§

ABSTRACT

OBJECTIVES The aim of this study was to compare the stroke/death rates between proximal embolic protection devices (P-EPDs) and distal filter embolic protection devices (F-EPDs) in elective carotid artery stenting (CAS).

BACKGROUND P-EPDs have theoretical advantages that may make them superior to F-EPDs for stroke prevention during CAS.

METHODS We examined 10,246 consecutive elective CAS procedures performed with embolic protection in the NCDR CARE registry between January 2009 and March 2013. We analyzed crude and propensity-matched rates of in-hospital combined death/stroke in patients treated with P-EPDs versus F-EPDs. Secondary analyses included 30-day adverse event rates and stroke rates by the involved cerebrovascular territory.

RESULTS P-EPDs were used in 590 of 10,246 cases (5.8%). Patients treated with P-EPDs had higher rates of symptomatic lesion status (46.8% vs. 39.7%, $p < 0.001$), atrial fibrillation/flutter (16.1% vs. 13.0%, $p = 0.03$), and history of a neurological event (51.2% vs. 46.6%, $p = 0.03$). In unadjusted and propensity-matched analyses, differences in in-hospital stroke/death between P-EPD and F-EPD cohorts were nonsignificant (1.5% vs. 2.4%, $p = 0.16$ and 1.6% vs. 2.0%, $p = 0.56$, respectively). For patients with available data ($n = 7,693$, 75.1%), 30-day adverse events rates were similar for P-EPDs and F-EPDs before (2.5% vs. 4.2%, $p = 0.07$) and after (2.7% vs. 4.0%, $p = 0.22$) propensity matching.

CONCLUSIONS Use of a P-EPD during CAS was associated with low rates of in-hospital stroke/death similar to those with an F-EPD in the first comparative effectiveness study of the devices. An adequately powered randomized trial comparing clinical outcomes between these devices is unlikely to be feasible. (J Am Coll Cardiol Intv 2015;8:609–15)

From the *Cardiovascular Medicine Division, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; †University Hospitals Harrington Heart and Vascular Institute and Case Western Reserve University School of Medicine, Cleveland, Ohio; ‡St. Luke's Mid-America Heart Institute, University of Missouri - Kansas City, Kansas City, Missouri; §The Institute for Heart, Vascular, & Stroke Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‖Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; ¶Division of Vascular Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; #Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado; **Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; and the ††John Ochsner Heart and Vascular Institute, Ochsner Medical Center, New Orleans, Louisiana. Dr. Yeh is an investigator at the Harvard Clinical Research Institute. Dr. White is the Steering Committee Chair for the NCDR CARE Committee. Dr. Rosenfield has received research grants from Abbott Vascular, Bard Peripheral Vascular, Medtronic/Invatec, and Atrium and consulting/advisory board fees from Abbott Vascular, Boston Scientific, Complete Conference Management, Harvard Clinical Research Institute, Contego, Micell, and Becker Ventures; has equity in Lumen Biomedical,

ABBREVIATIONS AND ACRONYMS

CAS = carotid artery stenting

dwMRI = diffusion-weighted magnetic resonance imaging

EPD = embolic protection device

F-EPD = distal filter embolic protection device

NIHSS = National Institutes of Health Stroke Scale

P-EPD = proximal embolic protection device

Carotid artery stenting (CAS) is a commonly used revascularization procedure for the treatment of asymptomatic and symptomatic carotid artery disease. Although CAS is performed to decrease a patient's long-term probability of stroke, periprocedural and 30-day strokes remain important procedural complications. Embolic protection devices (EPDs) provide a theoretical mechanism to reduce periprocedural strokes, although data regarding their effectiveness have been mixed (1,2). Nevertheless, EPDs are mandated for reimbursement by Medicare and used in more than 95% of all CAS cases in the United States (1). Two types of EPD are currently available, with different mechanisms for stroke prevention. Distal filter EPDs (F-EPDs) are small baskets deployed in the internal carotid artery distal to the lesion to catch any debris that may be produced by manipulation during angioplasty and stent placement. Proximal EPDs (P-EPDs) use balloons to arrest or reverse flow to the internal carotid artery so that angioplasty and stenting can be performed with less risk of antegrade embolization. Aspiration is performed either continuously or before balloon deflation, theoretically capturing any debris released by the procedure.

A P-EPD may be theoretically superior to an F-EPD for stroke prevention because the carotid lesion is never touched in an unprotected fashion when using a P-EPD. Three small single-center studies demonstrated significantly fewer surrogate events, such as transcranial Doppler-detected microembolic signals and diffusion-weighted magnetic resonance imaging (dwMRI) lesions with the use of P-EPDs (3–5). No large-scale analysis using the clinical outcomes of stroke and mortality has yet been performed to evaluate the potential utility of P-EPDs compared with F-EPDs. In the current study, we sought to compare outcomes of CAS using F-EPDs and P-EPDs in a large, nationally representative, multi-institutional registry.

METHODS

STUDY POPULATION. The CARE (Carotid Artery Revascularization and Endarterectomy) Registry is an initiative of the American College of Cardiology Foundation with partnering support from the Society for Cardiovascular Angiography and Interventions, the Society of Interventional Radiology, the American Academy of Neurology, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the Society for Vascular Medicine, and the Society of Vascular and Interventional Neurology. The registry enrolls U.S. patients with carotid stenosis who have undergone revascularization with either carotid endarterectomy or CAS (6). It was created to monitor clinical practice, assess patient outcomes, and provide a framework for quality improvement initiatives. As of July 2013, the registry included 17,064 CAS procedures performed at 184 hospitals.

All patients undergoing CAS from January 2009 through March 2013 were initially evaluated for inclusion in this analysis. Patients with acute evolving stroke (n = 378, 3.26%), spontaneous carotid artery dissection (n = 93, 0.8%), or fibromuscular dysplasia (n = 66, 0.6%) or requiring general anesthesia (n = 517, 4.5%) were excluded because these patients represented distinct, often nonelective, subgroups of patients with substantially higher procedural risk. Patients for whom no embolic protection was attempted were excluded as well (n = 278, 2.6%). Outcomes in these patients were reported previously and were not directly relevant to the present analysis (1).

OUTCOMES. The primary outcome of interest was the occurrence of in-hospital major adverse events, defined as the composite of stroke and death. Stroke was defined as a new neurological deficit persisting for more than 24 h. The occurrence of stroke was recorded by trained data abstracters. The Registry also collects National Institutes of Health Stroke Scale (NIHSS) scores before and after procedures, administered by a certified independent examiner. Formal independent adjudication of documented strokes by a board-certified neurologist was not routinely performed, and data regarding the proportion of patients who underwent this adjudication process were unavailable. To account for potential incomplete ascertainment of small strokes, we used a secondary expanded definition of stroke that included patients with documented changes in NIHSS score ≥2 as a result of the procedure, combined with those

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qualifying for stroke on the basis of the primary endpoint definition.

CLINICAL CHARACTERISTICS. For each patient, the registry was used to record demographics, comorbid conditions, cardiac history, neurological history, anatomic (carotid lesion and aortic arch) characteristics, and procedural information. Data definitions were consistent across study sites and are available at http://cvquality.acc.org~/media/QII/NCDR/Data%20Collection%20Forms/PVI%20Registry_DataDictionary.ashx. Demographic and other general descriptive variables included age, sex, insurance status, and ethnicity. Comorbid conditions assessed included hypertension, diabetes mellitus, dialysis dependence, dyslipidemia, peripheral artery disease, chronic lung disease, smoking status, major surgery planned within 8 weeks, previous neck radiation, and previous neck surgery. Cardiac history variables included ischemic heart disease, myocardial infarction within 6 weeks, class III/IV angina within 6 weeks, moderate/severe aortic stenosis, mechanical aortic valve, heart failure, New York Heart Association functional class III/IV within the previous 6 weeks, atrial fibrillation/flutter, moderate/severe mitral stenosis, and permanent pacemaker or implantable cardioverter-defibrillator. Neurological variables assessed included dementia, seizure disorders, previous carotid endarterectomy, previous CAS, previous transient ischemic attack, previous stroke, and previous hemorrhagic stroke. Anatomic and procedural variables included urgent cardiac surgery within 30 days, a symptomatic target lesion within the previous 6 months, carotid endarterectomy restenosis, CAS restenosis, contralateral occlusion, lesion difficult to access surgically, and bovine aortic arch.

The patients in the F-EPD cohort included those treated with the following devices: Accunet (Abbott Laboratories, Abbott Park, Illinois); Emboshield (Abbott); Angioguard (Cordis Corporation, Bridgewater, New Jersey); SpiderFx (ev3 Endovascular Inc., Plymouth, Minnesota); and Filterwire (Boston Scientific, Natick, Massachusetts). Relative rates of use of these devices in U.S. practice were previously reported (7). P-EPD patients were treated with 1 of 2 devices: Gore Flow Reversal System (W.L. Gore and Associates, Flagstaff, Arizona) or MO.MA Ultra Proximal Cerebral Protection Device (Medtronic, Santa Rosa, California).

STATISTICAL ANALYSIS. We performed unadjusted comparisons of characteristics for patients for whom F-EPDs were used versus those for whom P-EPDs were used, using the Student *t* test for continuous variables and the chi-square test for categorical variables.

TABLE 1 Patient Characteristics of the Study Population

	F-EPD (n = 9,656)	P-EPD (n = 590)	p Value
Demographic characteristics			
Age, yrs	70.8 ± 10.1	70.5 ± 11.5	0.494
Sex			0.014
Male	5,994 (62.1)	396 (67.1)	
Female	3,662 (37.9)	194 (32.9)	
Insurance (self-pay or none)	294 (3.0)	17 (2.9)	0.822
Caucasian	8,905 (92.2)	541 (91.7)	0.643
Body mass index	29.0 ± 13.3	31.7 ± 22.4	<0.001
Comorbid conditions			
Currently on dialysis	248 (2.6)	20 (3.4)	0.226
Smoker	7,112 (73.7)	460 (78.0)	0.021
Hypertension	8,857 (91.7)	539 (91.4)	0.746
Dyslipidemia	8,578 (88.8)	544 (92.2)	0.011
Peripheral arterial disease	4,149 (43.0)	255 (43.2)	0.906
Diabetes mellitus	3,717 (38.5)	208 (35.3)	0.116
Chronic lung disease	2,720 (28.2)	185 (31.4)	0.096
Major surgery planned w/in next 8 wk	334 (3.5)	12 (2.0)	0.063
Previous neck radiation	613 (6.3)	41 (6.9)	0.562
Previous neck surgery (other than CEA)	553 (5.7)	27 (4.6)	0.240
Cardiac history			
Ischemic heart disease	5,097 (52.8)	304 (51.5)	0.546
MI w/in 6 wk	227 (2.4)	14 (2.4)	0.973
Angina CCS class III/IV within 6 weeks	602 (6.2)	53 (9.0)	0.008
History of heart failure	1,584 (16.4)	92 (15.6)	0.603
NYHA functional class III or IV within 6 weeks	610 (6.3)	23 (3.9)	0.018
History of atrial fibrillation or flutter	1,257 (13.0)	95 (16.1)	0.031
Moderate to severe aortic stenosis	403 (4.2)	30 (5.1)	0.283
Moderate to severe mitral stenosis	101 (1.0)	11 (1.9)	0.063
Mechanical heart valve	227 (2.4)	25 (4.3)	0.004
Permanent pacemaker or ICD	817 (8.5)	56 (9.5)	0.367
Neurological history and risk factors pre-procedure			
Dementia or Alzheimer's disease	305 (3.2)	9 (1.5)	0.025
History of seizures	244 (2.5)	12 (2.0)	0.456
Previous CEA left or right	2,108 (21.8)	111 (18.8)	0.084
Previous CAS left or right	1,071 (11.1)	69 (11.7)	0.651
Previous transient ischemic attack	2,961 (30.7)	212 (35.9)	0.007
Previous ischemic stroke	1,446 (15.0)	84 (14.2)	0.625
Previous hemorrhage or hemorrhagic stroke	47 (0.5)	1 (0.2)	0.526
Procedure information			
Target carotid vessel			0.851
Right	4,752 (49.2)	288 (48.8)	
Left	4,904 (50.8)	302 (51.2)	
Urgent cardiac surgery within 30 days	305 (3.2)	10 (1.7)	0.046
Target lesion symptomatic within last 6 months	3,829 (39.7)	274 (46.8)	<0.001
CAS restenosis	292 (3.0)	12 (2.0)	0.169
CEA restenosis	1,441 (14.9)	75 (12.7)	0.142
Contralateral carotid artery occlusion	1,042 (10.8)	38 (6.4)	<0.001
Lesion difficult to access surgically	1,595 (16.5)	113 (19.2)	0.097
Bovine arch	1,281 (13.7)	86 (15.7)	0.192

Values are mean ± SD or n (%). Continuous variables compared using 1-way analysis of variance. Categorical variables compared using the chi-square or Fisher exact test.

CAS = carotid artery stenting; CCS = Canadian Cardiovascular Society; CEA = carotid endarterectomy; F-EPD = distal filter embolic protection; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association; P-EPD = proximal embolic protection.

To account for nonrandom treatment assignment to the devices being compared, we used propensity-score matching. Specifically, we used logistic regression to estimate the log odds of undergoing CAS with a P-EPD or an F-EPD for each patient, on the basis of the 40 variables discussed earlier. We then conducted 1:4 nearest-neighbor matching for each of the 590 patients in the P-EPD group to maximize the power of the sample. We used a caliper width of 0.2 times the SD of the logit of the propensity score. Compared with logistic regression, this propensity matching model allows for more complete risk adjustment when the number of events in any group is low, as well as proper assessment of balance of measured confounders before analysis (8,9). Standardized differences between matched groups were estimated for all covariates, and differences of <10 were considered evidence of the accepted threshold for successful matching (10). Outcomes between matched groups were then compared using conditional logistic regression. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

A P-EPD was used in a total of 590 of 10,246 cases (5.8%). The Gore Flow Reversal System (W.L. Gore and Associates) was used in 374 cases (63.4%) and the MO.MA Ultra Proximal Cerebral Protection Device (Medtronic) was used in 216 cases (36.4%). Patients treated with a P-EPD had higher rates of symptomatic lesion status (46.8% vs. 39.7%, p < 0.001) and atrial fibrillation/flutter (16.1% vs. 13.0%, p = 0.03) and a history of a neurological event (51.2% vs. 46.6%, p = 0.03) than those treated with an F-EPD (Table 1).

In the overall population studied, the in-hospital stroke/death rate was 2.6% and the in-hospital stroke rate was 2.2%. In unadjusted analyses, the in-hospital stroke/death rates in those treated with a P-EPD and an F-EPD were similar (1.5% vs. 2.4%, p = 0.16) (Table 2). For the 75.1% of patients with 30-day follow-up data available (n = 7,693), the stroke/death rates between the groups remained similar (2.5% vs. 4.2%, p = 0.07) (Table 2). Pre- and post-NIHSS scores were available for 74% of patients. When the definition of stroke was broadened to include patients with documented changes in pre- and post-NIHSS scores of ≥2, no significant differences were found between groups for the unadjusted in-hospital stroke rate (2.1% vs. 3.1%, p = 0.27). Rates of the primary outcome in patients treated with the Gore Flow Reversal System and the MO.MA Proximal Cerebral Protection Device were similar (1.3% vs. 1.9%, p = 0.73).

PROPENSITY-MATCHED COMPARISON. After 1:4 propensity matching along 40 variables (n = 2,450), patients were well-balanced on measured characteristics (Figure 1). Differences in in-hospital stroke/death rates were nonsignificant between the P-EPD and F-EPD groups (1.6% vs. 2.0%, p = 0.56) (Table 2). There was no difference in the ipsilateral stroke rate between the groups (0.8%% vs. 1.0%, p = 0.62) (Table 3). For the 76.5% of matched patients with 30-day follow-up data available (n = 1,875), differences in stroke/death rates between the groups remained nonsignificant (2.7% vs. 4.0%, p = 0.22) (Table 2). When the definition of stroke was broadened to include patients with documented changes in pre- and post-NIHSS scores of ≥2, no significant differences were found between the matched groups for in-hospital stroke rate (2.0% vs. 2.7%, p = 0.42). No difference in treatment effect of P-EPDs versus F-EPDs was observed in symptomatic compared with asymptomatic patients (p value for interaction = 0.60 for in-hospital stroke or death; p value for interaction = 0.66 for 30-day stroke or death).

DISCUSSION

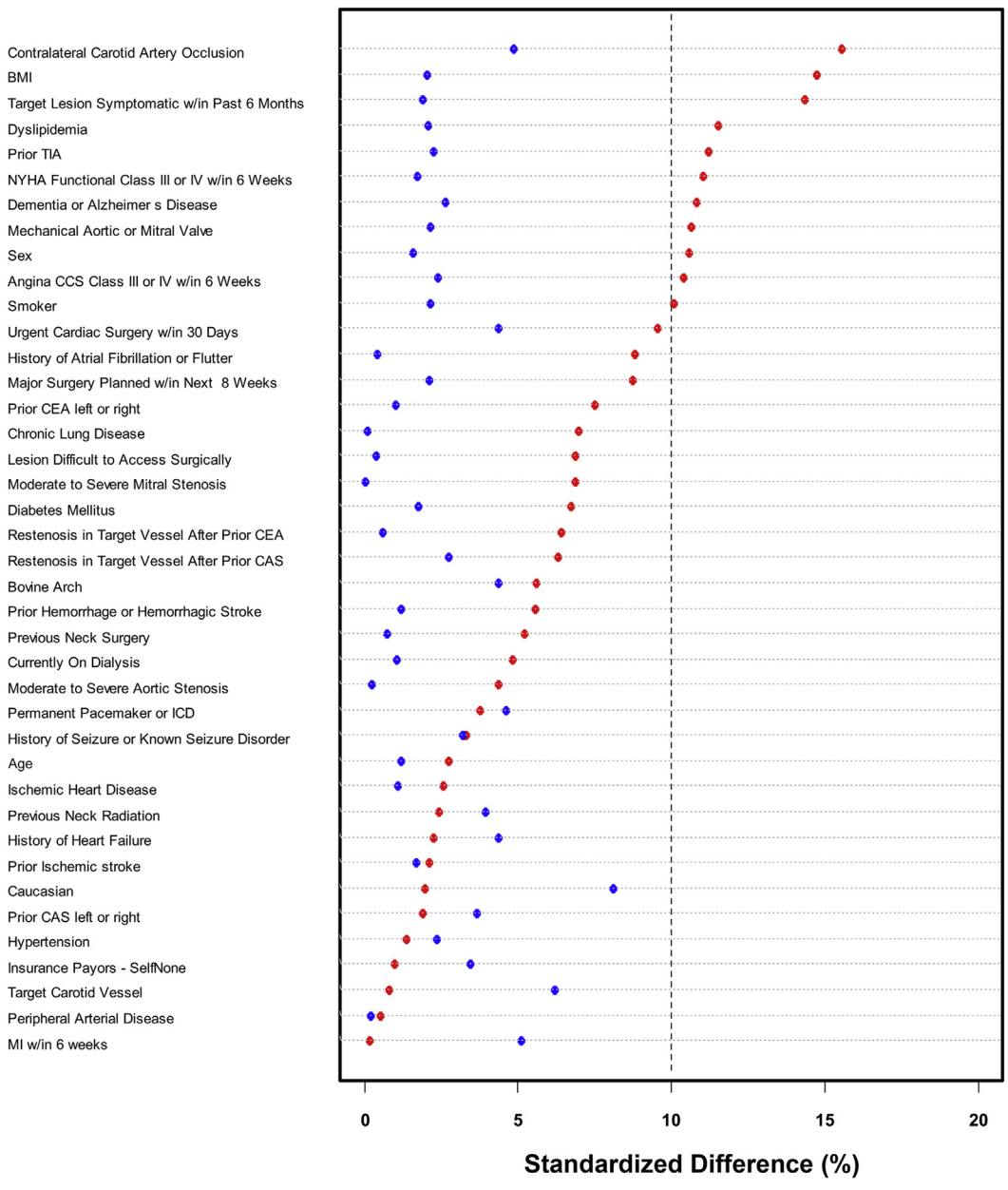
In this first large, multicenter, comparative effectiveness analysis of proximal versus distal embolic protection for CAS, we found that P-EPDs have been used in a small minority of U.S. patients. P-EPDs and F-EPDs were associated with similar periprocedural

TABLE 2 Major Adverse Events Based on Embolic Protection Type

	In-Hospital Outcomes						30-Day Outcomes					
	Before Propensity Matching			After Propensity Matching			Before Propensity Matching			After Propensity Matching		
	F-EPD (n = 9,656)	P-EPD (n = 590)	p Value	F-EPD (n = 2,032)	P-EPD (n = 508)	p Value	F-EPD (n = 7,211)	P-EPD (n = 482)	p Value	F-EPD (n = 1,469)	P-EPD (n = 406)	p Value
Death or stroke	234 (2.4)	9 (1.5)	0.164	40 (2.0)	8 (1.6)	0.560	300 (4.2)	12 (2.5)	0.072	59 (4.0)	11 (2.7)	0.219
Mortality	40 (0.4)	1 (0.2)	0.730	9 (0.4)	1 (0.2)	0.697	53 (0.7)	2 (0.4)	0.582	12 (0.8)	2 (0.5)	0.747
Stroke	209 (2.2)	9 (1.5)	0.296	33 (1.6)	8 (1.6)	0.937	264 (3.7)	11 (2.3)	0.114	49 (3.3)	10 (2.5)	0.373

Values are n (%).
Abbreviations as in Table 1.

FIGURE 1 Standardized Differences in Covariates Before and After Propensity Matching



Red dots and **blue dots** indicate pre- and post-matched comparisons of standardized differences of modeled covariates between patients treated with proximal and distal embolic protection devices. All post-match standardized differences are <10, indicating good balance of the measured characteristics. BMI = body mass index; CAS = carotid artery stenting; CCS = Canadian Cardiovascular Society; CEA = carotid endarterectomy; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association; TIA = transient ischemic attack; w/in = within.

and 30-day risks of stroke/death in both unadjusted and propensity-matched analyses.

Four previous randomized trials reported on the surrogate outcomes of new dwMRI lesions or transcranial Doppler-detected microembolic signals after P-EPD and F-EPD use (3-5,11). Three of these studies noted fewer new dwMRI lesions or micro-embolic signals in patients treated with P-EPD,

TABLE 3 In-Hospital Strokes Grouped by Involved Territory

	Before Propensity Matching			After Propensity Matching		
	F-EPD (n = 9,656)	P-EPD (n = 590)	p Value	F-EPD (n = 2,032)	P-EPD (n = 508)	p Value
All strokes	209 (2.2)	9 (1.5)	0.296	33 (1.6)	8 (1.6)	0.937
Ipsilateral strokes	139 (1.4)	4 (0.7)	0.126	21 (1.0)	4 (0.8)	0.615
Contralateral strokes	26 (0.3)	2 (0.3)	0.675	5 (0.2)	2 (0.4)	0.633
Vertebral/unknown strokes	44 (0.5)	3 (0.5)	0.751	7 (0.3)	2 (0.4)	0.99

Values are n (%).
Abbreviations as in Table 1.

whereas 1 trial noted more dwMRI lesions with P-EPDs. Each trial studied only 40 to 62 patients, so conclusions about stroke rates could not be made. Our results suggest that if P-EPDs do indeed decrease cerebral microemboli during CAS, this does not necessarily translate into robust differences in clinical outcomes.

A recently published meta-analysis reported 30-day clinical outcomes of nearly all the reported patients to date in clinical protocols who received a P-EPD during CAS (12). The authors reported a 30-day stroke/death rate of 2.1%. Importantly, these results may not be generalizable because all patients were treated at a limited number of experienced centers, most within the context of industry-sponsored clinical trials. Additionally, there were no control groups in the analyzed studies, making it impossible to draw conclusions about relative therapy effectiveness. Nevertheless, it is interesting that our observed 30-day stroke/death rate of 2.5% is fairly consistent with these results.

Certain characteristics, such as symptomatic lesion status, have been advocated by expert operators as reasons to choose a P-EPD over an F-EPD. The symptomatic subgroup did not show particular benefit of P-EPD use over F-EPD use in the current analysis. Additionally, we did not observe reduced rates of ipsilateral stroke with P-EPDs, the major presumed benefit of P-EPD use. It should be noted, however, that no signal of harm was noted with the use of P-EPDs, and there were trends toward improved outcomes at 30 days that did not meet statistical significance. As such, it is reasonable to defer to operator preference, experience, and judgment in specific clinical scenarios when choosing the type of embolic protection for an individual CAS procedure.

Because of the slow adoption of P-EPDs in the United States, the proximal protection group in this study was much smaller than the F-EPD group. We attempted to account for any selection bias with our propensity-matched analysis. Still, we cannot rule out the influence of unmeasured confounders in this analysis. These include operator experience, operator specialty, and anatomic characteristics (e.g., external carotid artery stenosis precluding effective proximal protection device placement) that may have biased the choice of protection device. Next, it is possible that operators were less familiar with P-EPD, implying that the currently observed stroke rates in P-EPD-treated patients may decrease over time. However, in an analysis of the first 295 procedures performed with P-EPDs versus the second 295 procedures performed, there were no significant differences in stroke rates (data not shown). Finally, despite being the largest national registry of CAS, the number of P-EPD devices used in the registry was modest, and the study may be underpowered to detect potentially meaningful differences in outcomes between the devices. However, given the rates of the primary endpoint observed in our cohort, a randomized trial of >34,000 subjects would be required to detect a significant difference between P-EPDs and F-EPDs with 80% power (a trial with a design on the basis of our observed 30-day event rates would require >6,000 patients). There are no known plans to organize such an effort, so it is likely that the current data will remain the best available evidence on this issue for the foreseeable future.

CONCLUSIONS

Use of a P-EPD during CAS was associated with similarly low rates of in-hospital stroke/death compared with F-EPD use in the first comparative analysis performed of this issue. An adequately powered randomized trial comparing clinical outcomes between these devices is unlikely to be feasible.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jay Giri, Hospital of the University of Pennsylvania Cardiovascular Medicine Division, Gates Pavilion, 9th Floor, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. E-mail: Giri.jay@gmail.com.

PERSPECTIVES

P-EPDs have theoretical advantages that may make them superior to distal F-EPDs for stroke prevention during CAS. In more than 10,000 patients treated with embolic protection for CAS, the use of P-EPDs was associated with low rates of in-hospital stroke/death similar to those with F-EPDs. Given the observed low event rates in the current analysis, an adequately powered randomized trial examining this issue is unlikely to be feasible.

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