Cerebrovascular Reserve and Stroke Risk in Patients With Carotid Stenosis or Occlusion: A Systematic Review and Meta-Analysis

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Background and Purpose—Impairments in cerebrovascular reserve (CVR) have been variably associated with increased risk of ischemic events and may stratify stroke risk in patients with high-grade internal carotid artery stenosis or occlusion. The purpose of this study is to perform a systematic review and meta-analysis to summarize the association of CVR impairment and stroke risk.

Methods—We performed a literature search evaluating the association of impairments in CVR with future stroke or transient ischemic attack in patients with high-grade internal carotid artery stenosis or occlusion. We included studies with a minimum of 1-year patient follow-up with baseline CVR measures performed by any modality and primary outcome measures of stroke and/or transient ischemic attack. A meta-analysis with assessment of study heterogeneity and publication bias was performed. Results were presented in a forest plot and summarized using a random-effects model.

Results—Thirteen studies met the inclusion criteria, representing a total of 1061 independent CVR tests in 991 unique patients with a mean follow-up of 32.7 months. We found a significant positive relationship between impairment of CVR and development of stroke with a pooled random effects OR of 3.86 (95% CI, 1.99–7.48). Subset analysis showed that this association between CVR impairment and future risk of stroke/transient ischemic attack remained significant regardless of ischemic outcome measure, symptomatic or asymptomatic disease, stenosis or occlusion, or CVR testing method.

Conclusions—CVR impairment is strongly associated with increased risk of ischemic events in carotid stenosis or occlusion and may be useful for stroke risk stratification. (Stroke. 2012;43:2884-2891.)

Key Words: cerebrovascular reactivity ▪ cerebrovascular reserve ▪ stroke ▪ meta-analysis ▪ risk ▪ systematic review ▪ TIA

Atherosclerotic disease occurs frequently at the common carotid artery bifurcation. Such extracranial atherosclerotic disease accounts for 15% to 20% of ischemic strokes.1 Traditional imaging-based risk assessment of stroke, focused on defining the degree of arterial narrowing, has not taken into account downstream hemodynamic effects distal to the stenosis and the cerebrovascular reserve (CVR). For example, when carotid stenosis is severe and reduces cerebral perfusion pressure, autoregulation of the vasculature will maximally dilate the cerebral arterioles to maintain cerebral blood flow. With further reduction in cerebral perfusion pressure and maximally dilated arterioles, the cerebral blood flow will also decrease and potentially increase the risk of stroke.

In symptomatic severe internal carotid artery (ICA) stenosis, carotid endarterectomy has been shown to significantly lower the risk of ipsilateral cerebral infarction.2 The benefit of carotid endarterectomy is less clear in patients with asymptomatic high-grade stenosis. For example, in the Asymptomatic Carotid Surgery Trial, the modest 5.4% reduction in absolute stroke risk at 5 years in patients with asymptomatic carotid stenosis who were treated with carotid endarterectomy requires serious consideration of the risks of surgery, including local surgical expertise in the procedure.3 In such a population, integration of cerebral hemodynamics such as CVR or oxygen extraction fraction derived from positron emission tomography into assessment of stroke risk could...
potentially help isolate a group of patients who might most benefit from surgical revascularization. On the other end of the spectrum, further risk stratification may improve prognosis and motivation for adherence to medical therapy in patients with symptomatic occlusion, because indications for surgical revascularization in this group also remain unclear with a recent randomized trial showing no benefit of surgical revascularization relative to medical therapy.

There have been 2 main approaches to measuring CVR. One approach attempts direct cerebral blood flow measurements of the brain tissue with flow-sensitive imaging techniques such as positron emission tomography, nuclear medicine techniques, CT perfusion, or MR perfusion before and after a vasodilatory stimulus. The second approach involves transcranial Doppler measurement of flow velocities (typically in the middle cerebral artery) distal to a lesion both before and after a vasodilatory stimulus with the increase flow velocity considered a surrogate for CVR. Vasodilatory stimuli include increasing levels of CO₂ (such as with breath-holding or inhalation of CO₂ gas mixtures) and pharmacological challenge with acetazolamide.

It is difficult to draw reliable conclusions about the role of CVR in predicting stroke based on individual research studies in the literature given their relatively small sample sizes. Although there have been attempts to summarize stroke risk based on existing studies evaluating CVR impairment in specific patients with a particular modality, no recent attempt at a systematic review and meta-analysis of the entire literature across all patient populations and modalities has been performed. It is important to improve our understanding of the role of CVR in patients with carotid artery stenosis for determining stroke prevention regimens. The purpose of this study is to perform a systematic review and meta-analysis to summarize the association of CVR impairment and stroke risk.

Methods
We used the methods described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria
We identified studies evaluating CVR impairment and association with future stroke or transient ischemic attack (TIA) in patients with high-grade carotid stenosis (≥70%) or occlusion. Inclusion criteria were (1) published English language articles; (2) original research studies (retrospective or prospective); (3) patients with high-grade carotid stenosis (≥70%) or occlusion measured by any imaging modality including ultrasound, CT angiography, MR angiography, or digital subtraction angiography; (4) administration of a physiological challenge and measurement of CVR after this challenge by any modality; (5) follow-up of ≥1 year assessing development of ipsilateral stroke and/or TIA; and (6) nonsurgical management of patients. In the case of duplicated published cohorts, we included the report with the longest follow-up and greatest number of patients. If a subset of patients underwent surgical revascularization during follow-up, we only included these studies in our meta-analysis if these patients were separately identified and analyzed by the authors so that they could either (1) be excluded from the meta-analysis; or (2) be included in the meta-analysis if the authors made clear that such patients were censored after revascularization so that follow-up up to but not after revascularization could be included. In addition, in any study in which more than one testing method for CVR was performed on the same set of patients, both methods were included separately in the statistical analysis.

Information Sources and Search
A systematic search was performed by an experienced medical librarian (D.D.) to identify studies according to the inclusion criteria. Potential articles were found by searching the electronic databases.
Table. Overview of Studies Evaluating the Association Between Baseline Measures of Cerebrovascular Reserve (CVR) and Risk of Ischemic Outcome

| Study No. | Author and Year | No. of Patients | Mean Age (SD) | Male (%) | Disease Site | Disease Severity | Symptomatic Versus Asymptomatic | Vasodilatory Stimulus | CVR Testing Modality | No. of Subjects With Normal CVR | No. of Subjects With Impaired CVR | Mean Follow-Up Duration, mo | Ischemic Events in Normal CVR Group | Ischemic Events in Impaired CVR Group | Outcome Measure |
|-----------|-----------------|----------------|---------------|----------|--------------|-----------------|-------------------------------|----------------------|------------------|----------------------|----------------------|-----------------------------|-------------------------------|--------------------------------|-------------------------------|-----------------------------|
| 1         | Gur et al., 1996 | 44             | 69 (6.5)      | 47.7     | ICA          | Stenosis        | Asymptomatic                | ACZ                  | TCD              | 23                    | 21                   | 24                          | 0                             | 7                             | Stroke                        | Stroke                        |
| 2         | Isozaki, 2010    | 30             | 59.6 (9.7)    | 86.7     | ICA and MCA  | Stenosis or occlusion | Symptomatic                | ACZ                  | H2O PET              | 16                    | 14                   | 49                          | 0                             | 0                             | Stroke or TIA                  | Stroke or TIA                  |
| 3         | Kimberger, 2010  | 35             | 68 (7.5)      | 60       | ICA          | Occlusion       | Asymptomatic                | ACZ                  | TCD              | 14                    | 21                   | 48                          | 1                             | 7                             | Stroke or TIA                  | Stroke or TIA                  |
| 4         | King, 2011       | 106            | 72.3 (8.1)    | 79.2     | ICA          | Stenosis        | Asymptomatic                | Varied (ACZ and inspired CO2 variation) | TCD              | 74                    | 32                   | 22.7                      | 2                             | 3                             | Stroke or TIA                  | Stroke or TIA                  |
| 5         | Kleiner, 1992    | 85             | Range 43 to 81| 90.6     | ICA          | Occlusion       | Both                        | inspired CO2 variation | TCD              | 48                    | 37                   | 38                         | 4                             | 12                            | Stroke                        | Stroke                        |
| 6         | Karoda, 2001     | 77             | 64 (SD N/A)   | 75.3     | ICA and MCA  | Occlusion       | Symptomatic                | ACZ                  | Xenon SPECT           | 52                    | 25                   | 42.7                       | 7                             | 9                             | Stroke                        | Stroke                        |
| 7         | Markus, 2001     | 107            | N/A           | N/A      | ICA          | Stenosis or occlusion | Asymptomatic                | Inspired CO2 variation | TCD              | N/A                   | N/A                  | 21.7                       | N/A                          | N/A                           | Stroke or TIA                  | Stroke or TIA                  |
| 8         | Ogasawara, 2002  | 70             | 57 (N/A)      | 75.7     | ICA and MCA  | Occlusion       | Asymptomatic                | ACZ                  | 133-Xenon SPECT       | 47                    | 23                   | 60                         | 5                             | 8                             | Stroke                        | Stroke                        |
| 8*        | Ogasawara, 2002  | 70             | 57 (N/A)      | 75.7     | ICA and MCA  | Occlusion       | Asymptomatic                | ACZ                  | 123-Imp SPECT         | 43                    | 27                   | 60                         | 6                             | 7                             | Stroke                        | Stroke                        |
| 9         | Reinhard, 2008   | 161            | 66 (8)        | 85.4     | ICA          | Stenosis or occlusion | Both                        | Inspired CO2 variation | TCD              | 128                   | 33                   | 24.5                       | 9                             | 7                             | Stroke or TIA                  | Stroke or TIA                  |
| 10        | Silverstein, 2000| 94             | 71.1 (5)      | 78.7     | ICA          | Stenosis        | Asymptomatic                | Inspired CO2 variation | TCD              | 54                    | 40                   | 28.5                       | 5                             | 11                            | Stroke or TIA                  | Stroke or TIA                  |
| 11        | Verrieri, 1999   | 65             | 67.8 (5.5)    | 76.9     | ICA          | Stenosis        | Both                        | Inspired CO2 variation | TCD              | 29                    | 36                   | 24                         | 1                             | 11                            | Stroke or TIA                  | Stroke or TIA                  |
| 12        | Webster, 1995    | 95             | 65.9 (N/A)    | 69.5     | ICA          | Stenosis or occlusion | Symptomatic                | ACZ                  | Xenon SPECT           | 43                    | 52                   | 19.6                       | 0                             | 12                            | Stroke                        | Stroke                        |
| 13        | Yamamoto, 2006   | 22             | N/A           | N/A      | ICA          | Stenosis        | Asymptomatic                | ACZ                  | 123-Imp SPECT         | 13                    | 9                    | 23                         | 0                             | 3                             | Stroke                        | Stroke                        |

N/A indicates data not available; ICA, internal carotid artery; MCA, middle cerebral artery; ACZ, acetazolamide; TCD, transcranial Doppler; PET, positron emission tomography; SPECT; single photon emission CT; IMP, isopropyl iodo-amphetamine; TIA, transient ischemic attack.

*Ogasawara et al performed 2 methods on the same cohort of patients; both are listed here.

Ovid MEDLINE, EMBASE, and The Cochrane Library. Relevant subject heading and free-text terms were used. Additional records were identified by using the Related Articles feature in PubMed and the Cited Reference Search in ISI Web of Science. All studies included in each database through September 2011 were searched. A representative primary search conducted through MEDLINE is available in online-only Data Supplement I.

Study Selection and Data Collection Process

After removal of duplicate articles, all potentially eligible articles were screened by a single reader with all screened articles read in their entirety by 3 readers. Two data extractors populated a form collecting key qualitative and quantitative data from the studies. Details of study selection and data collection are available in online-only Data Supplement II.

Assessment of Study Methods

Risk of bias estimates described by PRISMA are most applicable to randomized control trials and no such similar published tool exists to evaluate time-to-event or longitudinal studies according to our literature search. Therefore, 2 data extractors assessed each study’s methodology (with discrepancies resolved by consensus with a third reader) according to the following guidelines. First, an assessment of reference standard bias was made regarding the binding of observers to the CVR results when the clinical ischemic outcomes were determined. Heterogeneity between blinded versus nonblinded studies was made using the $I^2$ statistic described subsequently. Second, an assessment of confounding bias was made regarding statistical adjustment of pre-existing vascular risk factors for the ischemic outcomes. Third, we assessed the completeness of follow-up data by recording the number of patients lost to follow-up or censored during the follow-up period.

Statistical Analyses

Heterogeneity across studies was examined by both the $I^2$ statistic and Breslow-Day method that measure the proportion of inconsistency in individual studies that cannot be explained by chance. The upper 95% confidence limit of $I^2 >30\%$ was used as a cutoff for accepting studies that were moderately heterogeneous in which case the ORs were pooled using random-effects models. A fixed-effects model was chosen if studies were found statistically homogeneous according to the $I^2$ statistic. For the Breslow-Day method, all probability values <0.05 were considered statistically significant and indicative of significant heterogeneity. Continuity correction was used for sparse tables before pooling the ORs. We performed additional subset analysis to assess heterogeneity. Subsets were limited to presence or absence of symptoms, severity of disease, outcome measure used, location of disease, testing modality, and type of vasodilatory challenge. Publication bias was examined by Egger and Begg tests. A biostatistician conducted all analyses using StatsDirect Version 2.7.8.

Results

Study Selection

After the initial screening review of 2238 titles and abstracts, 21 potential articles were selected for further detailed review
(Figure 1). articles were excluded for failure to meet all of the inclusion criteria (n=5) and duplicated patient populations (n=3). The remaining 13 studies were included in the qualitative systematic review. Of these studies, 85% (11 of 13) divided ischemic outcomes into categories amenable to meta-analysis. In one of the 2 studies in which outcome data were originally presented in a fashion not amenable to meta-analysis, the original data were provided by the study corresponding author in a fashion amenable to meta-analysis, allowing for 92% (12 of 13) of studies used in the final analysis. In the remaining study, the data remained unavailable after several attempts to directly contact the corresponding authors.

**Qualitative Assessment and Study Characteristics**

The 13 studies meeting inclusion criteria (Table) were all prospective, time-to-event studies, with 4 conducted in Japan, 2 in Israel, 2 in Germany, 2 in Italy, and one in the United States. A total of 1061 independent CVR tests in 991 unique patients were included with a mean patient follow-up of 32.7 months. All study populations had a minimum of 70% stenosis of the ICA with some studies including patients with carotid occlusion or extension of occlusion from the ICA into the middle cerebral artery. Twelve of the 13 studies included exclusively ipsilateral ischemic outcomes measures and one study included 4 contralateral ischemic outcomes, which were excluded in the statistical analysis.

**Assessment of Study Methods**

Thirty-eight percent (5 of 13) of the studies reported that observers were blinded to the CVR results when assessing ischemic outcomes (F=0; CI, 0%–61%). In the remaining 8 articles, no blinding method was explicitly described (F=0; CI, 0%–58.5%). Sixty-nine percent (9 of 13) of the studies explicitly described a statistical correction or adjustment for pre-existing vascular risk factors in the assessment of ischemic outcome likelihood. In the remaining 4 studies, no adjustment was explicitly described. Finally, in the assessment of the completeness of follow-up, in Reinhard et al., 5 patients had carotid endarterectomy after a mean of 23.2 months; these patients were censored in their analysis and were included in the meta-analysis. In Yamamoto et al., 18 of 40 patients were surgically managed; these patients were excluded from our meta-analysis because the outcome data from this group were clearly separated from the remaining patients. In the remaining 11 studies, no loss to follow-up and no censoring from surgery were described by the authors.

**Meta-Analysis Results**

In pooling the results of the 13 eligible studies for the meta-analysis, both the F statistic and Breslow-Day statistic showed low heterogeneity (F=0; CI, 0%–48.6% and Breslow-Day=7.31, df=12, P=0.84). Begg tests did not reveal any publication bias of the meta-analyses (Begg-Mazumdar: Kendall τ=0.36; P=0.1). The summarized random-effects OR of 3.96 (CI, 2.60–6.04) indicates a significant positive relationship between baseline CVR impairment and future development of TIA and/or stroke (Figure 2). Each study had a positive association between baseline CVR impairment and future development of stroke/TIA, although 38% (5 of 13) of the studies did not have statistically significant ORs.

**Subset Analysis**

Additional subset analyses with heterogeneity measures were performed according to clinically relevant features using a random-effects model based on the criteria described previously.
A statistically significant random-effects OR was preserved in all of the following subset analyses: (1) symptomatic (Figure 3A) versus asymptomatic disease (Figure 3B); (2) outcome measure of only stroke (Figure 3C) versus combination of stroke and/or TIA (Figure 3D); (3) disease severity of high-grade stenosis (Figure 4A) versus occlusion (Figure 4B); (4) disease extent involving only the ICA (Figure 4C) versus ICA and middle cerebral artery disease (Figure 4D); (5) CVR testing modality of transcranial Doppler (Figure 5A) versus nuclear medicine single photon emission CT techniques (Figure 5B); and (6) CVR challenge using acetazolamide (Figure 5C) versus inspired carbon dioxide (Figure 5D).

Discussion

Most imaging-based risk assessments of stroke or TIA rely on the degree of arterial narrowing with the highest incidence of stroke associated with the most severe narrowing. The yearly incidence of stroke varies from approximately 1.2% to 5.9% per year for asymptomatic ICA stenosis\(^5\) to approximately 10% per year for symptomatic ICA occlusion.\(^21\) Although these estimates are integral to current treatment and stroke prevention paradigms, most consensus recommendations do not include assessments of cerebral hemodynamics in their management algorithms.\(^22\)

In this systematic review and meta-analysis of 1061 independent CVR tests in 991 unique patients with carotid stenosis or occlusion with a mean follow-up of 32.7 months, baseline CVR impairment was associated with increased risk of stroke/TIA. Our findings suggest a positive relationship between baseline CVR impairment and future ischemic events with a pooled OR suggesting that patients with impaired CVR are approximately 4 times more likely to develop stroke or TIA. To our knowledge, although there have been 2 previous published meta-analyses of the role of CVR in predicting future stroke risk, one was limited in scope because it examined only 3 studies limited to patients with asymptomatic disease\(^5\) and another was performed in 1997 before a majority of the current studies in the meta-analysis were published and was focused instead on baseline cerebral blood flow impairments.\(^6\) Our literature search found 5 studies limited to asymptomatic patients and is the first study to evaluate the effect of CVR impairment across different
Cerebrovascular Reserve and Stroke: A Meta-Analysis

Gupta et al.

Disease characteristics and by combining studies that used different methods to measure CVR. Importantly, our study suggests that CVR impairment is strongly associated with stroke or TIA in both high-grade stenosis and occlusion as well as in asymptomatic and symptomatic patients. These findings suggest that, in combination or in addition to the risk of embolic stroke arising from carotid atheromatous plaque, these patients face stroke risk from hypoperfusion in vascular territories where vasodilatory capacity is maximally exhausted.

The choice of modality for evaluating CVR varies. We found the association between CVR impairment and risk of stroke conserved across testing modality (transcranial Doppler or nuclear medicine techniques) as well as the nature of the vasodilatory stimulus (acetazolamide or variation in inspired CO2 levels). Transcranial Doppler is relatively inexpensive and fairly widely available but does not provide additional information of the brain parenchyma and is technically impossible in some cases due to lack of acoustic windows. Modalities that measure brain tissue perfusion such as nuclear medicine techniques often have limited use in the clinical setting due to expense, availability, and low spatial and temporal resolution. Although there are radiation and cost considerations for newer cross-sectional methods such as CT and MRI perfusion techniques, to our knowledge, no prospective studies assessing CVR impairment and stroke risk have been performed with these newer modalities, so their use requires further investigation.

Our study has some limitations that should be considered. Although no studies in the review described any differences in risk factors or treatment that might explain differences between normal and impaired CVR groups, an explicit statistical correction of these risk factors occurred in a majority (9 of 13) but not all of the studies. In addition, no methodology for blinding of investigators to the CVR results was explicitly made in a majority of the studies. Additional limitations inherent to the generalization of data for the purposes of pooled statistical analysis also should be acknowledged. Study end points (stroke or TIA) were defined variably by authors with many aggregating these outcomes and preventing distinction between them in our summary meta-analysis and also preventing a distinction between minor versus disabling stroke. In addition, definitions of normal versus impaired CVR and symptomatic versus asymptomatic disease varied, and although some similarities

Figure 4. A, High-grade stenosis. B, Occlusion. C, Internal carotid artery (ICA disease only). D, ICA and middle cerebral artery (MCA) mixed populations. OR and 95% CI for studies divided by patient disease characteristics, including studies of patients with only high-grade stenosis (A) or only vessel occlusion (B) and patients with disease only in the ICA only (C) or in both the ICA and MCA (D). The symbols and abbreviations are as in Figure 2.
 existed, no one standard definition could be applied across all studies. Similarly, more precise description of the severity of stenosis (percentages) and timing of this measurement relative to CVR determination was reported in a variable fashion and was difficult to generalize. Lastly, due to the nature of the data available for statistical analysis, assessment of risk per unit of time as a hazard ratio could not be performed.

Despite these potential limits, the preservation of association between CVR impairment and risk of stroke/TIA is robust across many patient subsets and methods of CVR assessment suggesting an important potential role in stroke/TIA risk assessment. The feasibility of integrating routine CVR measurements into the care of patients with carotid stenosis or occlusion and validation of newer methods of CVR using cross-sectional imaging techniques requires continued investigation.

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**Disclosures**
None.

**References**
Gupta et al  Cerebrovascular Reserve and Stroke: A Meta-Analysis  2891


Cerebrovascular Reserve and Stroke Risk in Patients With Carotid Stenosis or Occlusion: A Systematic Review and Meta-Analysis
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/11/2884

An erratum has been published regarding this article. Please see the attached page for:
/content/44/10/e137.full.pdf

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/10/23/43.11.2884.DC1
The version of the article, “Cerebrovascular Reserve and Stroke Risk in Patients With Carotid Stenosis or Occlusion: A Systematic Review and Meta-Analysis” that appears in the November issue (Stroke. 2012;43:2884–2891) had an error in the table. For study No. 5, Kleiser, under the column for “No. of Subjects With Impaired CVR,” the number 1112 is listed. The correct number should be 37.

The table has been corrected in the online version of the article.
ONLINE SUPPLEMENT 1

Supplemental Methods

exp Carotid Stenosis/ OR (carotid adj3 (stenos$ or ulcer$ or plaque$ or narrow$ or obstruct$ or occlus$ or constrict$)).tw. OR (steno$ occlus$ or stenoocclus$).tw. AND exp Cerebrovascular Circulation/ OR (cerebr$ adj3 (circulat$ or Autoregulat$ or reactivity or reserve or blood or flow or volume or resistance or pressure or hemodynamic$ or vasomotor$)).tw. OR(regional CBF or rCBF or CVR or CPP).tw. AND exp Stroke/ OR Stroke$.tw. OR cerebrovascular.tw. OR ((brain or vascular or lacunar or venous or cerebral or isch?emic) adj2 (accident$ or infarct$ or event$ or attack$)).tw. OR (cva or cvas).tw.

Legend: Representative primary search was conducted through MEDLINE using the terms above in an Ovid Medline Search from 1948 to September Week 4 2011.
ONLINE SUPPLEMENT 2

Supplemental Methods

Study Selection Process:

After removal of duplicate manuscripts, all potentially eligible manuscripts were screened by a single reader (A.G.) based on title and abstract content. After excluding manuscripts that did not meet the inclusion criteria, additional related manuscripts were identified via related articles, cited reference, and bibliography searches. The titles and abstracts of these manuscripts were reviewed and any additional potential manuscripts were identified. All screened manuscripts were carefully read in their entirety by three readers (A.G., J.L.C, and M.H.) for final inclusion.

Data collection process:

Two data extractors (J.L.C. and M.H.) reviewed the included manuscripts and populated a form collecting key data from each study including cohort age, gender, location and severity of carotid stenosis or occlusion, presence or absence of symptoms, CVR testing modality, type of vasodilatory stimulus, mean follow up length, and ischemic endpoint(s). If possible, for the purposes of this meta-analysis, the data extractors divided CVR measures into normal or impaired according to the classification scheme described in the manuscript. Based on this classification into normal and impaired CVR, the data extractors classified the number of patients and ischemic events in each group. If this raw data breakdown was not readily available in the manuscript, an attempt to directly contact the author was made. All data collected was confirmed by a third reader (A.G.) with discrepancies resolved by consensus.