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

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Abstract

Background and Purpose—Impairments in CVR have been variably associated with increased risk of ischemic events and may stratify stroke risk in patients with high grade internal carotid artery (ICA) 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 (TIA) in patients with high grade ICA stenosis or occlusion. We included studies with a minimum of one year patient follow up with baseline CVR measures performed via any modality and primary outcome measures of stroke and/or TIA. 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 odds ratio of 3.86 (95% CI, 1.99–7.48). Subset analysis showed that this association between CVR impairment and future risk of stroke/TIA 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.

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Disclosures: None

Keywords

cerebrovascular reserve; cerebrovascular reactivity; stroke; TIA; risk; systematic review; meta-analysis

Introduction

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 (CPP), autoregulation of the vasculature will maximally dilate the cerebral arterioles to maintain cerebral blood flow (CBF). With further reduction in CPP and maximally dilated arterioles, the CBF will also decrease and potentially increase the risk of stroke.

In symptomatic severe ICA stenosis, carotid endarterectomy (CEA) has been shown to significantly lower the risk of ipsilateral cerebral infarction[2]. The benefit of CEA 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 CEA 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 (PET) 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, as indications for surgical revascularization in this group also remain unclear with a recent randomized trial[4] showing no benefit of surgical revascularization relative to medical therapy.

There have been two main approaches to measuring CVR. One approach attempts direct CBF measurements of the brain tissue with flow sensitive imaging techniques such as positron-emission tomography (PET), nuclear medicine (NM) techniques, CT perfusion, or MR perfusion before and after a vasodilatory stimulus. The second approach involves transcranial Doppler (TCD) 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 pharmacologic 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. While there have been attempts to summarize stroke risk based on existing studies evaluating CVR impairment in specific patients with a particular modality[5,6] 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 employed the methods described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[7].

Eligibility Criteria

We identified studies evaluating CVR impairment and association with future stroke or TIA in patients with high grade carotid stenosis (≥70%) or occlusion. Inclusion criteria were 1) published English language manuscripts; 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 (CTA), MR angiography (MRA), or digital subtraction angiography (DSA); 4) administration of a physiologic challenge and measurement of CVR after this challenge via any modality; 5) follow up of 1 year or greater assessing development of ipsilateral stroke and/or TIA; and 6) non-surgical 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 where 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 Ovid MEDLINE, EMBASE and The Cochrane Library. Relevant subject heading and free text terms were used. Additional records were identified by employing 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 the online supplement (S1).

Study Selection and Data Collection Process

After removal of duplicate manuscripts, all potentially eligible manuscripts were screened by a single reader with all screened manuscripts read in their entirety by three 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 the online supplement (S2).

Assessment of Study Methods

Risk of bias estimates described by PRISMA are most applicable to randomized control trials [7]and no such similar published tool exists to evaluate time-to-event or longitudinal studies according to our literature search. Thereby, 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 blinding of observers to the CVR results when the clinical ischemic outcomes were determined. Heterogeneity between blinded versus non-blinded studies was made using the I^2 statistic described below. 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 greater than 30% was used as a cutoff for accepting studies that were moderately heterogeneous in which case the odds ratios were pooled using random effects models[8]. Fixed effects model was chosen if studies were found statistically homogeneous according to the I^2 statistic. For the Breslow-Day method, all P values less than 0.05 were considered statistically significant and indicative of significant heterogeneity. Continuity correction was used for sparse tables before pooling the odds ratios. 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's and Begg's tests. A biostatistician conducted all analyses using StatsDirect version 2.7.8.

Results

Study Selection

After the initial screening review of 2,238 titles and abstracts, 21 potential manuscripts were selected for further detailed review (Figure 1). Manuscripts were excluded for failure to meet all of the inclusion criteria (n=5) and duplicated patient populations (n=3). The remaining 13 studies[5,9–20] were included in the qualitative systematic review. Of these studies, 85% (11/13) divided ischemic outcomes into categories amenable to meta-analysis. In one of the two studies where outcome data was originally presented in a fashion not amenable to meta-analysis[16], the original data was provided by the study corresponding author in a fashion amenable to meta-analysis, allowing for 92% (12/13) of studies used in the final analysis. In the remaining study[14], 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 1) were all prospective, time-to-event studies, with 4 conducted in Japan[10,13,15,20] 2 in Israel[9,11], 2 in Germany[12,16], 2 in Italy[17,18], 1 in the United States[19], and 1 in multiple countries as a multi-center trial[5]. 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 1 study[19]included 4 contralateral ischemic outcomes which were excluded in the statistical analysis.

Assessment of Study Methods

Thirty-eight percent (5/13) of the studies[5,15–18] reported that observers were blinded to the CVR results when assessing ischemic outcomes (I^2=0, CI=0 to 61%). In the remaining 8 manuscripts, no blinding method was explicitly described (I^2=0, CI=0 to 58.5%). Sixty-nine percent (9/13) of the studies[5,13–20]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[16] five patients had CEA 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[20], 18 of 40 patients were surgically managed; these patients were excluded from our meta-analysis as the outcome data from this group was clearly separated from the remaining patients. In the remaining 11 studies, no loss to follow up and no censoring from surgery was described by the authors.

Meta-Analysis Results

In pooling the results of the 13 eligible studies for the meta-analysis, both the I^2 statistic and Breslow-Day statistic showed low heterogeneity (I^2=0, CI=0 to 48.6% and Breslow-Day=7.31, df=12, p=0.84). Begg's tests did not reveal any publication bias of the meta-analyses (Begg-Mazumdar: Kendall's tau = 0.36, p-value of 0.1). The summarized random effects odds ratio 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, though 38% (5/13) of the studies[5,10,11,13,20] did not have statistically significant odds ratios.

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 above. A statistically significant random effects odds ratio 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 MCA disease (Figure 4D), (5) CVR testing modality of TCD (Figure 5A) versus NM-SPECT 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[5,17] to about 10% per year for symptomatic ICA occlusion[21]. Though 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 odds ratio suggesting that patients with impaired CVR are approximately 4 times more likely to develop stroke or TIA. To our knowledge, though there have been two previous published meta-analyses of the role of CVR in predicting future stroke risk, one was limited in scope as 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 CBF 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 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 (TCD or NM techniques) as well as the nature of the vasodilatory stimulus (acetazolamide or variation in inspired CO2 levels). TCD 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 which measure brain tissue perfusion, such as NM techniques, often have limited use in the clinical setting due to expense, availability, and low spatial and temporal resolution. Though 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 utility requires further investigation.

Our study has some limitations that should be considered. Though 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 endpoints (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 though some similarities 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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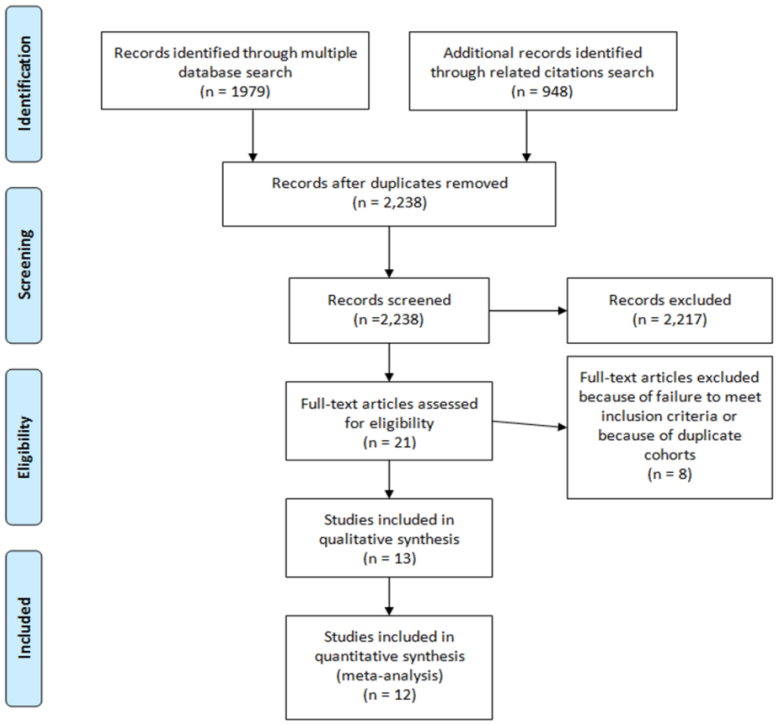


Figure 1.
Study selection flow diagram, adapted from the PRISMA group statement

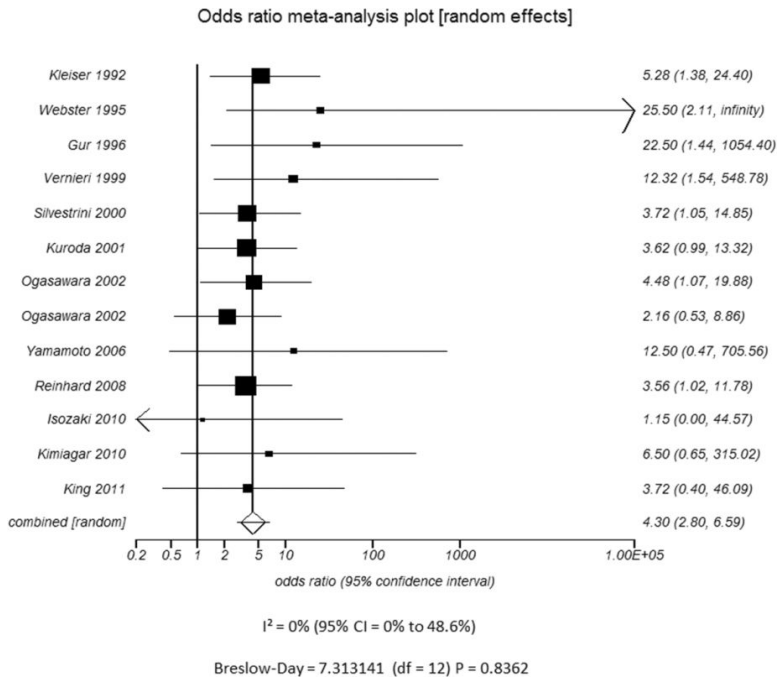
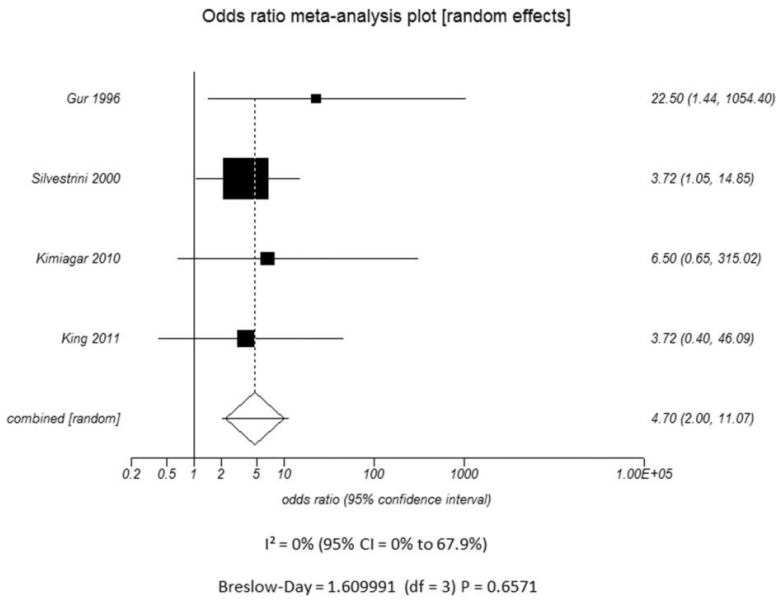


Figure 2.

Meta-analysis of the association between cerebrovascular reserve (CVR) and stroke/TIA. Studies are listed by date. Squares indicate point estimates for effect size (OR), with the size proportional to the inverse variance of the estimate. Diamonds indicate pooled estimates. Lines represent 95% CIs. Vertical line indicates the null effect. I^2 and Breslow-Day heterogeneity statistic listed below the forest plot.

A



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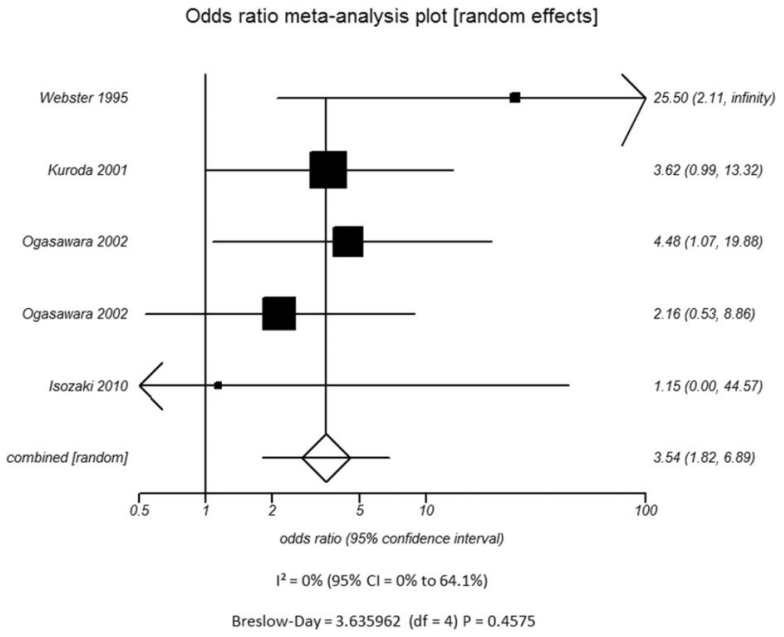

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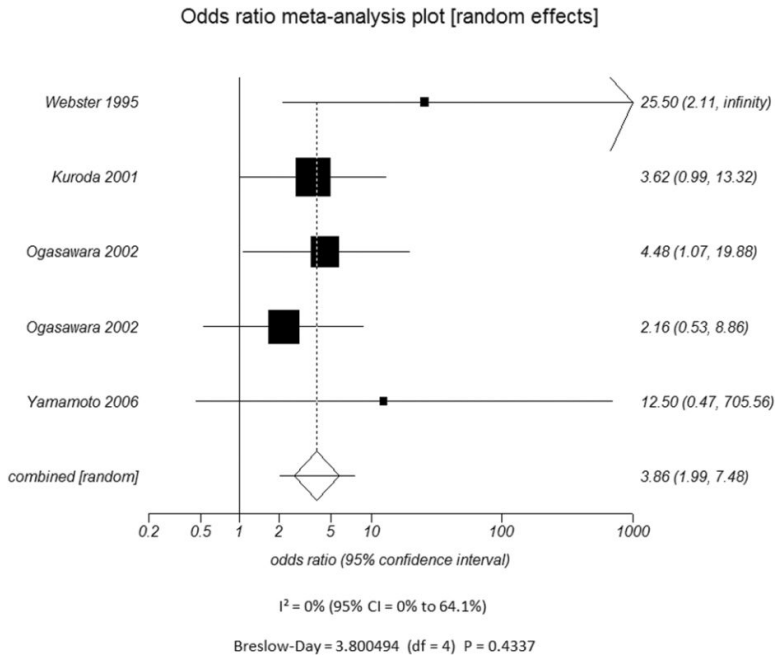

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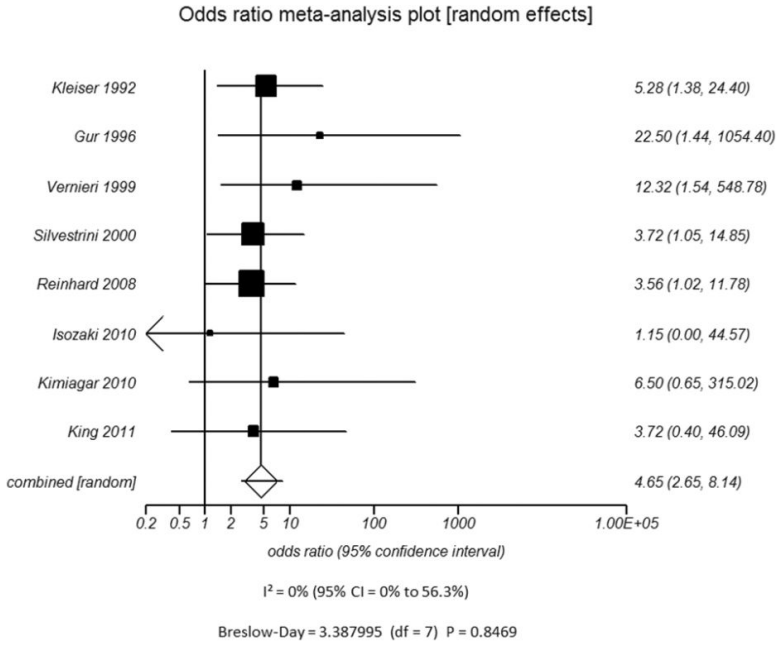


Figure 3.

Odds ratio and 95% confidence ratio for studies divided by the presence of n patients with only asymptomatic (A) or symptomatic (B) disease and whether the study outcome measure was only stroke (C) or stroke and TIA (D). The symbols and abbreviations are as in Figure 2.

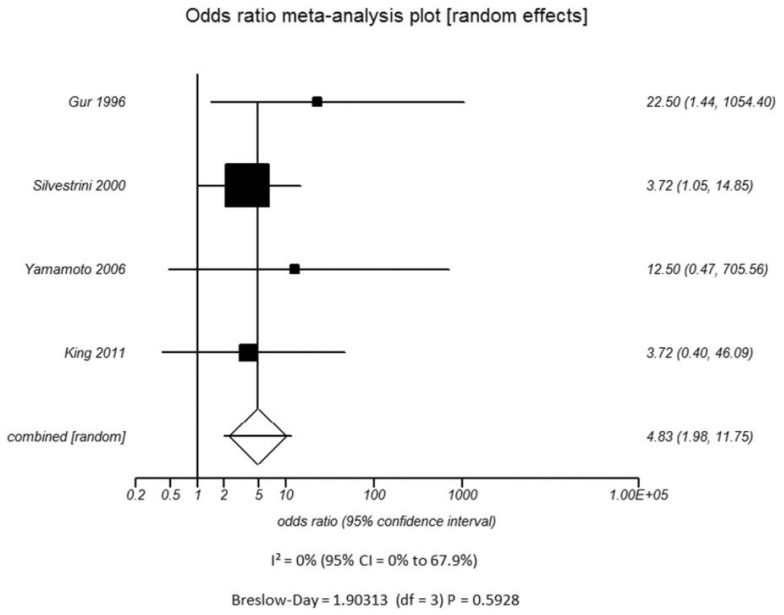
A - Asymptomatic Patients

B - Symptomatic Patients

C - Stroke only as outcome measure

D - Stroke and TIA as outcome measure

A



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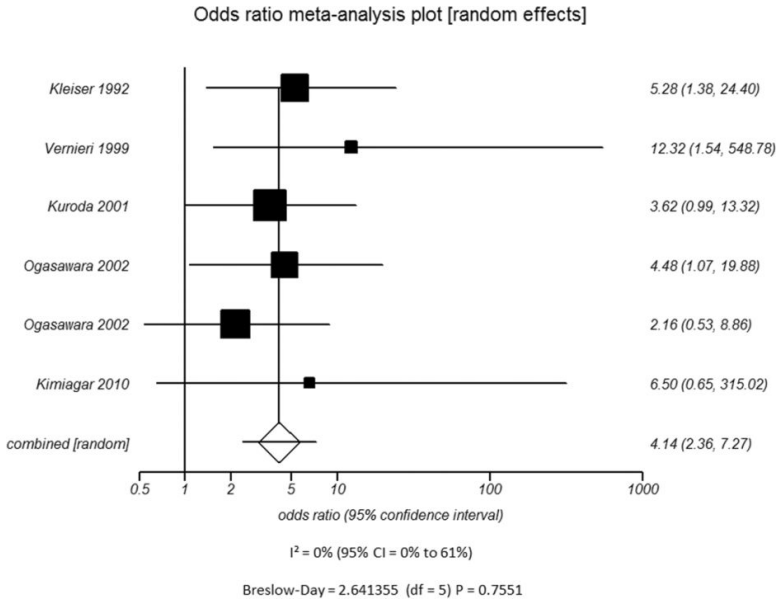

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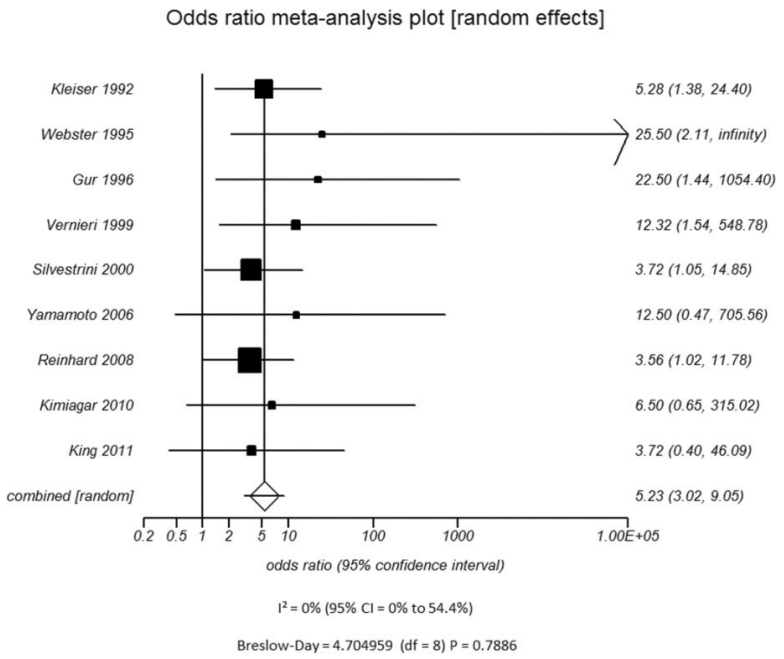

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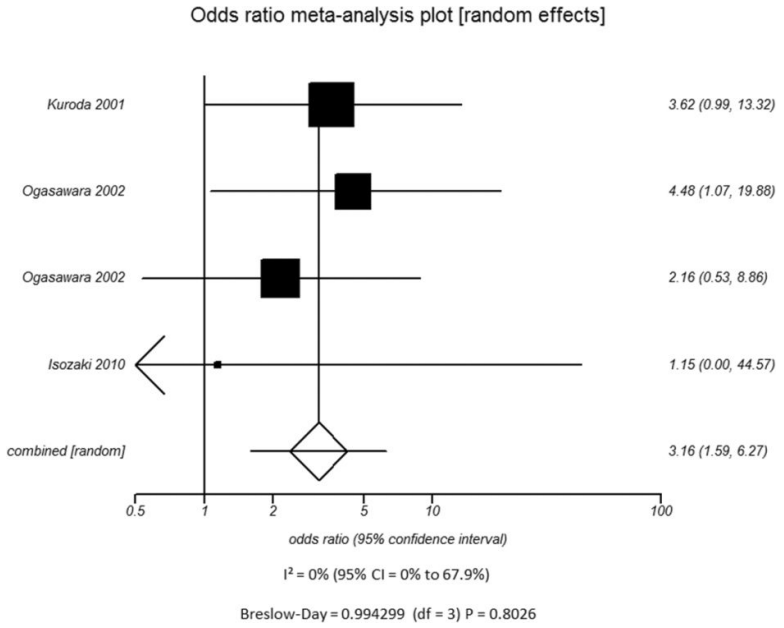


Figure 4.

Odds ratio and 95% confidence ratio 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.

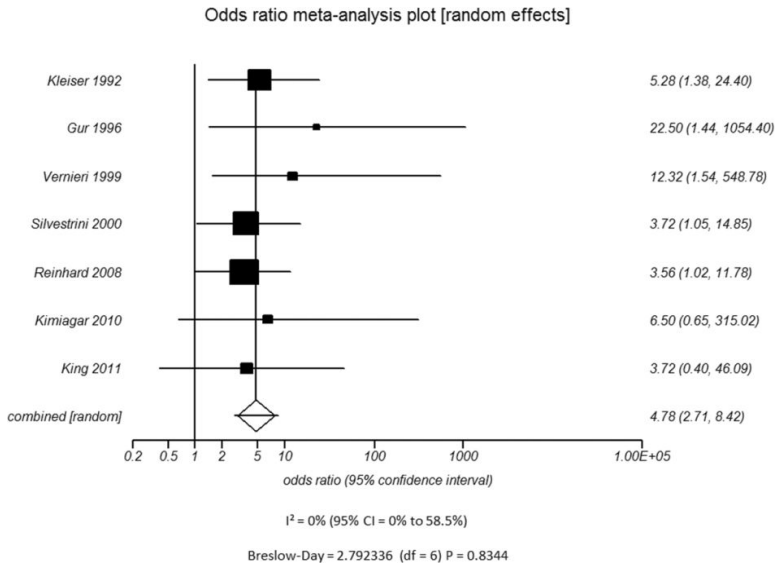
A - High Grade Stenosis

B - Occlusion

C - ICA disease only

D - ICA and MCA mixed populations

A



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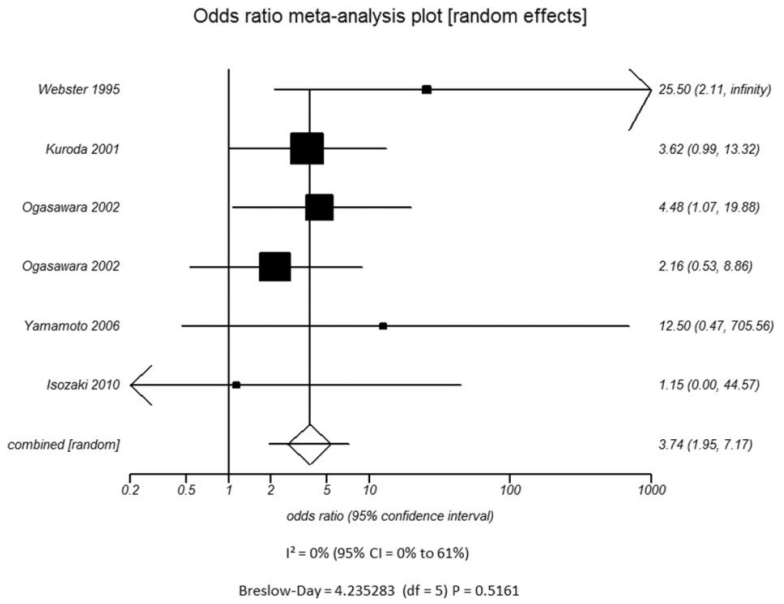

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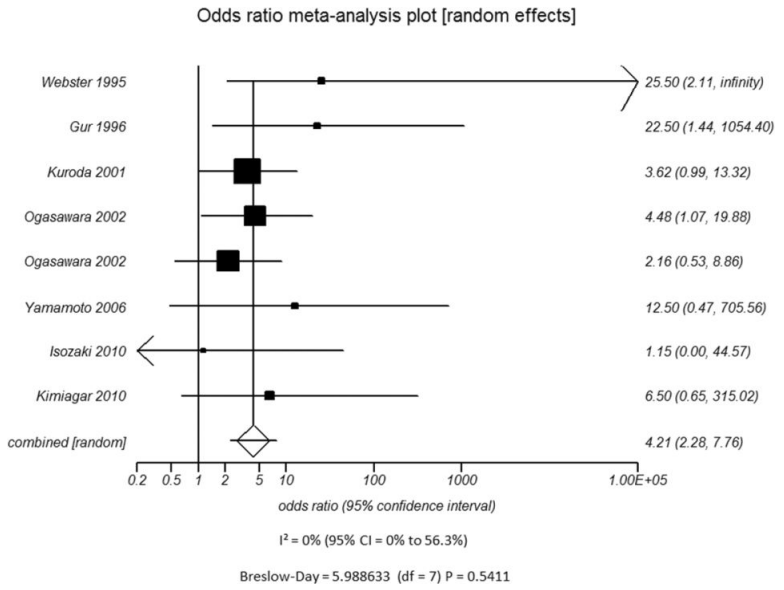

D

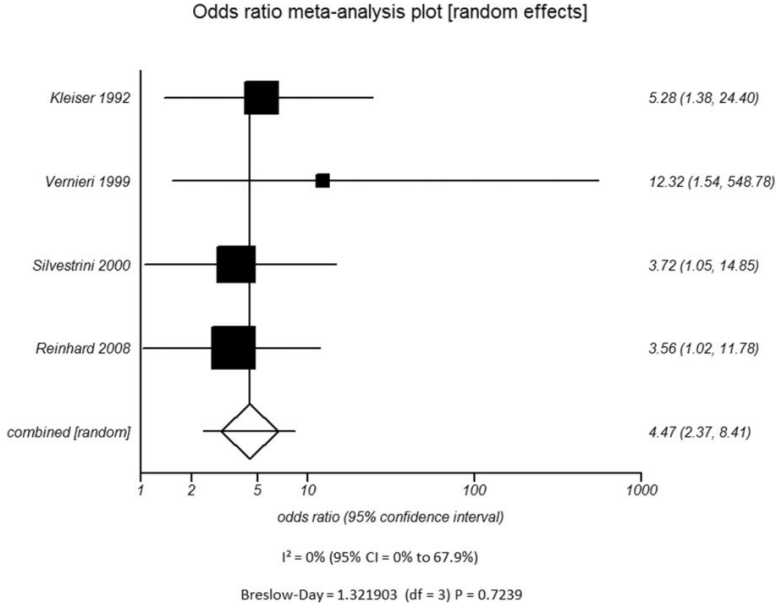

Figure 5.

A - Modality used to Measure CVR - TCD
B - Modality used to Measure CVR - Nuclear Medicine Scintigraphy
C - Type of Vasodilatory Challenge Used - Acetazolamide
D - Type of Vasodilatory Challenge Used - Variation in Inspired Carbon DioxideFigure 5.
Odds ratio and 95% confidence ratio for studies divided by distinguishing features of CVR testing methodology used, including whether TCD (A) or nuclear medicine techniques (B) was the modality of choice and whether acetazolamide challenge (C) or variations in inspired carbon dioxide (D) was the vasodilatory stimulus used. The symbols and abbreviations are as in Figure 2.

Table 1

Overview of Studies Evaluating the Association Between Baseline Measures of Cerebrovascular Reserve (CVR) and Risk of Ischemic Outcome.

Study Number	Author and Year	Number of Patients	Mean Age (SD)	Maie (%)	Disease Site	Disease Severity	Symptomatic versus Asymptomatic	Vasodilatory Stimulus	CVR Testing Modality	Number of Subjects with Normal CVR	Number 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[9] 1996	44	69 (6.5)	47.7	ICA	stenosis	asymptomatic	ACZ	TCD	23	21	24	0	7	stroke or TIA
2	Isozaki[10] 2010	30	59.6 (9.7)	86.7	ICA & MCA	stenosis or occlusion	symptomatic	ACZ	H2O PET	16	14	49	0	0	stroke or TIA
3	Kimiagar[11] 2010	35	68 (7.5)	60	ICA	occlusion	asymptomatic	ACZ	TCD	14	21	48	1	7	stroke or TIA
4	King 2011[5]	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
5	Kleiser[12] 1992	85	Range 43 to 81	90.6	ICA	occlusion	both	inspired CO2 variation	TCD	48	1112	38	4	12	stroke or TIA
6	Kuroda[13] 2001	77	64 (SD n/a)	75.3	ICA & MCA	occlusion	symptomatic	ACZ	Xenon SPECT	52	25	42.7	7	9	stroke
7	Markus[14] 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
8	Ogasawara[15] 2002	70	57 (n/a)	75.7	ICA & MCA	occlusion	symptomatic	ACZ	133-Xenon SPECT	47	23	60	5	8	stroke
8 *	Ogasawara[15] 2002	70	57 (n/a)	75.7	ICA & MCA	occlusion	symptomatic	ACZ	1231-IMP SPECT	43	27	60	6	7	stroke
9	Reinhard[16] 2008	161	66 (8)	85.4	ICA	stenosis or occlusion	both	inspired CO2 variation	TCD	128	33	24.5	9	7	stroke or TIA
10	Silvestrini[17] 2000	94	71.1 (5)	78.7	ICA	stenosis	asymptomatic	inspired CO2 variation	TCD	54	40	28.5	5	11	stroke or TIA
11	Vernieri[18] 1999	65	67.8 (5.5)	76.9	ICA	occlusion	both	inspired CO2 variation	TCD	29	36	24	1	11	stroke or TIA
12	Webster[19] 1995	95	65.9 (n/a)	69.5	ICA	stenosis or occlusion	symptomatic	ACZ	Xenon SPECT	43	52	19.6	0	12	stroke
13	Yamamoto[20] 2006	22	(n/a)	n/a	ICA	stenosis	both	ACZ	1231-IMP SPECT	13	9	23	0	3	stroke

ACZ=acetazolamide; CT=computed tomography; ICA=internal carotid artery; n/a = data not available; MCA=middle cerebral artery; PET=positron emission tomography; SPECT=single photon emission computed tomography; TCD=transcranial Doppler; TIA=transient ischemic attack; IMP=Isopropyl Iodo-Amphetamine;

*Ogasawara[15] et al performed two methods on the same cohort of patients, both are listed here