Cerebrovascular reactivity predicts stroke in high-grade carotid artery disease

Matthias Reinhard, MD
Guido Schwarzer, PhD
Matthias Briel, MD, MSc
Claudia Altamura, MD
Paola Palazzo, MD
Alice King, PhD
Natan M. Bornstein, MD
Nils Petersen, MD
Edith Motschall
Andreas Hetzel, MD
Randolph S. Marshall, MD, MS
Catharina J.M. Klijn, MD, PhD
Mauro Silvestrini, MD
Hugh S. Markus, FRCP
Fabrizio Vernieri, MD

Correspondence to Dr. Reinhard: matthias.reinhard@uniklinik-freiburg.de

ABSTRACT

Objective: To assess the usefulness of transcranial Doppler CO_2 reactivity (CO2R) for prediction of ipsilateral ischemic stroke in carotid artery stenosis and occlusion with a meta-analysis of prospective studies based on individual patient data.

Methods: We searched Medline, Biosis Previews, Science Citation Index, The Cochrane Library, and EMBASE for studies in which patients with severe carotid artery stenosis or occlusion underwent Doppler CO2R testing (inhalation of CO_2 or breath-holding) and were prospectively followed for ipsilateral ischemic stroke. Individual data from 754 patients from 9 studies were included. We used percentage cerebral blood flow velocity increase (pCi) during hypercapnia as the primary CO2R measure, and defined impaired reactivity as pCi <20% increase.

Results: In a multiple regression model, impaired CO2R was independently associated with an increased risk of ipsilateral ischemic stroke (hazard ratio [HR] 3.69; confidence interval [CI] 2.01, 6.77; $p < 0.0001$). Risk prediction was similar for recently symptomatic vs asymptomatic patients. Using continuous values of pCi, a significant association between decreasing pCi and increasing risk of ipsilateral stroke was found: HR of 1.64 (95% CI 1.33, 2.02; $p < 0.0001$) per 10% decrease in pCi. For patients with asymptomatic internal carotid artery stenosis only (n = 330), a comparable stroke risk prediction was found: increasing HR 1.95 (95% CI 1.26, 3.04; $p = 0.003$) per 10% decrease in pCi.

Conclusions: This analysis supports the usefulness of CO2R in risk prediction for patients with severe carotid artery stenosis or occlusion, both in recently symptomatic and asymptomatic patients. Further studies should evaluate whether treatment strategies in asymptomatic patients based on CO2R could improve patient outcomes. ***Neurology*® 2014;83:1424–1431**

GLOSSARY

CBFV = cerebral blood flow velocity; **CI** = confidence interval; **CO2R** = CO_2 reactivity; **CVR** = cerebrovascular reactivity; **HR** = hazard ratio; **ICA** = internal carotid artery; **IPD** = individual patient data; **MFP** = multiple fractional polynomial; **pCi** = percentage cerebral blood flow velocity increase during hypercapnia; **TCD** = transcranial Doppler sonography.

Carotid recanalization in patients with asymptomatic internal carotid artery (ICA) stenosis offers a marginal clinical benefit when all patients are considered together.[1] Given the advances in modern optimized medical therapy, identifying a subset of patients at high risk is thus of increasing importance.

Transcranial Doppler sonography (TCD) offers 2 prognostic tests that may allow risk stratification in ICA disease: detection of microembolic signal (MES) and determination of cerebrovascular reactivity (CVR). Detection of MES can identify asymptomatic patients with ICA stenosis at risk.[2] CVR, which assesses the increase in cerebral blood flow in response to a vasodilatory stimulus, was a significant predictor of future stroke in some TCD studies,[3–7] while other studies failed to show such an association.[8,9]

Supplemental data at Neurology.org

From the Department of Neurology (M.R., A.H.) and the Institute of Medical Biometry and Statistics (G.S., E.M.), University of Freiburg, Germany; Basel Institute for Clinical Epidemiology and Biostatistics (M.B.), University Hospital Basel, Switzerland; the Department of Clinical Epidemiology and Biostatistics (M.B.), McMaster University, Hamilton, Canada; Neurology Unit (C.A., P.P., F.V.), Università Campus Bio-Medico of Rome, Italy; School of Public Health (A.K.), Imperial College London, UK; the Department of Neurology (N.M.B.), Tel Aviv Sourasky Medical Center and Tel Aviv University, Israel; Columbia University Medical Center (N.P., R.S.M.), Neurological Institute of New York; the Department of Neurology and Neurosurgery (C.J.M.K.), Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands; the Department of Experimental and Clinical Medicine (M.S.), Marche Polytechnic University, Ancona, Italy; and Clinical Neurosciences (H.S.M.), University of Cambridge, UK.

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Previous conventional meta-analyses investigating CVR were limited by combining different methodologies of estimating cerebral blood flow (TCD vs nuclear medicine methods), different vasodilatory stimuli (CO_2 vs acetazolamide), and by including heterogeneous patient risk profiles (symptomatic vs asymptomatic disease), cutoff values, and clinical outcome events.[8,10]

Individual patient data (IPD) meta-analysis overcomes such limitations through standardized definitions and analyses across studies and adjustment for variations in individual patient prognosis at baseline. This allows for more powerful investigations of subgroup effects and specific endpoints.[11]

We therefore performed an IPD meta-analysis to investigate the usefulness of TCD CO_2 reactivity in the prediction of ipsilateral ischemic stroke in ICA stenosis or occlusion.

METHODS

Standard protocol approvals, registrations, and patient consents. A study protocol for this meta-analysis of IPD was written in advance and sent to all investigators involved. This study was approved by the Ethics Committee of the University of Freiburg. We prepared the present report according to PRISMA guidelines.[27]

Study selection and data collection. Eligible studies applied transcranial Doppler sonography of the middle cerebral artery with a vasodilatory CO_2 challenge (hypercapnia or breath-holding) in symptomatic or asymptomatic patients with severe (≥70%) carotid artery stenosis (not scheduled for intervention) or occlusion (not scheduled for extracranial/intracranial bypass) and prospectively reported clinical outcome (stroke and TIAs) in relation to the measured parameter of CO_2 reactivity (CO2R). Studies were excluded if they exclusively focused on acetazolamide as a stimulus or if they did not follow patients prospectively. There were no exclusions based on language or publication status of reports.

An experienced health science librarian (E.M.) identified suitable studies in July 2011 (the search was updated upon finalization of the manuscript on November 26, 2013) by a formal search in the following databases: Medline (since 1948), Medline In-Process & Other Non-Indexed Citations, Biosis Previews (since 1926), Cochrane Library: Cochrane Database of Systematic Reviews (issue 11/2013, Clinical Trials, issue 10/2013), Science Citation Index (since 1945), Embase, and Embase Alert (since 1974). Search terms, their synonyms, and, in databases with a thesaurus, appropriate controlled terms were combined. Combinations were according to the following aspects: cerebrovascular reactivity, CO_2 reactivity, transcranial Doppler, and carotid artery. Reference lists of retrieved relevant articles were screened and experts in the field contacted for additional eligible studies. Detailed search strategies are available from the authors by request.

Two reviewers (M.R., A.H.) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed. Because we built our own statistical models taking into account all relevant confounders and potential clustering effects, we focused in our assessment of the methodologic quality of included prognostic studies on 5 domains: representativeness of the population, loss to follow-up, prognostic factor measurement, outcome measurement, and confounding measurement[12] (table e-1 on the *Neurology*® Web site at Neurology.org). Study quality was assessed independently by 2 reviewers (M.R., A.H.). Discrepancies between reviewers were resolved by consensus or third party arbitration (M.B.), if required.

Data collection, subgroups, and outcomes. Individual patient data were requested from principal investigators of all eligible studies. All investigators were asked to provide a dataset including (1) baseline characteristics of each individual patient: age, sex, vascular risk factors, degree of ipsilateral and contralateral carotid stenosis, status of stenosis (symptomatic, asymptomatic), if applicable type and time of previous ischemic events in the territory supplied by the affected carotid artery; and (2) methodology of CO2R test: CO2R in terms of maximum % increase in cerebral blood flow velocity (CBFV) during the hypercapnic challenge, CO2R normalized to the amount of hypercapnia (% CBFV increase per mm Hg $PetCO_2$ increase), and local cutoff values of CO2R3 clinical endpoints: ischemic stroke or TIA attributed to the territory of the affected carotid artery, death during follow-up, and carotid recanalization without a prior ischemic event. Data from each study were first checked against reported results and queries were resolved with the principal investigator.

In order to reanalyze IPD with a common continuous CO2R measure, we asked all authors to contribute (published or unpublished) data on maximum % increase in CBFV during the hypercapnic challenge in their patients (pCi = percentage CBFV increase).

As a main outcome across studies, individual data on ipsilateral ischemic events were gathered for all patients. Ischemic stroke was defined as the sudden onset of new neurologic symptoms attributable to the affected ICA and lasting longer than 24 hours in all studies. Separate data for minor and major stroke and neuroimaging results were not consistently available across studies. As a further outcome, ipsilateral TIA (hemispheric or retinal, symptoms lasting <24 hours) were assessed across all studies.

Statistical analysis. Previous studies have reported percentage increase in CBFV and used a cutoff of 20%.[3] Therefore, we used this prespecified cutoff for the primary analysis as well as continuous pCi. Multiple fractional polynomials (MFPs)[13] were used to evaluate the functional form of continuous pCi and age (which was the other continuous covariable). We used the Stata programs stcox (for Cox proportional hazard regression model) as well as mfp and mfpi (for MFPs) with default settings, i.e., a p value of 0.05 was used for testing between MFP models.

We conducted the following prespecified sensitivity analyses: (1) considering interaction terms in multiple regression models between predictive value of pCi and (a) method of inducing hypercapnia (breath-holding vs CO_2 inhalation), (b) presence or absence of recent symptoms, and (c) carotid occlusion vs severe stenosis; and (2) addition of covariables hypertension and diabetes in multiple regression models. A meta-regression was conducted for the predictive value of pCi of <20% (unadjusted estimates) and year of publication to evaluate a potential trend over time. Furthermore, a heterogeneity test was conducted for unadjusted pCi <20% predictions.

In addition, a linear mixed effect model with study as a random effect was used to identify baseline variables with an influence on the percentage increase of CBFV during the hypercapnic challenge.[14]

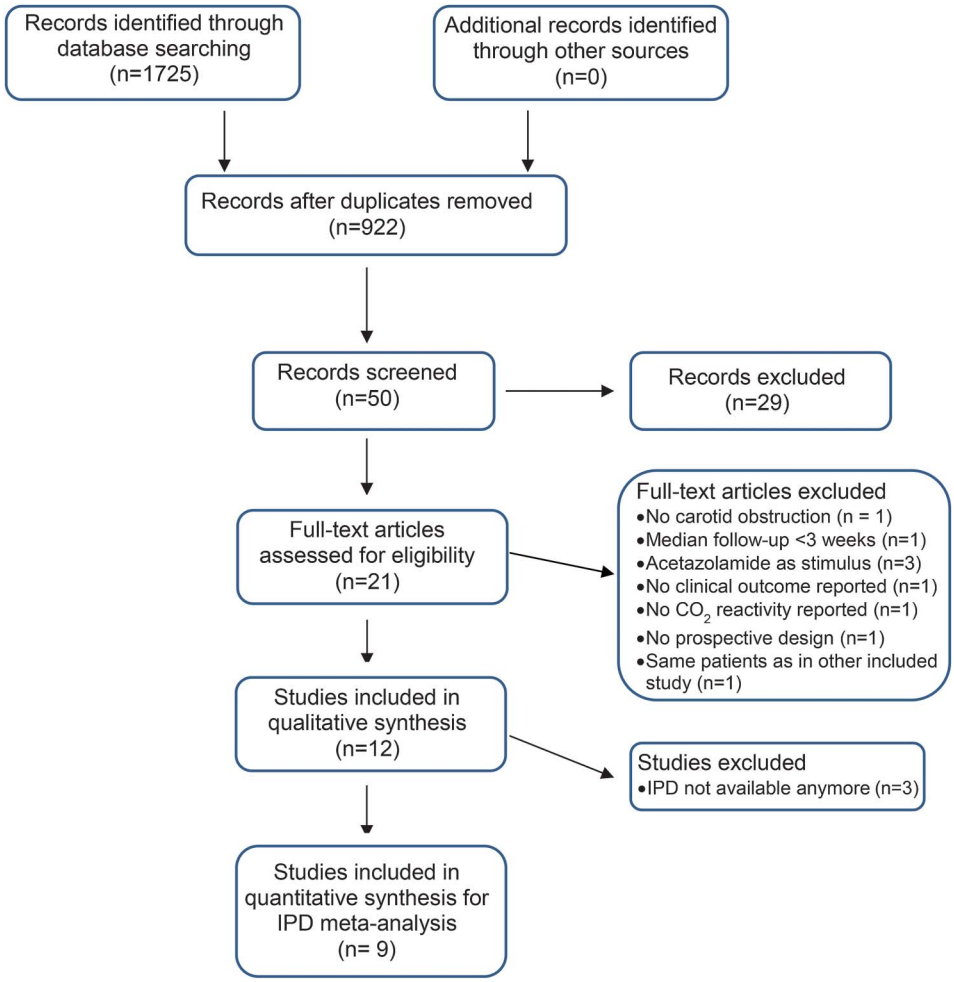
Cox proportional hazard models stratified by study (fixed effect model) were used to evaluate the prognostic value of percentage increase of CBFV during the hypercapnic challenge on the occurrence of TIA or stroke. The following covariables were considered in Cox regression models: age, sex, hypertension, diabetes, ICA stenosis ipsilateral, ICA stenosis contralateral, ischemic events during the last 3 months before study inclusion, and method of breath-holding.

RESULTS We identified 12 studies that met the inclusion criteria (figure 1). The median duration of follow-up was comparable across studies. There was, however, a considerable methodologic heterogeneity with respect to the type of CO_2 challenge (inhalation of CO_2 or breath-holding), the mode of calculating CO2R, and the cutoff used to define pathologic values (table 1). Clinical endpoints assessed were mostly ipsilateral ischemic events (stroke, cerebral TIA, and in some studies also retinal ischemia). The methodologic quality of all included studies was good; details are summarized in table e-1.

We were able to obtain IPD from 9 studies including a total of 762 patients. Data from 3 studies[4,15,16] were no longer available. These studies mostly analyzed patients with ICA occlusion: 2 of them reported an association of impaired CO2R with stroke. Because information on pCi could not be obtained in 8 patients, the total sample is based on 754 individual patients prospectively followed for stroke or TIA. Baseline characteristics of all included patients are presented in table 2. During a median follow-up time of 750 days, 59 patients (8%) had an ipsilateral ischemic stroke and 49 patients (6%) an ipsilateral TIA.

CO_2 reactivity at baseline. In a multivariable model, the common ipsilateral CO2R measure pCi was lower in patients with ipsilateral ischemic symptoms within the previous 3 months, in current smokers, in patients with more severe ICA stenosis or occlusion, and in patients with a significant contralateral ICA

Figure 1 **Flow diagram according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[27]**



IPD = individual patient data.

Table 1 Characteristics of included studies

Reference	Included in individual patient data meta-analysis	Country	Type of study	Clinical diagnosis	Type of CO2R testing and cutoff used	No. of patients followed with ipsilateral CO2R at baseline	Primary endpoint	Mean follow-up time, mo
16	No[a]	Germany	Prospective, single-center	ICA stenosis ≥50% or occlusion, asymptomatic	Inhalation of 7% CO_2 <8%/vol %	20	Ipsilateral TIA, stroke	36
4	No[a]	Germany	Prospective, single-center	ICA occlusion, symptomatic or asymptomatic	Inhalation of 5% CO_2 <10%/vol % (diminished) <5%/vol % (exhausted)	85	Ipsilateral stroke, death	38
15	No[a]	Germany	Prospective, single-center	ICA occlusion, symptomatic or asymptomatic	Inhalation of 5% CO_2 <9%/vol % (diminished) <3%/vol % (exhausted)	98	Not given	26
6	Yes[b]	Italy	Prospective, single-center	ICA occlusion, symptomatic or asymptomatic	Breath-holding 30 seconds <0.69%/s	65	Ipsilateral TIA, stroke; death	24
5	Yes	Italy	Prospective, single-center	ICA stenosis ≥70%, asymptomatic	Breath-holding 30 seconds <0.69%/s	94	Ipsilateral TIA, stroke; death	28.5
9[c]	Yes	The Netherlands	Prospective, single-center	ICA occlusion, symptomatic within ≤6 months	Inhalation of 5% CO_2 <18% CBFV increase[d]	110[d]	Ipsilateral TIA, stroke	24.2
23	Yes[b]	Italy	Prospective, single-center	ICA occlusion, symptomatic or asymptomatic	Breath-holding 30 seconds <0.69%/s	104	Ipsilateral stroke, contralateral stroke,[e] death	24
3	Yes	UK	Prospective, single-center	ICA stenosis ≥70% or occlusion, asymptomatic within previous 24 months	Inhalation of 8% CO_2	106	Ipsilateral TIA, stroke; death	20.9
24	Yes	USA	Prospective, single-center	ICA stenosis ≥80% or occlusion, symptomatic or asymptomatic	Inhalation of 5% CO_2	35	Ipsilateral TIA, stroke	6
7	Yes	Germany	Prospective, single-center	>70% ICA stenosis or ICA occlusion, symptomatic or asymptomatic	Inhalation of 7% CO_2 ≤0.70%/mm Hg	161	Ipsilateral TIA, stroke; death; carotid recanalization	24.2
25	Yes	Italy	Prospective, single-center	ICA occlusion, symptomatic or asymptomatic	Inhalation of 7% CO_2 <30% CBFV increase[d]	65	Ipsilateral stroke or vascular death	36
8	Yes	Multinational	Prospective, multicenter	ICA stenosis ≥70%, asymptomatic within previous 24 months	Inhalation of 6% CO_2	79[f]	Ipsilateral TIA, stroke	22.6[f]

Abbreviations: CBFV = cerebral blood flow velocity; CO2R = CO_2 reactivity; ICA = internal carotid artery.
[a] Studies not included in the individual patient data meta-analysis because individual data not available.
[b] Patients of both studies were partly overlapping, those with longer follow-up time being included in the present analysis.
[c] A very long-term follow-up of these patients has also been published,[26] but it has been decided to focus on data from the first publication of this population with a follow-up comparable to other studies.
[d] Reported post hoc by principal author.
[e] Contralateral stroke was not considered an endpoint in the present analysis.
[f] Only patients with a CO_2 reactivity test (hypercapnic challenge) were considered.

stenosis (table e-2). It was slightly higher with increasing age. The method of induction of hypercapnia did not significantly influence pCi results. In the subset of data with information on statin therapy available (4 studies, n = 380), no significant influence of statin treatment on pCi was found.

Multiple regression model using prespecified cutoff values for pCi. Impaired CO2R (pCi <20%) showed a highly significant and independent prognostic effect on the main endpoint of ipsilateral stroke and on the combined endpoint of ipsilateral stroke or TIA (table 3). Neither statistical heterogeneity nor a trend over time of study publication for the predictive effect of impaired CO2R was observed for either endpoint. Figure 2, A and B, shows incidence curves for the pooled patient group in the IPD analysis. Figure e-1 shows a forest plot for the prediction of ischemic events across studies.

In an interaction analysis, the specific predictive power of CO2R (relative risk increase) was not influenced by (1) the method used for induction of hypercapnia (breath-holding vs CO_2 inhalation, $p = 0.573$ for interaction), (2) the presence or absence of recent symptoms (within the previous 3 months) ($p = 0.293$ for interaction), and (3) the presence of different degrees of ipsilateral stenosis (70%–89%, 90%–99%)

Table 2 Baseline characteristics of patients included in the individual patient data meta-analysis

Parameter	Value (total n = 754)
Demographics	
Age, y, mean (SD)	67 (9.1)
Men, n (%)	580 (77)
Method of CO2R testing, n (%)	
Inhalation of CO_2	556 (74)
Breath-holding	198 (26)
Carotid artery status	
Ipsilateral carotid artery occlusion, n (%)	406 (54)
Ipsilateral carotid artery stenosis, n (%)	348 (46)
Degree of ipsilateral carotid artery stenosis, % ± SD	85 ± 7
Severe contralateral stenosis or occlusion, n (%)	57 (8)
Clinical status at entry, n (%)	
Asymptomatic within previous 3 months	535 (71)
Symptomatic within previous 3 months	219 (29)
Vascular risk factors, n (%)[a]	
Hypertension (107 missing values)	466 (72)
Dyslipidemia (108 missing values)	337 (52)
Diabetes (107 missing values)	150 (23)
Current smoking (106 missing values)	245 (38)
Treatments, n (%)	
Antiplatelet (111 missing values)	559 (87)
Oral anticoagulation (111 missing values)	86 (13)
Statin (374 missing values)	190 (50)
Follow-up	
Duration of follow-up, d, median (95% CI)	750 (741–773)
Ipsilateral stroke, n (%)	59 (8)
Ipsilateral TIA, n (%)	49 (6)

Abbreviations: CI = confidence interval; CO2R = CO_2 reactivity.
[a] Information on vascular risk factors was not available for one study[3] with 106 patients and few additional patients from other studies resulting in 646–648 patients with information on vascular risk factors.

and occlusion (p = 0.953 for interaction; detailed results of the respective proportional hazard regression models not shown).

A sensitivity analysis including the cofactors hypertension, diabetes, and smoking (data available for 647 patients, 8 studies) did not substantially change the independent predictive value of impaired CO2R for ipsilateral stroke (hazard ratio [HR] 2.54, 95% confidence interval [CI] 1.38, 4.69; p = 0.0029). Statin treatment (data available for 380 patients, 4 studies) was not associated with the risk of cerebral ischemic events and did not interact with predictive power of impaired CO2R (p = 0.90 for interaction).

Multiple regression model using continuous values of pCi. A single patient with very extreme pCi value of −73% was excluded from MFP analyses to evaluate the functional form of continuous pCi. We found a significant influence for pCi on ipsilateral stroke risk (table 3). Overall, a decrease of pCi by 10% translates to an increased risk for stroke of 64%. A sensitivity analysis considering stroke and TIA as an outcome event yielded comparable HRs (table 3).

Whereas ischemic symptoms within the previous 3 months were associated with an increase in stroke risk, the relative risk increase inferred by CO2R for the risk of ischemic stroke was similar regardless of the presence or absence of recent symptoms (interaction term p = 0.924). A Cox regression model including an interaction term between continuous pCi and method of induction of hypercapnia (breath-holding or CO_2 inhalation) showed a significant interaction between these 2 covariates with a steeper relation between pCi reduction and stroke risk increase for the breath-holding method.

Sensitivity analysis including the cofactors hypertension, diabetes, and smoking did not relevantly change the predictive value of 10% pCi decrease for ipsilateral stroke (HR = 1.49, 95% CI 1.19, 1.87; p = 0.0006).

Subanalysis in patients with asymptomatic severe ICA stenosis. Asymptomatic patients with severe stenosis were defined as patients without ipsilateral symptoms in the previous 6 months (n = 330). This typical definition could be applied as data on delay to last symptoms were more detailed for patients with stenosis than occlusion. Overall, risk prediction for ipsilateral stroke in an adjusted multivariate model (corrected for age, sex, presence of severe contralateral stenosis) was comparable to that for the overall group of patients: for the dichotomized pCi <20%: HR = 2.90 (95% CI 1.02, 8.30; p = 0.047), for pCi as a continuous value: HR = 1.95 (95% CI 1.26, 3.04; p = 0.003) per 10% decrease in pCi.

DISCUSSION This IPD meta-analysis included 754 patients with severe carotid artery stenosis or occlusion who underwent a TCD CO2R test and were prospectively followed for ischemic events. There was a strong and independent association between impaired CO2R with the risk of ipsilateral ischemic stroke and ischemic stroke or TIA. This association was similar for recently symptomatic and asymptomatic disease and for patients with severe carotid artery stenosis and occlusion. Of note, also in the specific subgroup of asymptomatic ICA stenosis, a highly predictive effect of impaired CO2R was found.

The use of IPD allows adjustment for patient characteristics across all studies. To increase comparability of studies and to identify a simple parameter for

Table 3 Prognostic effect of impaired CO_2 reactivity in severe carotid stenosis or occlusion

Parameter	Adjusted HR (95% CI)	p Value
Clinical endpoint: ipsilateral stroke		
Impaired CO2R (pCi <20%)	3.69 (2.01–6.77)	<0.0001
Age	1.08 (1.04–1.12)	0.0001
Female sex	1.22 (0.69–2.17)	0.50
Carotid occlusion vs 70%–99% stenosis	2.34 (0.66–8.28)	0.19
Contralateral stenosis ≥70%	0.77 (0.26–2.22)	0.62
Symptoms within previous 3 months	2.71 (1.07–6.86)	0.035
Clinical endpoint: ipsilateral stroke or TIA		
Impaired CO2R (pCi <20%)	2.65 (1.72–4.09)	<0.0001
Age	1.04 (1.02–1.07)	0.001
Female sex	1.40 (0.91–2.16)	0.13
Carotid occlusion vs 70%–99% stenosis	1.03 (0.50–2.15)	0.93
Contralateral stenosis ≥70%	0.57 (0.32–1.02)	0.06
Symptoms within previous 3 months	3.31 (1.80–6.10)	0.0001
Parameter	**Coefficient (95% CI)**	**p Value**
Clinical endpoint: ipsilateral stroke		
pCi (per 10% decrease, continuous values)	1.64 (1.33–2.02)	<0.0001
Age, y	1.08 (1.04–1.12)	<0.0001
Female sex	1.28 (0.72–2.29)	0.40
Carotid occlusion vs 70%–99% stenosis	1.59 (0.44–5.80)	0.48
Contralateral stenosis ≥70%	0.65 (0.23–1.88)	0.43
Symptoms within previous 3 months	2.08 (0.81–5.34)	0.13
Clinical endpoint: ipsilateral stroke or TIA		
pCi (per 10% decrease, continuous values)	1.33 (1.18–1.50)	<0.0001
Age, y	1.04 (1.02–1.07)	0.00051
Female sex	1.44 (0.93–2.23)	0.102
Carotid occlusion vs 70%–99% stenosis	0.90 (0.43–1.90)	0.79
Contralateral stenosis ≥70%	0.54 (0.30–0.97)	0.038
Symptoms within previous 3 months	3.12 (1.69–5.77)	0.00027

Abbreviations: CI = confidence interval; CO2R = CO_2 reactivity; HR = hazard ratio. Upper table: Using a pCi cutoff value of 20%. Cox regression models stratified by study. Lower table: Using continuous values of pCi. Cox regression model using multiple fractional polynomials. pCi = percentage change in cerebral blood flow velocity.

clinical risk prediction, we used the percentage CBFV increase (pCi) as a common CO2R measure across studies. This is the largest set of baseline data in patients to date, which enabled us to look for independent associations of impaired CO2R with clinical factors. Impaired CO2R was associated with contralateral severe stenosis or occlusion (indicating reduced potential of anterior crossover flow in this situation), recent symptoms (confirming the association between impaired CO2R and stroke risk), and current smoking.

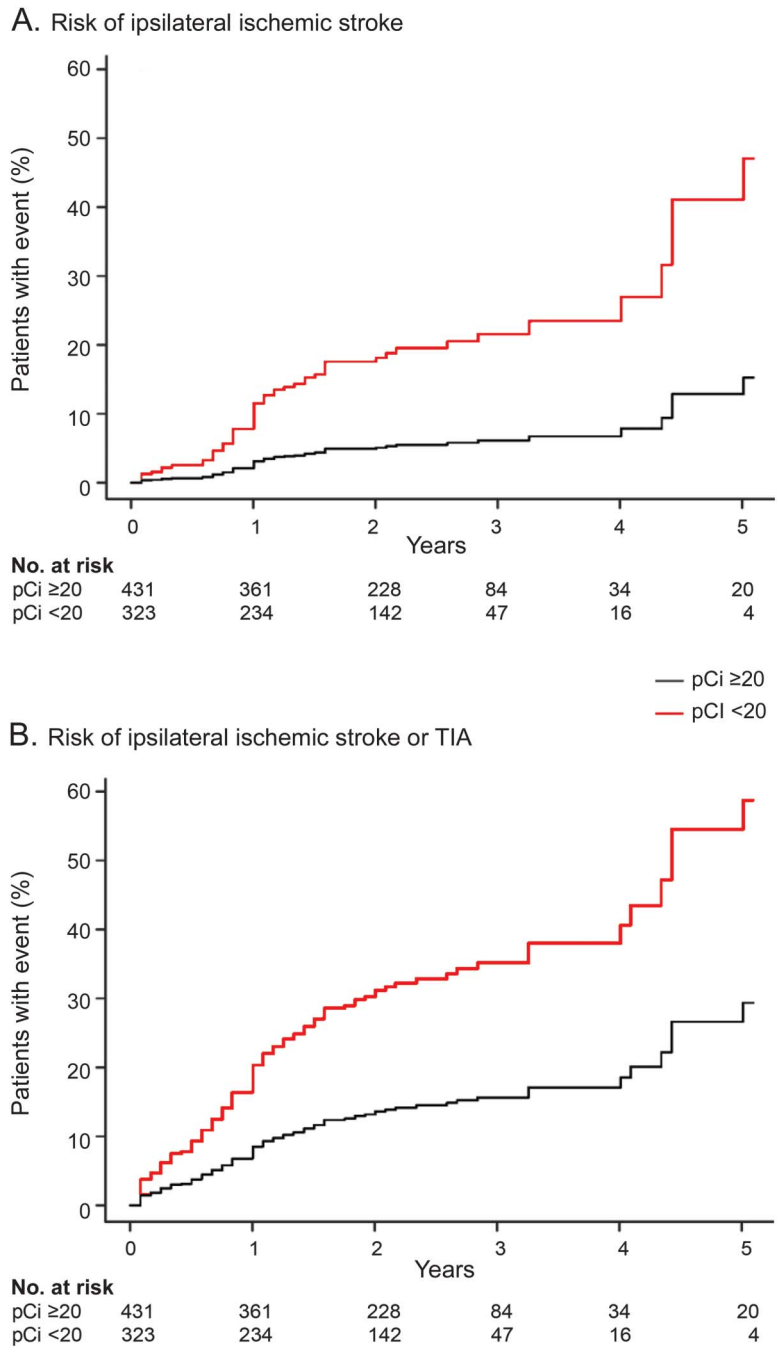
The use of cutoff values may have reduced power and has some methodologic weaknesses.[13,17] Therefore, a second analysis using continuous pCi values instead of cutoffs was performed to quantify the risk more accurately. The predictive power of pCi in this model was not relevantly affected by addition of vascular risk factors hypertension, diabetes, and smoking. This risk model needs validation in an external cohort. It might, however, be used in its present form as an indicator of the dimension of risk increase for experienced clinicians using Doppler CO_2 reactivity techniques.

In the continuous statistical model, studies using the breath-holding method showed a steeper association between pCi status and stroke risk. The reasons for this difference are unclear and potential unmeasured confounders across various study sites cannot be ruled out. Finally, chance might have played a role since IPD from 2 studies that showed a clear association using CO_2 inhalation could not be retrieved.[4,15] Thus, inferences regarding the superiority of the breath-holding method cannot be drawn.

The TCD detection of microembolic signals is another promising test to predict stroke in patients with asymptomatic carotid artery stenosis.[2] For practical reasons, the determination of CO2R, particularly using the breath-holding index, takes less time in comparison with detection of microemboli. Perhaps a combination of various ultrasound tests might improve the risk prediction. This has already been shown for the combination of plaque morphology and microemboli detection.[18] Combining CO2R testing with plaque morphology or with the detection of microemboli may improve risk prediction further. This combined approach would address 2 pathophysiologic mechanisms of stroke in carotid artery disease: microembolism due to unstable plaque and poor hemodynamic compensation leading to impaired washout of emboli or pure hemodynamic ischemia. In the Asymptomatic Carotid Emboli Study, a relation between lower CO2R and increased number of embolic signals was found but the number of outcome events was too small to establish its clinical value.[8]

Limitations of this study are that there was no information on changes in the degree of stenosis and medication details during the follow-up period. Factors like carotid revascularization without an ischemic event and varying length of follow-up within studies might have interfered with risk analysis. Although the definition of ischemic stroke was homogenous across studies, specific details (severity, borderzone or embolic pattern) were not available and therefore could not be considered in this analysis. The 3 oldest studies could not be included because of missing data. Looking at the reported results and patient characteristics of these studies, it is unlikely that they might have relevantly changed the overall results of this IPD analysis. We had a priori decided to focus this IPD meta-analysis on the more

Figure 2 **Relation between pCi and risk of ischemic stroke in carotid artery stenosis or occlusion**



Estimated incidence of ischemic events over time in the pooled group of all patients including all covariates listed in table 3. (A) Risk of ipsilateral ischemic stroke. (B) Risk of ipsilateral ischemic stroke or TIA. Hazard ratio for impaired CO_2 reactivity (pCi <20%) is slightly different from result in the Cox model used in table 3, which is additionally stratified by study (HR = 3.84 vs 3.69 for stroke, HR = 2.55 vs 2.65 for stroke or TIA; $p < 0.00001$ for all values). pCi = percentage increase in cerebral blood flow velocity (by hypercapnic stimulus).

frequently used CO_2 stimulus and did not consider studies using acetazolamide as an alternative vasodilatory stimulus.[19] This semi-invasive test may also be a risk indicator in carotid artery stenosis.[20,21]

Furthermore, CO_2 inhalation and breath-holding can induce blood pressure increases and thus overestimate the actual vasomotor reactivity.[22] In the present study, a correction for concomitant blood pressure increases was not possible since most of the studies did not monitor blood pressure during the hypercapnic challenge. However, any resultant rise in blood pressure would be expected to reduce, not increase, the association between impaired CO2R and stroke risk.

This meta-analysis based on IPD supports the usefulness of Doppler CO2R to predict the risk of ipsilateral ischemic stroke in patients with severe carotid stenosis or occlusion, with or without recent symptoms. There was no difference in prediction of clinical events; however, breath-holding may be easier to use in clinical practice than CO_2 inhalation as it does not require the use of additional equipment. The CO2R method needs to be prospectively verified in a cohort receiving current optimal medical therapy. It should be evaluated whether treatment strategies in asymptomatic patients based on CO2R could improve patient outcomes.

AUTHOR CONTRIBUTIONS

Drs. Reinhard, Schwarzer, Briel, and Vernieri conceived the study. E. Motschall performed the literature search. Drs. Reinhard and Hetzel assessed the eligibility of identified studies. Dr. Schwarzer performed the final data analysis. The following authors were chief investigators of studies included in the IPD meta-analysis or essentially contributed in providing the individual patient data: Drs. Altamura, Palazzo, King, Bornstein, Petersen, Hetzel, Marshall, Klijn, Silvestrini, and Markus. Dr. Reinhard drafted the manuscript, which was revised by all authors named above for intellectual content.

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DISCLOSURE

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