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ORIGINAL RESEARCH

Preconditioning by Preceding Ischemic Cerebrovascular Events

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BACKGROUND: Emerging yet contrasting evidence from animal and human studies associates ischemic preconditioning with improvement of subsequent stroke severity, although long-term outcome remains unclear. The purpose of this study was to analyze how preceding cerebral ischemic events influence subsequent stroke severity and outcome.

METHODS AND RESULTS: Data for this retrospective cohort study were extracted from ASTRAL (Acute Stroke Registry and Analysis of Lausanne). This registry includes a sample of all consecutive patients with acute ischemic strokes admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital, Switzerland. We investigated associations between preceding ischemic events (transient ischemic attacks or ischemic strokes) and the impact on subsequent stroke severity and clinical improvement within 24 hours, measured through National Institute of Health Stroke Scale, as well as 3-month outcome, determined through a shift in the modified Rankin Scale. Of 3530 consecutive patients with ischemic stroke (43% women, median age 73 years), 1001 (28%) had ≥1 preceding cerebral ischemic events (45% transient ischemic attack, 55% ischemic stroke; 31% multiple events). After adjusting for multiple prehospital, clinical, and laboratory confounders, admission stroke severity was significantly lower in patients preconditioned through a preceding ischemic event, but 24-hour improvement was not significant and 3-month outcome was unfavorable.

CONCLUSIONS: Preceding ischemic events were independently associated with a significant reduction in subsequent stroke severity but worsened long-term clinical outcome. These results, if confirmed by future randomized studies, may help design neuroprotective strategies. The unfavorable effect on stroke outcome is probably a consequence of the cumulative disability burden after multiple ischemic events.

Key Words: all cerebrovascular disease/stroke ■ all clinical neurology ■ outcomes research ■ preconditioning

Stroke remains one of the most important causes of morbidity and mortality worldwide, often affecting people in the most productive phase of their life.[1] Other than specialized care in stroke units, acute revascularization treatment, and specialized neurorehabilitation, neuroprotective therapy has been studied for several decades.[2] Ischemic preconditioning appears to promote natural adaptive mechanisms mediated by the brain itself in response to ischemia, leading to better ischemic tolerance.[3,4] It was first demonstrated in 1986 in transient coronary artery occlusion in anesthetized dogs, resulting in a decrease in subsequent myocardial infarct size.[5]

It is a promising mechanism that could lend itself to neuroprotection in patients or situations at high risk of acute, recurrent, or progressive ischemic damage. Various types of preconditioning stimuli have been used experimentally to protect the brain, heart, kidney, liver, and other organs. The tolerance can appear either early (within minutes) or later (after hours or days) with different underlying mechanisms; many stimuli can lead to both rapid and delayed tolerance. Interestingly, tolerance may also be triggered

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CLINICAL PERSPECTIVE

What Is New?

- Preceding ischemic events were independently associated with a significant reduction in subsequent stroke severity but worsened long-term clinical outcome.

What Are the Clinical Implications?

- The observed preconditioning effect of a preceding ischemic event, if confirmed by future randomized studies, may help design future neuroprotective strategies.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ASTRAL	Acute Stroke Registry and Analysis of Lausanne
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PIE	preceding ischemic event
TOAST	Trial of Org 10172 in Acute Stroke Treatment

by subjecting a remote organ or limb to a preconditioning stimulus.[3]

Multiple encouraging neuroprotective strategies in animal studies have not been reproduced in clinical trials in humans so far.[2,6] Better understanding of the mechanisms, timing, and magnitude of interventions in patients with stroke may generate new hypotheses and models to be tested in further trials. In this regard, results of previous analyses of preconditioning in patients with stroke have been variable or inconclusive.

A spontaneous preceding ischemic event (PIE) in the central nervous system can be considered a human model of ischemic preconditioning. Although most definitions of the ischemic penumbra stress a "time–brain volume" concept, few incorporate the idea that selective and delayed neuronal injury plays an important role.[7] Gray matter has a higher infarction threshold than white matter in patients within 24 hours of ischemic stroke onset. Hence, when assessing patients for potential therapies, tissue-specific rather than whole-brain thresholds may be a more precise measure of predicting the likelihood of infarction.[8] A mechanism of autoprotection within the white matter has been observed with gamma-aminobutyric acid B and adenosine A_1 receptors. Both act on a G protein linked to the protein kinase C pathway to limit axonal Na^+ and Ca^{2+} entry. This mechanism may play a protective role in so-called ischemic tolerance following transient ischemic attack (TIA) or minor ischemic stroke.[3,8]

Our objective was to study the potential protective effect of a PIE on subsequent ischemic stroke, using a large series of consecutive patients with acute ischemic stroke (AIS) admitted to a single stroke center over a long time period. Specifically, we wanted to know whether a PIE translates into a measurable reduction in stroke severity at onset and whether this effect depends on PIE duration or frequency, the timing between PIE and AIS, or the affected territory. We also wanted to ascertain whether PIE influences initial stroke recovery within 24 hours and long-term clinical outcome at 3 months.

METHODS

Study Population

PIE was defined as any documented cerebral (TIA or stroke) or ophthalmic (amaurosis fugax or retinal stroke) ischemic event that occurred before the index AIS. We prospectively collected and retrospectively analyzed consecutive patients from ASTRAL (Acute Stroke Registry and Analysis of Lausanne) from January 2003 to June 2015. This registry includes all consecutive patients who are admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital with a main discharge diagnosis of AIS, including recurrent AIS.[9]

In all patients, details of PIEs including the delay between the last PIE and the index AIS, the territory involved (same or other territory), and the total number of PIEs were recorded. For the duration of PIE, we selected to dichotomize the PIEs according to the historical time-based definition, ie, to classify them as TIAs if they lasted <24 hours, and as ischemic stroke if the lasted >24 hours, independently of imaging findings.[10] Furthermore, the following parameters were analyzed: demographics (age, sex, ethnicity), medical history, cardiovascular risk factors (prestroke modified Rankin Sale [mRS] score, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, symptomatic documented coronary artery disease, mechanical or biological valves, low ejection fraction <35%, symptomatic peripheral arterial disease, oncological disease, migraine, alcohol abuse), current medications (antiplatelets, anticoagulants, antihypertensives, lipid-lowering drugs, insulin, and oral antidiabetics), clinical symptoms and examination (ie, paresis, dysarthria, sensory deficit, visual field defects, eye deviation, oculomotor brainstem symptoms, cerebellar, ataxic or vestibular

signs, aphasia, neglect, level of consciousness), and other features of the stroke (affected vascular territory, National Institute of Health Stroke Scale (NIHSS) score at admission and at 24 hours, mRS score at admission and 3 months).

Comorbidities according to Charlson and Elixhauser indexes[11,12] were collected and vital signs (skin temperature, blood pressure, heart rate) and metabolic and hematologic parameters (glucose, creatinine, total cholesterol, white blood cells, hematocrit, platelet count) were measured at admission (usually in the emergency department). The NIHSS[13] was performed or supervised by NIHSS-certified personnel on admission and 24 hours later. Stroke onset time-to-hospital arrival was recorded. Stroke pathophysiology was classified according to TOAST (Trial of Org 10172 in Acute Stroke Treatment),[14] with dissections and multiple causes recorded as additional mechanisms. Acute stroke management followed European Stroke Organization and Swiss guidelines at the time of hospitalization.[15–17] The 3-month mRS was assessed both by ambulatory visits in person and sometimes by telephone.

Statistical Analysis

A professional biostatistician (M.A.) performed simple and multiple regression analyses using R statistical software (R Core Team 2014; R Foundation for Statistical Computing). For continuous variables, the coefficient represents the mean change in the outcome, associated with a unit change in the predictor variable. The summary indicates median and interquartile range. For categorical variables, categories are compared with all other categories merged. The coefficient is the difference in outcome. The intercept term is the mean value of the outcome in the merged categories, and the summary indicates numbers and proportions.

We first conducted a simple regression analysis of the above-mentioned variables with NIHSS at admission as a dependent variable. We thereafter forced the PIE characteristics (delay, duration, frequency, and territory) into a multiple regression analysis of the PIE effect, with variables included both based on statistical and clinical significance. We also conducted a multivariable-adjusted analysis of the PIE effect on delta NIHSS to quantify the effect on early improvement after stroke. The global effect of PIE and its characteristics on clinical outcome at 3 months was evaluated using an mRS shift analysis with adjustment for multiple confounders in addition to Bonferroni correction to limit chance findings. Confounders were selected as the ones that induced >10% change in the coefficient of PIE, without its variance inflation factor exceeding 5 and without causing loss of too many observations via missing values. The last condition was implemented by imposing at least 20 observations per explanatory variable in the multiple regression models.

Protocols and Ethical Approval

This study was conducted under the auspices of the ethical standards committee for research on

Table 1. Multivariable Analysis of Any PIE Effect on Admission NIHSS

Variable	β-coefficient	95% CI	
		Lower bound	Upper bound
Mean admission NIHSS without PIE (intercept)	13.04	11.73	14.34
PIE of any type	−1.35*	−2.03*	−0.67*
NIHSS prestroke	0.77*	0.55*	0.98*
Symptom onset to hospitalization	−0.16*	−0.21*	−0.11*
Private insurance	−1.05*	−1.81*	−0.28*
Silent infarction on imaging	−0.27	−0.91	0.38
Stroke localization			
Posterior circulation stroke	−4.03*	−4.76*	−3.30*
Anterior and posterior circulation stroke	−2.09	−4.83	0.64
Undetermined/other territory stroke	−3.66*	−4.53*	−2.80*
Stroke mechanism (TOAST)			
Cardiac	−0.86	−2.07	0.34
Lacunar	−2.44*	−3.47*	−1.41*
Dissection	1.43	−0.58	3.44
Unknown	−0.95	−1.98	0.07
Other determined/rare	0.38	−1.40	2.16
Multiple mechanisms	−1.28	−2.95	0.40
Risk factors			
Obesity	−1.41*	−2.01*	−0.82*
Hypercholesterolemia	−1.48*	−2.36*	−0.60*
Atrial fibrillation	2.54*	1.55*	3.52*
Symptomatic PAD	0.18	−1.05	1.41
Myocardial infraction	1.73*	0.61*	2.85*
Cancer	−0.68	−2.02	0.66
Pretreatment			
Hypolipidemic drugs	−0.41	−1.11	0.29
Antiplatelets	0.25	−0.42	0.91

This table includes several nonsignificant variables used for adjustment in addition to the ones specified in Figure 1. Confounders were selected as those inducing >10% change in the coefficient of preceding ischemic event (PIE), without its variance inflation factor exceeding 5 and without causing loss of too many observations via missing values. The last condition was implemented by imposing at least 20 observations per explanatory variable in the model. NIHSS indicates National Institutes of Health Stroke Scale; PAD, peripheral arterial disease; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Statistically significant results.

humans of the Canton of Vaud (CER-VD). Because of the retrospective nature of this study, the committee approved the use of data from ASTRAL for scientific purposes without requiring individual informed consent.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) method was applied to report results.[18]

Data Availability Statement

Anonymized data will be shared on request from qualified investigators.

RESULTS

Of 3530 consecutive patients with AIS (43% women, median age 73 years), 1001 (28.4%) had PIEs (45.0% TIA including amaurosis fugax, 55.0% ischemic stroke including retinal stroke; 30.7% had multiple events). In the prior stroke group, there were 385 cases with NIHSS ≤2 at the time of presentation of the prior ischemic stroke, and 49 with an NIHSS >2. In the prior TIA group, there were 261 cases with NIHSS ≤2 at the time of presentation of the prior TIA, and 3 with NIHSS >2. The median delay between the PIE and the subsequent stroke was 180 days (interquartile range, 5–1425 days), with 162 PIEs occurring 24 hours before the index AIS (Table S1).

PIEs correlated with a beneficial reduction in the admission NIHSS after adjusting for a wide variety of confounders (Table 1 and Figure 1). The overall reduction of NIHSS attained was 1.35 points, with a 95% CI of 0.67 to 2.03. Short-duration PIEs (TIAs, ie, symptom duration <24 hours) were more beneficial than long-duration PIEs (ie, stroke), the short versus long effect being an NIHSS reduction of 1.50 points, with a 95% CI of 0.30 to 2.70 (Table 2). Timing, frequency, and territory did not significantly influence admission NIHSS (Table 2 and Figure S1).

We observed a maximum effect on admission NIHSS in patients with a single, short-duration PIE (ie, TIA) in the same territory as the subsequent AIS (NIHSS reduction by 2.87 points; CI, 1.75–4.00) (Table 2 and Figure S1). This beneficial effect on admission NIHSS persisted over the whole range of latency before stroke (Figure 2). Patients with a single, short-duration PIE (ie, TIA) in other territories also had a lower admission NIHSS than patients without PIE, with an admission NIHSS reduction of 2.09 points (CI, 0.84–3.33).

When examining the association with change of stroke severity over the first 24 hours (delta NIHSS), no significant effect of PIE was found (Table S2 and Figure S2). Several other factors were associated with early improvement, such as early hospital arrival, lower initial NIHSS, and stroke cause. A total of 253 (25.3%)

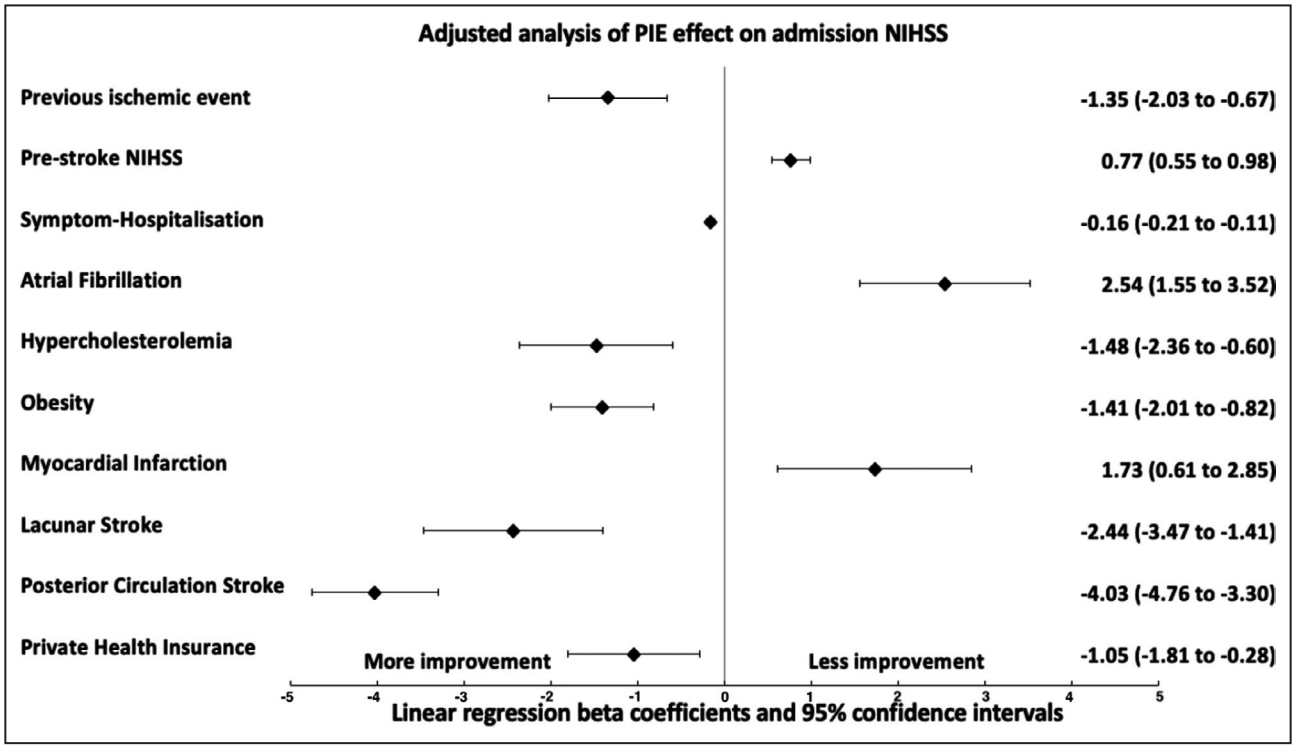

Figure 1. Multiple regression analysis of preceding ischemic event (PIE) effect on admission National Institutes of Health Stroke Scale (NIHSS) score.
Significant associations with admission NIHSS score. For more detailed results, see Table 1.

Table 2. Multiple Linear Regression Analyses of the Relationship Between Admission NIHSS and Different PIE Subtypes, Adjusted With Multiple Other Variables

Variable	β-coefficient	95% CI	
		Lower bound	Upper bound
Mean admission NIHSS without PIE (intercept)	13.40	12.06	14.73
PIE characteristics			
PIE duration (stroke vs TIA)	1.50*	0.30*	2.70*
PIE frequency (multiple vs single PIE)	0.57	−0.64	1.78
PIE territory (other vs same territory)	0.79	−0.42	1.99
PIE territory (unknown vs same territory)	0.50	−1.13	2.14
PIE timing	<0.0001	−0.0002	0.0003
PIE with strongest correlation (single, transient, same territory), timing 180 d (median timing)	−2.87*	−4.00*	−1.75*
NIHSS prestroke	0.65*	0.41*	0.89*
Symptom onset to hospitalization	−0.16*	−0.21*	−0.12*
Private insurance	−1.03*	−1.82*	−0.24*
Silent infarction	−0.25	−0.91	0.42
Stroke localization			
Posterior circulation stroke	−4.05*	−4.79*	−3.31*
Anterior and posterior circulation stroke	−2.24	−5.08	0.61
Undetermined/other territory stroke	−3.70*	−4.59*	−2.81*
Stroke mechanism (TOAST)			
Cardiac	−1.13	−2.36	0.10
Lacunar	−2.56*	−3.63*	−1.50*
Dissection	1.30	−0.74	3.34
Unknown	−1.09*	−2.16*	−0.03*
Other determined/rare	0.25	−1.60	2.10
Multiple mechanisms	−1.30	−3.03	0.44
Risk factors			
Hypercholesterolemia	−1.60*	−2.50*	−0.70*
Atrial fibrillation	2.44*	1.44*	3.43*
Obesity	−1.37*	−1.98*	−0.77*
Symptomatic PAD	−0.15	−1.37	1.08
Myocardial infarction	1.72*	0.56*	2.89*
Cancer	−0.63	−2.02	0.77
Pretreatment			
Hypolipidemic drugs	−0.34	−1.06	0.38
Antiplatelets	0.09	−0.60	0.78

Confounders were selected as those inducing >10% change in the coefficient of preceding ischemic event (PIE), without its variance inflation factor exceeding 5 and without causing loss of too many observations via missing values. The last condition was implemented by imposing at least 20 observations per explanatory variable in the model. The intercept corresponds to mean admission National Institutes of Health Stroke Scale (NIHSS) value for patients without PIE. PAD indicates peripheral arterial disease; TIA, transient ischemic attack; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Statistically significant results.

patients had a recurrent stroke in the PIE group as compared with 407 (16.1%) in the no-PIE group in the first 12 months poststroke.

Having a PIE was associated with an unfavorable shift of the mRS at 3 months after adjustment for multiple confounders (cumulative odds ratio [OR] for mRS shift, 0.83; CI, 0.72–0.96) (Table 3). When analyzing different combinations of the duration, number, delay, and territory of PIEs, we found that patients with PIE who had a single, short-duration PIE (ie, TIA) >6 months before the ensuing stroke in the same territory (cumulative OR, 2.13; CI, 1.22–3.72) were significantly associated with a better outcome at 3 months (Table S3). Bonferroni corrections for multiple testing were applied in the calculation of this last CI, since all combinations of PIE characteristics were investigated in order to find the most beneficial one.

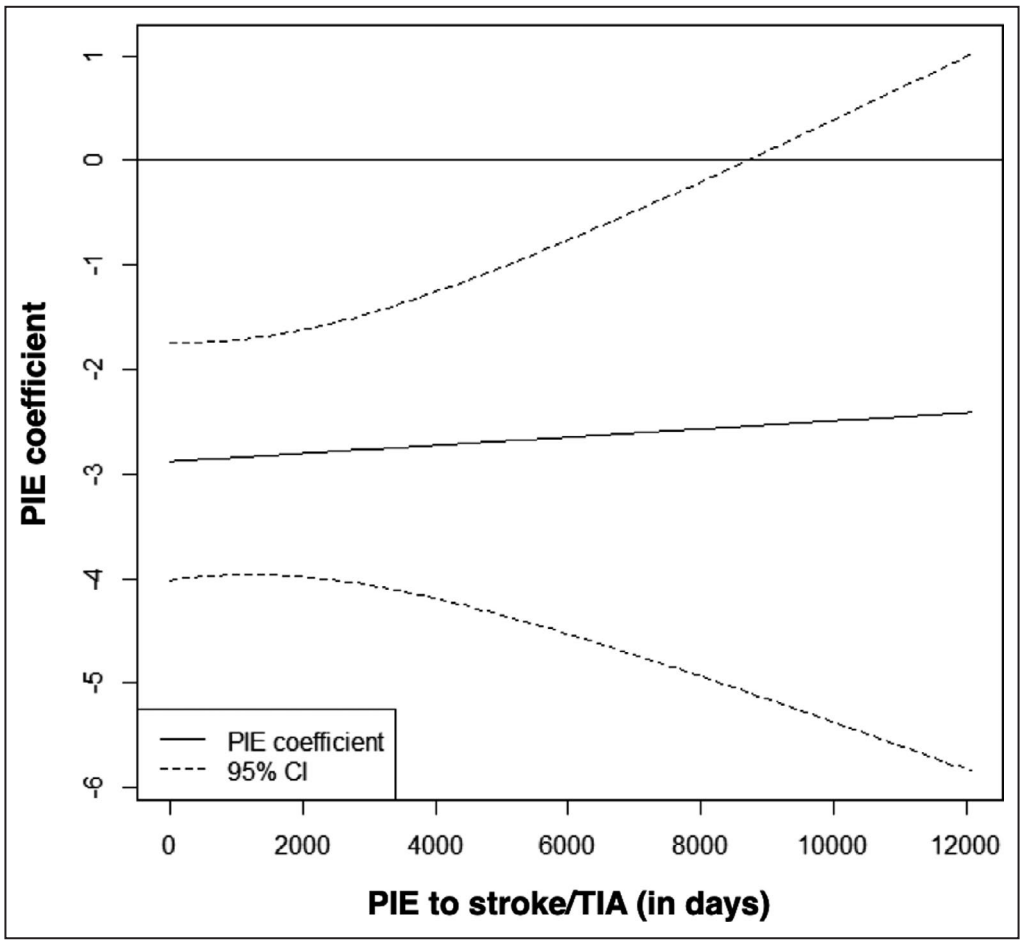

Figure 2. Graph illustrating the impact of preceding ischemic event (PIE) on stroke/transient ischemic attack (TIA) severity over time.
The graph shows that the beneficial effect of PIE (single, transient, in same territory) on stroke/TIA severity (PIE coefficient) remains relatively constant over time.

DISCUSSION

In a large consecutive cohort of patients with AIS retrospectively analyzed, we found an independent association between PIEs and reduced initial stroke severity. This beneficial effect was especially pronounced in the case of a single, short-duration event (TIA, ie, symptom duration <24 hours) in the same territory as the subsequent stroke. However, this did not translate into a long-term benefit, given that patients with PIEs had a less favorable 3-month outcome. Only temporally distant (>6 months), single, short-duration PIEs (ie, TIA) in the same territory as the ensuing AIS seem to provide a beneficial long-term effect. Furthermore, we did not observe a "dose effect," ie, a benefit of repetitive preconditioning stimuli seen in an earlier study.[19]

Previous studies have shown a favorable effect of ischemic preconditioning in animals[20,21] and humans.[19,22–24] Nevertheless, other studies did not confirm the association in humans.[25,26] The heterogeneity of results is echoed in our study, where, in spite of a beneficial influence on initial stroke severity, preconditioning seems to lead to a worse long-term functional outcome.

Effects on Admission NIHSS and Delta NIHSS

The beneficial effect of a short-duration PIE (ie, TIA) on initial stroke severity (admission NIHSS) is in line with published results showing a positive correlation between short-duration (10 to 20 minutes) TIAs and outcome.[22] Given that we have adjusted the admission NIHSS by prestroke NIHSS, residual deficits from a preceding long-duration PIE (ie, stroke) is an unlikely explanation for this finding.

A possible explanation is that the synthesis of neuroprotective proteins and the induction of neuroprotective mechanisms may be especially prevalent in short-duration events, since longer-duration events may lead to cell death, encumbering protein synthesis

Table 3. Adjusted Analysis of Global PIE Effect on mRS at 3 Months

Variable	Cumulative OR	95% CI	
		Lower bound	Upper bound
PIE effect on mRS at 3 mo	0.83*	0.72*	0.96*
Age	0.97*	0.97*	0.98*
Female sex	0.76*	0.66*	0.87*
Psychosis/depression	0.69*	0.57*	0.83*
Atrial fibrillation	0.62*	0.53*	0.73*
Congestive heart failure	0.81*	0.68*	0.97*
Coronary heart disease	1.02	0.85	1.23
Chronic renal failure	0.69*	0.56*	0.85*
Cancer	0.56*	0.41*	0.76*
Private insurance	1.43*	1.21*	1.70*
Symptom onset to hospitalization	1.00	0.99	1.01
Thrombolysis	0.64*	0.54*	0.76*
Thrombectomy	0.31*	0.21*	0.44*
Acute glucose	0.91*	0.89*	0.93*

The cumulative odds ratio (OR) for preceding ischemic event (PIE) corresponds to the effect of PIE towards better 3-month outcome (lower 3-month modified Rankin Scale [mRS]).

*Statistically significant results.

and overriding protective effects.[27] The balance between prosurvival and prodeath mechanisms has been shown in a murine model of a postischemic brain, where neuroprotective mechanisms stimulate the generation and migration of new cells from the dentate gyrus and the subventricular zone. Most of these, however, fail to efficiently integrate and ultimately die.[28,29]

Early changes in NIHSS, typically determined 24 hours after an AIS (ie, delta NIHSS), are influenced by a wide variety of factors including blood sugar, body temperature, blood pressure, and fibrinogen level.[30] We did identify multiple clinical and pathogenetic factors correlating with significantly improved 24-hour delta NIHSS, although PIE was not among these. Our research group has previously shown that factors such as stroke mechanism (eg, cervical artery dissection) and hemorrhagic transformation are associated with severe early worsening of ≥8 NIHSS points.[31] It is known that while spontaneous early improvement is common in AIS, the severity of stroke deficits becomes increasingly predictive of the final outcome over time.[32]

Effects on Long-Term Outcome

Possible explanations for the globally unfavorable association between PIEs and long-term outcome in our cohort could be that patients with recurrent cerebrovascular events have a higher risk for further strokes[33,34] or that patients with previous cerebrovascular events have a higher burden of disability, as seen in our cohort. The observed beneficial effect of a temporally distant (>180 days), single, short-duration PIE (ie, TIA) in the same territory as the subsequent AIS is an unexpected finding that requires confirmation in further studies in humans. In experimental models, ischemic tolerance does not seem to be maintained beyond a few days.[3] However, a recent study in mice showed that ischemic preconditioning could provide long-lasting neuroprotection by significantly reducing stroke-related deficits up to 35 days after the index event.[35] Previous clinical studies have looked for a preconditioning effect only days or a few weeks before the subsequent AIS, and not over longer periods of time.[19,22–24]

If our results are confirmed, preconditioning would be of benefit several months before an unpredictable future ischemic event, justifying its use as a preventive procedure. Inducing brief PIEs, especially in the territory at risk, may be difficult, but elective procedures in brain-supplying vessels, eg, carotid interventions, could serve as a testing ground for this approach.

The strengths of our study include the long-term prospective data collection and use of mutivariable-adjusted regression analyses to reduce the effect of confounders. The limitations of the study include its nonrandomized and observational nature in a single, tertiary stroke center. The use of admission NIHSS as a measure of stroke severity, rather than early infarct volume on imaging, can be questioned; still, this choice seems clinically relevant, as it is a widely used parameter to assess stroke severity and correlates reasonably well with acute infarct volumes.[36,37] Despite the multiple adjustments used in the statistical analyses, we cannot exclude that the observed association is related to other, unmeasured metabolic or genetic factors. We did not look for statistical interactions in our analysis as we aimed to primarily ascertain the overall effect of a preceding ischemic event. A more refined analysis that takes into account the effect in different patient subgroups could be the subject of future research.

CONCLUSIONS

We demonstrated that a preconditioning effect through preceding ischemic events (TIAs and/or ischemic strokes) could favorably impact the initial severity of a subsequent stroke. However, no influence on early stroke recovery could be observed and long-term clinical outcome was even worse after a preceding ischemic event. The unfavorable effect on stroke outcome is probably a consequence of the cumulative disability burden after multiple ischemic events. These results, if confirmed by future randomized studies, may help design neuroprotective strategies within the setting of elective procedures.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Simple regression analysis of admission NIHSS versus a set of variables including patient and stroke characteristics.

Variable	Total, n = 3530	PIE, n = 1001	No PIE, n = 2529	β admission NIHSS (mean)	95% CI admission NIHSS (mean)	Intercept (mean admission NIHSS of PIE Group)
Age (years)	73.1 (60.6 – 81.4)	74.4 (63.2 – 82.3)	72.4 (59.7 – 81.1)	0.03*	0.02 – 0.05*	6.59*
Female sex	1519 (43.1%)	392 (39.2%)	1127 (44.6%)	1.33*	0.82 – 1.85*	8.49*
Insurance (private)	650 (18.7%)	212 (21.2%)	438 (17.3%)	-1.44*	-2.1 – -0.79*	9.26*
Symptom onset to hospitalization delay (hours)	3.3 (1.4 – 10.7)	2.9 (1.3 – 9.7)	3.5 (1.5 – 11)	-0.23*	-0.27 – -0.19*	10.41*
mRS pre-stroke median (IQR)	0 (0 – 1)	1 (0 – 2)	0 (0 – 1)	0.98*	0.73 – 1.22*	8.25*
High mRS pre-stroke (3 to 5)	339 (9.7%)	145 (14.5%)	194 (7.7%)	3.13*	2.27 – 3.99*	8.68*
NIHSS pre-stroke median (IQR)	0 (0)	0 (0 – 1)	0 (0)	0.63*	0.37 – 0.9*	8.49*

Admission NIHSS median (IQR)	6 (3 – 14)	6 (3 – 12)	7 (3 – 15)	NA	NA	NA
Delta NIHSS median (IQR)	1 (0 – 3)	1 (0 – 3)	1 (0 – 3)	-0.38*	-0.43 – -0.32*	8.41*
Risk factors and comorbidities						
Hypertension	2491 (71 %)	766 (76.5%)	1725 (68.2%)	-0.69*	-1.25 – -0.12*	9.48*
Diabetes	645 (18.4%)	225 (22.5%)	420 (16.6%)	-0.10	-0.76 – 0.56	9.02
Hypercholesterolemia	2537 (72.7%)	772 (77.1%)	1765 (69.8%)	-2.91*	-3.47 – -2.34*	11.08*
Smoking	821 (23.9%)	459 (45.9%)	362 (14.3%)	-0.78*	-1.39 – -0.18*	9.13*
Atrial Fibrillation	993 (28.3%)	265 (26.5%)	728 (28.8%)	3.49*	2.93 – 4.05*	8.01*
Myocardial infarction	353 (10.3%)	104 (10.4%)	249 (9.8%)	1.22*	0.37 – 2.08*	8.90*
Obesity	1519 (44.9%)	451 (45.1%)	1068 (42.2%)	-2.01*	-2.53 – -1.5*	9.92*
Pyschosis /Depression	445 (13.3%)	76 (7.6%)	369 (14.6%)	-0.06	-0.83 – 0.71	9.05
Congestive heart failure	645 (18.9%)	175 (17.5%)	470 (18.6%)	1.34*	0.68 – 2.0*	8.78*
Chronic renal failure	455 (13.3%)	144 (14.4%)	311 (12.3%)	0.89*	0.13 – 1.66*	8.91*

Migraine	123 (3.6%)	34 (3.4%)	89 (3.5%)	-2.94*	-4.32 – -1.55*	9.11*
Peripheral arterial disease (PAD)	223 (6.4%)	93 (9.3%)	130 (5.1%)	-0.02	-1.06 – 1.03	8.75
Cancer	183 (5.3%)	137 (13.7%)	46 (1.8%)	-0.05	-1.19 – 1.09	9.00
Chronic alcoholism	404 (11.7%)	107 (10.7%)	297 (11.7%)	-0.24	-1.04 – 0.56	9.03
PIE duration						
Transient (<24 h, TIA)	450 (12.7%)	450 (45.0%)	NA	NA	NA	NA
Long (>24 h, stroke)	551 (15.6%)	551 (55.0%)	NA	1.69*	0.77 – 2.62*	7.43*
PIE frequency						
Single	694 (19.7%)	694 (69.3%)	NA	NA	NA	NA
Multiple	307 (8.7%)	307 (30.7%)	NA	-0.28	-1.28 – 0.72	8.45
PIE timing median (days)	NA	180 (5 – 1425)	NA	0.00	0-0	8.31
Stroke Characteristics						
Posterior	900 (26.1%)	244 (24.4%)	656 (25.9%)	-4.22*	-4.79 – -3.64*	10.17*
Anterior	2297 (66.7%)	664 (66.3%)	1633 (64.6%)	4.87*	4.35 – 5.4*	5.82*
Anterior+ Posterior	52 (1.5%)	28 (2.8%)	24 (0.94%)	0.77	-1.41 – 2.96	9.06

Undetermined/ Other territory	196 (5.7%)	67 (6.7%)	129 (5.1%)	-5.18*	-6.28 – -4.08*	9.37*
Stroke mechanism						
Large vessel Atherosclerosis	460 (13.5%)	175 (17.5%)	285 (11.3%)	0.43	-0.33 – 1.19	8.95
Cardiac	1163 (34.2%)	171 (17.1%)	992 (39.2%)	2.87*	2.33 – 3.41*	8.02*
Lacunar	424 (12.5%)	270 (26.9%)	154 (6.1%)	-5.54*	-6.3 – -4.77*	9.70*
Dissection	153 (4.5%)	123 (12.3%)	30 (1.2%)	2.32*	1.06 – 3.58*	8.90*
Unknown	861 (25.3%)	33 (3.3%)	828 (32.7%)	-1.35*	-1.95 – -0.75*	9.35*
Other determined	151 (4.4%)	61 (6.1%)	90 (3.6%)	0.83	-0.44 – 2.1	8.97
Multiple/coexisting	185 (5.4%)	59 (5.9%)	126 (5.0%)	0.66	-0.49 – 1.82	8.97
Pre-treatment						
Antiplatelets	1336 (38.4%)	550 (54.9%)	786 (31.1%)	-0.06	-0.59 – 0.46	8.96
Oral anticoagulants	403 (35.4%)	149 (14.9%)	254 (10.0%)	1.55*	0.76 – 2.35*	8.76*
Anti hypertensives	2040 (58.7%)	636 (63.5%)	1404 (55.5%)	-0.10	-0.62 – 0.42	8.98
Anti diabetics	429 (12.3%)	110 (10.9%)	319 (12.6%)	-0.64	-1.42 – 0.13	9.02
Lipid lowering agents	974 (27.8%)	402 (40.2%)	572 (22.6%)	-0.71*	-1.28 – -0.14*	9.16*

Acute physiology and laboratory values						
Temperature	36.3 (0.7)	36.3 (36 – 36.7)	36.3 (36 – 36.7)	-0.68*	-1.08 – -0.28*	33.70*
Systolic blood pressure	153 (36)	154 (139 – 171)	152 (287 – 324)	-0.01*	-0.02 – 0*	10.73*
Diastolic blood pressure	85 (23)	85 (74 – 96)	85 (74 – 98)	-0.02*	-0.03 – 0*	10.51*
Heart rate	79 (22)	78 (68 – 90)	80 (67 –90)	0.05*	0.04 – 0.07*	4.78*
Glucose	6.6 (2.2)	6.5 (5.7 – 7.8)	6.5 (5.8 – 7.9)	0.21*	0.11 – 0.31*	7.43*
Creatinine	87 (32)	89 (75-107)	86 (73 – 104)	0.00	-0.01 – 0	9.21
Total cholesterol	5.2 (1.7)	5 (4.3-6)	5.3 (4.5 – 6)	-0.06	-0.14 – 0.02	8.87

Statistically significant results are indicated by *.

β = beta coefficient; CI = confidence interval; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; PIE = previous ischemic event.

Table S2. Multiple regression analysis of PIE effect on NIHSS at 24 hours (Delta NIHSS)

	β	95% CI	
		lower bound	upper bound
Mean admission NIHSS without PIE (Intercept)	-0.97	-2.15	0.21
PIE	-0.24	-0.69	0.22
NIHSSadm	-0.17*	-0.21*	-0.13*
NIHSS pre-stroke	0.05	-0.10	0.21
Symptom onset to hospitalization	0.04*	0.02*	0.07*
mRS pre-stroke	0.16	-0.06	0.38
Private Insurance	-0.22	-0.75	0.31
Age	0.02*	0.00*	0.03*
Stroke localization			
Posterior Circulation Stroke	-0.22	-0.67	0.24
Anterior and Posterior circulation stroke	0.31	-0.91	1.53
Undetermined/ Other territory stroke	-0.45	-0.94	0.04
Stroke Mechanism (TOAST)			
Cardiac	-0.85*	-1.54*	-0.16*
Lacunar	-0.61	-1.26	0.04
Dissection	1.05	-0.48	2.59
Unknown	-0.80*	-1.50*	-0.11*
Other determined/rare	-0.81	-1.94	0.33
Multiple mechanisms	-0.39	-1.32	0.54
Risk factors			
Diabetes	-0.16	-0.64	0.32
Obesity	-0.14	-0.55	0.26
Cancer	0.35	-0.33	1.04
Migraine	-0.13	-0.93	0.68
Comorbidity PAD	0.22	-0.32	0.77

Symptomatic PAD	0.24	-0.70	1.18
Psychosis/Depression	0.60*	0.04*	1.16*
Pre-treatment			
Hypolipidemic drugs	-0.58*	-1.05*	-0.12*
Antiplatelets	0.26	-0.22	0.74
Anticoagulants	0.35	-0.35	1.06

This table includes several non-significant variables used for adjustment in addition to the ones specified in eFigure 2. In this analysis, the coefficient for PIE corresponds to the average effect of having any PIE (with all adjustment variables staying the same). Confounders have been selected as the ones that induced more than 10% change in the coefficient of PIE, without its variance inflation factor exceeding 5 and without causing loss of too many observations via missing values. The last condition was implemented by imposing at least 20 observations per explanatory variable in the model. Statistically significant results are indicated by *.

CI = confidence interval; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; PAD: Peripheral artery disease; PIE = previous ischemic event.

Table S3. Adjusted analysis of PIE effect on mRS at 3 months considering effects of PIE characteristics

	Cumulative OR	95% CI	
		lower bound	upper bound
PIE effect on mRS at 3 months (>180 days before stroke)	2.13*	1.50*	3.04*
PIE effect on mRS at 3 months (0 to 180 days before stroke)	0.49*	0.36*	0.66*
Age	0.97*	0.97*	0.98*
Female Sex	0.75*	0.65*	0.86*
Psychosis/Depression	0.69*	0.57*	0.83*
Atrial Fibrillation	0.64*	0.54*	0.75*
Congestive Heart Failure	0.82*	0.68*	0.98*
Coronary Heart Disease	1.01	0.83	1.21
Chronic Renal Failure	0.66*	0.53*	0.81*
Cancer	0.54*	0.40*	0.74*
Private Insurance	1.43*	1.21*	1.70*
Symptom onset to hospitalisation	1.00	0.99	1.01
Thrombolysis	0.62*	0.52*	0.74*
Thrombectomy	0.29*	0.20*	0.42*
Acute Glucose	0.91*	0.89*	0.94*
PIE characteristics			
PIE duration (TIA versus stroke)	0.53*	0.40*	0.70*
PIE frequency (single versus multiple PIE)	0.95	0.72	1.24
PIE territory (same versus other territory)	0.63*	0.47*	0.85*
PIE territory (same versus unknown territory)	0.59*	0.39*	0.89*

The cumulative OR for PIE corresponds to the effect of PIE towards better 3-month outcome (lower mRS at 3 months). Statistically significant results are indicated by *.

CI = confidence interval; OR = odds ratio; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; PIE = previous ischemic event.

Figure S1. Effect of PIE characteristics on admission NIHSS.

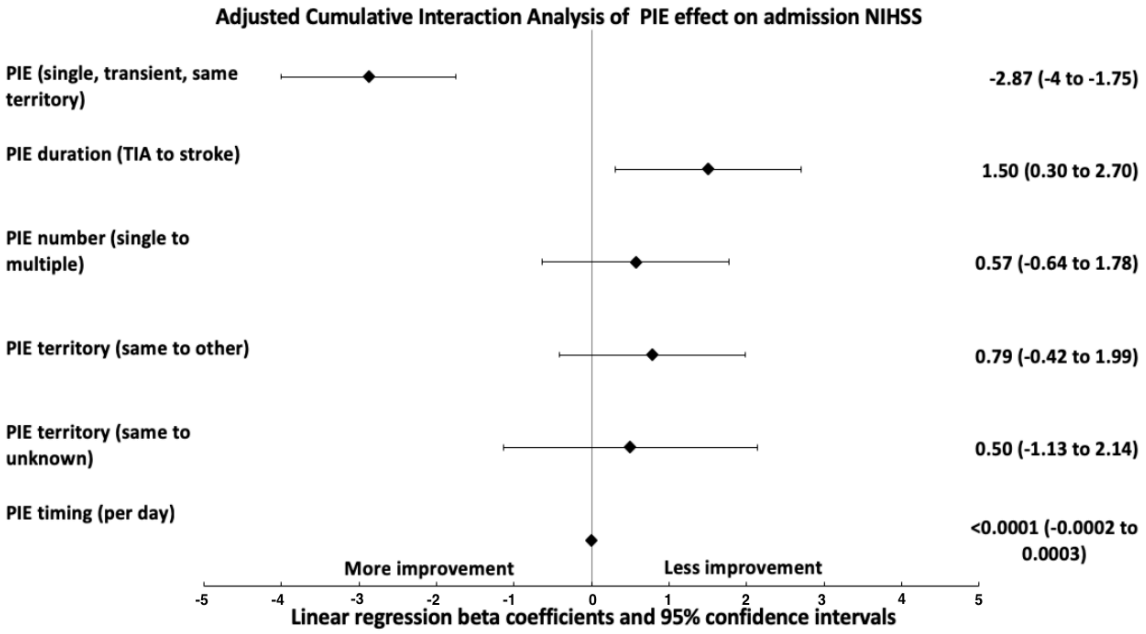

Figure S2. Multiple regression analysis of PIE effect on NIHSS at 24 hours (Delta NIHSS) Significant associations with delta NIHSS, including the (non-significant) PIE variable.