

The Quest for Early Predictors of Stroke Evolution

Can TCD Be a Guiding Light?

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Background and Purpose—The present study aimed at evaluating the prognostic value of transcranial Doppler ultrasonography (TCD) in the acute phase of ischemic stroke, when major therapeutic decisions must be made.

Methods—Seventy-three patients with a first-ever ischemic hemispheric stroke underwent neurological assessment according to the Unified Neurological Stroke Scale, clinical subgrouping according to the criteria of Bamford, CT scan, cervical duplex sonography, and TCD, all within 12 hours from stroke onset. TCD was repeated on days 2 and 7. Patients were followed for 90 days, during which we calculated the fatality rate and then assessed clinical outcome.

Results—Emergency TCD revealed middle cerebral artery (MCA) no-flow in 24 cases and MCA asymmetry in 30 subjects. Serial TCD showed early (<24 hours) MCA recanalization in 6 patients. After 90 days, no patient with MCA occlusion at admission was autonomous, while 17 of 19 patients (89.5%) with a normal baseline TCD were independent. The fatality rate at 3 months was 21% but was 46% in patients with MCA occlusion and 61% in patients without signs of early MCA recanalization. Total anterior circulation infarct and abnormal TCD were significantly correlated ($P<0.001$) with higher mortality rate and worse outcome (Barthel Index score ≤ 60), whereas early CT ischemic signs and severe carotid disease were not. Furthermore, TCD identified within the total anterior circulation infarct subgroup 2 prognostic clusters according to MCA patency at admission ($P<0.001$). Logistic regression selected normal baseline TCD as an independent predictor of good long-term outcome and MCA no-flow as an independent predictor of disability or death.

Conclusions—TCD findings play an important role in the early prognosis of anterior circulation stroke, providing possible guidance for therapeutic interventions. (*Stroke*. 2000;31:2942-2947.)

Key Words: cerebral ischemia ■ stroke outcome ■ ultrasonography, Doppler, transcranial

Transcranial Doppler ultrasonography (TCD) offers a noninvasive and rapid assessment of patients with acute ischemic stroke by localizing cerebral arterial occlusion or abnormal waveforms and indicating collateral compensatory pathways^{1,2}; this is especially true in the middle cerebral artery (MCA) territory, where TCD reaches very high specificity values, close to 100%.^{3,4} A previous study⁵ has indicated a very interesting correlation between TCD findings in the first 24 hours from stroke onset, MCA territory infarction pattern, and clinical outcome. Nevertheless, such relevant information on intracranial hemodynamics has not entered the decision-making process of therapeutic interventions and still remains merely an academic, unexplored notion.

The National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Trial⁶ has shown that intravenous recombinant tissue plasminogen activator (tPA) improves, although only slightly, the outcome of acute cerebral ischemia when administration is started within 3 hours of symptom onset; moreover, the Second European Cooperative Acute Stroke Study (ECASS II) and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke

(ATLANTIS) trial were unable to demonstrate a benefit from the same treatment beyond the 3-hour time window, even though carefully selected patients with anterior circulation ischemia might improve their outcome if tPA therapy is given within 6 hours.^{7,8} Paradoxically, in all these trials the decision of following this therapeutic approach was not based on cerebral vessel status but on clinical examination and CT only; in particular, the European study excluded from treatment those patients with early ischemic CT signs because of a previously reported higher risk of intracerebral hemorrhage and poor outcome.^{9,10} However, we know from daily practice that in the very early stages of stroke, patients with only transient ischemic attacks cannot be identified clinically and that among patients presenting with the same symptomatology, some improve spontaneously while others do not. Furthermore, early CT changes are burdened by a significant interobserver variability, and, among patients with a hyperdense MCA sign, those who are given tPA have a better neurological recovery than those who received placebo.¹¹ Therefore, in light of evidence from previous trials, there is a great need to find early reliable prognostic factors to tailor the treatment of cerebral ischemia.

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In the present study we sought to evaluate the prognostic value of TCD in the acute phase of ischemic stroke and its possible role in guiding and monitoring therapeutic interventions.

Subjects and Methods

This was a multicenter prospective study on first-ever acute ischemic MCA stroke. Seventy-three patients were enrolled according to the following criteria. Inclusion criteria were as follows: (1) acute cerebral ischemia in the MCA territory with a neurological deficit lasting >1 hour to minimize the enrollment of patients with transient ischemic attack, since episodes that last >1 hour are usually minor infarctions¹²; (2) brain CT, color-coded extracranial duplex ultrasonography, and TCD¹³ performed within 12 hours of clinical onset (for those patients who awakened with symptoms, the time of falling asleep was defined as stroke onset); (3) age between 35 and 85 years; (4) a Unified Neurological Stroke Scale (UNSS) score between 5 and 24, with a motor power score <9; and (5) patent temporal bone windows. Exclusion criteria were as follows: (1) stupor or coma; (2) previous ischemic stroke; (3) cerebral hemorrhage on CT; (4) preexisting neurological, psychiatric, or other illness that would confound the neurological evaluations; (5) severe concomitant medical condition (eg, metastatic cancer, AIDS); and (6) pregnancy.

On admission, neurological deficit was quantified according to the UNSS score, and patients were classified according to the criteria of Bamford et al¹⁴ into 3 clinical subgroups: total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), and lacunar infarcts (LACI). All patients underwent a cerebral CT to exclude a hemorrhagic stroke and to disclose early signs of cerebral ischemia such as effacement of cortical sulci, parenchymal hypodensity, hyperdense MCA sign, loss of insular ribbon sign, and lenticular sign. Finally, a complete color-coded duplex ultrasonographic assessment of the extracranial vessels and a TCD of the basal cerebral arteries were performed within 12 hours of the onset of symptoms. We repeated the CT scan after a few days and the TCD on days 2 and 7. TCD findings were classified as follows: (1) MCA occlusion, when no flow signal was detected in the symptomatic MCA while it was present in the ipsilateral anterior cerebral artery and posterior cerebral artery; (2) MCA asymmetry, when the side-to-side flow velocity difference was >30%; (3) normal MCA, when side-to-side flow velocity difference was <30%; and (4) no temporal bone window, when normal extracranial internal carotid artery findings were associated with no flow signal in the symptomatic MCA, ipsilateral anterior cerebral artery, and posterior cerebral artery; in case of suspected distal internal carotid artery occlusion, an examination of the carotid siphon and of the anterior cerebral artery was performed through the transorbital window. Serial TCD findings were compared with those at entry, and we considered a change from no flow to asymmetry or to normal velocity as MCA recanalization, whereas the disappearance of blood flow signal was defined as a marker of a new MCA occlusion.

During hospitalization, no patient received thrombolysis (a therapy not yet registered in Italy for acute ischemic stroke), but patients received osmotic agents, antiplatelet agents, subcutaneous heparin, intravenous heparin, or oral anticoagulants when indicated.

We followed the patients for 90 days, during which we calculated the fatality rate; afterward, we evaluated the residual activities of daily living of survivors, considering a Barthel Index¹⁵ (BI) score ≤60 to be a poor functional outcome.

Statistical Analysis

Statistical analysis was performed with the use of Statistica software. Univariate tests (χ^2 , Fisher's exact test, Spearman's ρ) were used to correlate age, risk factors for stroke, early and repeated CT scan findings, clinical characteristics (UNSS and Bamford's classification), stroke treatment, cervical duplex ultrasonography, and TCD findings with clinical outcome (BI score). A logistic regression analysis was used to determine independent predictors of clinical evolution among those baseline parameters that showed a statistical

significance in univariate tests. A *P* value <0.05 was considered significant.

Results

Demographic data, baseline clinical characteristics, baseline investigational findings, and 90-day clinical outcome are summarized in the Table. On admission, of the 73 patients studied with acute cerebral ischemia in the MCA territory, 52 (71%) were clinically classified as TACI, 14 (19%) as PACI, and the remaining 7 (10%) as LACI; the mean UNSS score was 12.7 ± 8.6 . Eleven patients (7 TACI, 3 PACI, and 1 LACI) were not enrolled because of an insufficient temporal bone window.

The clinical outcome at 3 months was scored by the BI: 30 patients (41%) were independent (BI score >60), while 28 patients (38%) were disabled (BI score ≤60); 15 patients died within 90 days and 11 within 7 days, so that the overall mortality rate was 21%. There were no differences in outcome regarding sex, age, stroke side, presence of hypertension, diabetes, smoking, previous transient ischemic attack, peripheral arteriopathy, and cardiopathies except for atrial fibrillation, which was significantly more frequent in patients with poor outcome (*P*=0.01). The TACI subgroup had a significantly worse prognosis than PACI and LACI (*P*<0.001), while the UNSS score showed an overall good correlation with outcome (Spearman's ρ , *P*<0.001). Regarding drug therapy, osmotic agents, antiplatelet agents, intravenous heparin, subcutaneous heparin, and oral anticoagulants were given to improving patients just as frequently as to deteriorating patients.

In the baseline CT, we observed early ischemic signs in 27 subjects (37%); 9 of these (12%) presented a hyperdense MCA sign. Of the 65 patients who underwent a second cerebral CT scan, 4 had a lacunar infarct (<1.5 cm), 23 had a medium-sized infarct (<3 cm), and 38 had a large infarct (>3 cm); 3 patients died before the second CT was performed.

Ultrasonographic assessment of the extracranial vessels revealed an ipsilateral internal carotid artery occlusion in 25 patients (34%), whereas in 8 cases (11%) we found an ipsilateral severe carotid stenosis (>70%).

The baseline TCD displayed MCA blood flow velocity asymmetry in 30 subjects (41%) and MCA occlusion in 24 patients (33%). Serial TCD showed MCA recanalization in 9 patients, 6 of whom recanalized within 24 hours. All MCA occlusions were observed in the TACI subgroup. The fatality rate was 46% (11/24) in patients with MCA occlusion, and it increased to 61% (11/18) in those cases in which MCA did not recanalize within 24 hours. In these patients death was most often caused by massive brain edema, a feature of the "malignant MCA syndrome."¹⁶ Late recanalization did not alter clinical outcome. Finally, in one patient who neurologically deteriorated and died on day 2, TCD findings changed from MCA asymmetry at admission to MCA no-flow at the 24-hour control.

In univariate analysis, early ischemic CT signs and carotid disease did not predict clinical evolution (Figure 1). TACI subgroup and baseline TCD findings did not correlate with the presence of early CT changes but showed a strong

Demographic Data, Baseline Characteristics, Risk Factors for Stroke, Repeated CT, Therapy, and Clinical Outcome

Total		90-Day Outcome			P
		Dead	Disabled	Independent	
No. of patients	73	15 (21%)	28 (38%)	30 (41%)	...
Sex	43 men	9 (60%)	15 (54%)	19 (63%)	NS
	30 women	6 (40%)	13 (46%)	11 (37%)	...
Age	65.8±12.8 y	70.3±11.7	67.1±12.5	62.6±13.1	NS
Time window	5.8±3.5 h	6±3.87	6.1±3.5	5.7±3.5	NS
	<3 h, 32% of pts	5 (33%)	9 (32%)	10 (33%)	...
	<6 h, 65% of pts	9 (60%)	18 (64%)	21 (70%)	...
Stroke side	37 left	10 (67%)	11 (39%)	16 (53%)	NS
	36 right	5 (33%)	17 (61%)	14 (47%)	...
Clinical subgroups	52 (71%) TACI	15 (100%)	25 (89%)	12 (40%)	<0.001
	14 (19%) PACI	0	3 (11%)	11 (37%)	...
	7 (10%) LACI	0	0	7 (23%)	...
Baseline UNSS	12.7±8.6	5.1±2.4	9.1±5.4	19.7±7.6	<0.001
Baseline CT	46 (63%) normal	8 (53%)	18 (64%)	20 (67%)	NS
	27 (37%) early ischemic signs	7 (47%)	10 (36%)	10 (33%)	...
Repeated CT	4 (6%) lacunar (<1.5 cm)	0	0	4 (16%)	...
	23 (35%) medium (<3 cm)	1 (8%)	9 (32%)	13 (52%)	<0.01
	38 (59%) large (>3 cm)	11 (92%)	19 (68%)	8 (32%)	...
Ipsilateral carotid disease	25 (34%) occlusion	7 (47%)	10 (36%)	8 (27%)	NS
	8 (11%) stenosis >70%	0	1 (4%)	7 (23%)	...
	40 (55%) normal	8 (53%)	17 (60%)	15 (50%)	...
Baseline TCD	24 (33%) MCA occlusion	11 (73%)	13 (46%)	0	<0.001
	30 (41%) MCA asymmetry	4 (27%)	13 (46%)	13 (43%)	...
	19 (26%) normal	0	2 (7%)	17 (57%)	...
Therapy	Heparin	1 (7%)	3 (11%)	1 (3%)	NS
	Antiplatelet agents	14 (93%)	25 (89%)	29 (97%)	NS
	Osmotic agents	14 (93%)	26 (93%)	23 (77%)	NS
Risk factors	12 Atrial fibrillation	6 (40%)	5 (18%)	1 (3%)	0.01
	16 Other cardiopathies	2 (13%)	5 (18%)	9 (28%)	NS
	42 Hypertension	10 (67%)	16 (57%)	16 (53%)	NS
	13 Diabetes	3 (20%)	5 (18%)	5 (17%)	NS
	13 Previous TIA	1 (7%)	7 (25%)	5 (17%)	NS
	23 Cigarette smoking	3 (20%)	9 (32%)	11 (37%)	NS

Data are mean±SD or as shown. Time window indicates the time elapsed from stroke onset to recruitment; TIA, transient ischemic attack.

correlation with outcome ($P<0.001$; Figure 2). Particularly, none of the patients with MCA occlusion was autonomous at 90 days, while almost all patients (17/19, 89.5%) were independent when basal TCD was normal.

TACI, MCA occlusion, and MCA asymmetry were significantly correlated with mortality rate ($P<0.001$) and with worse outcome (BI score ≤ 60) in survivors at 3 months ($P<0.001$), but TCD was able to identify within the same clinical subgroup (TACI) 2 clusters with significantly different prognosis on the basis of MCA patency at admission ($P<0.001$, Fisher's exact test; Figure 3). The size of the infarct, as shown by the second CT scan, was also significantly correlated with clinical outcome ($P<0.01$, Pearson χ^2),

even though this finding is temporally inadequate for planning acute treatment.

Finally, a logistic regression analysis was performed to determine independent predictors of clinical evolution among those baseline parameters that showed a statistical significance in univariate tests. We found that TCD at admission was an independent strong predictor of outcome, while coexisting atrial fibrillation and clinical subgrouping did not add any significant contribution to prognosis.

Discussion

In our study we have shown the feasibility of TCD in unmasking the presence and site of an arterial occlusion; this

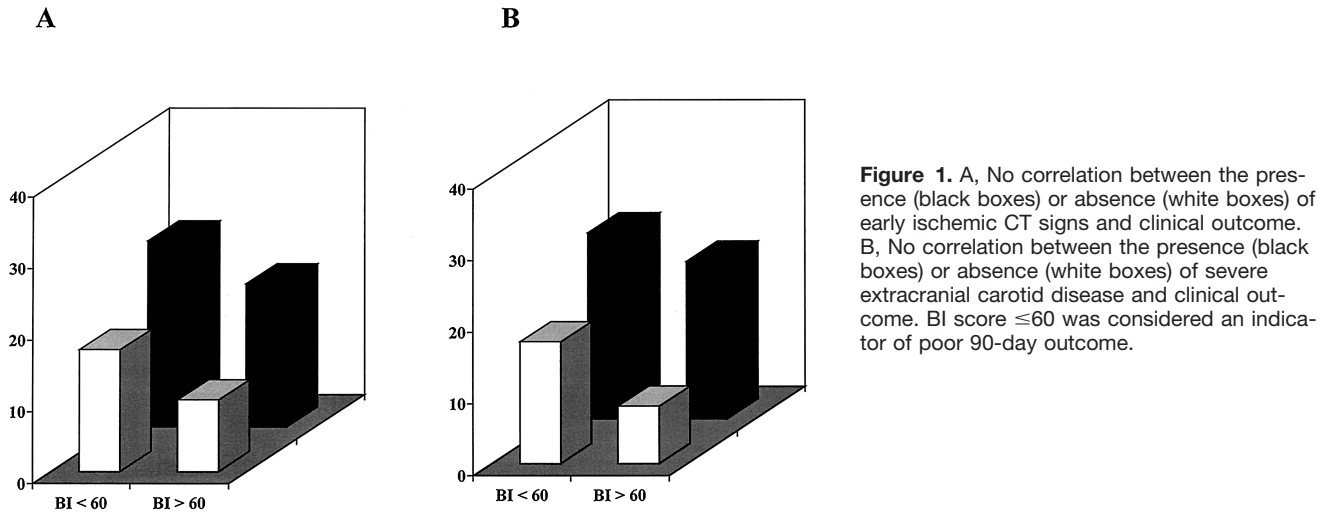


Figure 1. A, No correlation between the presence (black boxes) or absence (white boxes) of early ischemic CT signs and clinical outcome. B, No correlation between the presence (black boxes) or absence (white boxes) of severe extracranial carotid disease and clinical outcome. BI score ≤ 60 was considered an indicator of poor 90-day outcome.

would offer both interesting insights into the pathophysiological mechanisms and new reliable prognostic elements that could guide a tailored treatment of acute stroke.

In addition to TCD, early brain CT scanning, pivotal in the exclusion of cerebral hemorrhage or stroke-like disease, has been proposed as a prognostic tool. The presence of early ischemic signs involving an extended area of the MCA territory has been correlated with a poor outcome in the ECASS I trial,⁹ and it became an exclusion criterion in ECASS II. Even though our sample size is smaller than those of the aforementioned studies, our findings are consistent with those of Bornstein et al¹⁷ and Goertler et al¹⁸ showing no significant correlation between early ischemic CT signs and 90-day outcome. This should not be too surprising because in the hyperacute phase (within 3 hours of symptom onset), a CT is often normal even when a large area of brain parenchyma has been damaged.¹⁹ On the other hand, false-positive CT signs can be present; for example, a hyperdense MCA has been observed in asymptomatic patients with a high hematocrit or with atherosclerotic calcifications.^{20–23} Moreover, from a therapeutic point of view, in the NINDS study those patients with early ischemic CT signs treated with recombinant tPA had a better 3-month outcome than those patients

treated with placebo, confirming the weak prognostic role of CT in stroke patients.

Similar to CT, color-coded duplex ultrasonography does not seem to provide any additional critical data. In our study extracranial carotid occlusion or severe stenosis has shown no significant impact on clinical evolution, confirming the paramount importance of the circle of Willis in preventing hemodynamic ischemic damage.^{24–26}

The clinical presentation at onset is known to be very important in terms of outcome; our patients showed a significant correlation between the Bamford categorization (especially those patients in the TACI subgroup) or UNSS score and the BI at 3 months, thus confirming that patients with a severe clinical presentation are more likely to have a poor outcome compared with patients presenting with mild symptoms. However, even in the same clinical subgroup, we observed a wide spectrum of outcomes. Indeed, it is known from daily clinical practice and from recent single-photon emission CT studies²⁷ that patients presenting with the same symptoms may subtend diverse etiologies and perfusional deficits. This variability, which remains unrevealed in Bamford's classification, may explain the different therapeutic response and the clinically relevant frequency of intracranial

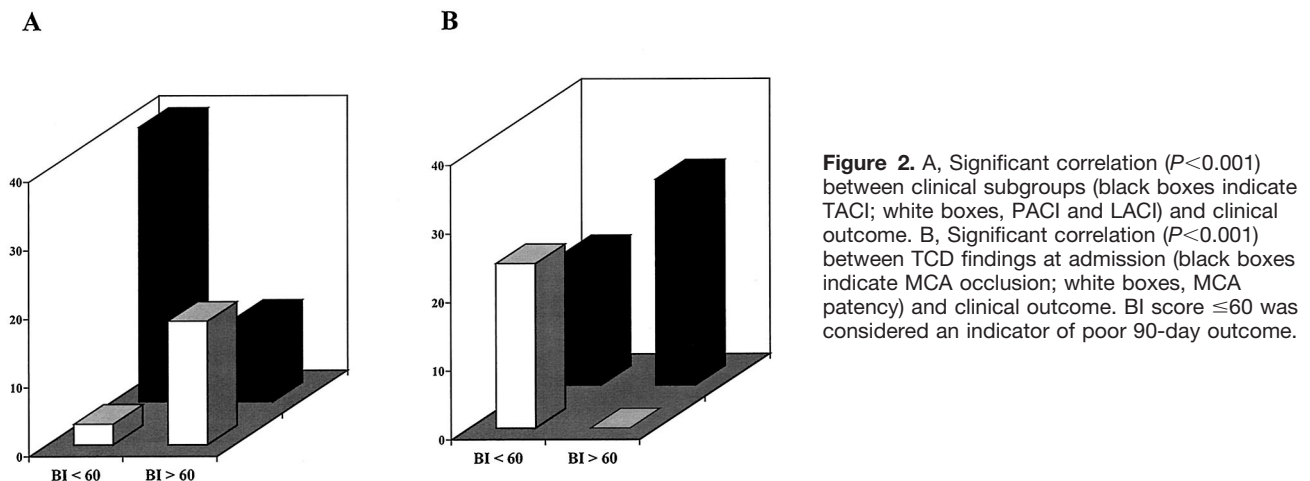


Figure 2. A, Significant correlation ($P < 0.001$) between clinical subgroups (black boxes indicate TACI; white boxes, PACI and LACI) and clinical outcome. B, Significant correlation ($P < 0.001$) between TCD findings at admission (black boxes indicate MCA occlusion; white boxes, MCA patency) and clinical outcome. BI score ≤ 60 was considered an indicator of poor 90-day outcome.

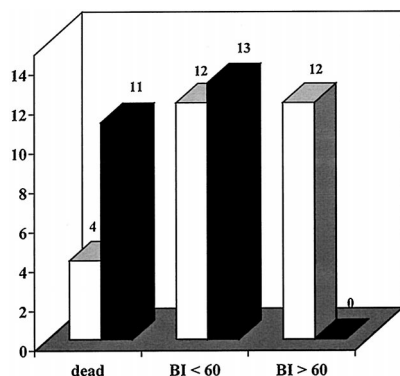


Figure 3. Strong correlation ($P<0.001$) between TCD findings at admission and 90-day outcome in patients with TACI. Black boxes indicate MCA occlusion; white boxes, MCA patency.

hemorrhage after thrombolysis.²⁸ A noninvasive bedside and expeditious investigational tool such as TCD is able to add key prognostic information even in patients with a similar clinical presentation and apparently similar outcome: in our TACI subgroup, TCD was indeed able to distinguish different prognostic clusters, and, in particular, the finding of an MCA occlusion seemed to predict death or disability at 3 months. These patients, many of whose conditions evolved into a malignant MCA syndrome, might not benefit from the same therapeutic approach as those TACI patients with a patent MCA, so that more aggressive therapeutic interventions such as induced hypothermia or decompressive craniotomy should be taken into account. Those patients with a patent MCA, early clinical improvement, and mild symptoms at admission seemed to have a much better prognosis, in accordance with Toni and coworkers,²⁹ who found similar results in an angiographic study performed within 5 hours of stroke onset.

In addition to depicting early vascular status, serial TCD allowed the monitoring of subsequent cerebral hemodynamic changes. Our data suggest that early spontaneous recanalization even beyond the first 6 hours is associated with a lower fatality rate, underscoring the relevance and the individual variability of the window of opportunity, ie, the time within which a therapeutic or a spontaneous recanalization can save ischemic brain tissue. In contrast, late (>24 hours) hemodynamic changes do not influence clinical evolution. These results are similar to those reported in a previous study which showed that early recanalization of embolic MCA occlusions has a favorable impact on infarct size.³⁰

Unfortunately, TCD cannot be performed in all acute stroke patients because some of them present an inadequate acoustic window. In our study the incidence of an insufficient temporal bone window for TCD was 13.1%, in accordance with that recently reported by Alexandrov and coworkers.¹ The application of contrast-enhanced transcranial color-coded duplex sonography has obtained equivalent percentages, but "old-fashioned" TCD is significantly less expensive, can be easily brought to the patient's bedside, and is totally noninvasive.

In conclusion, cerebral CT and duplex scanning of the cervical arteries have shown scarce prognostic value, while TCD findings were able to predict clinical evolution. After logistic regression analysis, only emergency TCD remained a

strong independent predictor of poor outcome by revealing an MCA occlusion or its failure to recanalize.

Further studies are needed to verify whether these patients would benefit from a more aggressive treatment (such as decompressive craniotomy or moderate hypothermia) or whether thrombolytic therapy would still be feasible beyond the 3-hour time window. Conversely, a normal baseline TCD was predictive of a good long-term outcome, and this finding should be taken into consideration when pharmacological trials for acute ischemic stroke are designed.

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