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Research Article

Changes in Cerebral Hemodynamics and Efficacy of Revascularization Procedures in Ischemic Stroke

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Introduction: We evaluated the possibility of identifying predictors of efficacy of revascularization treatments in patients with acute ischemic stroke (AIS) through mean flow velocity (MFV) changes in middle cerebral arteries (MCAs).
Patients and Methods: Color-coded transcranial Doppler ultrasound (TCCD) was used to assess vessel status and cerebral hemodynamics of 40 consecutive AIS patients (19 females [47.5%], median age 72 years) with distal occlusion of the internal carotid artery (ICA) or MCA immediately after reperfusion treatments.
Results: Proximal occlusion was observed in 80% of cases. Seventy-five percent of cases had successful recanalization, defined as Grade 2b or 3 score at the modified thrombolysis in cerebral infarction (mTICI), while partial recanalization (Grade 2a mTICI) was achieved in 17.5%. Ipsilateral MFV in the mTICI 2b-3 subgroup was 86.1 ± 14.2 and 64.2 ± 6.2 cm/s in the contralateral side ($p < 0.05$, *t*-test for independent samples). In patients with other mTICI values, there was no statistically significant difference in MFV values between the sides. The MFV ratio (MFV of occluded side/contralateral MFV) was significantly associated with NIHSS improvement after 3 months.
Discussion and Conclusions: Higher MFV values in the vessel undergoing mechanical thrombectomy compared with the contralateral side are associated with successful revascularization. The increase in MFV was statistically significant in cases involving the distal ICA and proximal segment of the MCA (M1) and nonsignificant in cases involving the distal segment of the vessel (M2). Performing a TCCD examination in stroke patients can be a valuable bedside approach to evaluate the effectiveness of treatments.

Keywords: acute ischemic stroke; arterial flow velocity; color-coded transcranial Doppler ultrasound; endovascular procedures

1. Introduction

About one-third of ischemic strokes are the result of acute large vessel occlusion (LVO) of the anterior circulation [1]. These types of strokes tend to manifest with more severe symptoms and are very often associated with poor outcomes. Many researches [2, 3], including randomized interventional studies, have consistently shown that the combination of endovascular treatment (EVT) with intravenous thrombolysis (IVT) offers a significant advantage over IVT alone [4]. Consequently, the combination of IVT and EVT is increasingly considered the preferred approach for the treatment of patients with LVO-related acute ischemic stroke.

Although digital subtraction angiography remains the gold standard for the diagnosis of LVO, its invasive and expensive nature limits its use for posttreatment follow-up. On the other hand, color-coded transcranial Doppler sonography (TCCD) offers a noninvasive and inexpensive alternative for assessing vessel patency. TCCD enables real-time visualization of morphological changes in cerebral blood vessels and provides valuable information on hemodynamic changes. This capability complements traditional radiological data and can improve rapid assessment of patients' circulatory conditions [5].

Given its potential, TCCD appears to be a promising method for evaluating the efficacy of EVT. This is particularly important because EVT does not guarantee successful recanalization in the whole population of LVO stroke patients. In addition, some patients may show no improvement despite appropriate treatment, while others may show significant recovery even if arterial recanalization remains only partial. It should be noted that there is a surprising lack of research on the hemodynamic changes that occur after interventional procedures. Therefore, we conducted a TCCS study to investigate whether changes in blood flow velocity could shed light on the efficacy of EVT.

2. Materials and Methods

This prospective study involved consecutive patients with ischemic stroke of the anterior circulation due to occlusion of a large artery, specifically the internal carotid artery (ICA) or middle cerebral artery (MCA) in segments M1 or M2. These patients underwent revascularization treatment and were admitted to a neurological unit from January 2023 to June 2023. The protocol was approved by the local ethics committee, and the patients gave informed consent.

EVT was performed by two experienced interventional neuroradiologists, and patients underwent this procedure in accordance with clinical practice and current international guidelines [6]. Therapeutic success from the radiological point of view was evaluated using the modified thrombolysis in cerebral infarction (mTICI) system [7], an angiographic tool to assess vessel recanalization after the procedure.

Immediately after the endovascular procedure, mean flow velocity (MFV) was measured in the previously occluded vascular segments of the anterior circulation and the corresponding contralateral segments using TCCD.

Demographic data, clinical characteristics, treatments for the ischemic event (other than endovascular therapy), radiological data, and clinical outcome measures were collected for each patient. Demographic variables included patients' age and sex. The risk factors considered were systemic hypertension (HTN), defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg, or chronic use of antihypertensive drugs; hypercholesterolemia, defined as total cholesterol level greater than 200 mg/dL or LDL levels greater than 100 mg/dL, or chronic therapy with oral lipid-lowering drugs; diabetes mellitus (DM), defined as fasting blood glucose levels ≥ 126 mg/dL or sample blood glucose levels ≥ 200 mg/dL, or taking oral antidiabetic drugs or subcutaneous insulin therapy; any history of atrial fibrillation (AF), whether newly diagnosed during hospitalization or preexisting.

Clinical characteristics of patients included NIH Stroke Scale (NIHSS) scores assessed at different time points.

Radiologic features were evaluated using reports from neuroradiologists, along with CT and conventional angiography images obtained at the time of admission. The parameters evaluated for each patient included the location of the ischemic lesion and the site of vessel occlusion. Supra-aortic trunk ultrasound examinations were performed during hospitalization to identify and exclude patients with ICA stenosis greater than 50%. Radiological features were reassessed at least 24 h after the acute event. Hemorrhagic transformation (HT), if present, was assessed using CT images obtained at least 24 h after the event and was classified according to the size of the lesion.

Acute reperfusion therapies were classified into two primary subgroups: thrombolysis and intracranial stent placement at the site of vessel occlusion. Patient outcomes were assessed using NIHSS scores at two key time points: 7 days after the event and at 3 months after clinical onset.

Clinical and demographic characteristics were summarized using percentages for categorical variables and averages with standard deviations for continuous variables. Noncontinuous variables, such as "thrombolysis in cerebral infarction (TICI) grade," "HT," and "vessel site," were reclassified as follows: TICI Grades 2b and 3 were classified as successful recanalization, while the other TICI values were considered unsuccessful recanalization. HT was classified as HT 1 for very mild, HT 2 for mild, and HT 3 and 4 for moderate to severe HT. Vessel occlusions in the ICA or M1 segment were classified as proximal, while occlusions in M2 or more distal segments were classified as distal.

Exclusion criteria included carotid stenosis of 50% or greater, detected by color Doppler ultrasound of the supra-aortic trunks or CT angiography. Additional exclusion criteria were significant clinical deterioration after the procedure that required transfer to the intensive care unit, mortality, or age less than 18 years.

3. Statistical Analysis

All statistical analyses were conducted using the SPSS Software Program Version 25 and Jamovy Version 2.3.28.0.

A descriptive analysis and frequency distribution of demographic and clinical characteristics were performed on the study sample.

In order to use parametric tests for statistical calculations, the distributions of the continuous variables "mean occluded vessel velocity" (MFV X) and "mean contralateral vessel velocity" (MFV CL) were examined by a numerical method (Shapiro–Wilk test) and a graphical method, respectively.

The independent-samples t-test was used to assess potential differences and sources of error in the variables MFV X and MFV CL among population subgroups classified by sex, HTN, smoking, DM, AF, hypercholesterolemia, and laterality.

The t-test was also used to explore variations in the above variables according to recanalization success or failure (TICI), site of occlusion (proximal or distal), and use or nonuse of fibrinolysis or stenting.

Finally, to evaluate the relationship between flow dynamics and neurological recovery, we introduced a new hemodynamic parameter, the MFV ratio, defined as the ratio of the MFV of the treated artery to the MFV of the corresponding contralateral untreated artery. A multiple linear regression model was run to study the association between ΔNIHSS (NIHSS before thrombectomy minus NIHSS at 3 months) and MFV ratio, adjusting for potential confounders. The following variables were included in the model based on their clinical relevance: age (continuous variable, years), HT (categorized as 0 = no hemorrhage, 1 = minor hemorrhage [H1–H2], 2 = major hemorrhage [H3–H4]), TICI score (categorized as 0 = successful recanalization [TICI 2b or 3], 1 = incomplete recanalization [TICI 0–2a]), smoking history (coded as 0 = never smoker or total smoking history < 5 years, 1 = active smoker or former smoker with ≥ 5 years of exposure), DM (0 = no, 1 = yes), HTN (0 = no, 1 = yes), AF (0 = no, 1 = yes), hypercholesterolemia (defined as total cholesterol > 200 mg/dL; 0 = no, 1 = yes), IVT (alteplase administration) (0 = no, 1 = yes), and stent placement (0 = no, 1 = yes). Model assumptions were evaluated through residual plots, normality tests, and variance inflation factor (VIF) analysis to exclude multicollinearity. Regression coefficients (β) were reported with their standard errors (SEs), t values, and p values. The coefficient of determination (R^2) was reported to quantify the percentage of variance of ΔNIHSS explained by the model.

A significance level of $p < 0.05$ was chosen for the analyses.

4. Results

During the study period, 40 patients (including 19 women) with ischemic stroke in the anterior circulation underwent EVT. In 80% of cases, the occlusion was located in the ICA or the first segment of the MCA. The mean NIHSS score was 15 (range 3–24). Intravenous fibrinolysis was administered to 55% of patients before the endovascular procedure, and in more than 85% of cases, no or minimal HT occurred. A complete summary of demographic and clinical characteristics is given in Table 1.

Successful recanalization (defined as mTICI Grade 2b or 3) was achieved in 75% of cases, while partial recanalization (mTICI Grade 2a) was obtained in 17.5% of patients (Figure 1).

The TCCD was performed as soon as possible after the endovascular procedure, but no later than 6 h from the onset of symptoms. The MFV in the treated vessel was 80 cm/s (SD = 17), while in the corresponding contralateral vessel, MFV was 64 cm/s (SD = 8).

Using the Student t-test for independent samples, no statistically significant differences were found in the subgroups based on gender, HTN, smoking, DM, AF, hypercholesterolemia, or laterality with regard to the continuous variables MFV X and MFV CL. This analysis allowed us to test the homogeneity of the sample, confirming that the sample was homogeneous.

When applying the t-test for independent samples to compare the following subgroups, the results were as follows:

- A statistically significant difference in mean blood flow velocity in the treated vessel was observed when effective recanalization was achieved (mTICI Grade 2b or 3): The mean values of MFV X in the "mTICI 2b or 3" subgroup was 86.1 cm/s (SD = 14.2); the mean MFV CL in the "mTICI 2b or 3" subgroup was 64.2 cm/s (SD = 6.2). No statistically significant difference was found between MFV X and MFV CL in the "other mTICI values" subgroups. This is illustrated graphically in Figure 1.

- A statistically significant difference was observed in the MFV of the vessel undergoing endovascular procedure when the treated vessel was a proximal one (ICA or M1 segment of the MCA): Mean values of MFV X in the "proximal" subgroup were 83.9 cm/s with a SD of 16.4 cm/s, while the mean values of MFV CL in the "proximal" subgroup were 64.7 cm/s with a SD of 8.7 cm/s. No statistically significant difference was found between MFV X and MFV CL in the respective "distal" subgroups.

- No statistically significant differences were found in the MFV of the vessel undergoing endovascular procedure and its corresponding contralateral vessel when the sample was divided into those who received intravenous fibrinolysis and those who did not.

TABLE 1: Descriptive and frequency analysis of the sample.

Demographic characteristics	
Age [years, median (1st–3rd quartile)]	72 [61.5–84]
Gender [females, n (%)]	19 (47.5%)
Clinical characteristics	
Smoking [smokers or nonsmokers ≤ 5 years, n (%)]	16 (40%)
Diabetes mellitus [n (%)]	6 (15%)
Hypertension [n (%)]	29 (72.5%)
Atrial fibrillation [n (%)]	12 (30%)
Hypercholesterolemia [n (%)]	10 (25%)
NIHSS 1 [mean ± SD]	14.55 ± 4.95
NIHSS 2 [mean ± SD]	10.26 ± 5.62
Neuroradiological characteristics	
Stroke side [left, n (%)]	21 (52.5%)
Vessel [proximal, n (%)]	32 (80%)
TICI [2b or 3, n (%)]	30 (75%)
Hemorrhagic transformation (HT) [n (%)]	Minimal or absent ≤ H1 34 (87.2%) Mild H2 4 (10.3%) Moderate–severe ≥ H3 1 (2.6%)
Treatments in addition to endovascular therapy	
Stent [n (%)]	13 (32.5%)
rtPA [n (%)]	22 (55%)
Mean flow velocity in the MCA	
MFV X = treated vessel [mean ± SD]	80 ± 17
MFV CL = contralateral vessel [mean ± SD]	64 ± 8

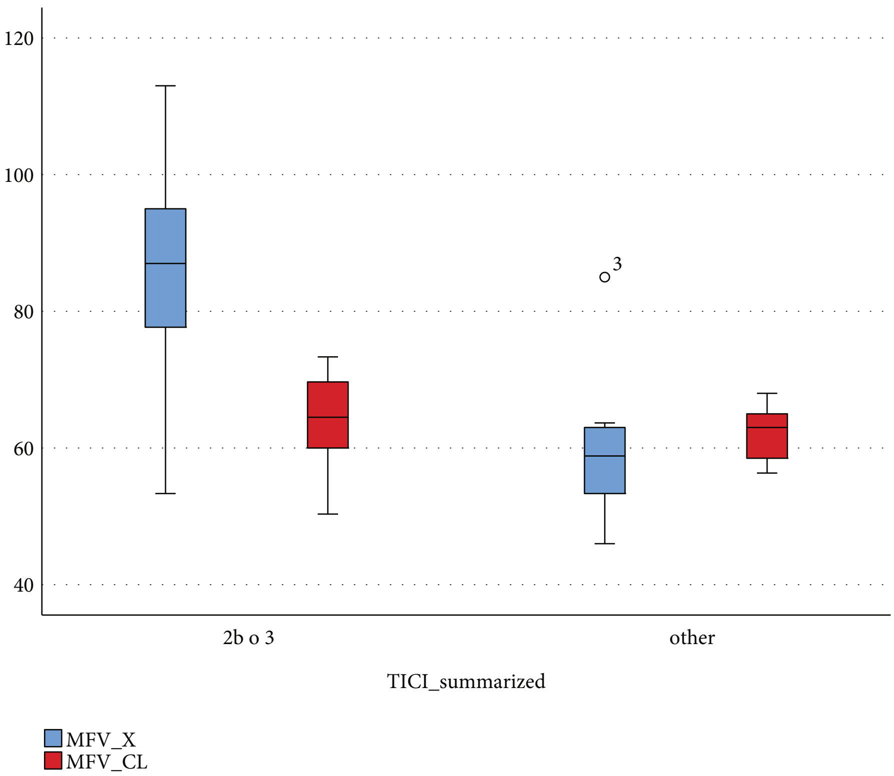

FIGURE 1: Box plot comparing the continuous variables MFV X and MFV CL in the two subgroups based on mTICI grading.

– No statistically significant differences were observed in the mean MFV values of the vessel subjected to endovascular procedure and its respective contralateral vessel when the sample was divided between those who underwent stent placement and those who did not. The results are graphically presented in Figure 2.

Finally, a linear regression analysis assessing predictors of NIHSS improvement at 3 months yielded an R^2 value of 0.337, indicating that the included variables accounted for approximately 33.7% of the variance in clinical recovery (Figure 3).

Among the examined predictors, the MFV ratio was the only variable significantly associated with NIHSS improvement ($\beta = 7.983$, SE = 3.857, $t = 2.070$, $p = 0.049$), suggesting that higher MFV ratios correlate with greater neurological recovery. Severe HT (H3/H4) approached statistical significance ($\beta = -10.126$, SE = 5.138, $t = -1.971$, $p = 0.060$), indicating a potential negative impact on recovery.

Age ($p = 0.969$), recanalization grade (TICI score, $p = 0.979$), DM ($p = 0.662$), HTN ($p = 0.925$), AF ($p = 0.391$), hypercholesterolemia ($p = 0.563$), smoking history ($p = 0.553$), fibrinolysis ($p = 0.932$), and stenting ($p = 0.282$) were not significant predictors of ΔNIHSS.

5. Discussion

This study evaluated cerebral hemodynamic changes in patients with ischemic stroke of the anterior cerebral circulation immediately after EVT by neurosonological investigation. The continuous variables examined (MFV in the vessel undergoing thrombectomy and in the contralateral vessel) were compared among different subgroups of the study population.

As a main result, we described a correlation between MFV values and recanalization success, confirming the reliability of TCCD in providing meaningful information related to treatment efficacy in the acute phase of ischemic stroke. In addition, when comparing MFV values in the occluded side with the contralateral side, a significant difference was observed in the case of proximal occlusion. This difference was less pronounced in the presence of distal occlusion (M2 segment of MCA or more distal cerebral arteries). The reason could be related to basal differences in blood flow velocity values between these two different anatomical locations.

Although a trend toward higher blood flow velocities was observed in vessels treated with stent insertion compared with those treated without stents, it did not reach a level of statistical significance. To explain this result, it is possible to speculate that early vascular remodeling due to the presence of the stent did not produce a hemodynamic effect detectable by TCCD. The lack of significant differences in MFV changes between the group that received both endovascular and fibrinolytic treatment versus the group that received only EVT seems to highlight that the latter approach, through its direct action on the vessel, is the main determinant of the observed changes in blood flow velocity values. Finally, postthrombectomy flow dynamics, as measured by MFV ratio, may be a major predictor of

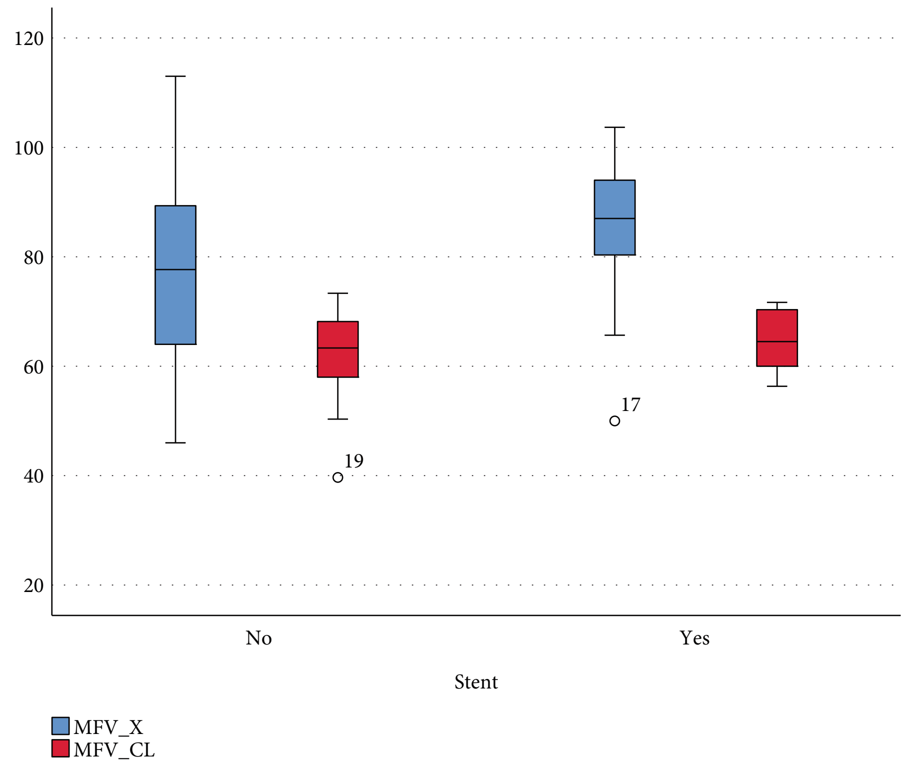

Figure 2: Box plot comparing the continuous variables MFV X and MFV CL for the subgroups with and without stent placement.

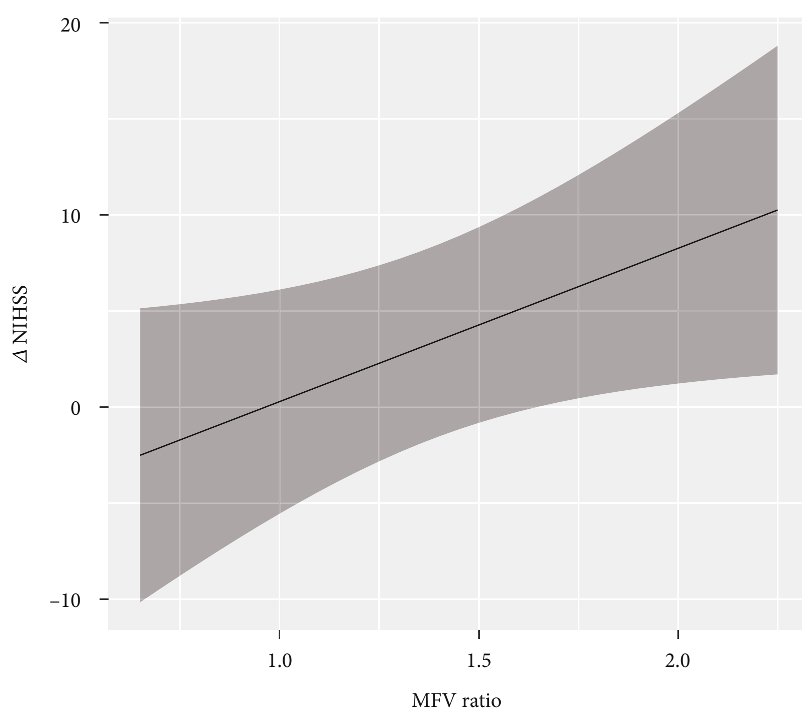

Figure 3: Marginal means' plot illustrating the relationship between MFV ratio and delta NIHSS, derived from a linear regression analysis. The black line represents the estimated regression line, while the shaded area indicates the 95% confidence interval.

neurological recovery, independent of conventional vascular risk factors. This result indirectly suggests that higher blood flow velocity may be related to better prognosis, as already suggested in a recent original study [8].

Previous studies have shown that EVT combined with fibrinolytic therapy is effective in restoring blood perfusion in major intracranial artery occlusions in a time-dependent manner [9]. Prognosis after endovascular procedures is closely related to the success of the procedure, with better outcomes described in association with an mTICI grade of 2b or 3 [10]. TCCD emerges as a useful tool to noninvasively assess treatment efficacy. A previous study on the hemodynamics of brain vessels undergoing EVT demonstrated no increase in blood flow velocity values [11]. The discrepancy with our results is probably due to the fact that in that study the neurosonological examination was performed within 72 h of the endovascular procedure, thus excluding the possibility of early detection of flow changes.

Our study has some limitations. The first, common to all studies using neurosonologic assessment, is that the examination is operator-dependent, making the approach very difficult to standardize; this is even more true for TCCD than for other ultrasound methods because of its relatively recent introduction into clinical practice. For this reason, the use of TCCD in clinical settings should be preceded by careful and thorough training of operators to gain standardization of results. A second limitation is the lack of neurosonologic follow-up due to the transfer of patients to peripheral stroke units, very often within a week from stroke onset. Further, the timing of TCCD assessment was not standardized across patients, even if all participants were evaluated immediately after revascularization procedures. Finally, our sample size was relatively small. In this regard, our investigation should be considered a pilot study with the aim of suggesting the possibility of providing a meaningful correlation between neurosonological information and clinical data. The promising results obtained can be considered encouraging and support the planning of larger multicenter studies for definitive validation of the use of TCCD as a reliable method for studying cerebral hemodynamics in stroke patients.

In conclusion, our investigation suggests that TCCD assessment of cerebral hemodynamic changes can be a useful, accessible, and noninvasive method enabling a rapid diagnostic approach at the patient's bedside to obtain pathophysiological information and may also be useful in monitoring the clinical effects of revascularization procedures.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Statement

Ethical approval for this study was obtained from the ethics committee (Marche Region Territorial Ethics Committee, Italy, Prot. 167/2023).

Consent

All patients were asked for informed consent by personal communication. For patients not able to give consent, the closest relative could approve inclusion in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

S. Salvemini: conceptualization, writing, formal analysis. G. De Vanna: result analysis, contributions to the conception or design of the work. R. Gigli: patients' inclusion, contributions to the conception or design of the work. G. Polonara: helped supervise the project, review, and editing. P. Rosettani: acquisition, analysis, or interpretation of data for the work. G. Viticchi: patients' inclusion, contributions to the conception or design of the work. M. Bartolini: result analysis, contributions to the conception or design of the work. M. Silvestrini: revising the work critically for important intellectual content.

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