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RESEARCH PAPER

# Asymmetric and symmetric dimethylarginine as markers of endothelial dysfunction in cerebrovascular disease: A prospective study

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**KEYWORDS**
Asymmetric dimethylarginine;
Symmetric dimethylarginine;
Endothelial dysfunction;
Stroke;
Transient ischemic attack

**Abstract** *Background and aim:* Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) have been proposed as mediators of endothelial dysfunction. In this study, we aimed to investigate the diagnostic and prognostic role of ADMA and SDMA in acute cerebrovascular disease.

*Methods and results:* A prospective case-control study was performed, enrolling 48 patients affected by ischemic stroke with no cardioembolic origin, 20 patients affected by TIA, 40 subjects at high cardiovascular risk and 68 healthy subjects.

ADMA levels were significantly lower in high-risk subjects (18.85 [11.78–22.83] μmol/L) than in patients with brain ischemic event, both transient (25.70 [13.15–40.20] μmol/L; $p = 0.032$) and permanent (24.50 [18.0–41.33] μmol/L; $p = 0.001$). SDMA levels were different not only between high-risk subjects and ischemic patients, but also between TIA and stroke patients, reaching higher levels in TIA group and lower levels in stroke group (1.15 [0.90–2.0] vs 0.68 [0.30–1.07] μmol/L; $p < 0.001$). SDMA was also correlated with short-term prognosis, with lower levels in case of adverse clinical course, evaluated by type of discharge ($p = 0.009$) and need of prolonged rehabilitation ($p = 0.042$).

*Conclusions:* The present study highlights the relationship between L-arginine, ADMA, SDMA and acute cerebrovascular events. Therefore, our results suggested a potential role of SDMA as a specific marker of transient ischemic damage and as a short-term positive prognostic marker.



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## 1. Introduction

Asymmetric dimethylarginine (ADMA) and Symmetric dimethylarginine (SDMA) are derived from the proteolysis of methylated arginine residues during intracellular protein degradation and are both processed by Protein-Arginine Methyl-Transferase (PRMT) enzymes I and II [1]. SDMA is partially cleared by the kidneys, whereas ADMA is metabolized by Dimethyl-Arginine Dimethyl-Hydrolase (DDAH) to L-citrulline and only minimally excreted through kidneys (20% of total amount) [2]. Nitric oxide (NO), produced by endothelial NO synthase (eNOS) from L-arginine, plays a central role in the maintenance of endothelial homeostasis, through its antithrombotic, vasodilating, anti-inflammatory and anti-proliferative properties [3]. It is well known that endothelial NO loss is related to endothelial dysfunction [4]. ADMA is an endogenous competitive inhibitor of L-arginine for eNOS binding, due to its similar structure. Therefore, it decreases endothelial NO synthesis, leading to the loss of NO bioavailability [5]. Moreover, the exposure to oxidative stress interferes with arginine-NO pathway, promoting the expression of PRMT, as well as the inhibition of DDAH, thus increasing ADMA production and reducing its degradation [6]. Although less studied, SDMA is also able to inhibit NO production indirectly, by competing with L-arginine at its transport protein human cationic amino acid transporter (hCAT)-2B and thus reducing the availability of L-arginine to eNOS [7]. As ADMA, also SDMA generation could be increased by the exposure to oxidative stress via modulation of PRMT. There is growing evidence that elevated plasma ADMA levels are associated with endothelial disfunction, supporting a pro-atherogenic role [8]. Specifically, ADMA was identified as a potential “Uber Marker”, namely a biochemical factor able to mediate negative vascular effects induced by several cardiovascular (CV) risk factors [9]. In fact, elevated plasma ADMA concentrations have been reported to be associated with traditional and novel CV risk factors, such as age [10], hypertension [11], diabetes mellitus [12], hypercholesterolemia [13], hyperhomocysteinemia [14], coronary artery disease [15], atrial fibrillation [16], left ventricular hypertrophy [17], as well as clinical and subclinical carotid and systemic atherosclerosis and intima-media thickness [18]. Much less is known about SDMA, but literature data suggested its function as biomarker of renal function or kidney injury in children and adolescents [19] and its role in several CV pathological conditions such as hypertension, coronary artery disease [15] and diabetes mellitus. Furthermore, SDMA has been recently identified as an independent predictor of all-cause and CV mortality in a large population-based cohort of European ancestry [20]. Therefore, ADMA and SDMA, through their interaction with NO pathway, play multifunctional roles in many human diseases [21].

Despite many evidence concerning the relationship between ADMA/SDMA levels and heart disease, chronic renal failure, and typical CV risk factors, studies investigating their correlation with cerebral ischemic events are scarce. Based on these assumptions, we aimed to investigate, in the short and in the long term, the diagnostic and prognostic role of methylarginines in a cohort of patients affected by cerebrovascular disease or at high risk for acute vascular events, in order to contribute to the evidence on this topic.

## 2. Methods

### 2.1. Design and study population

We designed a prospective case-control study, enrolling subjects referring to the City of Health and Science University Hospital of Turin between July 2021 and December 2022.

Cases were defined as patients presented acute cerebrovascular disease or at high cardio-cerebrovascular risk, and were divided into three groups: a) subjects with acute cerebral dysfunction which completely regresses within 24 h (transient ischemic attack - TIA group, n = 20); b) subjects with ischemic stroke with no cardioembolic origin (STROKE group, n = 48); c) subjects free from an acute cerebral event but superimposable to ischemic patients due to clinical demographic characteristics (age, gender and CV risk factors) (High Risk - HR group, n = 40). Ischemic stroke was defined as “acute neurological deficit, with focal or global dysfunction, of non-traumatic vascular origin, whose symptoms are present for more than 24 h or resulting in patient’s death within 24 h”. Cerebral infarction was documented by brain computed tomography (TC) and/or diffusion magnetic resonance imaging (MRI). TIA was defined as “acute episode of cerebral or visual focal dysfunction due to a blood supply deficit, which completely regresses within 24 h”.

Exclusion criteria were: a) known cardioembolic sources considered at “high risk”: mechanical prosthetic valve; paroxysmal, persistent, or permanent atrial fibrillation with non-target INR; mitral stenosis with atrial fibrillation; recent myocardial infarction (within the 4 weeks after the enrolment); dilated cardiomyopathy; atrial myxoma; sick sinus syndrome; b) stroke of uncommon cause: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Moyamoya, Fabry disease, mitochondrial diseases; c) cryptogenic stroke.

Controls were healthy blood donors (Control group - CTRL group, n = 68), without evidence of cerebrovascular disease or related risk factors (absence of hypertension, diabetes mellitus or dyslipidemia; no previous medical history, and no drug assumption).

The study was performed in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of City of Health and Science University Hospital of Turin. Written informed consent was obtained from all enrolled patients.

### 2.2. Clinical and biochemical investigations

We recorded patients’ clinical history, including demographic characteristics, presence of cardio-cerebrovascular risk factors (smoking, hypertension,

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dyslipidemia, and diabetes mellitus), previous ischemic heart disease or previous stroke/TIA, stroke severity and etiology. For each subject age, gender, weight, height, body mass index (BMI), total cholesterol, HDL-cholesterol, triglycerides, creatinine, glycated haemoglobin (HbA1c), L-arginine, ADMA and SDMA were evaluated.

Stroke severity was assessed using the National Institutes of Health Stroke Scale/Score (NIHSS) [22]. This scale is formed by 11 items to define the integrity of the state of consciousness, vision, motility, sensibility, language, in a multimodal evaluation. Total score range between 0 (absence of deficit) and 48 (patient in coma unresponsive to stimuli). An NIHSS of 0–1 was considered mild, 2–8 moderate, and ≥9 severe.

The short-term outcome of stroke patients was defined according to the type of discharge within two weeks of hospitalization. Patients transferred to rehabilitation clinic or vascular surgery were considered with adverse prognosis, while patients discharged home were defined with favourable prognosis. Long-term outcome was evaluated at 5 months of follow-up in only 37 patients, through a telephone interview aimed at identifying the level of disability quantified by Modified Rankin Scale (mRS) [23].

### 2.3. Analytical methods

ADMA, SDMA and L-arginine levels were measured by High Performance Liquid Chromatography (HPLC) on purified and OPA-derivatizated plasma samples, using a commercial kit for the quantification of amino acids in human plasma (EsseCi Group Srl, Como, Italy). Blood samples were centrifuged (3000 rpm at 4 °C for 15 min) and the obtained plasma was treated with trichloroacetic acid (TCA) in order to purify it. To ensure analytical accuracy an internal standard (Norvalin) was also added. Briefly: 100 μl of TCA 10% and 20 μl of Norvalin 10 mg/L were added to 200 μl of plasma; after an incubation of 10 min in ice, the samples were centrifuged (8000 rpm at 4 °C for 10 min) and supernatants were collected and stored at −80 °C prior analysis. Before chromatographic analysis, samples were derivatized in a fluorescent compound by reaction of ADMA, SDMA and L-arginine amino groups with Orto Phtalaldeide (OPA) in a solution of boric acid and mercaptoethanol in order to increase sensitivity and selectivity. This pre-column derivatization was performed by an autosampler that can ensure ruggedness, ease of use as well as high precision and reliability in results. ADMA, SDMA and L-arginine were then identified by isocratic chromatographic separation, and the retention times were respectively 11.5 (±0.5), 19.0 (±0.5) and 19.5 (±0.5). Finally, all molecules were quantified by using commercial calibrators (Eureka Srl – Lab Division, Ancona, Italy).

### 2.4. Statistical analysis

The considered variables resulted non-normally distributed at the Kolmogorov-Smirnov test. So, data were presented as median and 25th – 75th percentile and as absolute and relative frequencies for categorical variables. Between-group comparisons for continuous variables were performed using Mann-Whitney *U* test and Kruskal-Wallis test, where appropriate. Correlation between categorical variables were calculated by Fisher's exact test. A p-value <0.05 was considered statistically significant. For the calculation of sample size, we hypothesized, according to literature evidence available on this topic, an expected 30% increase in ADMA levels in patients with brain ischemic event compared to ADMA mean levels detected in healthy subjects. Therefore, a sample size of at least 38 patients was needed to obtain a statistical power of 80% (beta error 0.2), with an alpha error of 0.05.

Data analysis was performed by GraphPad Prism (version 9.5.1).

## 3. Results

We enrolled 68 patients with acute cerebral event (20 patients with TIA and 48 patients with stroke), 40 patients at high cardiovascular risk and 68 healthy controls.

Anthropometrics characteristics, smoking habit, and biochemical assessment of methylarginines and their ratio with arginine of the CTRL group subjects are summarized in Table 1.

In CTRL group, median age was 40.0 [24.0–48.8] years and median BMI value was 22.38 [20.63–24.59] kg/m$^2$. CTRL group was approximately equally represented in males (47.1%) and females (52.9%). About a third of subjects was smoker (33.8%). Concerning biochemical median values, they were, respectively, 27.95 [20.63–35.03] μmol/

**Table 1** Clinical and biochemical characteristics in CTRL group, CTRL <40 and CTRL ≥40 subgroups.

| Variables/parameters | CTRL (n = 68) | CTRL <40 (n = 32) | CTRL ≥40 (n = 36) | p-value |
|---|---|---|---|---|
| Age (years) | 40.0 [24.0–48.8] | 24.0 [22.0–25.0] | 48.0 [43.0–54.0] | |
| BMI (kg/m$^2$) | 22.38 [20.63–24.59] | 21.38 [19.91–22.66] | 24.17 [21.69–25.73] | <0.001 |
| Male gender (n, %) | 32, 47.1 | 15, 46.9 | 17, 47.2 | >0.999 |
| Smoke (n, %) | 23, 33.8 | 10, 31.3 | 13, 36.1 | 0.799 |
| Arginine (μmol/L) | 27.95 [20.63–35.03] | 31.10 [23.70–46.90] | 25.15 [16.43–31.85] | 0.012 |
| ADMA (μmol/L) | 15.20 [7.20–24.80] | 9.45 [5.13–15.15] | 20.50 [12.40–30.10] | <0.001 |
| SDMA (μmol/L) | 0.63 [0.33–0.90] | 0.53 [0.31–0.72] | 0.78 [0.42–1.01] | 0.017 |
| Arginine/ADMA | 1.76 [1.06–4.32] | 3.23 [1.66–10.35] | 1.27 [0.80–2.09] | <0.001 |
| Arginine/SDMA | 42.43 [25.14–84.47] | 64.58 [40.65–107.70] | 34.17 [20.97–46.84] | <0.001 |

Data are expressed as median [25th-75th percentile] and frequency count, as appropriate.
Abbreviations: ADMA, asymmetric dimethylarginine; BMI, body mass index; CTRL, control group; SDMA, symmetric dimethylarginine.

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L for L-arginine, 15.20 [7.20–24.80] μmol/L for ADMA, 0.63 [0.33–0.90] μmol/L for SDMA, 1.76 [1.06–4.32] for L-arginine/ADMA ratio and 42.43 [25.14–84.47] for L-arginine/SDMA ratio.

We also divided CTRL group in two subgroups (CTRL< 40, and CTRL ≥40) according to the median age in the overall group, as shown in Table 1.

With the age increasing, there was a significant decrease in L-arginine (31.10 [23.70–46.90] vs 25.15 [16.43–31.85] μmol/L; $p = 0.012$), L-arginine/ADMA ratio (3.23 [1.66–10.35] vs 1.27 [0.80–2.09]; $p < 0.001$) and L-arginine/SDMA ratio (64.58 [40.65–107.70] vs 34.17 [20.97–46.84]; $p < 0.001$) and a significant increase in ADMA (9.45 [5.13–15.15] vs 20.50 [12.40–30.10] μmol/L; $p < 0.001$) and SDMA (0.53 [0.31–0.72] vs 0.78 [0.42–1.01] μmol/L; $p = 0.017$), as reported in Fig. 1.

Anthropometrics characteristics, smoking habit, CV risk factors and biochemical markers for the three pathological groups we have examined (HR, STROKE and TIA) are reported in Table 2.

ADMA values progressively increased from HR (18.85 [11.78–22.83] μmol/L) to STROKE (24.50 [18.0–41.33] μmol/L) and TIA (25.70 [13.15–40.20] μmol/L) patients ($p = 0.004$). Conversely, L-arginine levels were higher in HR group (21.70 [15.53–37.83] μmol/L) than in STROKE (15.30 [8.30–27.85] μmol/L) and TIA (13.95 [10.28–18.95] μmol/L) ($p = 0.001$). The higher value of SDMA was observed in TIA patients (1.15 [0.90–2.0] μmol/L), while lower levels were noted in the STROKE (0.68 [0.30–1.07] μmol/L) and in the HR (0.78 [0.55–1.30] μmol/L) groups ($p = 0.001$). L-aginine/ADMA ratio decreased from HR (1.51 [0.96–2.46]) to TIA (0.63 [0.30–1.08]) and STROKE (0.55 [0.25–1.10]) groups ($p < 0.001$) and also L-arginine/SDMA ratio was higher in HR (27.16 [18.42–41.23]) than in STROKE (22.61 [11.08–44.01]) and TIA (10.38 [5.70–22.57]) ones ($p < 0.001$). Concerning the CV risk factors analyzed, only the presence of previous TIA event was differently distributed among the three groups ($p = 0.017$).

### 3.1. Comparisons between groups

#### 3.1.1. HR vs STROKE

The comparison between HR and STROKE groups showed that ADMA levels were statistically significantly higher in STROKE group ($p = 0.001$), while L-arginine and L-arginine/ADMA ratio progressively decreased in patients with ischemic event, as shown in Fig. 2 ($p = 0.002$ and $p < 0.0001$, respectively).

#### 3.1.2. HR vs TIA

Comparing HR and TIA groups, we found that TIA patients were significantly different from high-risk patients according to higher levels of ADMA ($p = 0.032$) and SDMA

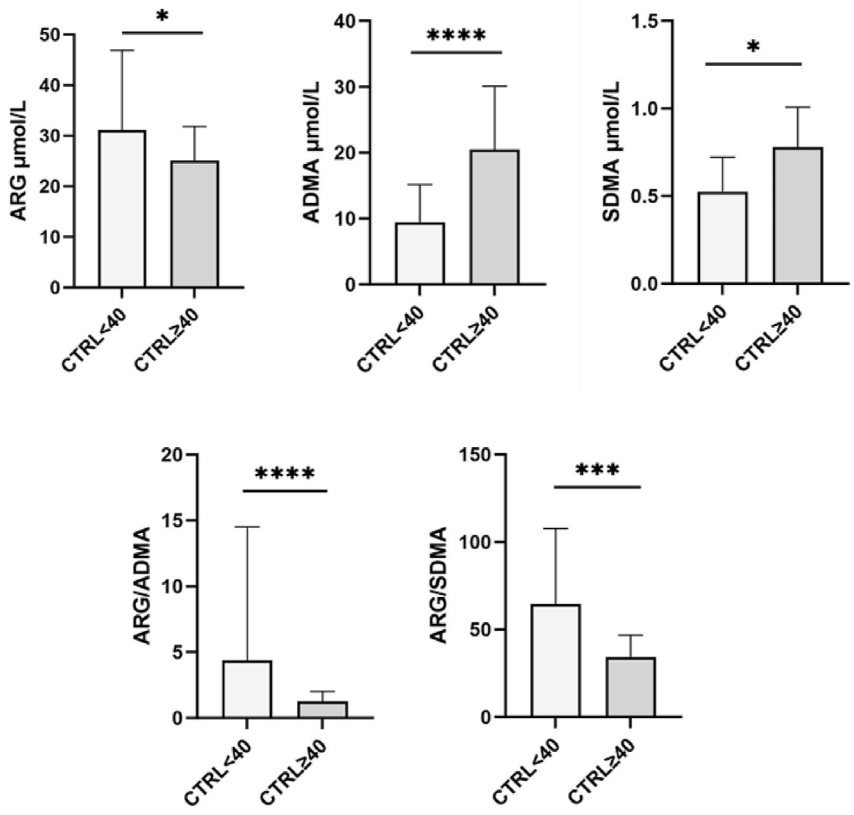


**Figure 1** Arginine, ADMA, SDMA, Arginine/ADMA and Arginine/SDMA (expressed as median with interquartile range) in CTRL <40 and CTRL ≥40 subgroups. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Abbreviations: ARG, arginine; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; CTRL, control group.

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**Table 2** Clinical and biochemical characteristics in HR, STROKE and TIA groups.

| Variables/parametes | HR (n = 40) | STROKE (n = 48) | TIA (n = 20) | p-value |
|---|---|---|---|---|
| Age (years) | 72.0 [60.5–78.8] | 70.5 [62.5–78.8] | 68.5 [62.5–74.8] | 0.487 |
| BMI (kg/m$^2$) | 25.00 [23.04–27.90] | 25.05 [22.12–27.92] | 29.41 [24.50–31.50] | 0.036[c] |
| Male gender (n, %) | 27, 67.5 | 30, 62.5 | 14, 70 | 0.803 |
| Smoke (n, %) | 14, 35 | 17, 35.4 | 11, 55 | 0.262 |
| Hypertension (n, %) | 33, 82.5 | 40, 83.3 | 12, 60 | 0.077 |
| ACEi/ARB (n, %) | 22, 55 | 23, 47.9 | 10, 50 | 0.800 |
| β-blockers (n, %) | 12, 30 | 10, 25 | 6, 30 | 0.558 |
| CCB (n, %) | 13, 33 | 10, 25 | 4, 20 | 0.385 |
| Diuretics (n, %) | 14, 35 | 11, 28 | 4, 20 | 0.332 |
| Other antihypertensive drugs (n, %) | 6, 15 | 4, 8 | 2, 10 | 0.603 |
| Dyslipidemia (n, %) | 17, 42.5 | 24, 50 | 7, 35 | 0.501 |
| Statin therapy (n, %) | 14, 35 | 13, 27 | 7, 35 | 0.534 |
| Diabetes mellitus (n, %) | 10, 25 | 12, 25 | 6, 30 | 0.899 |
| Ischemic heart disease (n, %) | 4, 10 | 6, 12.5 | 6, 30 | 0.101 |
| Previous TIA (n, %) | 0, 0 | 8, 16.7 | 4, 20 | 0.017[a,b] |
| Total cholesterol (mg/dL) | 170.0 [128.0–198.0] | 174.0 [140.0–216.0] | 161.0 [142.0–209.0] | 0.582 |
| HDL (mg/dL) | 43.0 [37.50–52.0] | 44.0 [34.0–54.0] | 45.0 [37.0–61.0] | 0.672 |
| LDL (mg/dL) | 110.0 [69.9–170.0] | 109.0 [80.0–126.0] | 88.0 [74.0–129.0] | 0.356 |
| Triglycerides (mg/dL) | 111.0 [66.0–159.5] | 103.0 [79.0–154.0] | 101.0 [88.0–124.0] | 0.839 |
| Creatinine (mg/dL) | 0.86 [0.77–1.35] | 0.85 [0.73–0.98] | 0.96 [0.79–1.13] | 0.189 |
| HbA1c (mmol/mol) | 6.4 [5.7–7.0] | 6.1 [5.6–6.5] | 6.1 [5.8–6.9] | 0.339 |
| Arginine (μmol/L) | 21.70 [15.53–37.83] | 15.30 [8.30–27.85] | 13.95 [10.28–18.95] | 0.001[a,b] |
| ADMA (μmol/L) | 18.85 [11.78–22.83] | 24.50 [18.0–41.33] | 25.70 [13.15–40.20] | 0.004[a,b] |
| SDMA (μmol/L) | 0.78 [0.55–1.30] | 0.68 [0.30–1.07] | 1.15 [0.90–2.0] | 0.001[b,c] |
| Arginine/ADMA | 1.51 [0.96–2.46] | 0.55 [0.25–1.10] | 0.63 [0.30–1.08] | <0.001[a,b] |
| Arginine/SDMA | 27.16 [18.42–41.23] | 26.61 [11.03–44.01] | 10.38 [5.79–22.57] | <0.001[b,c] |

Data are reported as median [25th-75th percentile] and frequency count, as appropriate.
Abbreviations: HR, high risk group; TIA, transient ischemic attack; BMI, body mass index; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated haemoglobin; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.
[a] Significant difference between HR and STROKE.
[b] Significant difference between HR and TIA.
[c] Significant difference between TIA and STROKE.

(p = 0.003), and lower levels of L-arginine (p = 0.002), L-arginine/ADMA ratio (p = 0.006) and L-arginine/SDMA ratio (p < 0.0001), as shown in Fig. 2.

### 3.1.3. TIA vs STROKE

Comparing TIA and STROKE groups, we found that these groups statistically significantly differed from SDMA levels that were higher in TIA patients (p < 0.001), and also from its ratio with Arginine that, conversely, was higher in STROKE patients (p = 0.003), as shown in Fig. 2.

### 3.1.4. Cases vs controls

As shown in Fig. 2, we also compared the distribution of the considered variables between cases (HR, STROKE and TIA groups) and controls (CTRL group). We found that: a) L-arginine levels were significantly higher in CTRL group (27.95 [20.63–35.03] μmol/L) than in TIA group (13.95 [10.28–18.95] μmol/L; p < 0.001) and in STROKE group (15.30 [8.30–27.95] μmol/L; p < 0.0001); ADMA levels were significantly lower in CTRL group than in TIA group (15.20 [7.20–24.80] vs 25.70 [13.15–40.20] μmol/L; p = 0.010) and in STROKE group (24.50 [18.0–41.33] μmol/L; p < 0.0001); c) SDMA levels were only statistically different between CTRL group (0.63 [0.33–0.90] μmol/L) and TIA group (1.15 [0.90–2.0] μmol/L), with higher values found in TIA patients (p < 0.0001); L-arginine/ADMA ratio was significantly lower in TIA group (0.63 [0.30–1.08]) and STROKE group (0.55 [0.25–1.10]) compared to controls (1.76 [1.06–4.32]; p = 0.001 and p < 0.0001, respectively); d) L-arginine/SDMA ratio significantly varied between CTRL (42.43 [25.14–84.47]) and all other pathological groups, reaching lower values in TIA patients (10.38 [5.79–22.57]; p < 0.0001), than in stroke patients (26.61 [11.03–44.01]; p < 0.001), and finally in high-risk patients (27.16 [18.42–41.23]; p = 0.035); e) control subjects were significantly younger (40.0 [24.0–48.75] years) than high-risk patients (72.0 [60.50–78.75]; p < 0.001) and patients affected by TIA (68.50 [62.50–74.75] years; p < 0.001) or stroke (70.50 [62.50–78.75] years; p < 0.001).

### 3.1.5. Clinical outcome after stroke

We also evaluated STROKE group according to two main disease course indicators: the extent of the neurological deficit, assessed by means of the NHISS score and the short-term outcome, considering patients in need of continuation of treatments as an adverse prognosis. We divided the surviving patients (n = 47) into two different groups, in relation to the expected discharge at home and to the need of rehabilitation after acute event. Anthropometrics characteristics, smoking habit, CV risk factors and biochemical markers for these different groups of prognoses are reported in Table 3.

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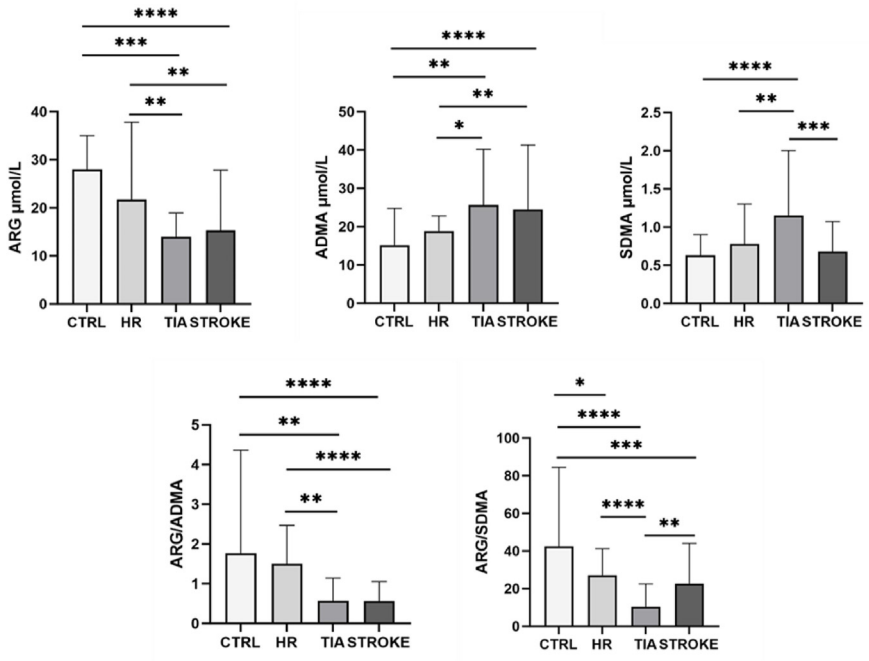


**Figure 2** Arginine, ADMA, SDMA, Arginine/SDMA and Arginine/SDMA (expressed as median with interquartile range) in CTRL, HR, TIA and STROKE group. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. Abbreviations: ARG, arginine; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; CTRL, control group; HR, high risk group; TIA, transient ischemic attack.

As shown in Fig. 3, concerning the type of discharge, we observed a statistically significant difference concerning SDMA levels and Arginine/SDMA ratio. SDMA concentrations were higher in patients destined to return directly at home compared those requiring further institutionalization (0.69 [0.50–1.60] vs 0.63 [0.25–0.80]; p = 0.009), while Arginine/SDMA ratio progressively increased between the two groups (16.60 [7.64–34.42] vs 30.77 [17.15–62.04]; p = 0.027). Instead, dividing patients according to the need of rehabilitation, we found that subjects undergone rehabilitation project had lower SDMA levels (0.67 [0.33–0.83] vs 0.69 [0.26–1.60]; p = 0.042) and higher L-arginine/SDMA ratio (30.77 [16.37–69.73] vs 19.62 [7.72–37.71]; p = 0.036).

Instead, we did not find a statistically significant correlation between methylarginines levels and stroke severity score evaluated with NHISS. Similarly, no association emerged from the analysis of the distribution of the methylarginines and the long-term outcome.

## 4. Discussion

In the present study, we analyzed the distribution of L-arginine and its metabolites in 68 healthy subjects and in a cohort of 108 patients affected by acute cerebrovascular disease or at high cardio-cerebrovascular risk, aimed to evaluate the distribution of these biomarkers both in the physiological and in the pathological context. The main results showed that: a) in the cohort of healthy subjects, increasing age was associated with higher levels of ADMA and SDMA and with lower levels of L-arginine and of the aforementioned ratios; b) as expected, ADMA concentrations significantly increased in patients affected by TIA or stroke, compared to high-risk and healthy subjects, without any significant difference between TIA and stroke groups; c) unexpectedly, SDMA could also distinguish between TIA and stroke patients, reaching higher levels in case of transient ischemic event, and d) SDMA elevation could represent a short-term positive prognostic marker.

We reported, in healthy subjects, an association between age and a) the increase of ADMA and SDMA levels and b) a reduction in their ratio with L-arginine.

As ADMA and SDMA have been reported to be increased in several pathological conditions of altered endothelial function [9], the evidence that ADMA and SDMA increase with age, while L-arginine/ADMA and L-arginine/SDMA ratio declines, is consistent with literature data. In fact, the main available evidence showed that in adult plasma ADMA levels typically increase with age [24] and that age, considered as a non-modifiable CV risk factor, is associated with endothelial dysfunction [25], mainly due to increased oxidative stress on vessel wall.

Instead, regarding the analysis of pathological groups, we observed higher ADMA levels in patients affected by cerebral ischemic events, both transient and permanent, compared to subjects at high CV risk. This difference, however, did not appear from the comparison between TIA and stroke groups. This finding is consistent with literature evidence, that extensively underline a relation between ADMA levels and CV risk, included its role as an independent marker of acute stroke and TIA [26–30]. In fact, elevated ADMA and SDMA concentration have been found in plasma and liquor of patients affected by acute cerebral

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**Table 3** Clinical and biochemical characteristics in stroke patients divided according to the type of discharge and need of rehabilitation.

| Variables/parameters | Home discharge (n = 23) | Non home discharge (n = 24) | p-value | Rehabilitation (n = 22) | Non rehabilitation (n = 25) | p-value |
|---|---|---|---|---|---|---|
| Age (years) | 67.0 [62.0–69.0] | 72.50 [62.5–80.3] | 0.506 | 72.5 [61.5–78.8] | 67.0 [63.0–80.5] | 0.565 |
| BMI (kg/m$^2$) | 24.9 [22.80–28.30] | 25.20 [21.55–27.78] | 0.712 | 25.20 [21.24–27.10] | 24.90 [23.0–28.55] | 0.583 |
| Male (n, %) | 27, 67.5 | 30, 62.5 | >0.999 | 14, 63.6 | 16, 64 | >0.999 |
| Smoke (n, %) | 11, 47.8 | 6, 25 | 0.135 | 5, 22.7 | 12, 70.6 | 0.127 |
| Hypertension (n, %) | 19, 82.6 | 20, 83.3 | >0.999 | 18, 81.8 | 21, 84 | >0.999 |
| ACEi/ARB (n, %) | 12, 52 | 11, 46 | 0.773 | 10, 45 | 13, 52 | 0.773 |
| β- blockers (n, %) | 6, 26 | 4, 17 | 0.494 | 3, 14 | 7, 28 | 0.297 |
| CCB (n, %) | 4, 17 | 6, 25 | 0.724 | 6, 27 | 4, 16 | 0.480 |
| Diuretics (n, %) | 5, 21 | 6, 25 | >0.999 | 6, 27 | 5, 20 | 0.732 |
| Other antihypertensive drugs (n, %) | 3, 13 | 1, 4 | 0.348 | 1, 5 | 3, 12 | 0.612 |
| Dyslipidemia (n, %) | 16, 69.6 | 8, 33.3 | 0.020 | 7, 31.8 | 17, 68 | 0.020 |
| Statin therapy (n, %) | 6, 26 | 7, 29 | >0.999 | 7, 32 | 6, 24 | 0.745 |
| Diabetes mellitus (n, %) | 7, 30.4 | 5, 20.8 | 0.517 | 5, 22.7 | 7, 28 | 0.747 |
| Ischemic heart disease (n, %) | 2, 8.7 | 4, 16.7 | 0.666 | 4, 18.2 | 2, 8 | 0.398 |
| Previous TIA (n, %) | 2, 8.7 | 9, 37.5 | 0.036 | 6, 27.3 | 2, 8 | 0.123 |
| Total cholesterol (mg/dL) | 206.0 [169.5–253.3] | 153.0 [135.3–183.5] | 0.013 | 151.0 [133.8–179.8] | 202.5 [171.3–232.8] | 0.004 |
| HDL (mg/dL) | 46.5 [39.0–51.8] | 41.50 [32.0–56.3] | 0.567 | 49.50 [31.8–57.0] | 47.0 [39.3–50.8] | 0.345 |
| LDL (mg/dL) | 119.0 [99.5–156.3] | 101.0 [76.0–122.3] | 0.052 | 95.0 [75.8–121.0] | 119.5 [100.3–154.5] | 0.024 |
| Triglycerides (mg/dL) | 113.5 [81.0–180.8] | 99.0 [79.0–133.3] | 0.416 | 91.0 [78.3–124.3] | 126.0 [83.3–174.0] | 0.198 |
| Creatinine (mg/dL) | 0.84 [0.62–1.01] | 0.86 [0.75–0.99] | 0.697 | 0.86 [0.75–0.99] | 0.84 [0.65–0.97] | 0.554 |
| HbA1c (mmol/mol) | 6.2 [5.8–7.1] | 6.0 [5.5–6.4] | 0.119 | 5.85 [5.4–6.4] | 6.25 [5.8–7.0] | 0.056 |
| Arginine (μmol/L) | 11.50 [8.26–27.40] | 15.30 [8.90–27.13] | 0.837 | 17.95 [10.25–28.33] | 10.90 [7.40–27.05] | 0.263 |
| ADMA (μmol/L) | 22.50 [18.0–38.20] | 30.75 [10.75–41.33] | 0.837 | 34.40 [11.85–42.55] | 22.50 [18.0–35.8] | 0.543 |
| SDMA (μmol/L) | 0.69 [0.50–1.60] | 0.63 [0.25–0.80] | 0.009 | 0.67 [0.33–0.83] | 0.69 [0.26–1.60] | 0.043 |
| Arginine/ADMA | 0.46 [0.24–1.15] | 0.61 [0.27–1.02] | 0.662 | 0.64 [0.29–1.20] | 0.41 [0.23–1.12] | 0.333 |
| Arginine/SDMA | 16.60 [7.64–34.42] | 30.77 [17.15–62.04] | 0.026 | 30.77 [16.37–69.73] | 19.62 [7.72–37.71] | 0.036 |

Data are reported as median [25th-75th percentile] and as frequency count, as appropriate.
Abbreviations: BMI, body mass index; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated haemoglobin; ADMA, asymmetric dimethylarginine; SDMA, symmetric di-methylarginine.

ischemic event, both permanent [28,31] and transient [27,32]. Yoo and Lee found that serum ADMA levels were significantly higher in 52 patients with stroke than in 36 healthy controls [28]. Ercan et al. [26] showed that, in another study performed on a similar population, ADMA levels were also significantly different between patients undergone ischemic stroke and control group, reaching higher values in the first group. Wanby et al. [27] examined a large population of 342 patients affected by acute cerebrovascular disease and 48 controls, demonstrating that ADMA resulted a week independent marker for acute stroke and a strong marker for TIA and that relative arginine deficiency was present in acute cerebrovascular disease. Instead, fewer studies have examined the role of SDMA in this topic, with results partially conflicting.

In our study, unexpectedly, we found significantly higher levels of SDMA only in subjects with TIA, if compared with the high-risk or the stroke groups. In addition, considering comparisons between healthy subjects and patients affected by ischemic disease or at high CV risk, SDMA was able to distinguish control subjects only from TIA patients. This finding suggested that SDMA could be configured as a specific marker of transient ischemic damage. Our results also suggested that, apart from absolute ADMA and SDMA levels, the evaluation of ratios between L-arginine and its metabolites is crucial to distinguish between subjects belonging to different risk groups. In fact, we found that L-arginine/ADMA ratio progressively decreases from HR to TIA and STROKE group. This is consistent with literature evidence that underlined the importance of L-arginine/ADMA ratio, as shown by the "L-arginine paradox", postulated by Bode-Boger et al. [4]. In fact, several studies demonstrated that lower L-arginine/ADMA ratio was a risk factor for all-cause mortality and atherosclerosis [33,34], but literature data regarding ischemic stroke are less consistent. Our study also highlighted the importance of L-aginine/SDMA ratio, that was the only biochemical parameter able to distinguish between all groups analyzed, reaching the lower level in TIA group. Concerning the potential prognostic role of these methylarginines, our data showed that SDMA was correlated with the short-term outcome, reaching higher levels in case of favourable course of acute event. So, SDMA could be considered a positive prognostic marker in the short-term outcome. However, this finding seems to be partially in contrast with the available evidence on this topic. In fact, Worthmann et al. [35] suggested that an increase in both ADMA and SDMA levels after acute ischemic stroke could predict poor functional outcome at 90 days after stroke. Luneburg et al. [36] showed, in a cohort of 137 patients affected by acute ischemic cerebral event, a strong association between SDMA levels and primary outcome (death, stroke recurrence, ischemic heart disease and rehospitalization) but in relation to renal function. Instead, Schulze et al. [37]

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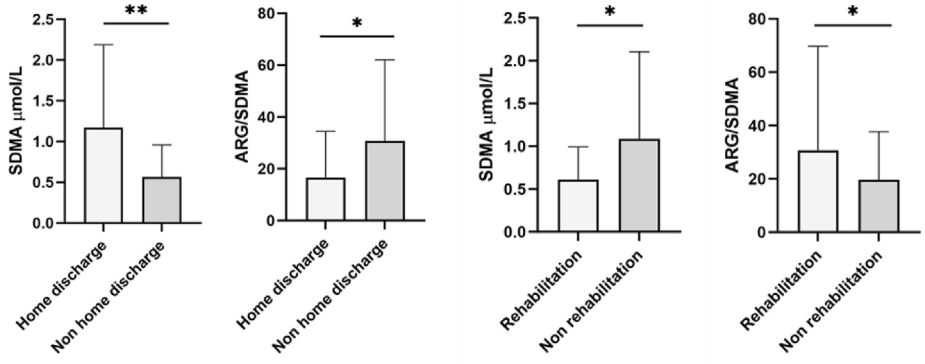


**Figure 3** SDMA and Arginine/SDMA ratio event (expressed as median with interquartile range) in relation of the type of discharge after acute ischemic. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.

pointed out, on a large series of 394 patients followed up for 7.4 years after acute ischemic stroke, that SDMA was an independent predictor of all-cause mortality, irrespective of renal function. The outperforming role of SDMA was also evaluated in other fields, such as in chronic kidney disease. In fact, Emrich et al. [38] performed a large prospective study on 528 patients affected by non-dialysis chronic kidney disease, suggesting that, among the other methylarginines, SDMA was more consistently associated with CV and renal outcomes.

Based on the present data, our group formulated a hypothesis, aimed at interpreting SDMA excursion observed in ischemic patients. Knowing how SDMA and ADMA compete for the same transporter, we have assumed that in the acute phase of a cerebral ischemic event, the increased intracellular concentration of the two metabolites is uniquely attributable to nuclear proteolysis process, which results in an equivalent transition of SDMA and ADMA in the extracellular compartment. Otherwise, in the subacute phase, and therefore exclusively in case of an ischemic lesion that persists beyond 24 h, this process would be associated with the enzymatic perturbation due to oxidative stress which in fact results in an increased expression of PRMTs and an inhibition of DDAH. This determines an overproduction of ADMA and SDMA, with the reduction of metabolism only in the first one. In this way, high intracellular concentrations of ADMA would prevent the transit of SDMA into the extracellular compartment competing for the cationic amino acid transporter (hCAT-2B). It follows that, in patients affected by stroke, after few hours from the acute ischemic injury, SDMA is compartmentalized in the cellular district, resulting significantly reduced in plasma. According to this hypothesis, we could therefore explain the statistically significant difference between plasma SDMA concentrations observed in patients affected by TIA and stroke. This hypothesis could justify the discordance with some literature evidence. In fact, the study of Wanby et al. [33] and Brouns et al. [32] have evaluated dimethylarginines levels in plasma and in liquor, respectively, in the first hours after the onset of symptoms, so in the phase in which SDMA values could be indistinctly elevated in patients affected by a transient or permanent event, according to our hypothesis. Instead, samples of our study were taken between the third and seventh day of hospitalization, when the distribution curves of ADMA e of SDMA could diverge sufficiently to obtain significantly different values of SDMA, but not of ADMA, in the TIA group compared to stroke group. The interpretation of SDMA as an indirectly proportional marker of oxidative stress could explain its potential role as a positive short-term prognostic indicator. The inconsistency of previous case control studies aimed at investigating the short-term prognostic role of SDMA could be attributable to the timing of its detection. In fact, in previous studies SDMA was measured in a very early stage. Conversely, in our study, the measurement a few days after the acute phase could express, in an indirect and inversely proportional way, the degree of oxidative stress in the ischemic area, thus configuring a positive prognostic marker. The strengths of the present study are the collection of data from a prospective single center register and the high quality of the laboratory that performed the analysis of L-aginine, ADMA and SDMA. Moreover, with this study, we aimed to provide simultaneously both the differential diagnostic and the prognostic role of the methylarginines in cerebrovascular disease. However, it is important to acknowledge certain limitations within this study. Firstly, the long-term follow-up was conducted only on a minority of stroke patients, resulting in a scarcity of data that may have partially influenced the statistical significance of SDMA as a prognostic marker for long-term outcomes. Secondly, parameters related to endothelial dysfunction or oxidative stress were not included in the analysis. Thirdly, the sample size of our cohort may not have been sufficient to draw definitive conclusions regarding the hypothesis of SDMA excursion in ischemic patients, thus necessitating further confirmation through larger subsequent studies. Thirdly, this study did not explore additional markers of endothelial function or oxidative stress.

## 5. Conclusions

The results of the present study confirmed the main literature evidence concerning the diagnostic role of ADMA, SDMA and, particularly, their ratio with L-arginine,

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in predicting the risk of an acute cerebrovascular event. Furthermore, we also evaluate the differential methylarginine expression pathways, in order to distinguish between transient or permanent ischemic event. We postulated that SDMA could be configured as a specific marker of transient ischemic damage. In fact, we hypothesized that, through the mechanisms above mentioned, while ADMA increased, significantly but indistinctly, both in TIA and stroke patients, the increase in SDMA levels was significantly associated only with TIA. As endothelial dysfunction precedes clinical atherosclerosis, its early identification may represent a clinical diagnostic tool in the primary prevention of cardio-cerebrovascular diseases. Moreover, assuming that the levels of SDMA are inversely proportional to oxidative stress degree, it is also possible to suppose the role of this metabolite both as a laboratory indicator of the extent of the neurological deficit and as a short-term positive prognostic marker in the patients affected from ischemic stroke. So, our study pointed out the potential diagnostic and prognostic role of both methylarginine and their ratio with L-arginine in acute cerebrovascular ischemic event, although these data need to be confirmed by a larger cohort in a prospective study.

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