

## **Role of asymmetric dimethyl-arginine and NOX-2 in activation of leptomeningeal collaterals after acute ischemic stroke**

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**Table S1. Demographics and clinical characteristics of the overall study population and by collateral status**

|                                       | All patients<br>N=101 | Good<br>n=44 | Moderate<br>n=35 | Poor<br>n=22   | p value                  |
|---------------------------------------|-----------------------|--------------|------------------|----------------|--------------------------|
| <b>Other clinical characteristics</b> |                       |              |                  |                |                          |
| Coagulopathy (%)                      | 1/96 (1.0)            | 0            | 1/33 (3.0)       | 0              | 0.381                    |
| Valvulopathy (%)                      | 20/97 (20.6)          | 8/43 (18.6)  | 6/33 (18.2)      | 6/21 (28.6)    | 0.595                    |
| Peripheral vasculopathy (%)           | 6/94 (6.4)            | 1/41 (2.4)   | 4/33 (12.1)      | 1/20 (5.0)     | 0.229                    |
| Migraine (%)                          | 1/96 (1.0)            | 0            | 1/34 (2.9)       | 0              | 0.398                    |
| Neoplasm (%)                          | 17/100 (17.0)         | 6 (13.6)     | 3/34 (8.8)       | 8 (36.4)       | <b>0.020</b>             |
| Stressful event (%)                   | 9/100 (9.0)           | 3/43 (7.0)   | 4 (11.4)         | 2 (9.1)        | 0.792                    |
| Recent infection (%)                  | 5 (5.0)               | 2 (4.5)      | 1 (2.9)          | 2 (9.1)        | 0.565                    |
| <b>Medications prior to stroke</b>    |                       |              |                  |                |                          |
| Anticoagulant (%)                     | 26/94 (27.7)          | 11/41 (26.8) | 8/32 (25.0)      | 7/21 (33.3)    | 0.793                    |
| - Warfarin                            | 8/26 (30.8)           | 4/11 (36.4)  | 2/8 (25.0)       | 2/7 (28.6)     |                          |
| - Acenocumarol                        | 3/26 (11.5)           | 0            | 2/8 (25.0)       | 1/7 (14.3)     |                          |
| - Enoxaparin                          | 5/26 (19.2)           | 2/11 (18.2)  | 2/8 (25.0)       | 1/7 (14.3)     |                          |
| - Warfarin/enoxaparin                 | 1/26 (3.8)            | 0            | 1/11 (12.5)      | 0              |                          |
| - Dabigatran                          | 1/26 (3.8)            | 1/11 (9.1)   | 0                | 0              |                          |
| - Apixaban                            | 2/26 (7.7)            | 0            | 1/8 (12.5)       | 1/7 (14.3)     |                          |
| - Edoxaban                            | 2/26 (7.7)            | 2/11 (18.2)  | 0                | 0              |                          |
| - Rivaroxaban                         | 4/26 (15.4)           | 2/11 (18.2)  | 0                | 2/7 (28.6)     |                          |
| Antiplatelet (%)                      | 36/92 (39.1)          | 15/41 (36.6) | 15/31 (48.4)     | 6/20 (30.0)    | 0.382                    |
| - ASA                                 | 20/35 (57.1)          | 7/14 (50.0)  | 9/15 (60.0)      | 4/6 (66.7)     |                          |
| - Clopidogrel                         | 7/35 (20.0)           | 3/14 (21.4)  | 2/15 (13.3)      | 2/6 (33.3)     |                          |
| - ASA+clopidogrel                     | 5/35 (14.3)           | 3/14 (21.4)  | 2/15 (13.3)      | 0              |                          |
| - Cardirene                           | 2/35 (5.7)            | 1/14 (7.1)   | 1/15 (6.7)       | 0              |                          |
| - Ticlopidina                         | 1/35 (2.9)            | 0            | 1/15 (6.7)       | 0              |                          |
| Lipid lowering drugs (%)              | 28/91 (30.8)          | 13/40 (32.5) | 10/31 (32.3)     | 5/20 (25.0)    | 0.818                    |
| ACE-I/AREB (%)                        | 47/92 (51.1)          | 16/41 (39.0) | 19/31 (61.3)     | 12/20 (60.0)   | 0.116                    |
| Diuretics (%)                         | 30/93 (32.3)          | 11/41 (26.8) | 11/31 (35.5)     | 8/21 (38.1)    | 0.598                    |
| Beta-blockers (%)                     | 40/93 (43.0)          | 18/41 (43.9) | 13/31 (41.9)     | 9/21 (42.9)    | 0.986                    |
| Calcium antagonists (%)               | 10/92 (10.9)          | 4/41 (9.8)   | 4/31 (12.9)      | 2/20 (10.0)    | 0.905                    |
| PPI (%)                               | 29/93 (31.2)          | 13/41 (31.7) | 11/31 (35.5)     | 5/21 (23.8)    | 0.669                    |
| Oral glucose lowering drugs (%)       | 16/93 (17.2)          | 7/41 (17.1)  | 6/31 (19.4)      | 3/21 (14.3)    | 0.893                    |
| Insulin (%)                           | 6/90 (6.7)            | 1/38 (2.6)   | 5/31 (16.1)      | 0              | <b>0.031</b>             |
| Nitrates (%)                          | 6/74 (8.1)            | 1/30 (3.3)   | 3/28 (10.7)      | 2/16 (12.5)    | 0.452                    |
| <b>Stroke characteristics</b>         |                       |              |                  |                |                          |
| SBP, mean (SD)                        |                       |              |                  |                |                          |
| - T0                                  | 144 (26.6)            | 144.7 (29.1) | 145.1 (25.3)     | 143.1 (24.6)   | 0.962                    |
| - T1                                  | 141.2 (22.8)          | 139.7 (22.8) | 139.2 (21.4)     | 148.8 (25.3)   | 0.321                    |
| - T2                                  | 142.7 (21.6)          | 139.7 (20.5) | 145.7 (20.9)     | 143.4 (25.5)   | 0.518                    |
| DBP, mean (SD)                        |                       |              |                  |                |                          |
| - T0                                  | 79.8 (14.3)           | 80.6 (14.6)  | 78.6 (12.9)      | 80.4 (16.4)    | 0.824                    |
| - T1                                  | 76.5 (16.5)           | 75.7 (12.2)  | 75.7 (16.7)      | 80.1 (24.4)    | 0.617                    |
| - T2                                  | 78.3 (14.3)           | 78.2 (13.0)  | 78.2 (13.1)      | 78.6 (19.10)   | 0.995                    |
| HR, mean (SD)                         |                       |              |                  |                |                          |
| - T0                                  | 78.3 (15.6)           | 77.1 (14.7)  | 81.7 (15.6)      | 74.7 (17.0)    | 0.250                    |
| - T1                                  | 80.5 (18.4)           | 75.4 (13.8)  | 85.7 (17.7)      | 82.8 (26.5)    | <b>0.046<sup>b</sup></b> |
| - T2                                  | 81.8 (22.3)           | 81.3 (21.1)  | 80.9 (18.8)      | 84.4 (30.4)    | 0.866                    |
| BT, mean (SD)                         |                       |              |                  |                |                          |
| - T0                                  | 36.3 (0.4)            | 36.2 (0.4)   | 36.3 (0.4)       | 36.2 (0.3)     | 0.805                    |
| - T1                                  | 37.0 (0.6)            | 37.0 (0.6)   | 37.1 (0.7)       | 37.0 (0.6)     | 0.763                    |
| - T2                                  | 37.0 (0.6)            | 36.9 (0.5)   | 36.9 (0.7)       | 37.1 (0.6)     | 0.503                    |
| HGT, mean (SD)                        |                       |              |                  |                |                          |
| - T0                                  | 143.3 (55.6)          | 138.7 (49.4) | 149.2 (70.2)     | 141.90 (37.83) | 0.722                    |
| - T1                                  | 128.8 (45.6)          | 114.3 (30.4) | 145.7 (55.7)     | 132.9 (47.7)   | <b>0.025<sup>c</sup></b> |
| - T2                                  | 116.0 (30.4)          | 110.7 (24.5) | 118.8 (36.2)     | 121.6 (30.2)   | 0.423                    |
| ASPECTS                               |                       |              |                  |                | 0.158                    |
| - mean (SD)                           | 8.22 (1.32)           | 8.48 (1.19)  | 8.24 (1.25)      | 7.86 (1.21)    |                          |
| - median (IQR)                        | 8 (7-9)               | 9 (8-9)      | 8 (7.50-9)       | 8 (7-8.25)     |                          |
| Collateral status (%)                 |                       | -            | -                | -              |                          |
| - good (17-20)                        | 44/102 (43.1)         |              |                  |                |                          |
| - moderate (11-16)                    | 36/102 (35.3)         |              |                  |                |                          |

|                                            |               |            |              |              |       |
|--------------------------------------------|---------------|------------|--------------|--------------|-------|
| - poor (0-10)                              | 22/102 (21.6) |            |              |              |       |
| Imaging for V measurement:                 |               |            |              |              | 0.688 |
| - RM (%)                                   | 83/99 (83.8)  | 36 (81.8)  | 30/34 (88.2) | 17/21 (81.0) |       |
| - CT (%)                                   | 16/99 (16.2)  | 8 (18.2)   | 4/34 (11.8)  | 4/21 (19.0)  |       |
| Corticosteroid therapy in the first 48 hrs | 6/97 (6.2)    | 1/43 (2.3) | 2 (5.7)      | 3/19 (15.8)  | 0.126 |

One-Way ANOVA: a. HR at T1: good vs. moderate p=0.042 (Tukey) or p=0.021 (Games-Howell); b. HGT at T1: good vs. moderate p=0.020 (Tukey); p=0.035 (Games-Howell)

**Table S2. Biomarkers from peripheral blood in the overall study population and by collateral status**

|                                                  | All patients<br>N=105     | Good<br>n=44              | Moderate<br>n=36          | Poor<br>n=22              | p value                  |
|--------------------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|--------------------------|
| <b>Admission (T0)</b>                            |                           |                           |                           |                           |                          |
| Onset-to-blood sample time, min,<br>median (IQR) | 120.0<br>(80-194.25)      | 105.0<br>(65-190)         | 120.0<br>(90-250)         | 90.0<br>(75.0-180.0)      | 0.611                    |
| Total leukocyte                                  |                           |                           |                           |                           | 0.215                    |
| - mean (SD)                                      | 8.69 (2.64)               | 8.54 (2.47)               | 8.31 (2.46)               | 9.54 (3.10)               |                          |
| - median (IQR)                                   | 8.10<br>(6.86-10.15)      | 7.87<br>(6.65-10.08)      | 8.06<br>(6.58-9.38)       | 9.07<br>(7.02-11.36)      |                          |
| Neutrophils (absolute count)                     |                           |                           |                           |                           | 0.757                    |
| - mean (SD)                                      | 6.12 (2.41)               | 6.04 (2.27)               | 6.01 (2.49)               | 6.46 (2.58)               |                          |
| - median (IQR)                                   | 5.54<br>(4.44-7.20)       | 5.35<br>(4.38-7.12)       | 5.99<br>(4.17-7.24)       | 5.74<br>(4.87-8.31)       |                          |
| Neutrophils (percentage)                         |                           |                           |                           |                           | 0.585                    |
| - mean (SD)                                      | 69.50 (11.43)             | 69.98 (10.64)             | 70.36 (12.55)             | 67.29 (11.23)             |                          |
| - median (IQR)                                   | 70.60<br>(61.0-79.0)      | 70.40<br>(62.10-77.90)    | 72.15<br>(61.30-79.23)    | 64.55<br>(57.58-78.38)    |                          |
| Lymphocytes (absolute<br>count)                  |                           |                           |                           |                           | 0.122                    |
| - mean (SD)                                      | 1.80 (1.03)               | 1.75 (0.90)               | 1.61 (1.03)               | 2.18 (1.18)               |                          |
| - median (IQR)                                   | 1.56<br>(1.19-2.13)       | 1.56<br>(1.09-2.13)       | 1.40<br>(1.06-1.92)       | 2.0<br>(1.33-2.93)        |                          |
| Lymphocytes (percentage)                         |                           |                           |                           |                           | 0.390                    |
| - mean (SD)                                      | 20.98 (9.93)              | 21.17 (9.49)              | 19.38 (10.49)             | 23.10 (9.84)              |                          |
| - median (IQR)                                   | 20.45<br>(12.60-27.33)    | 21.10<br>(13.75-27.08)    | 17.45<br>(11.60-24.73)    | 25.45<br>(15.78-30.13)    |                          |
| PCR                                              |                           |                           |                           |                           | 0.526                    |
| - mean (SD)                                      | 1.83 (2.81)               | 1.91 (0.17)               | 1.38 (1.80)               | 2.49 (3.34)               |                          |
| - median (IQR)                                   | 0.37<br>(0.12-2.16)       | 0.17<br>(0.10-2.03)       | 0.48<br>(0.17-2.08)       | 0.42<br>(0.15-6.55)       |                          |
| Cortisol                                         |                           |                           |                           |                           | 0.523                    |
| - mean (SD)                                      | 190.94 (40.85)            | 185.95 (43.81)            | 192.20 (37.49)            | 200.20 (40.82)            |                          |
| - median (IQR)                                   | 197.76<br>(155.22-215.62) | 187.33<br>(150.01-211.37) | 197.76<br>(163.32-219.27) | 203.72<br>(160.73-215.62) |                          |
| NO                                               |                           |                           |                           |                           | 0.860                    |
| - mean (SD)                                      | 49.64 (19.45)             | 48.36 (20.33)             | 50.80 (18.94)             | 50.64 (19.22)             |                          |
| - median (IQR)                                   | 48.34<br>(36.40-61.07)    | 47.82<br>(29.81-59.0)     | 52.17<br>(38.07-65.23)    | 49.26<br>(39.34-60.46)    |                          |
| ET-1                                             |                           |                           |                           |                           | 0.182                    |
| - mean (SD)                                      | 12.02 (5.70)              | 10.80 (4.51)              | 12.81 (6.61)              | 13.55 (6.26)              |                          |
| - median (IQR)                                   | 10.81<br>(8.52-14.18)     | 10.43<br>(7.96-13.38)     | 10.67<br>(8.63-16.0)      | 12.42<br>(8.86-17.56)     |                          |
| NOX2                                             |                           |                           |                           |                           | 0.808                    |
| - mean (SD)                                      | 13.91 (10.14)             | 13.45 (6.97)              | 14.93 (14.96)             | 13.22 (5.40)              |                          |
| - median (IQR)                                   | 12.56<br>(8.16-16.38)     | 12.40<br>(7.83-16.65)     | 12.53<br>(8.64-14.51)     | 12.56<br>(8.65-16.98)     |                          |
| ADMA                                             |                           |                           |                           |                           | <b>0.028<sup>a</sup></b> |
| - mean (SD)                                      | 112.55 (31.75)            | 102.40 (25.72)            | 119.80 (29.30)            | 123.85 (42.36)            |                          |
| - median (IQR)                                   | 113.59<br>(88.08-131.49)  | 98.04<br>(78.77-123.65)   | 118.10<br>(99.95-137.58)  | 115.38<br>(90.85-135.70)  |                          |
| <b>24 h (T1)</b>                                 |                           |                           |                           |                           |                          |
| Onset-to-blood sample time, min,<br>median (IQR) | 26.54<br>(25.0-25.50)     | 25.63<br>(25-27.36)       | 26.25<br>(25.37-29.50)    | 25.50<br>(24.50-27.0)     | 0.925                    |
| Total leukocyte                                  |                           |                           |                           |                           | 0.368                    |

|                                                               |                                             |                                             |                                             |                                             |                          |
|---------------------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------|
| - mean (SD)<br>- median (IQR)                                 | 10.07 (3.50)<br>9.00<br>(7.54-12.25)        | 9.61 (3.34)<br>8.93<br>(7.35-12.28)         | 10.13 (3.83)<br>8.79<br>(7.82-12.64)        | 11.28 (3.32)<br>10.72<br>(8.80-14.75)       |                          |
| Neutrophils (absolute count)<br>- mean (SD)<br>- median (IQR) | 8.17 (3.52)<br>7.60<br>(5.67-10.34)         | 7.75 (3.35)<br>7.21<br>(5.29-10.15)         | 8.3 (3.94)<br>7.41<br>(5.62-10.03)          | 9.12 (3.31)<br>8.57<br>(6.82-12.78)         | 0.509                    |
| Neutrophils (percentage)<br>- mean (SD)<br>- median (IQR)     | 78.6 (9.98)<br>81.10<br>(72.10-85.90)       | 77.37 (10.89)<br>79.60<br>(70.53-87.63)     | 80.09 (9.79)<br>82.30<br>(72.70-87.10)      | 79.30 (7.61)<br>82.10<br>(74.58-84.70)      | 0.600                    |
| Lymphocytes (absolute count)<br>- mean (SD)<br>- median (IQR) | 1.22 (0.57)<br>1.14<br>(0.79-1.56)          | 1.26 (0.61)<br>1.10<br>(0.75-1.69)          | 1.11 (0.55)<br>0.92<br>(0.80-1.39)          | 1.32 (0.48)<br>1.32<br>(1.04-1.74)          | 0.543                    |
| Lymphocytes (percentage)<br>- mean (SD)<br>- median (IQR)     | 13.80 (7.99)<br>11.30<br>7.80-20.0)         | 14.64 (8.55)<br>13.65<br>(7.28-20.70)       | 12.94 (8.03)<br>10.50<br>(7.85-19.20)       | 12.91 (6.49)<br>11.25<br>(7.83-18.90)       | 0.686                    |
| PCR<br>- mean (SD)<br>- median (IQR)                          | 1.96 (2.10)<br>1.22<br>(0.53-2.72)          | 1.91 (2.37)<br>1.09<br>(0.55-1.85)          | 2.14 (2.11)<br>1.22<br>(0.30-3.68)          | 1.72 (1.45)<br>1.68<br>(0.69-1.99)          | 0.884                    |
| Cortisol<br>- mean (SD)<br>- median (IQR)                     | 184.18 (50.27)<br>189.84<br>(146.50-216.13) | 170.48 (48.06)<br>168.40<br>(128.07-197.27) | 185.75 (49.62)<br>188.37<br>(154.76-216.88) | 210.90 (48.17)<br>207.73<br>(185.11-236.36) | <b>0.033<sup>b</sup></b> |
| NO<br>- mean (SD)<br>- median (IQR)                           | 23.87 (12.00)<br>24.49<br>(14.84-32.13)     | 21.54 (13.37)<br>20.20<br>(8.76-31.54)      | 24.79 (9.68)<br>25.52<br>(18.11-29.65)      | 27.44 (12.79)<br>31.62<br>(16.40-36.71)     | 0.239                    |
| ET-1<br>- mean (SD)<br>- median (IQR)                         | 16.77 (8.21)<br>15.57<br>(11.46-21.01)      | 16.42 (10.03)<br>15.21<br>(9.97-20.68)      | 16.96 (6.39)<br>16.02<br>(11.90-20.67)      | 17.20 (7.35)<br>14.55<br>(11.51-23.66)      | 0.941                    |
| NOX2<br>- mean (SD)<br>- median (IQR)                         | 19.16 (10.00)<br>16.70<br>(11.93-24.08)     | 18.33 (9.47)<br>15.95<br>(10.65-25.21)      | 19.69 (9.31)<br>16.93<br>(12.25-26.15)      | 19.86 (12.93)<br>16.85<br>(13.55-22.78)     | 0.818                    |
| ADMA<br>- mean (SD)<br>- median (IQR)                         | 132.18 (30.26)<br>131.0<br>(107.51-150.41)  | 127.42 (29.13)<br>127.70<br>(104.47-145.46) | 132.09 (25.09)<br>140.19<br>(112.11-150.41) | 142.84 (40.73)<br>134.26<br>(105.10-192.78) | 0.265                    |
| <b>48 h (T2)</b>                                              |                                             |                                             |                                             |                                             |                          |
| Onset-to-blood sample time, min,<br>median (IQR)              | 50.0<br>(49-52)                             | 49.9<br>(49-51-63)                          | 50.0<br>(49.10-53.50)                       | 49.40<br>(48.63-51.0)                       | 0.540                    |
| Total leukocyte<br>- mean (SD)<br>- median (IQR)              | 10.23 (4.46)<br>9.39<br>(7.59-11.65)        | 9.42 (3.26)<br>8.71<br>(7.32-11.28)         | 10.06 (5.24)<br>9.16<br>(7.56-11.67)        | 11.98 (4.69)<br>9.79<br>(8.81-14.24)        | 0.202                    |
| Neutrophils (absolute count)<br>- mean (SD)<br>- median (IQR) | 8.14 (4.40)<br>7.07<br>(5.68-9.51)          | 7.47 (3.21)<br>6.58<br>(5.36-8.58)          | 7.88 (5.32)<br>6.89<br>(5.18-9.39)          | 9.77 (4.36)<br>8.18<br>(6.85-12.23)         | 0.252                    |
| Neutrophils (percentage)<br>- mean (SD)<br>- median (IQR)     | 77.05 (11.99)<br>78.40<br>(73.20-84.60)     | 75.10 (15.40)<br>76.90<br>(72.70-82-70)     | 77.26 (10.38)<br>78.40<br>(70.85-86.30)     | 80.20 (5.88)<br>80.60<br>(75.10-85.30)      | 0.422                    |
| Lymphocytes (absolute count)<br>- mean (SD)<br>- median (IQR) | 1.42 (1.32)<br>1.12<br>(0.81-1.55)          | 1.19 (0.51)<br>1.04<br>(0.82-1.44)          | 1.52 (1.60)<br>1.25<br>(0.79-1.65)          | 1.68 (1.77)<br>1.13<br>(0.83-1.83)          | 0.478                    |
| Lymphocytes (percentage)<br>- mean (SD)<br>- median (IQR)     | 13.57 (7.45)<br>12.45<br>(8.22-16.58)       | 13.83 (6.41)<br>13.10<br>(9.20-17.90)       | 14.48 (9.30)<br>11.50<br>(7.16-19.68)       | 11.54 (5.41)<br>10.70<br>(7.90-15.30)       | 0.471                    |

|                                           |                                             |                                             |                                             |                                             |       |
|-------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|-------|
| PCR<br>- mean (SD)<br>- median (IQR)      | 4.59 (5.43)<br>2.70<br>(1.01-6.33)          | 2.77 (3.11)<br>1.67<br>(0.92-4.11)          | 6.69 (8.09)<br>3.79<br>(1.17-9.80)          | 4.90 (3.55)<br>4.25<br>(2.35-7.19)          | 0.082 |
| Cortisol<br>- mean (SD)<br>- median (IQR) | 183.91 (52.16)<br>180.47<br>(138.20-227.54) | 183.90 (52.38)<br>181.41<br>(138.10-229.68) | 176.50 (47.30)<br>170.75<br>(137.75-206.36) | 201.03 (61.86)<br>193.57<br>(142.70-249.76) | 0.372 |
| NO<br>- mean (SD)<br>- median (IQR)       | 16.82 (8.54)<br>15.36<br>(10.79-23.90)      | 14.81 (8.48)<br>14.06<br>(6.54-22.12)       | 18.71 (8.87)<br>15.92<br>(11.93-24.08)      | 17.71 (7.54)<br>17.40<br>(13.22-23.28)      | 0.167 |
| ET-1<br>- mean (SD)<br>- median (IQR)     | 16.10 (6.62)<br>15.44<br>(11.43-20.90)      | 16.17 (6.56)<br>17.34<br>(11.47-21.74)      | 16.85 (5.92)<br>16.21<br>(12.13-20.77)      | 14.53 (8.06)<br>13.24<br>(8.22-18.85)       | 0.532 |
| NOX2<br>- mean (SD)<br>- median (IQR)     | 21.83 (9.06)<br>19.49<br>(15.72-28.41)      | 20.72 (7.29)<br>19.49<br>(13.90-27.72)      | 22.50 (10.97)<br>19.58<br>(15.62-27.70)     | 23.02 (8.93)<br>20.11<br>(16.18-29.71)      | 0.622 |
| ADMA<br>- mean (SD)<br>- median (IQR)     | 146.42 (33.25)<br>142.97<br>(121.31-164.61) | 139.03 (31.57)<br>135.02<br>(118.01-156.57) | 149.23 (31.36)<br>144.57<br>(129.57-169.45) | 158.09 (39.43)<br>156.64<br>(120.01-191.66) | 0.184 |

One-Way ANOVA: a. ADMA at T0: good vs. moderate p=0.073 (Tukey) or p=0.045 (Games-Howell); good vs. poor p=0.065 (Tukey) or p=0.189 (Games-Howell); b. Cortisol at T1: good vs. poor p=0.025 (Tukey) or p=0.031 (Games-Howell).

**Table S3. Biomarkers from the intracranial blood (pre- and post-occlusion) in the overall study population and by collateral status**

|                       | All patients<br>N=105  | Good<br>n=44           | Moderate<br>n=36       | Poor<br>n=22           | p value |
|-----------------------|------------------------|------------------------|------------------------|------------------------|---------|
| <b>Admission (T0)</b> |                        |                        |                        |                        |         |
| Cortisol              |                        |                        |                        |                        |         |
| <i>Pre-occlusion</i>  | n=40                   | n=21                   | n=13                   | n=6                    | 0.177   |
| - mean (SD)           | 161.07 (46.75)         | 148.17 (41.51)         | 172.77 (49.25)         | 180.87 (52.98)         |         |
| - median (IQR)        | 169.93 (125.43-190.80) | 145.58 (109.26-190.73) | 175.73 (142.36-190.41) | 180.99 (128.96-215.85) |         |
| <i>Post-occlusion</i> | n=5                    | n=2                    | n=2                    | n=1                    | -       |
| - mean (SD)           | 202.97 (29.15)         | 211.57 (14.97)         | 189.21 (50.41)         | 213.30                 |         |
| - median (IQR)        | 213.30 (177.27-213.50) | -                      | -                      | -                      |         |
| NO                    |                        |                        |                        |                        |         |
| <i>Pre-occlusion</i>  | n=19                   | n=7                    | n=8                    | n=4                    | 0.848   |
| - mean (SD)           | 47.60 (8.80)           | 48.62 (9.42)           | 46.17 (10.09)          | 48.69 (6.35)           |         |
| - median (IQR)        | 47.69 (40.94-55.22)    | 44.50 (40.94-58.43)    | 47.02 (36.13-55.22)    | 50.55 (42.0-53.53)     |         |
| <i>Post-occlusion</i> | n=5                    | n=2                    | n=2                    | n=1                    | -       |
| - mean (SD)           | 39.48 (12.81)          | 43.68 (20.03)          | 42.25 (3.28)           | 25.56                  |         |
| - median (IQR)        | 39.93 (27.54-51.21)    | -                      | -                      | -                      |         |
| ET-1                  |                        |                        |                        |                        |         |
| <i>Pre-occlusion</i>  | n=39                   | n=21                   | n=12                   | n=6                    | 0.354   |
| - mean (SD)           | 9.60 (5.46)            | 9.10 (4.16)            | 11.39 (7.70)           | 7.77 (3.76)            |         |
| - median (IQR)        | 8.86 (5.23-11.50)      | 8.86 (6.78-10.0)       | 9.78 (4.77-19.17)      | 8.75 (3.30-11.17)      |         |
| <i>Post-occlusion</i> | n=5                    | n=2                    | n=2                    | n=1                    | -       |
| - mean (SD)           | 3.56 (0.30)            | 3.42 (0.30)            | 3.64 (0.45)            | 3.67                   |         |
| - median (IQR)        | 3.63 (3.27-3.82)       | -                      | -                      | -                      |         |
| NOX2                  |                        |                        |                        |                        |         |
| <i>Pre-occlusion</i>  | n=40                   | n=21                   | n=13                   | n=6                    | 0.680   |
| - mean (SD)           | 14.52 (9.43)           | 15.71 (12.41)          | 13.66 (3.93)           | 12.20 (5.03)           |         |
| - median (IQR)        | 12.52 (10.18-15.62)    | 12.49 (9.74-16.53)     | 13.04 (10.42-15.47)    | 10.87 (8.51-16.23)     |         |
| <i>Post-occlusion</i> | n=5                    | n=2                    | n=2                    | n=1                    | -       |
| - mean (SD)           | 16.22 (4.26)           | 17.16 (4.55)           | 13.58 (4.94)           | 19.61                  |         |
| - median (IQR)        | 17.07 (12.01-20.0)     | -                      | -                      | -                      |         |
| ADMA                  |                        |                        |                        |                        |         |
| <i>Pre-occlusion</i>  | n=40                   | n=21                   | n=13                   | n=6                    | 0.833   |
| - mean (SD)           | 106.43 (29.03)         | 106.37 (29.52)         | 103.70 (28.92)         | 112.58 (31.87)         |         |
| - median (IQR)        | 105.25 (83.76-131.50)  | 103.60 (83.15-136.10)  | 106.52 (79.55-126.99)  | 112.32 (82.56-140.79)  |         |
| <i>Post-occlusion</i> | n=5                    | n=2                    | n=2                    | n=1                    |         |

|                |                        |                |               |        |   |
|----------------|------------------------|----------------|---------------|--------|---|
| - mean (SD)    | 131.12 (12.89)         | 126.47 (14.53) | 127.34 (9.84) | 147.99 |   |
| - median (IQR) | 134.30 (118.29-142.37) | -              | -             | -      | - |

**Table S4. Clinical outcome measures of the overall study population and by collateral status**

|                        | <b>All patients<br/>N=101</b> | <b>Good<br/>n=44</b> | <b>Moderate<br/>n=35</b> | <b>Poor<br/>n=22</b> | <b>p value</b> |
|------------------------|-------------------------------|----------------------|--------------------------|----------------------|----------------|
| mRS at 90 days (%)     |                               |                      |                          |                      | 0.468          |
| - 0                    | 18/96 (18.8)                  | 11/41 (26.8)         | 6/34 (17.6)              | 1/21 (4.8)           |                |
| - 1                    | 11/96 (11.5)                  | 3/41 (7.3)           | 3/34 (8.8)               | 5/21 (23.8)          |                |
| - 2                    | 9/96 (9.4)                    | 3/41 (7.3)           | 5/34 (14.7)              | 1/21 (4.8)           |                |
| - 3                    | 9/96 (9.4)                    | 5/41 (12.2)          | 4/34 (8.8)               | 1/21 (4.8)           |                |
| - 4                    | 17/96 (17.7)                  | 7/41 (17.1)          | 5/34 (14.7)              | 5/21 (23.8)          |                |
| - 5                    | 10/96 (10.4)                  | 5/41 (12.2)          | 3/34 (8.8)               | 2/21 (9.5)           |                |
| - 6                    | 22/96 (22.9)                  | 7/41 (17.1)          | 9/34 (26.5)              | 6/21 (28.6)          |                |
| mRS 0-1 at 90 days (%) | 29/96 (30.2)                  | 14/41 (34.1)         | 9/34 (26.5)              | 6/21 (28.6)          | 0.758          |
| mRS 0-2 at 90 days (%) | 38/96 (39.6)                  | 17/41 (41.5)         | 14/34 (41.2)             | 7/21 (33.3)          | 0.803          |
| mRS 2-6 at 90 days (%) | 67/96 (69.8)                  | 27/41 (65.9)         | 25/34 (73.5)             | 15/21 (71.4)         | 0.758          |
| mRS 3-6 at 90 days (%) | 58/96 (60.4)                  | 24/41 (58.5)         | 20/34 (58.8)             | 14/21 (66.7)         | 0.803          |
| In-hospital death (%)  | 16/96 (16.7)                  | 4/41 (9.8)           | 6/34 (17.6)              | 6/21 (28.6)          | 0.167          |
| Death at 90 days (%)   | 22/96 (22.9)                  | 7/41 (17.1)          | 9/34 (26.5)              | 6/21 (28.6)          | 0.493          |

mRS=modified Rankin Scale

**Table S5. Binary logistic regression analysis for good functional outcome (mRS 0-2) at 90 days**

|                                        | <b>OR</b> | <b>95% CIs</b> | <b>p value</b> |
|----------------------------------------|-----------|----------------|----------------|
| <b>Age</b>                             | 0.917     | 0.865-0.973    | <b>0.004</b>   |
| <b>Sex</b>                             | 2.597     | 0.613-11.008   | 0.195          |
| <b>NIHSS at T0</b>                     | 0.812     | 0.715-0.922    | <b>0.001</b>   |
| <b>Acute therapy (IVT, MT, IVT+MT)</b> | 1.787     | 0.060-53.246   | 0.738          |
| <b>ADMA levels at T0</b>               | 0.988     | 0.968-1.010    | 0.282          |
| <b>NOX2 levels at T0</b>               | 0.976     | 0.861-1.106    | 0.704          |
| <b>Collateral status</b>               |           |                | 0.464          |
| -good as reference                     | -         | -              | -              |
| -moderate                              | 2.468     | 0.535-11.390   | 0.247          |
| -poor                                  | 1.014     | 0.159-6.447    | 0.989          |

NIHSS=National Institutes of Health Stroke Scale

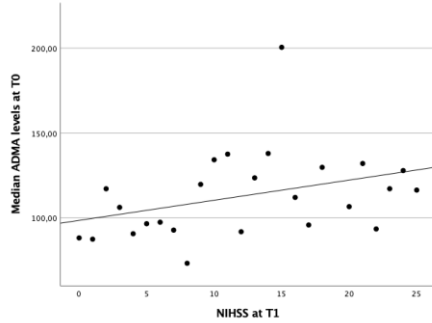
**Table S6. Binary logistic regression analysis for death at 90 days**

|                                        | <b>OR</b> | <b>95% Cis</b> | <b>p value</b> |
|----------------------------------------|-----------|----------------|----------------|
| <b>Age</b>                             | 1.032     | 0.974-1.093    | 0.283          |
| <b>Sex</b>                             | 1.024     | 0.296-3.545    | 0.970          |
| <b>NIHSS at T0</b>                     | 1.077     | 0.965-1.201    | 0.185          |
| <b>Acute therapy (IVT, MT, IVT+MT)</b> | 0.421     | 0.030-5.813    | 0.518          |
| <b>ADMA levels at T0</b>               | 1.012     | 0.992-1.034    | 0.246          |
| <b>NOX2 levels at T0</b>               | 1.018     | 0.904-1.147    | 0.769          |
| <b>Collateral status</b>               |           |                | 0.948          |
| -good as reference                     | -         | -              | -              |
| -moderate                              | 1.304     | 0.338-7.462    | 0.765          |
| -poor                                  | 1.284     | 0.242-6.808    | 0.769          |

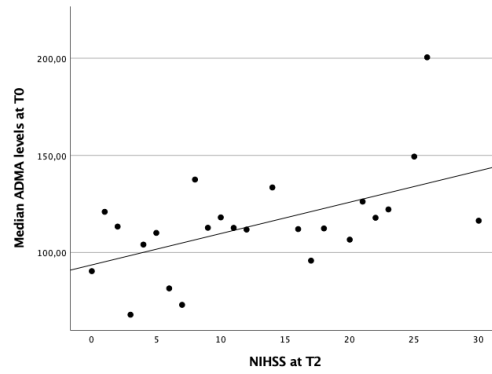
NIHSS=National Institutes of Health Stroke Scale

**Figure S1. ADMA levels and stroke severity**

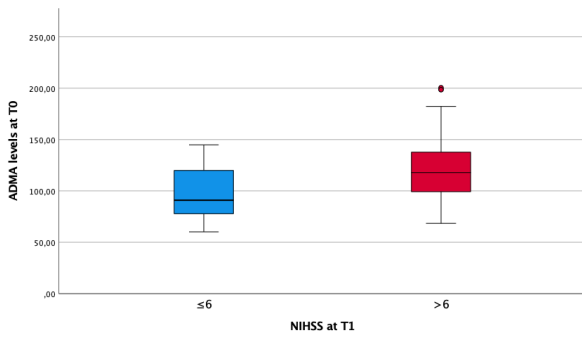
A.



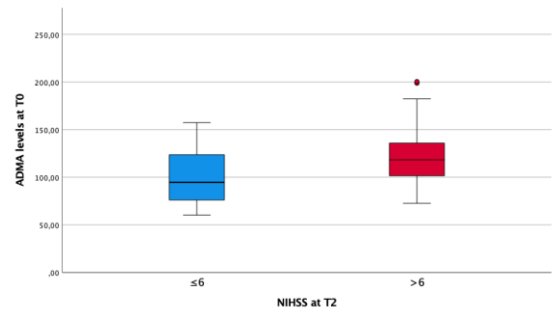
B.



C.



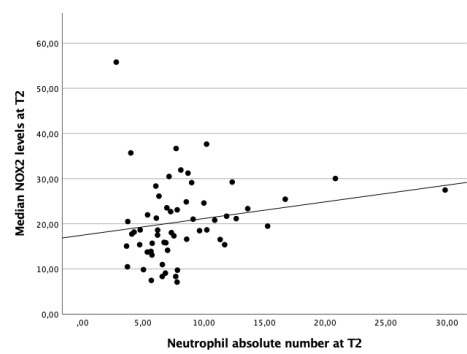
D.



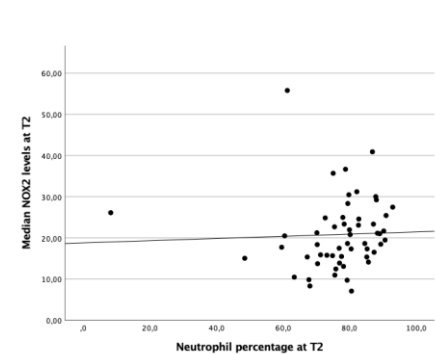
A, B Correlations between ADMA levels at admission and NIHSS score at the different timepoints;  
C, D Associations between ADMA levels at admission and mild ( $\text{NIHSS} \leq 6$ ) versus moderate to severe ( $\text{NIHSS} > 6$ ) stroke at T1 and T2.

**Figure S2. Correlation between NOX2 levels at T2 and blood cells**

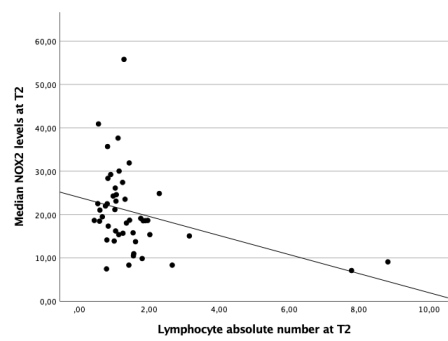
**A.**



**B.**



**C.**



**D.**

