SUPPLEMENTAL MATERIAL
Supplemental Methods

Trial Design and Participants

CATIS was a multicenter, single-blind, blinded end-points randomized clinical trial conducted in 26 hospitals across China. A total of 4071 patients aged over 22 years who had first-ever ischemic stroke confirmed by computed tomography or magnetic resonance imaging within 48 hours of symptom onset and had an elevated systolic blood pressure (BP) between 140 mmHg and 220 mmHg were recruited. Participants with a BP ≥220/120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis (≥70%), resistant hypertension, deep coma, or treatment with intravenous thrombolytic therapy were excluded. Patients treated with intravenous thrombolytic therapy (ie, intravenous recombinant tissue plasminogen activator [rtPA]) at baseline were excluded because of different requirements for blood pressure reduction.

The present observational study was based on a preplanned ancillary study, which aimed to investigate whether early antihypertensive treatment would reduce poststroke cognitive impairment and PSD in patients with acute ischemic stroke at 3 months after randomization among a random sample of the CATIS. In this ancillary study, 660 CATIS participants were systemically selected before randomization from 7 participating hospitals for cognitive function and psychological state evaluation at their...
3-month follow-up visit. Specifically, each of the 7 participating hospitals recruited 80-100 patients consecutively. The exclusion criteria for the ancillary study were visual, hearing, or psychiatric impairment substantial enough to hinder performance on evaluation. The recruitment was completed by November 2012. In the present study, we further excluded 88 participants without GDF-15 data or available follow-up. Finally, 572 participants were included in this analysis (Figure S1).

**Data collection**

Baseline data on demographic characteristics, lifestyle risk factors, medical history, and clinical features were collected at the time of enrollment. Admission ischemic stroke severity was evaluated with the National Institutes of Health Stroke Scale (NIHSS) by trained neurologists. Ischemic stroke subtype was classified as large artery atherosclerosis (thrombotic), cardiac embolism (embolic), and small artery occlusion lacunae (lacunar) according to patients’ clinical symptoms and imaging data. Baseline BP was calculated from three BP measurements conducted at admission by trained nurses when the patients were in the supine position using standard mercury sphygmomanometers according to a common protocol adapted from the procedures recommended by the American Heart Association. Serum galectin-3 concentrations were tested using a commercially available ELISA kit (R&D Systems). Routine laboratory measurements (e.g., blood glucose) were obtained at the participating hospitals at admission.

**Serum GDF-15 measurement**
Blood samples were collected after at least 8 hours of fasting within 24 hours of hospital admission. All blood samples were separated in the clinical laboratories of participating hospitals and stored at -80 °C until laboratory testing. A quantitative sandwich ELISA was performed using the Quantikine Human GDF-15 Immunoassay kit (R&D Systems) to measure serum GDF-15 concentrations at Soochow University. A standard curve was constructed, from which GDF-15 concentrations of unknown samples were determined. The intra- and interassay coefficients of variation were <1.8% and <6.0%, respectively. Laboratory technicians who performed serum GDF-15 measurements were blinded to the baseline characteristics and clinical outcomes of the study participants.

This study was approved by the Ethical Committees at Soochow University and the Institutional Review Boards at Tulane University. Written consent was obtained from all study participants or their immediate family members. The CATIS is registered at clinicaltrials.gov (Identifier: NCT01840072).

**Supplemental Results**

**Baseline characteristics**

Most baseline characteristics were well balanced between patients who were assayed for serum GDF-15 and all CATIS patients (Table S1), indicating that those assayed basically represent all CATIS participants. The 572 participants in this analysis had a mean age of 60 years, and 399 (69.8%) were men. The median serum GDF-15
concentration was 940.47 ng/L (interquartile range, 702.66-1386.70 ng/L). The participants with higher serum GDF-15 tended to be older; had higher serum galectin-3; and had lower body mass index and prevalence of thrombotic stroke than those with lower serum GDF-15 (Table S2).

Association between serum GDF-15 and PSD

At the 3-month follow-up, a total of 231 patients (40.4%) had PSD. The serum GDF-15 level in patients with PSD was higher than that in patients without PSD [1035.58 (753.89-1481.27) vs. 896.06 (679.86-1310.61) ng/L; \(P=0.003\)]. Patients in the third tertile of serum GDF-15 had the highest incidence of PSD (48.2%; \(P=0.002\)). After adjustment for confounders, the OR of PSD associated with the highest tertile of serum GDF-15 was 2.92 (95% CI: 1.36-6.27; \(P_{\text{trend}}=0.006\); Table 1) compared with the lowest tertile. In continuous analysis, a per-SD increase in raw GDF-15 and log-transformed GDF-15 was associated with 43% (95% CI: 3%-98%) and 42% (95% CI: 2%-97%) increased risk of PSD, respectively. Moreover, multivariate ordinal logistic regression analysis showed a significant association between serum GDF-15 and PSD severity (OR: 2.09; 95% CI 1.07-4.10; \(P_{\text{trend}}=0.030\); Table 1; Figure 1). In addition, multivariable-adjusted spline regression models showed a linear dose-response association between serum GDF-15 and PSD (\(P\) for nonlinearity=0.140; \(P\) for linearity=0.006; Figure 2). In addition, we also found that baseline NIHSS score and clinical center were significantly associated with the risk of PSD in the multivariable analysis (Table S3).
**Subgroup and sensitivity analyses**

High serum GDF-15 levels were associated with PSD (OR: 1.91; 95% CI: 1.04-3.51; \( P=0.038 \); Figure S2) after adjustment for potential confounders. In subgroup analyses stratified by age, sex, education, time from onset to hospitalization, systolic BP, history of hypertension, baseline NIHSS score, body mass index, and receiving immediate blood pressure reduction, ORs of PSD were significant in older participants, those with higher education, baseline NIHSS score, BMI, history of hypertension, and receiving immediate blood pressure reduction. No significant interaction between serum GDF-15 levels and these interesting factors on PSD was observed (all \( P \) for interaction >0.05). Sensitivity analyses showed that after considering blood pressure variability at different time points, the significance of the association between GDF-15 and PSD still exists (Table S4).

**Incremental prognostic value of serum GDF-15 in patients with ischemic stroke**

We further examined whether adding serum GDF-15 to conventional risk factors improved the risk prediction of PSD. As shown in Table S5, the likelihood ratio test showed that model fit was significantly improved after adding GDF-15 to the model (\( P <0.001 \)). In addition, NRI was 28.21% (95% CI: 10.35%-46.07%; \( P=0.002 \)), and IDI was 1.86% (95% CI: 0.63%-3.08%; \( P=0.003 \)). The C statistic was 0.740 in the conventional model and 0.754 in the conventional model+GDF-15 (\( P=0.109 \)). Adding GDF-15 to a model containing conventional risk factors did not significantly improve the C statistics but did significantly improve risk reclassification and discriminatory power for 3-month PSD among patients.
Table S1. Baseline characteristics between patients who were enrolled and those were excluded.

| Characteristics       | Enrolled          | Excluded         | P value |
|-----------------------|-------------------|------------------|---------|
| Number of participant | 572               | 3489             |         |
| Demographics          |                   |                  |         |
| Age, years            | 59.98 ± 10.31     | 62.28 ± 10.94    | <0.001  |
| Male                  | 399 (69.8)        | 2205 (63.0)      | 0.002   |
| Education, years      | 6.0 (5.0-9.0)     | 6.0 (4.0-9.0)    | <0.001  |
| Current cigarette smoking | 214 (37.4) | 1271 (36.3)      | 0.616   |
| Current alcohol drinking | 196 (34.3) | 1057 (30.2)      | 0.057   |
| Clinical features     |                   |                  |         |
| Time from onset to randomization, h | 11.5 (5.0-24.0) | 10.0 (4.5-24.0) | 0.607   |
| Systolic BP, mm Hg    | 167.21 ± 16.60    | 165.96 ± 16.95   | 0.102   |
| Diastolic BP, mm Hg   | 98.11 ± 9.97      | 96.44 ± 11.26    | <0.001  |
| Blood glucose, mmol/L | 5.7 (5.0-7.1)     | 5.8 (5.1-7.3)    | 0.376   |
| Body mass index, kg/m² | 24.7 (22.9-26.4) | 24.8 (22.9-26.8) | 0.441   |
| Galectin-3, ng/ml     | 8.18 (5.81-11.35) | 8.76 (6.05-12.19) | 0.025   |
| Baseline NIHSS score  | 4.0 (3.0-7.0)     | 4.0 (2.0-8.0)    | 0.260   |
| Medical history       |                   |                  |         |
| History of hypertension | 438 (76.6) | 2771 (79.2)      | 0.155   |
| History of hyperlipidemia | 41 (7.2)  | 236 (6.7)        | 0.710   |
| History of diabetes mellitus | 95 (16.6) | 624 (17.8)      | 0.476   |
| History of coronary heart disease | 61 (10.7) | 383 (11.0)      | 0.841   |
| Family history of stroke | 95 (16.6) | 658 (18.8)      | 0.210   |
BP, blood pressure; NIHSS, National Institute of Health Stroke Scale.

*Continuous variables are expressed as mean ± standard deviation, or as median (interquartile range). Categorical variables are expressed as frequency (percent).
Table S2. Baseline characteristics of study participants according to serum GDF-15 tertiles.

| Characteristics*       | Total  | <792.94 | 792.94-1234.66 | ≥1234.66 | P value for trend |
|------------------------|--------|---------|----------------|----------|------------------|
| Number of participants | 572    | 190     | 191            | 191      |                  |
| **Demographics**       |        |         |                |          |                  |
| Age, years             | 59.98 ± 10.31 | 55.14 ± 9.49 | 59.24 ± 9.19 | 65.53 ± 9.52 | <0.001 |
| Male                   | 399 (69.8) | 129 (67.9) | 134 (70.2) | 136 (71.2) | 0.772 |
| Education, years       | 6.0 (5.0-9.0) | 8.0 (5.0-10.0) | 6.0 (5.0-9.0) | 6.0 (4.0-9.0) | 0.084 |
| Current cigarette smoking | 214 (37.4) | 76 (40.0) | 75 (39.3) | 63 (33.0) | 0.298 |
| Current alcohol drinking | 196 (34.3) | 70 (36.8) | 73 (38.2) | 53 (27.8) | 0.064 |
| **Clinical features**  |        |         |                |          |                  |
| Time from onset to randomization, h | 11.5 (5.0-24.0) | 12.0 (5.0-24.0) | 12.0 (6.0-24.0) | 10.0 (4.0-24.0) | 0.351 |
| Systolic BP, mm Hg     | 167.21 ± 16.60 | 167.58 ± 16.96 | 166.05 ± 15.83 | 167.99 ± 17.02 | 0.487 |
| Diastolic BP, mm Hg    | 98.11 ± 9.97 | 99.03 ±10.22 | 98.18 ± 9.30 | 97.12 ± 10.32 | 0.175 |
| Medical history               | 438 (76.6) | 148 (77.9) | 141 (73.8) | 149 (78.0) | 0.546 |
|------------------------------|------------|------------|------------|------------|-------|
| History of hypertension      | 41 (7.2)   | 18 (9.5)   | 14 (7.3)   | 9 (4.7)    | 0.196 |
| History of hyperlipidemia    | 95 (16.6)  | 22 (11.6)  | 36 (18.9)  | 37 (19.4)  | 0.074 |
| History of diabetes mellitus | 61 (10.7)  | 15 (7.9)   | 18 (9.4)   | 28 (14.7)  | 0.081 |
| History of coronary heart disease | 95 (16.6) | 29 (15.3)  | 35 (18.3)  | 31 (16.2)  | 0.714 |

| Ischemic stroke subtype      | 364 (63.6) | 130 (68.4) | 127 (66.5) | 107 (56.0) | 0.026 |
|------------------------------|------------|------------|------------|------------|-------|
| Thrombotic                   | 23 (4.0)   | 3 (1.6)    | 10 (5.2)   | 10 (5.2)   | 0.111 |
| Embolic                      | 194 (33.9) | 59 (31.1)  | 58 (30.4)  | 77 (40.3)  | 0.072 |
| Lacunar                      |            |            |            |            |       |
Receiving immediate BP reduction  282 (49.3)  97 (51.1)  91 (47.6)  94 (49.2)  0.801

BP, blood pressure; NIHSS, National Institute of Health Stroke Scale; GDF-15, Growth Differentiation Factor 15.

*Continuous variables are expressed as the mean ± standard deviation or as the median (interquartile range). Categorical variables are expressed as frequencies (percentages).
Table S3. The OR and 95% CI of covariates.

| Variables                              | Univariate OR (95% CI) | P value | Multivariate Adjusted OR (95% CI) | P value |
|----------------------------------------|------------------------|---------|----------------------------------|---------|
| Age, years                             | 1.02 (1.00-1.03)       | 0.039   | 1.02 (0.99-1.05)                 | 0.167   |
| Male                                   | 1.27 (0.88-1.84)       | 0.203   | 1.48 (0.77-2.84)                 | 0.243   |
| Education, years                       | 0.96 (0.91-1.00)       | 0.070   | 0.99 (0.91-1.07)                 | 0.701   |
| Current cigarette smoking              | 1.30 (0.92-1.84)       | 0.131   | 1.66 (0.91-3.03)                 | 0.098   |
| Current alcohol drinking               | 1.03 (0.72-1.46)       | 0.879   | 1.32 (0.69-2.53)                 | 0.400   |
| Time from onset to randomization, h    | 1.01 (0.99-1.02)       | 0.504   | 1.00 (0.98-1.03)                 | 0.683   |
| Systolic BP, mm Hg                     | 0.97 (0.96-0.98)       | <0.001  | 0.98 (0.97-1.00)                 | 0.061   |
| Blood glucose, mmol/L                  | 1.02 (0.96-1.08)       | 0.604   | 1.02 (0.94-1.12)                 | 0.602   |
| Galectin-3, ng/ml                      | 0.94 (0.91-0.98)       | 0.003   | 1.00 (0.94-1.07)                 | 0.993   |
| Body mass index, kg/m²                 | 1.00 (0.95-1.06)       | 0.914   | 1.08 (0.98-1.18)                 | 0.116   |
| Baseline NIHSS score                   | 1.33 (1.11-1.60)       | 0.002   | 1.85 (1.04-3.30)                 | 0.036   |
|                        | Center 1 | Center 2               | Center 3               | Center 4               | Center 5               | Center 6               | Center 7               |
|------------------------|----------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| History of hypertension| 1.37 (0.93-2.03) | 1.68 (0.70-4.05)       | 0.92 (0.31-2.70)       | 38.88 (15.81-95.60)    | 0.58 (0.25-1.33)       | 0.28 (0.08-0.97)       | 5.41 (2.29-12.76)      |
| History of hyperlipidemia| 1.50 (0.76-2.96) | 2.27 (1.38-3.73)       | 0.92 (0.31-2.70)       | 1.53 (1.28-1.84)       | 0.58 (0.25-1.33)       | 0.28 (0.08-0.97)       | 38.88 (15.81-95.60)    |
| History of coronary heart disease| 1.23 (0.71-2.13) | 1.68 (0.70-4.05)       | 0.92 (0.31-2.70)       | 1.23 (0.71-2.13)       | 0.58 (0.25-1.33)       | 0.28 (0.08-0.97)       | 1.23 (0.71-2.13)       |
| Family history of stroke| 2.27 (1.38-3.73) | <0.001                | 0.086                  | <0.001                | <0.001                | <0.001                | <0.001                |
| Ischemic stroke subtype| 1.53 (1.28-1.84) | <0.001                | 0.086                  | <0.001                | <0.001                | <0.001                | <0.001                |
| Receiving immediate BP reduction| 0.92 (0.66-1.28) | 0.623                  | 0.086                  | 0.92 (0.66-1.28)       | 0.623                  | 0.086                  | 0.92 (0.66-1.28)       |

*Taking Center 1 as the reference group.
### Table S4. Reclassification and discrimination statistics (95% CI) for poststroke depression by serum GDF-15.

| HRSD score≥8 | Continuous NRI, % | IDI, % | C statistics | Likelihood ratio test, P value |
|--------------|--------------------|--------|--------------|------------------------------|
|              | Estimate (95% CI)  | P value| Estimate (95% CI) | P value| Estimate (95% CI) | P value | Reference | Reference |
| Conventional model | Reference | Reference | 0.740 (0.699–0.779) | Reference | 28.21 (10.35–46.07) | 0.002 | 1.86 (0.63–3.08) | 0.003 | 0.754 (0.713–0.792) | 0.109 | <0.001 |
| Conventional model + GDF-15 | 28.21 (10.35–46.07) | 0.002 | 1.86 (0.63–3.08) | 0.003 | 0.754 (0.713–0.792) | 0.109 | <0.001 |

IDI, integrated discrimination index; NRI, net reclassification improvement; GDF-15, growth differentiation factor 15. The conventional model included age, sex, education level, time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction.
Table S5. Sensitivity analyses of the association between high serum GDF-15 and poststroke depression.

| GDF-15, ng/L | < 792.94 | 792.94-1234.66 | ≥1234.66 | P value for trend |
|--------------|-----------|----------------|----------|------------------|
| Events, n (%)| 62 (32.6) | 77 (40.3)      | 92 (48.17)|                  |
| Unadjusted   | 1.00      | 1.39 (0.92-2.12) | 1.92 (1.27-2.91) | 0.002 |
| Model 1      | 1.00      | 1.63 (0.81-3.28) | 2.92 (1.36-6.27) | 0.006 |
| Model 2      | 1.00      | 1.74 (0.85-3.58) | 2.81 (1.27-6.23) | 0.011 |
| Model 3      | 1.00      | 1.69 (0.82-3.48) | 3.26 (1.48-7.20) | 0.003 |
| Model 4      | 1.00      | 1.69 (0.84-3.40) | 2.97 (1.36-6.46) | 0.006 |
| Model 5      | 1.00      | 1.68 (0.79-3.60) | 3.33 (1.46-7.59) | 0.004 |
| Model 6      | 1.00      | 1.71 (0.85-3.44) | 3.02 (1.40-6.52) | 0.005 |

Model 1, adjusted for age, sex, education level, time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction.
Model 2, adjusted for Model 1 and further adjusted for the ratio of 12-hour systolic blood pressure to baseline systolic blood pressure.

Model 3, adjusted for Model 1 and further adjusted for the ratio of 24-hour systolic blood pressure to baseline systolic blood pressure.

Model 4, adjusted for Model 1 and further adjusted for the ratio of 3-day systolic blood pressure to baseline systolic blood pressure.

Model 5, adjusted for Model 1 and further adjusted for the ratio of 7-day systolic blood pressure to baseline systolic blood pressure.

Model 6, adjusted for Model 1 and further adjusted for the ratio of 3-month systolic blood pressure to baseline systolic blood pressure.
Figure S1. Flowchart of participants’ selection.

4071 patients from CATIS trail

Pre-planned to receive 3-month cognitive function tests (N=660)

Lost to follow-up at 3 months (N=15)  Died during 3 months (N=7)

Completing psychological state evaluation at 3 months (N=638)

Did not have blood samples or failed to measure GDF-15 levels (N=66)

Patients eligible for analysis (N=572)
Figure S2. Subgroup analyses of the association between high serum GDF-15 and poststroke depression.

| Subgroup                        | Low GDF-15 | High GDF-15 | OR (95% CI)   | P_interaction |
|--------------------------------|------------|-------------|---------------|---------------|
| **Overall**                    | 87/255 (34.1) | 144/317 (45.4) | 1.91 (1.04-3.51) | 0.096         |
| Age, years                     |            |             |               |               |
| <65                             | 72/207 (34.8) | 62/162 (38.3) | 1.84 (0.97-4.32) |               |
| ≥65                             | 18/48 (37.5)  | 79/155 (51.0)  | 2.10 (1.06-4.18) |               |
| Sex                             |            |             |               | 0.550         |
| Men                             | 65/176 (36.9) | 103/223 (46.2) | 1.76 (0.92-3.36) |               |
| Women                           | 22/79 (27.9)  | 41/94 (43.6)   | 2.14 (0.82-4.43) |               |
| Education                       |            |             |               | 0.782         |
| Primary                         | 37/120 (30.8) | 74/181 (40.9)  | 1.62 (0.97-3.38) |               |
| Middle or high                  | 50/135 (37.0) | 70/136 (51.5)  | 2.19 (1.03-4.22) |               |
| Time from onset to hospitalization |            |             |               | 0.282         |
| <12                             | 40/121 (33.1) | 80/167 (47.9)  | 1.96 (0.96-3.53) |               |
| ≥12                             | 47/134 (35.1) | 64/150 (42.7)  | 1.61 (0.73-2.67) |               |
| History of hypertension         |            |             |               | 0.392         |
| No                              | 24/56 (42.9)  | 38/78 (48.7)   | 1.34 (0.53-4.17) |               |
| Yes                             | 63/199 (31.7) | 106/239 (44.4) | 1.97 (1.04-3.76) |               |
| Baseline NIHSS score            |            |             |               | 0.836         |
| <4                              | 30/113 (26.6) | 41/107 (38.3)  | 1.58 (0.76-3.78) |               |
| ≥4                              | 57/142 (40.1) | 103/210 (59.7) | 2.25 (1.22-4.15) |               |
| Body mass index, kg/m²          |            |             |               | 0.473         |
| <24                             | 25/88 (28.4)  | 67/152 (44.1)  | 1.31 (0.78-3.67) |               |
| ≥24                             | 62/167 (37.1) | 77/165 (46.7)  | 1.92 (1.01-4.35) |               |
| Receiving immediate blood pressure reduction |            |             |               | 0.646         |
| No                              | 47/131 (35.9) | 73/159 (45.9)  | 1.89 (0.82-3.31) |               |
| Yes                             | 40/124 (21.9) | 71/158 (44.9)  | 2.26 (1.14-4.49) |               |
High serum GDF-15 was defined as ≥885.68 ng/L (optimal cut point obtained from the receiver operating characteristic curve). In the multivariate models, confounding factors, such as age, sex, education level, time from onset to randomization, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction, were included unless the variable was used as a subgroup variable. OR indicates odds ratio.