

# Ginkgo biloba extract improved cognitive and neurological functions of acute ischaemic stroke: a randomised controlled trial

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## ABSTRACT

**Purpose** To evaluate the efficacy and safety of Ginkgo biloba extract (GBE) in acute ischaemic stroke and its impact on the recurrence of vascular events.

**Methods** We conducted a multicentre, prospective, randomised, open label, blinded, controlled clinical trial enrolling patients with an onset of acute stroke within 7 days from five hospitals in China Jiangsu Province. Participants were assigned to the GBE group (450 mg GBE with 100 mg aspirin daily) or the control group (100 mg aspirin daily) for 6 months. The primary outcome was the decline in the Montreal Cognitive Assessment score at 6 months. Secondary outcomes were other neuropsychological tests of cognitive and neurological function, the the incidence of adverse events and vascular events.

**Results** 348 patients were enrolled: 179 in the GBE group and 169 in the control group. With 18 patients lost to follow-up, the dropout rate was 5.17%. Admission data between two groups were similar, but in the GBE group there was a marked slow down in the decline in the Montreal Cognitive Assessment scores ( $-2.77 \pm 0.21$  vs  $-1.99 \pm 0.23$ ,  $P=0.0116$  (30 days);  $-3.34 \pm 0.24$  vs  $-2.48 \pm 0.26$ ,  $P=0.0165$  (90 days);  $-4.00 \pm 0.26$  vs  $-2.71 \pm 0.26$ ,  $P=0.0004$  (180 days)) compared with controls. The National Institutes of Health Stroke Scale scores for independent rate at 30, 90 and 180 days, and the Barthel Index scores at 30, 90 and 180 days in the GBE group were significantly improved compared with controls. Improvements were also observed in GBE groups for Mini-Metal State Examination scores of 30, 90 and 180 days, Webster's digit symbol test scores at 30 days and Executive Dysfunction Index scores at 30 and 180 days. No significant differences were seen in the incidence of adverse events or vascular events.

**Conclusions** We conclude that GBE in combination with aspirin treatment alleviated cognitive and neurological deficits after acute ischaemic stroke without increasing the incidence of vascular events.

**Trial registration number** ChiCTR-TRC-12002688.

## INTRODUCTION

Stroke is one of the leading causes of disability and mortality worldwide. Thrombolysis

and intra-artery therapy, the only two effective strategies, are available to only a minority of patients with stroke due to the limited time window.<sup>1</sup> However, a great many stroke survivors suffer from cognitive decline. One cross sectional study performed in 10 countries found that the prevalence of post stroke dementia was approximately 30% determined by Mini-Metal State Examination (MMSE)  $<27$ .<sup>2</sup> Cognitive decline after stroke can result in vascular cognitive impairment (VCI) and Alzheimer's disease.<sup>3</sup> Thus effective and safe interventions are urgently needed to tackle this public health burden of stroke and VCI.

Ginkgo biloba is an ancient Chinese tree and its extract has long been used in China as a traditional herb for memory, depression, tinnitus and confusion.<sup>4</sup> In the UK, Europe, Canada and the USA, Ginkgo biloba extract (GBE) is a commercially available food supplement available without prescription. The ingredients of GBE are complicated, and vary by age, cultivation source and gender of the Ginkgo biloba tree.<sup>5</sup> EGb761 is a well defined GBE, produced by Dr Willmar Schwabe Pharmaceuticals in the early 1990s, which contains approximately 24% flavone glycosides (primarily quercetin, kaempferol and isorhamnetin), 6% terpene lactones (ginkgolides A, B and C, and bilobalide), 0.8% Ginkgolide B and  $<5$  ppm harmful ginkgoic acid. Most of the clinical trials to date have been performed based on the standardised EGb761.<sup>6</sup> The Ginkgo ketone ester dispersible tablets produced by Jiangsu Shenlong Pharmaceutical Co include 44% flavone glycosides, 10% terpene lactones, 2.5% Ginkgolide B and  $<2$  ppm harmful ginkgoic acid. The chemical structures and chromatograms are presented in the online Supplementary figure S1 and S2.

Hence the GBE in this study has more protective chemicals and less harmful constituents and is expected to exert a better therapeutic effect than EGb761.<sup>6</sup>

It is reported that EGb761 protected against ischaemic brain injury by scavenging free radicals, including superoxide radicals, ONOO<sup>-</sup>, OH<sup>•</sup> and NO<sup>•</sup>, and other lipid peroxide radicals.<sup>7–9</sup> EGb761 can also suppress the activity of ACE, thereby inhibiting the contraction of small arteries, dilation of cerebral blood vessels and increase in cerebral blood flow.<sup>10</sup> Despite the protective effect of GBE,<sup>11</sup> there is still a lack of compelling evidence to recommend its use in the management of ischaemic stroke. Clinical trials focussing on the therapeutic effect of GBE in VCI are lacking.

In this study, we investigated 348 patients with acute stroke with the aim of evaluating the potential use of GBE in the treatment of ischaemic stroke and its secondary effects on cognitive decline. In addition, we evaluated the side effects of an oral dose of GBE 450 mg daily. We also provide more evidence for neurologists regarding the application of GBE.

## METHODS

### Patients

This was a multicentre, prospective study approved by the ethics committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School and registered in the clinical trial centre (ChiCTR-TRC-12002688). All data were obtained from five tertiary hospitals in the Jiangsu Stroke Research Collaborative Group in China. From August 2012 to June 2014, 348 patients met the inclusion criteria and were successfully enrolled in the study. All subjects or their statutory guardians provided informed signed consent. Inclusion criteria were: (1) age 18–80 years; (2) acute ischaemic stroke onset within 7 days, confirmed by CT scan or MRI, corresponding to large artery atherosclerosis or small vessel occlusion type, according to the classification of the trial of Org 10 172 in acute stroke treatment (TOAST), and CT or MR angiography; (3) admission National Institutes of Health Stroke Scale (NIHSS) score of 4–20; (5) first onset stroke or patients with recrudescence stroke with a legacy of a modified Rankin Scale (mRS) score of  $\leq 1$ ; and (6) willing to cooperate with the follow-up examinations. Exclusion criteria were: (1) history of intracranial haemorrhage or subarachnoid haemorrhage; (2) cardiogenic cerebral embolism confirmed by atrial fibrillation incentive, typical history, or by CT or MR; (3) low platelet count, antiplatelet contraindication or receiving other antiplatelet drugs during the study; (4) severe cardiac, hepatic or renal insufficiency, pulmonary infection, terminal stage of disease or physical disability; (5) severe mental or cognitive disorder and uncooperative with the study; (6) allergy sufferer, or known allergy to Ginkgo biloba; (7) participation in another trial within 3 months; and (8) other conditions not appropriate for this study.

### Study intervention

Participants were randomised to the GBE group (three daily doses of 150 mg Ginkgo ketone ester dispersible tablets, combined with a daily dose of 100 mg aspirin) or the control group (aspirin 100 mg daily) for 6 months after stroke onset, with a regular treatment strategy, including lipid lowering, antihypertension, glucose lowering and neuroprotection. The 450 mg dose of GBE was chosen based on medical instructions, and previous clinical studies suggested a dose–response relationship of up to 450 mg.

### Randomisation

Assignment to the GBE or control group was determined by a random allocation sequence generated by a computer random number generator. Randomisation was done at the Affiliated Drum Tower Hospital, Nanjing University, and each participant was assigned a batch number. All professional neurological investigators were uniformly trained and responsible for strictly executing the study protocol, monitoring serious adverse events and reporting to the study's Data and Safety Monitoring Board (DSMB). To minimise the systematic error of a single blind trial, some neurological investigators were responsible for allocating suitable participants to random groups, and others, who were blinded to the treatment details, were responsible for the follow-up visits and data acquisition. All participants were blinded to the treatment assignment for the duration of the study. The primary centre conductor was responsible for monitoring serious adverse events and reporting the results to the data and safety monitoring board (DSMB). Study statisticians and the DSMB reviewed unblinded data for safety and efficacy, but strict confidentiality of results was maintained.

### Study outcomes

The primary efficacy endpoint was a decline in the Montreal Cognitive Assessment (deMoCA) score (0–30) at 180 days. The Montreal Cognitive Assessment (MoCA) is a neuropsychological test evaluating cognitive executive function and has a higher sensitivity in screening for mild cognitive disorders. This test was performed at admission, and at 12, 30 and 90 days. Lower scores indicate a more serious degree of cognitive function impairment, especially executive function.

Secondary measures at admission and at 12, 30, 90 and 180 days included the following:

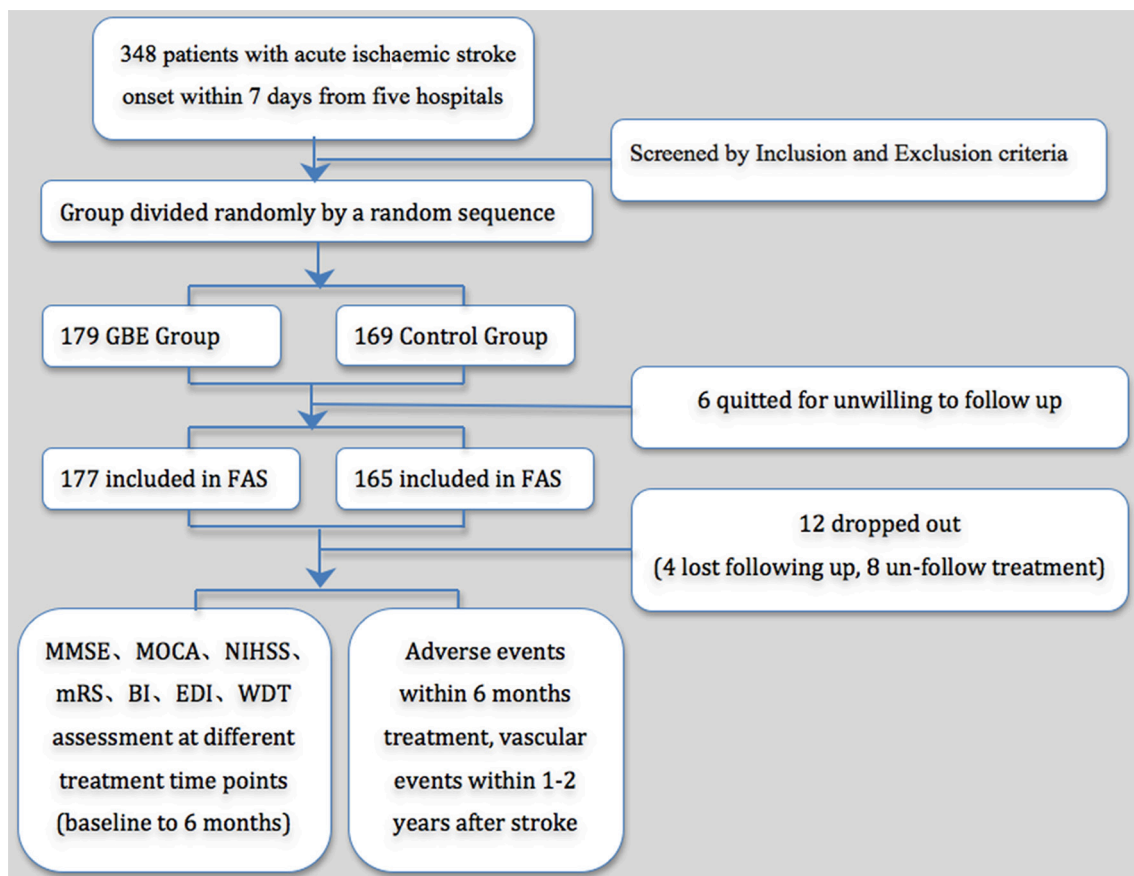
1. NIHSS and mRS independent rate. The NIHSS score, measured from 0 to 42, was used to assess the clinical severity and functional ability of patients with ischaemic stroke quantitatively during the acute stage, with smaller scores implying better neurological function. The mRS score, measured from 0 to 6, was used to assess the clinical severity and functional ability of patients with ischaemic stroke, with the higher mRS independent rate (defined as an mRS score of  $\leq 2$ ) implying favourable neurological function for follow-up.

2. The Barthel Index (BI) measured global function and the activities of daily living, with a total score of 100 points (a higher score indicates more severe impairment).
3. A neuropsychological test of cognitive function was performed using the MMSE, which is more effective and convenient for patients with dementia with multiple domain impairment. The test has scores from 0 to 30, with higher scores indicating better cognitive function;
4. Neuropsychological tests of executive function were performed using the Executive Dysfunction Index (EDI) and Webster's digit symbol test (WDT). Higher scores for EDI and lower scores for WDT indicate more severe impairment of executive function.
5. The incidence of vascular events, including cerebrovascular events, within 1–2 years was also a secondary endpoint. Events included ischaemic stroke, cerebral haemorrhage, subarachnoid haemorrhage, transient ischaemic attack, cardiovascular events (coronary heart disease and myocardial infarction), pulmonary embolism, deep venous thrombosis, peripheral arterial occlusive disease and other vascular events.

These neuropsychological evaluations were administered to all participants by professional neurological investigators. Adverse events were monitored throughout the study and hepatorenal function tests were administered to all participants at 12, 90 and 180 days for safety evaluations.

### Statistical methods

All data were analysed using SPSS V.19.0 statistical analysis software (SPSS). To estimate the sample size, we conducted a pilot study ( $n=40$ ). From previous studies, we hypothesised that the mean deMoCA values were  $-2.46\pm 0.51$  in the GBE group and  $-2.31\pm 0.43$  in the control group. Accordingly, a total sample size of 316 was needed for a power of 0.8 (type II error 0.2, 0.05, two tailed). Because of the considerable uncertainty, enrolment was extended to 348 patients (10% increment). A test for normality was performed using the Kolmogorov–Smirnov test. Continuous variables are expressed as mean $\pm$ SE for normal variables and medians (P25, P75) for non-normal variables. Categorical variables are expressed as a percentage. Intergroup differences were analysed using the independent t test for normal variables, the Mann–Whitney U test for non-normal variables and the  $\chi^2$  test for categorical variables. Intragroup differences were evaluated using the paired t test. The significance level was 0.05 by two tailed tests.



**Figure 1** Flowchart illustrating the trial design. BI, Barthel index; EDI, Executive Dysfunction Index; FAS, full analysis set; GBE, Ginkgo biloba extract; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; WDT, Webster's digit symbol test.

**Table 1** Baseline characteristics of the enrolled patients in the Ginkgo biloba extract and control groups

	GBE group (n=177)	Control group (n=165)	Difference (P value)
Age (years) (mean±SEM)	64.53±0.76	63.27±0.83	0.265
Women (n (%))	120 (67.80)	96 (58.18)	0.066
SBP (mm Hg) (mean±SEM)	143.09±1.54	145.89±1.51	0.196
DBP (mm Hg) (mean±SEM)	82.34±0.86	84.30±1.01	0.141
Stroke history (n (%))	143 (80.79)	134 (81.21)	0.921
Hypertension history (n (%))	108 (61)	107 (64.8)	0.537
Diabetes mellitus history (n (%))	42 (23.7)	46 (27.9)	0.770
CHD history (n (%))	8 (4.5)	5 (3)	0.518
Hyperlipidaemia history (n (%))	7 (3.5)	5 (3)	0.216
FBS (mmol/L) (mean±SEM)	6.65±0.22	6.71±0.22	0.853
BUN (µmol/L) (mean±SEM)	5.23±0.13	7.39±1.78	0.224
Creatinine (µmol/L) (mean±SEM)	73.45±1.72	71.24±2.31	0.451
ALT (U/L) (mean±SEM)	18.80±0.83	20.90±1.09	0.129
AST (U/L) (mean±SEM)	19.58±0.62	20.43±0.81	0.402
Triglycerides* (n (%))	16 (9.04)	20 (12.12)	0.419
Thrombin time*(s) (n (%))	1 (0.56)	1 (0.61)	0.493
APTT (s) (mean±SEM)	26.60±0.51	25.61±0.45	0.162
Fibrinogen (g/L) (mean±SEM)	4.56±1.38	3.76±0.82	0.635
NIHSS median (P25, P75)	5 (4, 7)	5 (4, 7)	0.625
BI (mean±SEM)	60.56±1.80	57.79±1.85	0.284
Independent mRS (n (%))	66 (37.29)	59 (35.76)	0.769
MMSE (mean±SEM)	22.60±0.45	22.59±0.49	0.988
MoCA (mean±SEM)	18.79±0.51	18.72±0.54	0.929
EDI (mean±SEM)	12.94±0.70	13.17±0.71	0.820
WDT (mean±SEM)	18.75±1.50	18.61±1.56	0.950

\*Values were abnormal and clinically significant.

ALT, alanine aminotransferase; APTT, activated partial thromboplastic time; AST, aspartate aminotransferase; BI, Barthel Index; BUN, blood urea nitrogen; CHD, coronary heart disease; DBP, diastolic blood pressure; EDI, Executive Dysfunction Index; FBS, fasting blood sugar; GBE, Ginkgo biloba extract; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; WDT, Webster's digit symbol test.

## RESULTS

From October 2012 to June 2014, 348 patients were enrolled in the study: 179 patients (51.4%) receiving GBE combined with aspirin (GBE group) and 169 patients (48.6%) receiving aspirin only (control group).

Eighteen patients were lost to follow-up or had health problems, including six patients who left at the beginning of the study (see figure 1). Hence 342 patients were included in the full analysis set and 330 were involved in the per protocol set. There was no difference between the two groups in baseline characteristics, including age, gender, history of stroke, diabetes mellitus, hypertension, coronary heart disease, hyperlipidaemia history, fasting blood sugar levels and hepatorenal function (table 1). Mean age was 64.53±0.76 years, and 67.80% were women in the GBE group. Mean MMSE and MoCA scores were 22.60±0.45 and 18.79±0.51 in the GBE group, which were not significantly different from the control group (22.59±0.49 and 18.72±0.54, P>0.05 vs controls). In addition, baseline NIHSS, independent mRS rate, EDI and WDT in the GBE group were similar to those in the control group (P>0.05).

## Primary efficacy measures

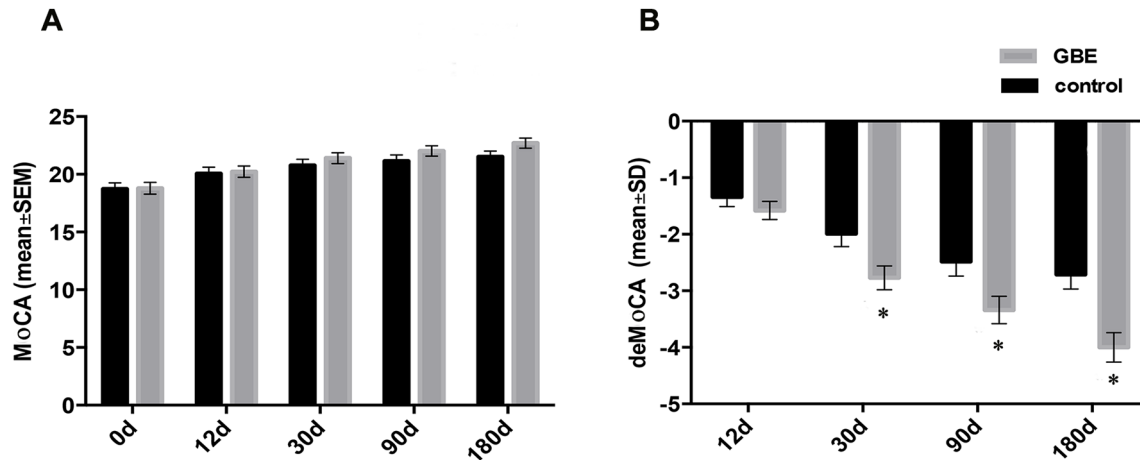
### Cognitive and executive function

As shown in figure 2A, MoCA scores after 12, 30, 90 and 180 days were overall higher in the GBE group than in controls. A statistically significant difference was detected in deMoCA, indicating that GBE combined with aspirin treatment may promote MoCA improvement, mainly at 30, 90 and 180 days (mean deMoCA in GBE group vs control group: -2.77±0.21 vs -1.99±0.23 at 30 days, P=0.0116; -3.34±0.24 vs -2.48±0.26 at 90 days, P=0.0165; -4.00±0.26 vs -2.71±0.26 at 180 days, P=0.0004) (figure 2B).

## Secondary efficacy measures

### Neurological function and global function

At 12 and 30 days after treatment, significant differences were seen between the GBE and control groups for NIHSS scores and decline in NIHSS scores compared with baseline (deNIHSS) (median NIHSS: 3 (2, 5) vs 4 (2, 6) at 12 days, P=0.0077; 2 (1, 4) vs 3 (1, 4) at 30 days, P=0.0015; Median deNIHSS: 2 (1, 3) vs 2 (0, 3) at 12 days, P=0.0123; 3 (2, 5) vs 3 (2, 4) at 30 days, P=0.0037) (figure 3A, B). These data demonstrate a favourable improvement in neurological deficit function with GBE treatment from acute ischaemic stroke onset to 1 month. Also, as shown in figure 4A, B, independent mRS rate (attainment of mRS≤2) and mRS scores were significantly improved in the GBE group compared with the control group from 30 to 180 days of follow-up. These data indicate better global functional outcome in the GBE group (independent mRS rate: 73.68% vs 59.75% at 30 days, P=0.0072; 84.80% vs 71.70% at 90 days, P=0.0038; 90.64% vs 78.62% at 180 days, P=0.0023). BI scores reflect activities of daily living. The study found an improvement in mean BI scores at 30, 90 and 180 days in the GBE group (mean BI: 80.85±1.58 vs 75.46±1.88 at 30 days, P=0.0279; 87.42±1.34 vs 80.96±1.76 at 90 days, P=0.0034; 90.56±1.15 vs 84.95±1.51 at 180 days, P=0.0031). However, these improvements were not significantly different from those in the control group (figure 3C, D).

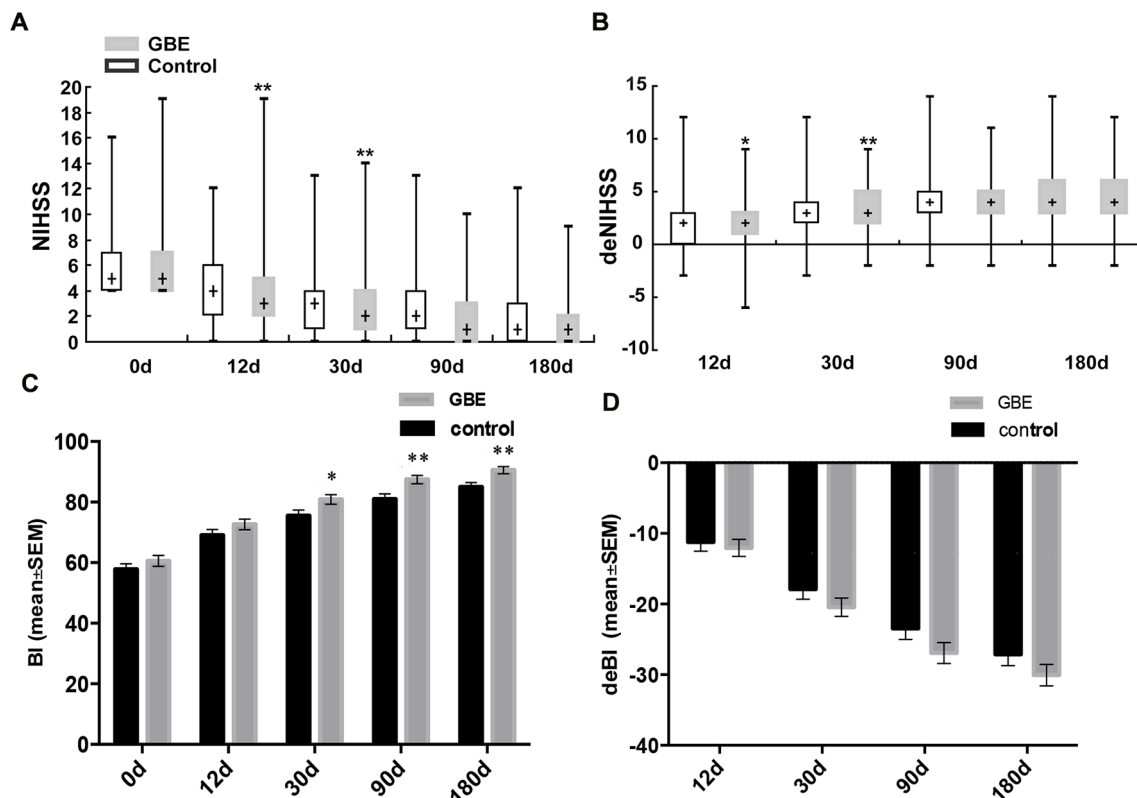


**Figure 2** Montreal Cognitive Assessment (MoCA) scores were evaluated as a measure of post stroke cognitive function in each participant during the study period. (A) MoCA scores after acute stroke in the Ginkgo biloba extract (GBE) group and in the control group at admission, and at 12, 30, 90 and 180 days. (B) Decline in MoCA scores (deMoCA) after acute stroke in the GBE and control groups at 12, 30, 90 and 180 days. deMoCA, MoCA score at admission–MoCA score at the indicated time points. \* $P < 0.05$  versus control group.

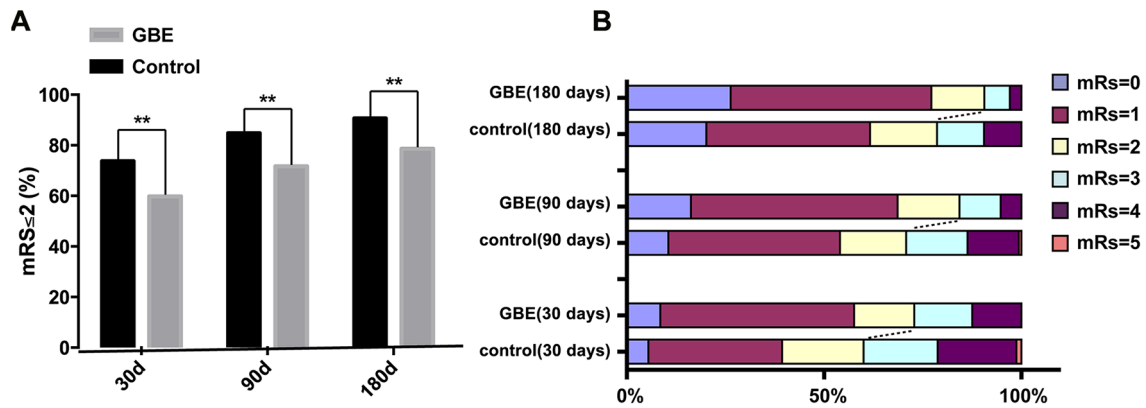
### Cognitive and executive function

Figure 5A shows that in the GBE group, MMSE scores at 12, 30, 90 and 180 days were higher than in the control group. At 30, 90 and 180 days, deMMSE scores in the GBE

group were significantly higher than those in the control group (mean deMMSE:  $-2.39 \pm 0.23$  vs  $-1.70 \pm 0.22$  at 30 days,  $P = 0.0279$ ;  $-3.11 \pm 0.26$  vs  $-2.34 \pm 0.27$  at 90 days,  $P = 0.0397$ ;  $-3.55 \pm 0.28$  vs  $-2.54 \pm 0.28$  at 180 days,  $P = 0.0110$ )



**Figure 3** National Institutes of Health Stroke Scale (NIHSS) scores were evaluated as a measure of neurological deficit in patients within 30 days, and the Barthel index (BI) scores were defined as activities of daily living within 180 days of acute stroke onset. (A) NIHSS scores at admission, and at 12 and 30 days after acute stroke in the Ginkgo biloba extract (GBE) group and the control group. (B) Decline in NIHSS scores (deNIHSS) after acute stroke in the GBE and control groups at 12 and 30 days. (C) BI scores after acute stroke in the GBE and control groups at admission, and at 12, 30, 90 and 180 days. (D) Decline in BI scores (deBI) at 12, 30, 90 and 180 days. deNIHSS, NIHSS score at admission–NIHSS score at the indicated time points. deBI, BI score at admission–BI score at the indicated time points. \* $P < 0.05$ , \*\* $P < 0.01$  versus control group.



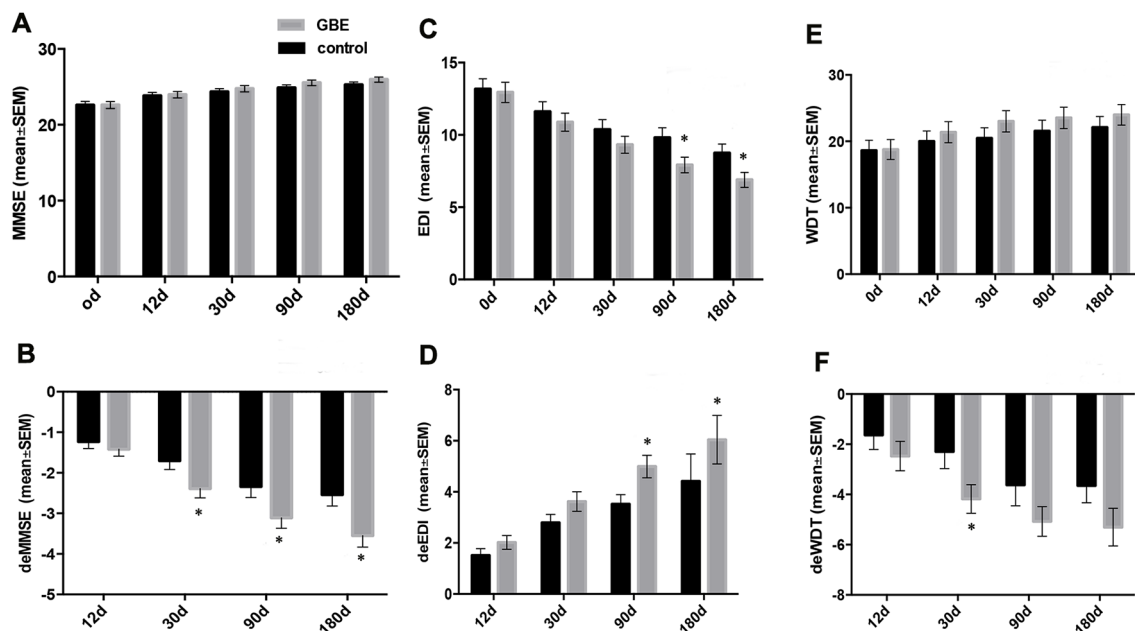
**Figure 4** Modified Rankin Scale (mRS) scores were evaluated as a measure of neurological outcome function of participants from 30 to 180 days after stroke. (A) Independent mRS rate after acute stroke in the Ginkgo biloba extract (GBE) group and the control group at 30, 90 and 180 days. (B) Distribution of mRS scores after acute stroke in the GBE and control groups at 30, 90 and 180 days. Independent mRS rate was defined as an mRS score of  $\leq 2$ . \*\* $P < 0.01$  versus control group.

(figure 5B). EDI score was used as a measure of the degree of executive dysfunction. In this study, EDI was improved in both groups but more obviously in the GBE group (mean EDI:  $7.92 \pm 0.54$  vs  $9.80 \pm 0.69$  at 90 days,  $P = 0.0294$ ;  $6.89 \pm 0.52$  vs  $8.74 \pm 0.63$  at 180 days,  $P = 0.0241$ ; mean deEDI:  $4.99 \pm 0.44$  vs  $3.52 \pm 0.37$  at 90 days,  $P = 0.0111$ ;  $6.04 \pm 0.95$  vs  $4.41 \pm 1.07$  at 180 days,  $P = 0.0135$ ) (figure 5C, D). As shown in figure 5E, WDT scores were improved slightly after treatment in both groups, with the GBE group showing the most improved trend. However, the differences in WDT and deWDT values were not considered

significant, except at the 30 day evaluation (mean deWDT:  $-4.18 \pm 0.57$  vs  $-2.29 \pm 0.68$  at 30 days,  $P = 0.0321$ ) (figure 5F).

#### Incidence of vascular events

We evaluated the recurrence of vascular events for nearly 2 years. A total of 339 of the 348 patients completed the last telephone call follow-up in April 2015. As shown in table 2, 36 patients (10.6%) had vascular events—16 in the GBE group (9.1%) and 20 in the control group (12.3%)—but there was no significant difference in the incidence of vascular events. In the GBE group, 13 reported



**Figure 5** Mini-Mental State Examination (MMSE) scores, Executive Dysfunction Index (EDI) scores and Webster's digit symbol test (WDT) scores were evaluated as a measure of post stroke cognitive executive function in patients at each time point. (A, C, E) MMSE, EDI and WDT scores after acute stroke in the Ginkgo biloba extract (GBE) group and in the control group at admission, and at 12, 30, 90 and 180 days. (B, D, F) Decline in MMSE scores (deMMSE), EDI scores (deEDI) and WDT scores (deWDT) at 12, 30, 90 and 180 days. deMMSE, MMSE score at admission–MMSE score at the indicated time points; deEDI, EDI score at admission–EDI score at the indicated time points; deWDT, WDT score at admission–WDT score at the indicated time points. \* $P < 0.05$  versus control group.

**Table 2** Occurrence of vascular events within 1 to 3 years after acute stroke onset in the Ginkgo biloba extract and control groups (follow-up in April 2015)

	GBE group (n=176)	Control group (n=163)	Difference (P value)
Vascular event (n (%))	16 (9.1)	20 (12.3)	0.343
Cerebrovascular event (n (%))	13 (7.4)	16 (9.8)	0.424
Cardiovascular event (n (%))	3 (1.7)	3 (1.8)	1.000
Other events (n (%))	1 (0.6)	0 (0)	1.000
Death (n (%))	4 (2.3)	1 (0.6)	0.415

GBE, Ginkgo biloba extract.

cerebrovascular events, including 9 recurrent strokes and 4 transient ischaemic attacks. Three patients reported cardiovascular events, one had an aortic dissecting aneurysm and one had both transient ischaemic attacks and cardiovascular events (atrial fibrillation). In the control group, 14 recurrent strokes, 2 transient ischaemic attacks, 3 cardiovascular events and 1 intestinal obstruction were reported. Five patients (1.5%) died before the end of the study, including one death due to recurrent stroke and one death due to intestinal obstruction in the control group, and three deaths of unknown cause (the families declined to disclose) in the GBE group.

### Safety analysis

During the 6 month period study, 10 adverse events were reported. One vomiting episode was considered to be possibly related to the study; a recurrent stroke event and a pneumonia event were considered possibly not related to the study; four events, including myocardial infarction, nephritis, sick sinus syndrome and respiratory failure, were considered to be definitely not related to the study; and for two other events (diabetes mellitus and vomiting) the cause could not be ascertained.

Adverse events were assessed at each visit from baseline to 180 days. As shown in table 3, the 10 adverse events (2.89%) in 346 patients included 5 in the GBE group (2.81%) and 5 in the control group (2.98%). No overall significant difference was reported between the groups (P=1.000). The rates of serious adverse events for the GBE and control groups were similar, including mortality and

**Table 3** Incidence of adverse events in the Ginkgo biloba extract and control groups

	GBE group (n=178)	Control group (n=168)	Difference (P value)
Adverse event (n (%))	5 (2.81)	5 (2.98)	1.0000
Severe adverse event (n (%))	1 (0.56)	4 (2.38)	0.2032

GBE, Ginkgo biloba extract.

incidence of coronary heart disease, stroke of any type and major bleeding, with one in the GBE group (0.56%) and four in the control group (2.38%) (P=0.2032). The same was true for the laboratory evaluation and the evaluation of vital signs and concomitant medication. Therefore, there was no indication of a safety risk associated with 450 mg/day GBE combined with aspirin.

### DISCUSSION

The aim of this initial randomised multicentre study was to evaluate the therapeutic efficacy of GBE on neurological deficit and cognitive decline after acute stroke injury. The study demonstrated that patients with stroke who received GBE manifested better memory function, executive functions, neurological function and daily life. Additionally, the safety data analysis demonstrated that GBE did not increase the incidence of adverse events.

Over the past decades, substantial evidence has supported the hypothesis that GBE protects against neuronal death caused by ischaemia in animal stroke models.<sup>12</sup> The possible molecular mechanism may include anti-apoptosis<sup>13–15</sup> and increasing cerebral blood flow.<sup>16</sup> One double blind, placebo controlled, randomised controlled trial of 102 patients with ischaemic stroke concluded that regarding neurological function, the GBE group fared much better than a placebo group over a 4 month follow-up period.<sup>17</sup> In the current study, 348 patients with stroke were enrolled with an extended follow-up time of 6 months. At 12 and 30 days, a significant improvement in neurological function was seen in the GBE group, in terms of mean NIHSS scores and decline in mean NIHSS scores (deNIHSS) compared with the control group. Similar improvements occurred in mRS scores at 30, 90 and 180 days. These data suggest that GBE is effective and could be recommended in the treatment of acute ischaemic stroke.

GBE can partially delay the progression of cognitive decline after stroke. In the current study, it was found that GBE may be a promising medication for patients with VCI. Regarding the therapeutic effect of GBE in dementia, the published literature is less conclusive.

Study designs can be divided into three categories: reduce the risk of developing dementia in older people; treat patients with dementia; and compare the effect of a strategy with other therapeutic strategies. In prophylactic studies, large scale clinical trials concluded that EGB761 (240 mg daily) did not reduce progression to Alzheimer's disease in older normal adults.<sup>18–20</sup> Compelling evidence regarding dementia treatment is still lacking. A meta-analysis involving 15 randomised, placebo controlled trials and 2684 outpatients concluded that EGB761 is a potential option for patients with dementia with good tolerability and efficacy.<sup>21</sup> Compared with donepezil (5 mg daily) in the treatment of Alzheimer's dementia, GBE (160 mg daily) showed comparable efficacy.<sup>22</sup> Heterogeneity will require further scrutiny in GBE therapeutic trials. Differences in evaluation systems, GBE dosage

and administration time points likely contribute to this discrepancy. Data from the current study support the notion that GBE improves the cognitive function of VCI. Compared with previous published studies, the current study used higher VCI and GBE dosages (450 mg daily). Moreover, daily life in the GBE group was significantly better than in the control group, including BI score and EDI score. Overall, administration of GBE in patients with acute stroke is recommended for its ability to improve cognition and the quality of daily life.

In the current study, no significant differences were noted between the GBE group and the control group regarding the percentages of participants experiencing any adverse events. These results are consistent with most published studies.<sup>18</sup> However, a randomised, placebo controlled trial conducted by Dodge *et al* reported that elderly patients (age >85 years) taking 240 mg GBE daily experienced more incidences of ischaemic stroke and transient ischaemic attack than people taking a placebo.<sup>23</sup> These data indicate that patients older than 85 years should receive a lower dose of GBE. Additionally, a few studies have proposed that GBE may increase the risk of bleeding due to its inhibition of platelet aggregation and platelet activating factor function.<sup>24,25</sup> From 1966 to 2004, 15 case reports described the association between GBE and bleeding events, including eight episodes of intracranial bleeding.<sup>26</sup> Among them, some patients had previous bleeding risk factors, including liver cirrhosis, hypertension and warfarin or high dose aspirin consumption.<sup>26</sup> As intracranial haemorrhage is a serious complication, sometimes leading to death, clinicians should be careful when giving GBE to patients with these risk factors. Patients with antiplatelet contraindications, low platelet count or liver insufficiency, and those taking other antiplatelet drugs were excluded from the current study. The average patient age was 64.53±10.09 years. In the current study, even though patients were taking 450 mg GBE daily, a higher incidence of cerebrovascular events was not observed in the GBE group compared with the control group.

There were some limitations in this study. First, the study was single not double blinded, which may have caused some bias in the analysis and conclusions. Second, most of the efficacy parameters were based on clinical scales and thus research bias by researchers cannot be entirely excluded. Third, the follow-up period was not very long, and the effect of long term exposure to GBE should be verified in further investigations. Lastly, further larger trials are needed for subgroup analysis of the degree of stroke severity and cognitive function impairment.

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