

Anti-thrombosis, Brain protection from stroke, Guideline recommended



- *It has dual effects of antagonizing platelet activating factors and protecting neurovascular units. Ginkgolide ABC and bilobalide have synergistic effects.
- *The results of the GIANT study show that Ginkgolide Injection significantly improves the 90-day clinical outcomes of patients with acute ischemic stroke, and effectively improves neurological function in the early stages of treatment; intravenous thrombolysis does not increase the risk of bleeding when administered within 24 hours.
- *The results of the GISAA study show that Ginkgolide Injection significantly improves the clinical outcomes of stroke patients; the earlier it is used, the better the effect, and the best effect is if used within 24 hours.
- * Post-marketing pharmaco-economic evaluation of Ginkgolide Injection, the cost-effectiveness ratio is better
- *Drugs recommended by "Chinese Clinical Management Guidelines for Cerebrovascular Disease" (Class IIb recommendation, Level B evidence)

Ginkgolide Injection

Anti-thrombosis
Brain protection from stroke
Guideline recommended

Simple prescription

[Name] Ginkgolide injection

[Ingredients] The main ingredients are bilobalide, ginkgolide A, ginkgolide B and ginkgolide C. The excipients are glycerin and ethanol.

[Characteristics] This product is colorless or light yellow clear liquid

[Functions and Indications] Promoting blood circulation to remove blood stasis, dredging meridians and activating collaterals. Ginkgolide Injection is indicated for the patients with apoplexy involving the channels and collaterals (mild to moderate cerebral infarction) and syndrome of static blood blocking collaterals in the convalescence, manifested by hemiplegia, distortion of mouth and tongue, dysphasia and numbness of limbs, etc.

[Usage and Dosage] Intravenous infusion. Ginkgolide Injection should be administered by intravenous infusion with 5 ampoules (10 mL) once. Slowly dilute the 5 ampoules (10 mL) of Ginkgolide Injection with 250 mL of 0.9% sodium chloride injection or 250 mL of 5% glucose injection before use. The admixture should be administered by intravenous infusion slowly, once daily, during which the infusion rate should be strictly controlled and no more than 40 drops/min to 60 drops/min. The course of treatment is 14 days.

[Packaging] 2ml/ampoule (contains 10mg of terpene lactones); 10 ampoules/box.

[Validity period] 36 months.

[Approval number] National drug approval number Z20110035



CHENGDU BAIYU PHARMACEUTICAL CO., LTD.
No. 433 Western Section of Liutai Avenue, Chengdu National Cross-Straits
Science and Technology Industrial Development Park, Wenjiang District,
Chengdu, P. R. China.
Tel +862861557793 Website: <http://www.baiyu.cn> Post Code 611130



1 Chinese Stroke Society: "Clinical Management Guidelines for Cerebrovascular Disease in China" (2019) (Class IIb recommendation, Level B evidence)

Ginkgolide Injection mainly inhibits platelet aggregation and promotes the recovery of neurological function by antagonizing platelet activating factors. It is recommended for use in the acute phase.

2 Encephalopathy Branch of the China Association of Chinese Medicine: "Evidence-based Practice Guidelines for Integrated Traditional Chinese and Western Medicine for Stroke" (2020)

For patients with cerebral infarction, Ginkgolide Injection can be given for treatment; the timing of administration should be early, at least in the acute phase.

3 "Research and Application Series of Famous and Excellent Chinese Patent Medicines-Ginkgolide Injection" (2020)

The ingredients, quality control, pharmacology and toxicology research, clinical application, and adverse reactions of Ginkgolide Injection are comprehensively described.

4 Chinese Academy of Medical Sciences: "Interpretation of Clinical Pathway and therapeutic drugs Internal Medicine Volume" (2020)

Recommendation: Ginkgolide Injection is a standardized treatment drug for transient ischemic attack, cerebral infarction, and coronary atherosclerosis.

5 Academician Zhang Boli: "Manual for the Rational Clinical Use of Traditional Chinese Medicine Injections" (2016)

Ginkgolide Injection has a low incidence of adverse reactions, no serious adverse events, and can significantly improve patients' neurological deficits.

6 "Guidelines for Community Prevention and Treatment of Cerebrovascular Disease" (2020)

For cerebral infarction with phlegm-heat/phlegm-dampness type, it is recommended to use Ginkgolide Injection.




Expert perspective

7 **Stroke** 2019.6.28

GISAA research: Exploration of antiplatelet therapy in atherosclerotic stroke

--Interview with Professor Dong Qiang from the Department of Neurology, Huashan Hospital Affiliated to Fudan University



GISAA research: Exploration of antiplatelet therapy in atherosclerotic stroke

"The GISAA study is an internationally registered randomized, double-blind, placebo-controlled, multi-center RCT study. The study was launched in 2016 and lasted for 3 years. A total of 61 centers participated in the study and 949 subjects were enrolled. We are pleased that the research achieved its intended purpose. Ginkgolide Injection can effectively improve the degree of neurological deficit in patients with acute ischemic stroke, improve clinical outcomes, and have a significant improvement trend in the end-point event of death/recurrence. Stratified analysis found that the earlier Ginkgolide Injection is used in patients with acute ischemic stroke, the better the effect, especially in patients within 24 hours of onset; patients with moderate to severe ischemic stroke with an NIHSS score of ≥ 8 , and Patients with cerebral atherosclerotic stenosis $<50\%$ have better outcomes. This means that on the basis of guideline standard treatment, a significant difference is still seen."

8 **Expert opinion** 2019.6.25

Current status and thoughts on research on "brain protection" in stroke

--Interview with Professor Yang Qingwu from the Department of Neurology, Xinqiao Hospital, Army Medical University



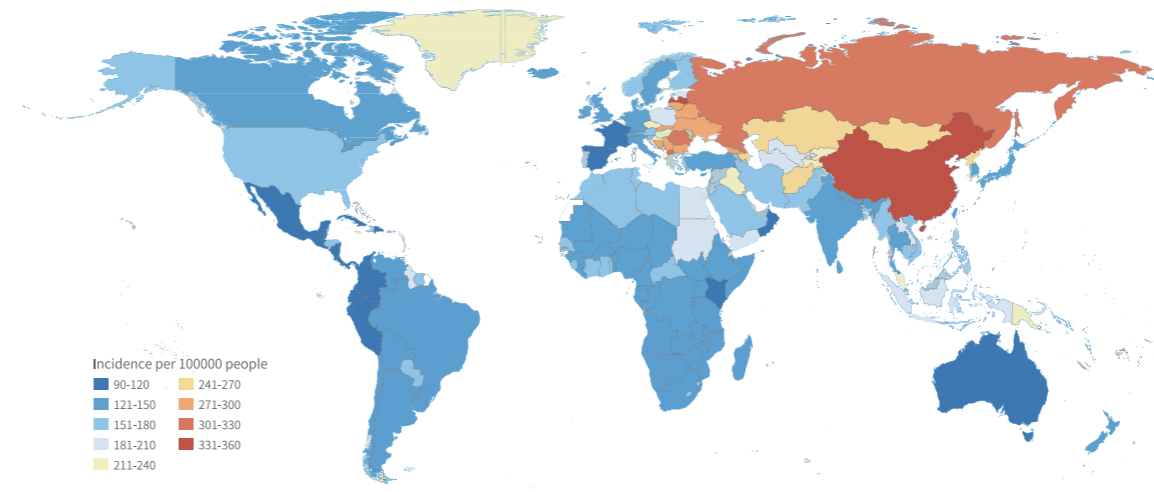
Current status and thoughts on research on "brain protection" in stroke

"The brain injury mechanism of stroke is complex. Neurons, glial cells, and vascular endothelial cells will all be damaged, so the concept of neurovascular unit has been proposed internationally. Therefore, brain protective drugs must fully consider the protection of the neurovascular unit!"

"Ginkgolide Injection has a dual mechanism of action. Ginkgolide ABC is a natural antagonist of platelet activating factor (PAF), which plays an anti-platelet aggregation and anti-inflammatory role. It also inhibits cerebral ischemia-reperfusion injury by antagonizing PAF. It has more benefits; bilobalide has a clear role in protecting the neurovascular unit, can protect neurons, glial cells, and blood vessels, and can also promote the regeneration of neural stem cells; especially there are the effect of synergy".

Stroke is the No.1 cause of death and disability in China, and the treatment situation for stroke is grim

Age-standardized incidence of stroke in different countries, 2016



On March 11, 2019, the journal "Lancet Neurology" released the 2016 Global Burden of Disease Study (GBD) analysis data on stroke. The results showed:

*The age-standardized incidence rate of stroke in China is the highest in the world (354/100,000 person-years).

*The average number of strokes worldwide has decreased by 8.1% compared with 1990, and the number of strokes in China has increased by 5.4% compared with 1990. The incidence trend of stroke in China is still very serious.

Antiplatelets are the cornerstone of ischemic stroke treatment

Recommendation of Chinese Stroke Guidelines

- Antiplatelet therapy for non-cardioembolic stroke/TIA I-A
- 24 hours, high recurrence risk TIA or minor stroke, DAPT for 21 days ★ I-A
- Within 30 days, intracranial artery stenosis, DAPT for 90 days ★ II-B
- Stroke with aortic arch atheroma, antiplatelet therapy, non-anticoagulation II-B
- Long-term DAPT is not recommended for non-cardioembolic stroke/TIA I-A

Aspirin/clopidogrel resistance affects clinical outcomes in stroke

58.8% of Chinese people belong to clopidogrel low-responsive type³
 Clopidogrel is an ADP pathway antiplatelet drug that needs to be metabolized by hepatic enzymes. The CHANCE study found that clopidogrel hyporesponsiveness was common among Chinese (58.8%).

Original Investigation

Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack

Yilong Wang, MD, PhD; Xingquan Zhao, MD, PhD; Jinli Lin, MD, PhD; Hao L, PhD; S. Claborne Johnston, MD, PhD; Yi Lin, MD, PhD; Yuesong Pan, MD; Liping Liu, MD, PhD; David Wang, DO, FAHA, FAAN; Chunxue Wang, MD, PhD; Xia Meng, MD, PhD; Jianfeng Xu, MD, PhD; Yongjun Wang, MD, for the CHANCE Investigators

The average incidence of aspirin resistance is 27.7%²

Aspirin resistance is associated with increased stroke severity and infarct volume

Marcel M.C. Hovens, MD, Jaapjan D. Snopce, MSc, Jeroen C.J. Eikenboom, MrPhD, Johanna G. van der Bom, MD, PhD, Bart J.A. Mertens, PhD, and Menno V. Huisman, MD, PhD Leiden, The Netherlands

47.4% of people who are resistant to aspirin are also resistant to clopidogrel⁴

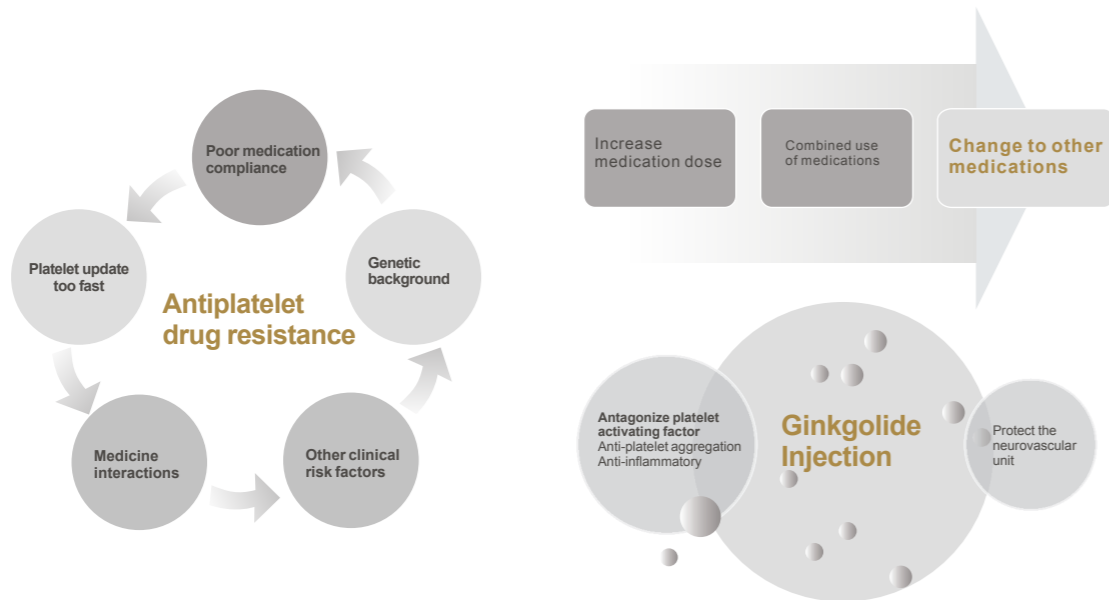
CLINICAL RESEARCH

Intervention Cardiology

Aspirin and Clopidogrel Drug Response in Patients Undergoing Percutaneous Coronary Intervention

The Role of Dual Drug Resistance
 Eli I. Lev, MD,* Rajnikant T. Patel, MD,* Kelly J. Maresh, RN, BSN,* Sasidhar Guthikonda, MD,* Juan Granada, MD, Timothy DeLao, MLT,* Paul F. Bray, MD,* Neal S. Kleiman, MD* Houston, Texas

Clinical Decision Making in Antiplatelet Drug Resistance Phenomenon



★ International authority: Ginkgolide and bilobalide are the core medicinal ingredients of ginkgo leaf preparations⁵



Professor Koji Nakanishi published in "Angew Chem Int Ed Engl" in 2004: Ginkgolide and bilobalide are the core medicinal ingredients of ginkgo leaf preparations. Their unique cage-like molecular formula cannot be synthesized artificially at present.



Therefore, he is known as the first person to discover the structures of ginkgolide and bilobalide.

Professor Koji Nakanishi

★ Ginkgolide Injection opens the door for global Ginkgo leaf preparations to move from the "extract era" to the "molecular era"

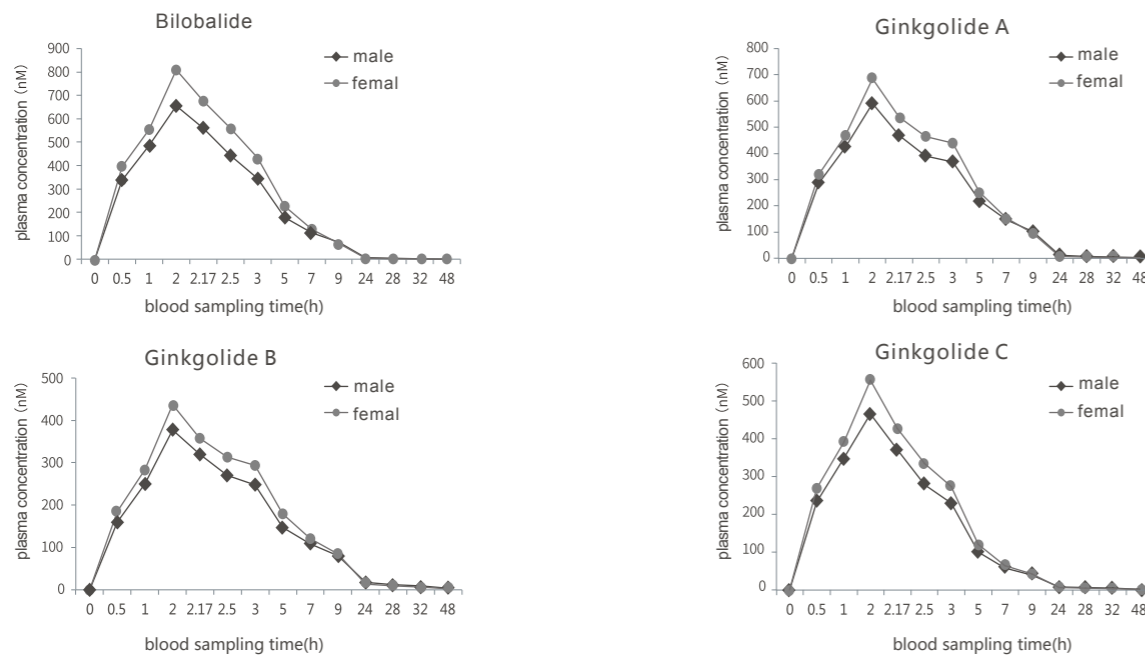
Ginkgolide Injection		VS		Traditional ginkgo leaf preparation	
Ginkgolide Injection (Active ingredient ≥99%)				Traditional ginkgo leaf preparation (Active ingredient ≤30%)	
Ginkgolide ABC 51%	Bilobalide 48%	Ginkgo flavonoids 24%	Ginkgolide ≤6%	unknown ingredients 70%	
		Water soluble: difficult to penetrate the blood-brain barrier	Lipid soluble: easily penetrates the blood-brain barrier		
R ¹ R ² R ³ molecular weight	molecular weight				
Ginkgolide A (GA) H H OH	408.4				
Ginkgolide B (GB) OH H OH	424.4				
Ginkgolide C (GC) OH OH OH	440.4				
Fingerprint				Fingerprint	

★ 10 Advantages of Ginkgolide Injection

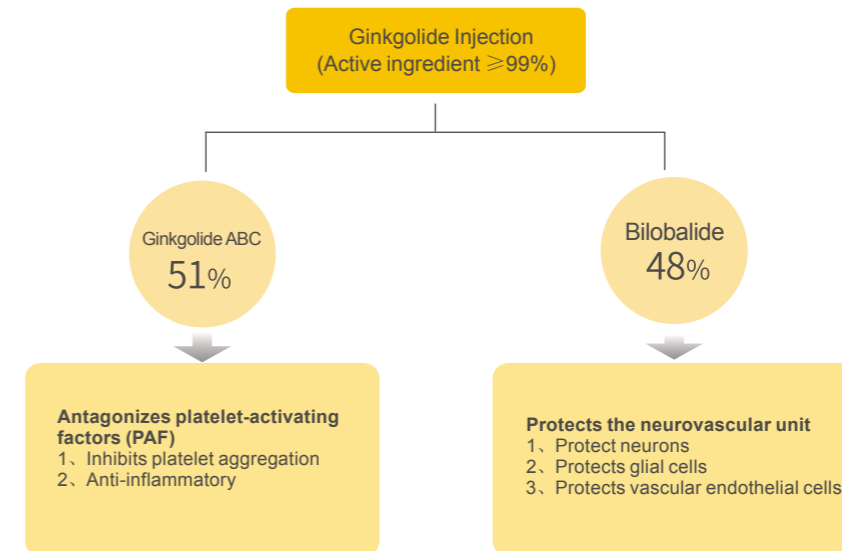
Product Features	Advantages	Ginkgolide Injection	Ginkgo diterpene lactone meglumine injection
Effectiveness	1. Anti-thrombosis and brain protection, synergistic effect	Ginkgolide ABCJ (anti-thrombotic)+ Bilobalide (brain protection)	Ginkgolide ABK, no bilobalide, no neurovascular protective effect
	2. Twice the daily therapeutic dose of active ingredients	10mg/vial (2ml), 5 vials per day, 50mg/day	25mg/vial, 1 vial per day, 25mg/day
	3. Better efficacy	Pre-marketing clinical studies have shown that the product has better efficacy than Ginkgo biloba extract injection 20ml (Therapeutic dose)	Pre-marketing studies are only better than Ginkgo biloba extract injection 5ml (non-therapeutic dose)
Convenience	4. Dosing is more flexible	5% glucose injection or 0.9% sodium chloride injection	Only 0.9% sodium chloride injection
	5. Better patient compliance	Conventional dripping speed, 40-60 drops/minute, only takes 1 hour	The dripping rate must be controlled to 10-30 drops/minute, and it takes 3 hours to complete the infusion, which leads to poor compliance.
	6. Wider application population	Only prohibited for allergic, pregnant and lactating women	Not suitable for allergic, pregnant and lactating women. It is contraindicated for those with hemorrhagic diseases or bleeding tendency. Disabled for those with venous thrombosis of lower limbs
Safety	7. No serious adverse events (death)	No serious adverse reactions found	It has an impact on blood pressure and may cause serious adverse events (death).
	8. Safer	Does not affect liver function, no need to test liver function during medication	In phase 1, II, and III clinical studies, there were many cases of liver function indicators rising 2-3 times. Liver function needs to be tested during medication.
	9. Excipients have no potential risks	The excipients contain ethanol and glycerin, which are safer and have no potential risks.	Excipient meglumine, NCBI (National Center for Biotechnology Information): has a series of potential risks such as eye damage, cancer risk, damage to fetus and fertility, damage to breastfed babies, etc.
	10. Better stability and longer validity period	Routine transportation and storage Valid for 36 months	Must be transported in cold chain and stored at 0-10°C away from light, Valid for 18 months

Note: The content comes from the product manual

★ Human pharmacokinetics study of Ginkgolide Injection shows that there is no accumulation in 24-hour metabolism



Ginkgolide Injection antagonizes platelet activating factors and protects the neurovascular unit.



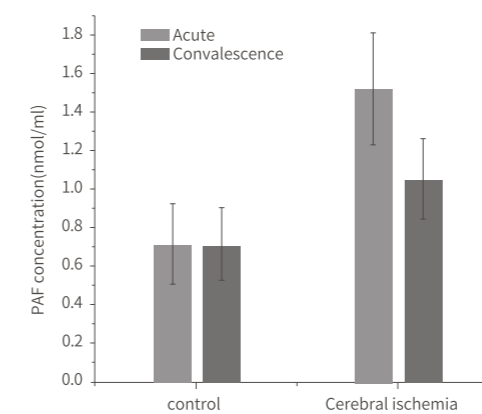
Mechanism of Action 1 of Ginkgolide Injection: Antagonizes platelet activating factor (PAF)

★ Stroke causes a significant increase in PAF content, and PAF has a strong effect on inducing platelet aggregation^{7,8}.

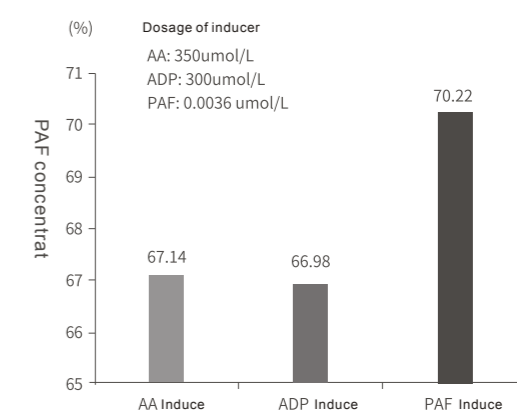


In 1972, French scholar Benveniste et al. discovered a new inflammatory factor. This compound was observed to promote platelet aggregation, so it was named platelet activating factor (PAF).
Jacques Benveniste (1935-2004)

PAF levels are significantly elevated during stroke

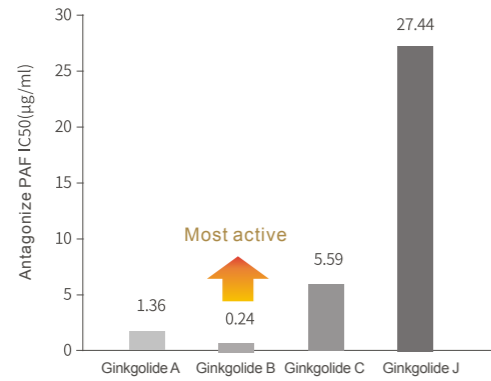


PAF induces platelet aggregation stronger than AA and ADP

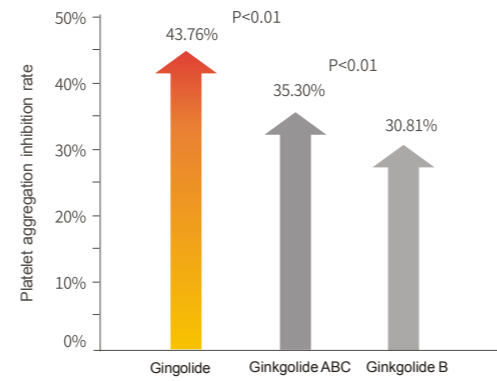


★ Ginkgolide significantly inhibits PAF-induced platelet aggregation⁹

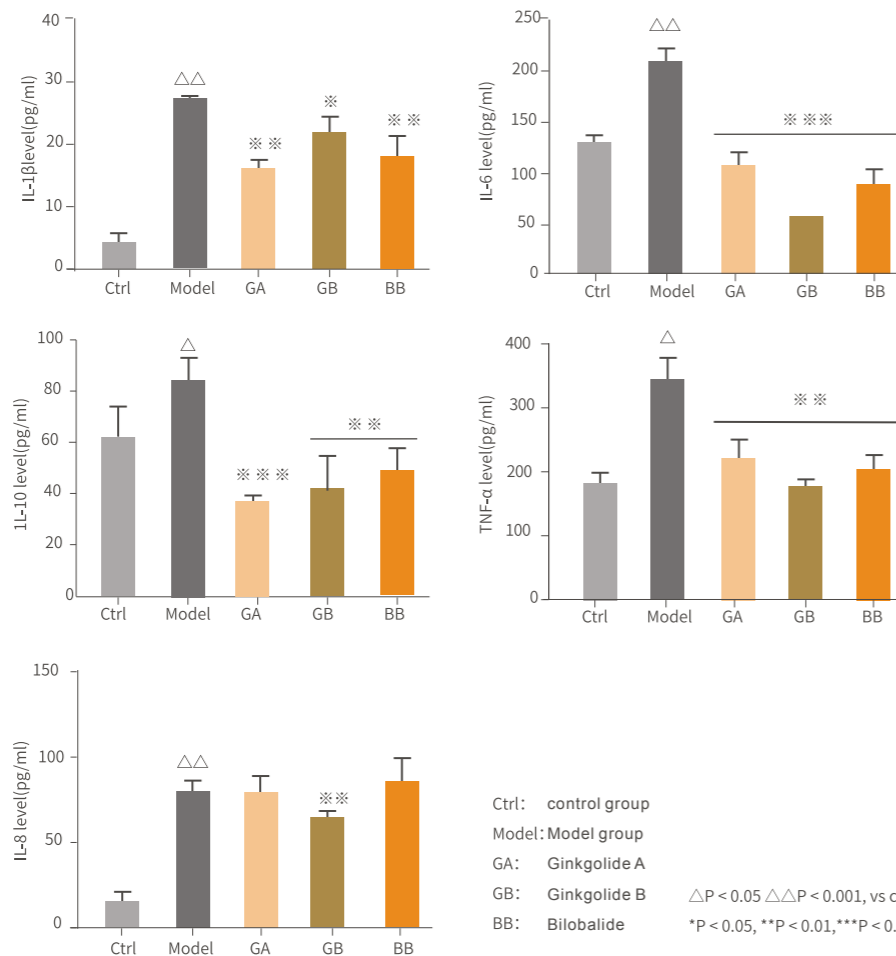
Ginkgolide ABC inhibits platelet aggregation Among them, ginkgolide B is the most active



Bilobalide and Ginkgolide ABC synergize



★ Ginkgolide and bilobalide significantly inhibit the release of inflammatory factors¹⁰

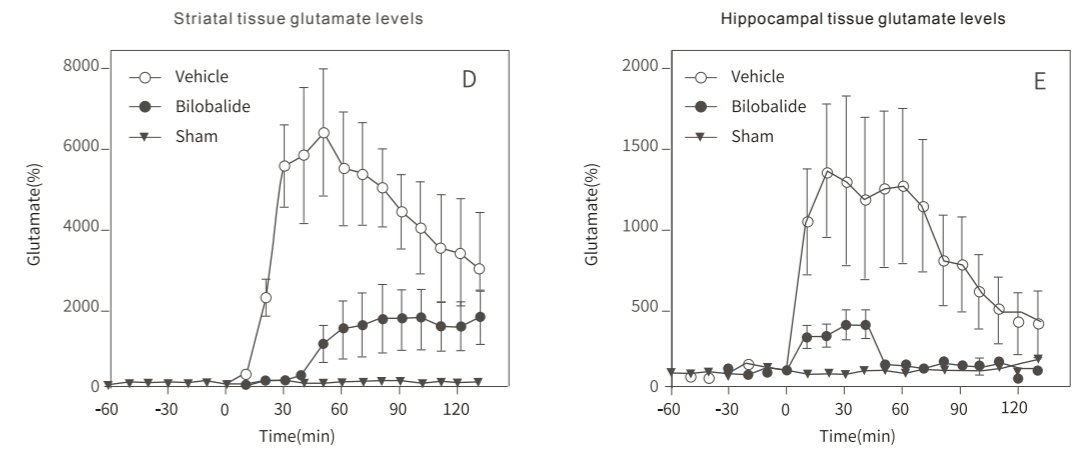


Mechanism of action 2 of Ginkgolide Injection: Protecting the neurovascular unit¹¹



Neurovascular unit: consists of neurons, microvessels, and glial cells and extracellular matrix composition. During ischemic stroke, nerves and vascular units can be severely damaged.

★ Bilobalide rapidly reduces glutamate release, resists excitotoxicity, and protects neurons¹²



Measured concentrations from 60 minutes before stroke induction (taking MCAO as time zero) to 130 minutes after stroke

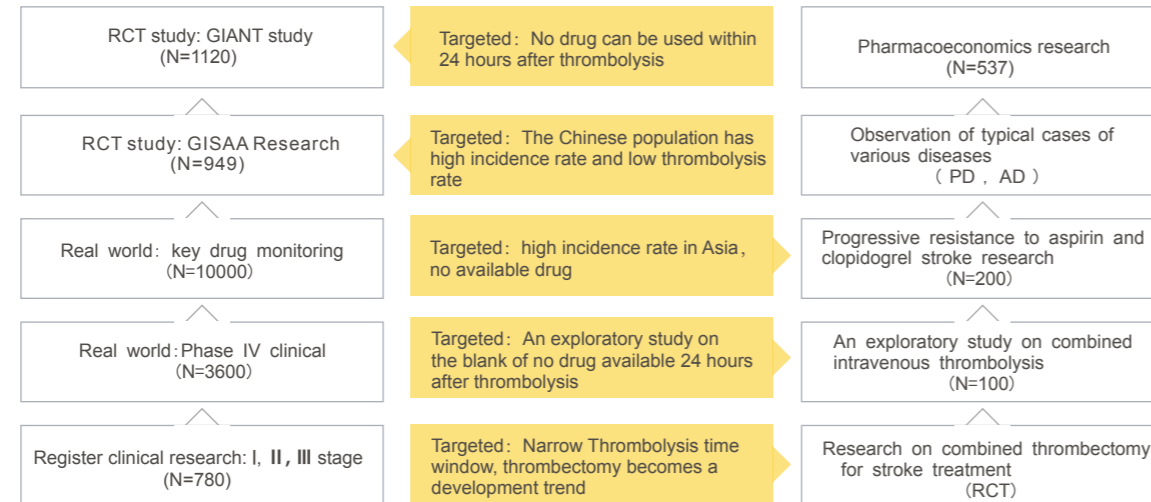
★ Bilobalide promotes glial cells and vascular endothelial cells to secrete endogenous protective factors¹³

Tab 1. Effects of bilobalide on the expression of GDNF mRNA and VEGF mRNA in cultured rat astrocytes. The ratio of $A_{GDNF}/A_{\beta-actin}$ and $A_{VEGF}/A_{\beta-actin}$ were used to express the level of GDNF mRNA and VEGF mRNA in astrocytes, respectively. $x \pm s$. ^bP < 0.05, ^cP < 0.01 vs control.

Time/h	n	Bilobalide/ $\mu\text{mol}\cdot\text{L}^{-1}$				
		0	5	15	50	100
GDNF mRNA						
12	3	0.35 ± 0.04	0.36 ± 0.07	0.39 ± 0.16	0.60 ± 0.06	0.66 ± 0.09
24	3	0.36 ± 0.07	0.38 ± 0.10	0.49 ± 0.07	0.66 ± 0.10	0.67 ± 0.08
48	3	0.37 ± 0.07	0.38 ± 0.07	0.51 ± 0.05	0.67 ± 0.11	0.69 ± 0.05
VEGF mRNA						
12	3	0.13 ± 0.06	0.17 ± 0.12	0.30 ± 0.10	0.67 ± 0.16	0.80 ± 0.12
24	3	0.16 ± 0.06	0.18 ± 0.09	0.42 ± 0.03	0.81 ± 0.17	0.83 ± 0.22
48	3	0.18 ± 0.08	0.18 ± 0.05	0.43 ± 0.12	0.82 ± 0.01	0.79 ± 0.11

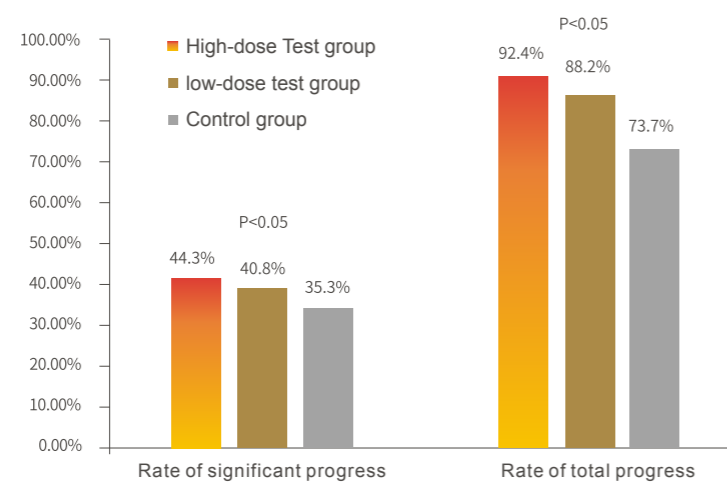
Ginkgolide Injection Exploring evidence-based medicine over ten years, with sufficient evidence-based evidence

Modern evidence-based medicine: it is safe and effective in treating cerebrovascular disease. the only traditional Chinese medicine recommended by the "Chinese Guidelines for the Clinical Diagnosis and Treatment of Cerebrovascular Disease"



Phase II Clinical Trial shows: Sufficient dosage, Sufficient treatment course, Better efficacy.

Test group: high-dose and low-dose groups (79 cases/76 cases): Ginkgolide Injection 10 ml /day, 6 ml / days, 14 days
Control group (76 cases): Ginkgo biloba extract injection 20ml/day, 14 days



Conclusion: Ginkgolide Injection were significantly better than Ginkgo biloba extract injection on the efficacy of the high-dose and low-dose group, the high-dose 10ml group had better efficacy.

Ginkgolide Injection significantly improves neurological deficits in acute phase patients¹⁴

The effect of intravenous ginkgolide on clinical improvement of patients with acute ischemic stroke

Yi Dong, Huiqin Li & Qiang Dong

	Pvalue	Odds ratio (95%CI)
Grouping (post-marketing studies as reference)	<0.001	2.169 (1.462, 3.216)
Sex (female as reference)	0.003	1.532 (1.152, 2.037)
Time of onset to enrollment (Time of onset to enrollment > 30 days as reference)	<0.001	1.915 (1.452, 2.526)
NIHSS score at baseline (NIHSS score ≤ 8 points as reference)	<0.001	15.140 (11.436, 20.045)

Treatment options

4089 patients from 7 days to 180 days after acute exacerbation were given ginkgolide injection 10 ml daily for 14 days.

Primary endpoint

NIHSS Score and mRS score

Conclusion

NIHSS and mRS for patients treated with Ginkgolide Injection for 14 days compared with baseline at enrollment were significantly reduced (P<0.001)

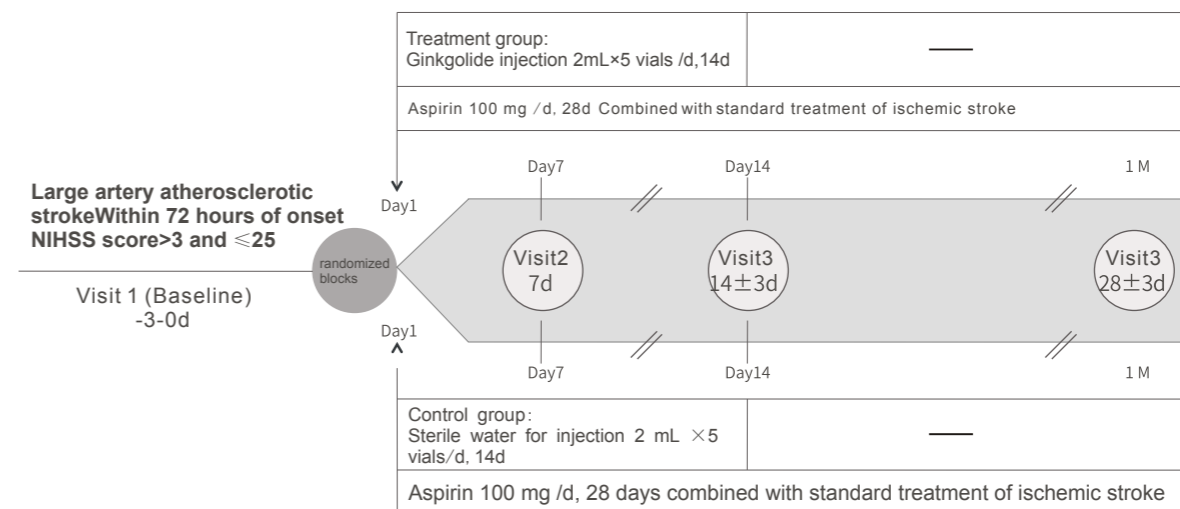
Ginkgolide Injection Research on clinical treatment of large artery atherosclerotic ischemic stroke (GISAA)¹⁵

International registration number: ChiCTR-IPR-17012310

Study design: Randomized, double-blind, multicenter, placebo-controlled clinical study

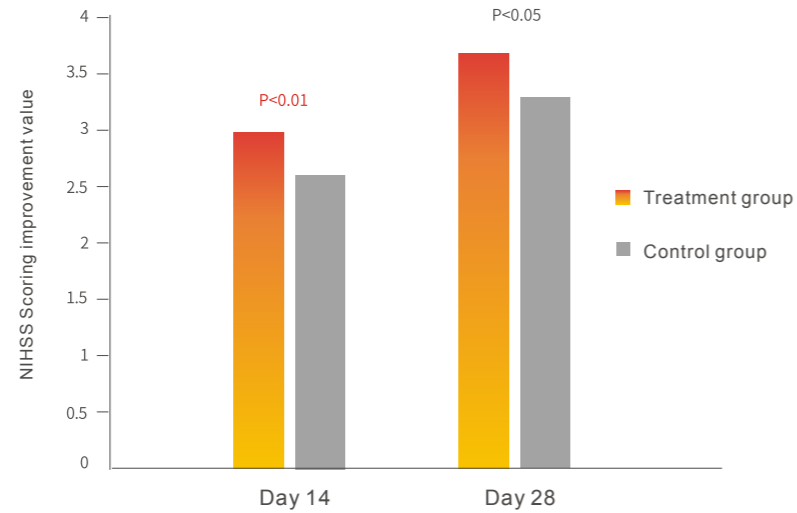
Sample size: 949 cases
Number of centers: 61

Leading unit: Huashan Hospital Affiliated to Fudan University
Main researcher: Professor Dong Qiang
Statistical unit: West China School of Public Health, Sichuan University



GISAA Research result

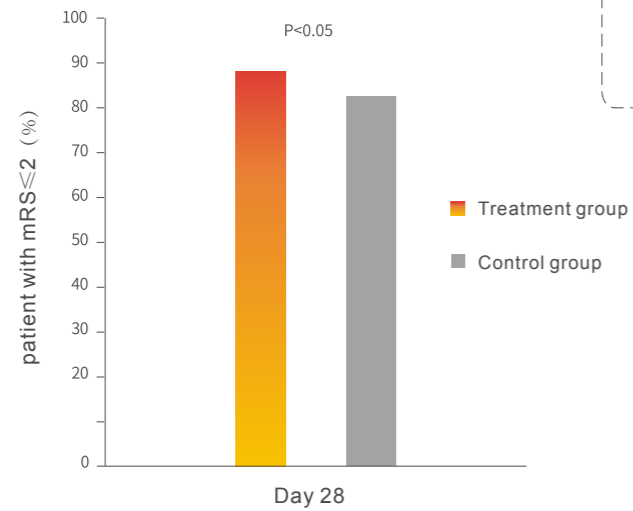
★ **Result 1: The treatment group significantly improved the neurological deficits of the patients.**



★ **Result 2: The treatment group significantly improved the clinical outcomes of patients**

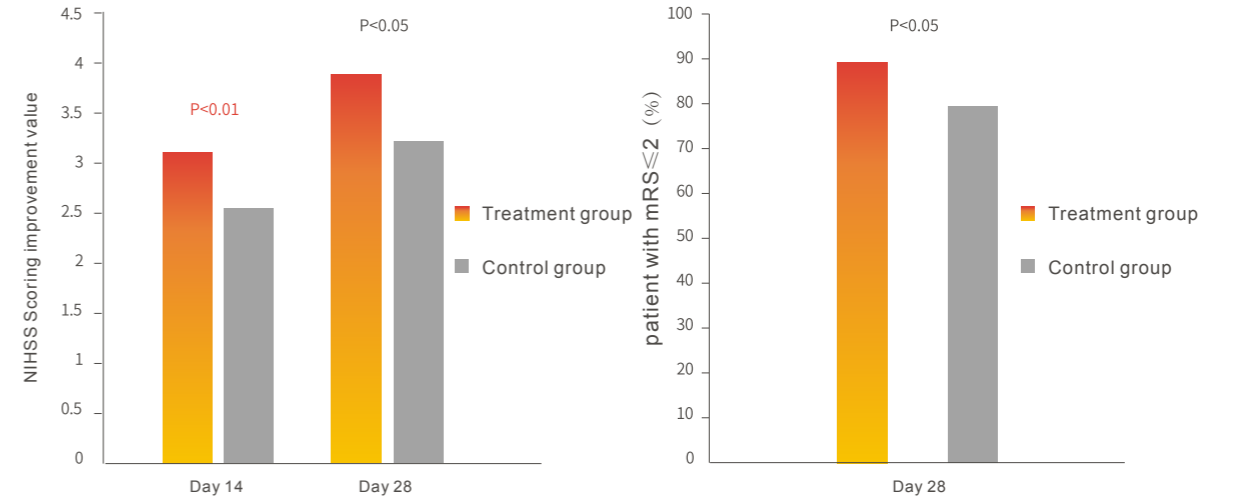
The treatment group significantly improved patients' 28-day clinical outcomes

Treatment showed a trend toward significant improvement in patients' 28-day endpoints



Outcome event on day 28 (death/recurrence of stroke)
 treatment group 0 death 0 recurrence
 control group 2 death 3 recurrence

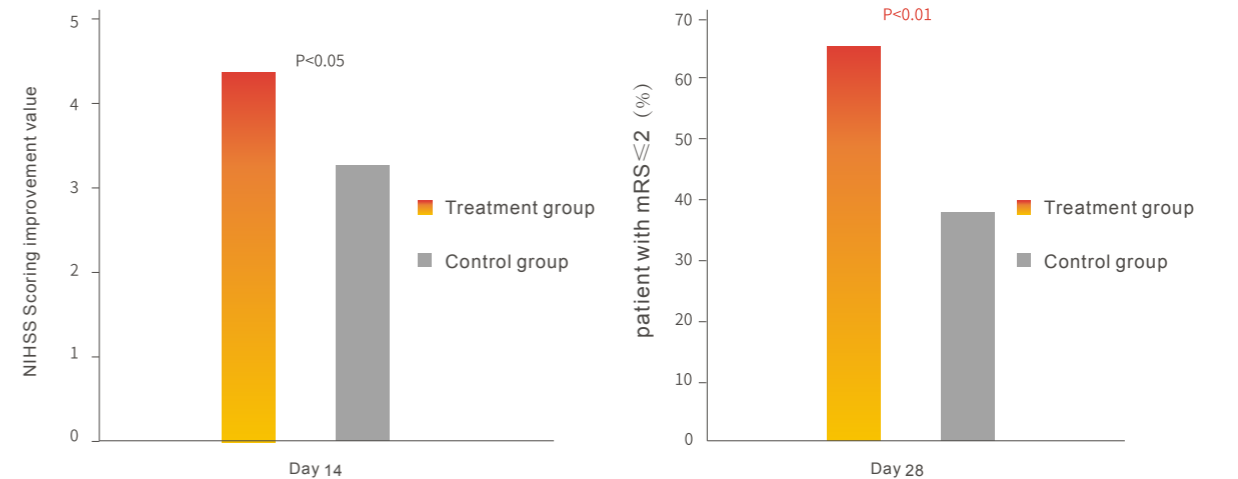
★ **Result 3: The earlier it is used, the better the effect will be**



Patients who use the drug within 24 hours have improved NIHSS scores. There is a very significant difference between the treatment group and the control group.

Patients who use the drug within 24 hours, the proportion of patients with mRS ≤ 2 on day 28 in the treatment group is significantly different from that in the control group.

★ **Result 4: The curative effect is more significant in moderate to severe patients**

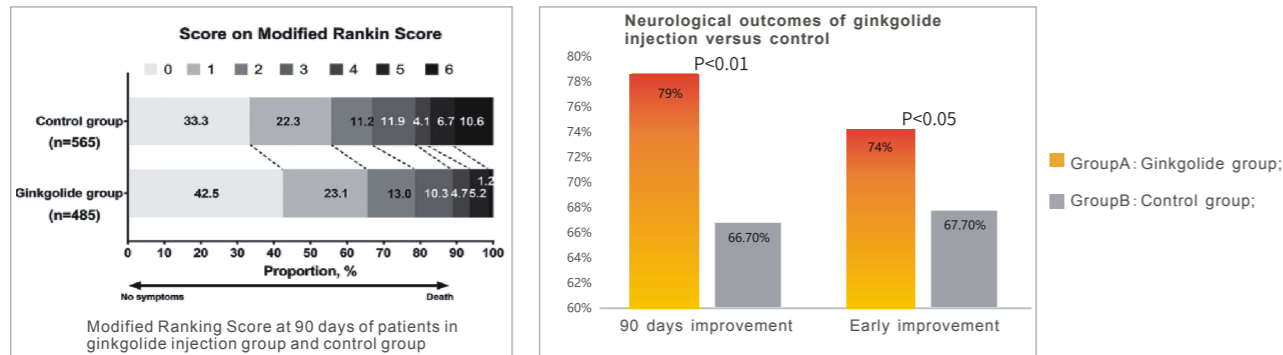


Moderate to severe patients (NIHSS Rating ≥ 8). Day 14 The scores NIHSS improved, there was a significant difference between the treatment group and the control group.

Moderate to severe patients (NIHSS score ≥ 8), the proportion of patients with mRS ≤ 2 on day 28 in the treatment group has a very significant difference compared with the control group.

GIANT Research Results¹⁷

★ Result 1: Ginkgolide Injection significantly improved the 90-day clinical outcomes of patients with acute ischemic stroke. And effectively improve neurological function in the early stage of treatment



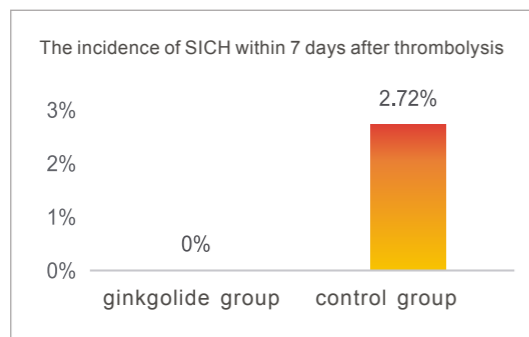
Compared with the control group, patients in the ginkgolide injection group were more likely to have a good outcome (78.6 vs. 66.7%, $P < 0.01$). That is, modified Rankin Score at 90 days (mRS) ≤ 2 . Patients in the ginkgolide group were more likely to experience early neurological improvement compared with the control group (74.0 vs. 67.7%, $P = 0.02$). That is, (NIHSS at baseline - NIHSS at 7 days / NIHSS at baseline * 100%) $\geq 18\%$.

★ Result 2: Intravenous thrombolysis administered within 24 hours will not increase the risk of bleeding

TABLE 2 | Neurological Outcome and Complication Among Ginkgolide intervention vs. Control Group after binary logistic regression.

Variables	ICC	Ginkgolide group, no. of events/Total patients (%)	Control group, no. of events/Total patients (%)	Odds ratio (95% CI) ^a	p Value
Primary outcome					
Good outcome at 90 days, No. (%)	0.033	381/485 (78.6)	377/565 (66.7)	1.498 (1.106-2.029)	0.009
Secondary outcome					
Early neurological improvement, No. (%)	0.002	372/503 (74.0%)	405/598 (67.7%)	1.392 (1.068-1.814)	0.014
Safety outcome					
sICH, No. (%)	0.031	0/403 (0%)	12/441 (2.72%)	-	-
Hemorrhage transformation, No. (%)	0.041	24/403 (6.0%)	42/441 (9.5%)	0.708 (0.412-1.218)	0.212

^aAdjusted for age, hypertension, atrial fibrillation, smoking and baseline NIHSS.

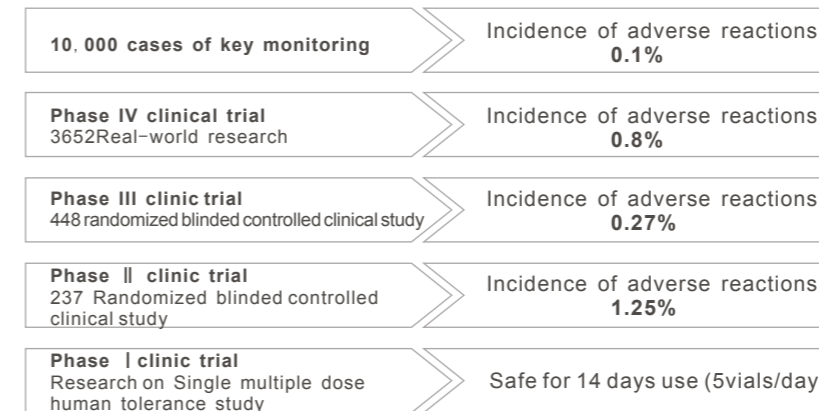


Compared with the control group, Patients in the ginkgolide group were more likely to experience lower symptoms intracranial hemorrhage (sICH) occurrence rate (0 vs. 2.72%, $P < 0.01$).

Compared with the control group, Patients in the Ginkgolide group showed a lower incidence of hemorrhagic transformation, but there was no significant difference between the groups. ($P > 0.05$)

Ginkgolide Injection has good safety and cost-effective

★ Good safety

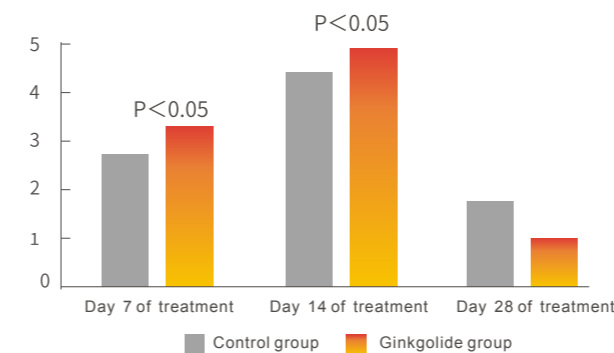


Since Ginkgolide Injection going public There were no serious adverse effects

Rare mild to moderate adverse effects mainly as follows: facial flushing, mild dizziness, and headache

★ Ginkgolide Injection better cost-effectiveness ratio on pharmacoeconomic evaluation¹⁶

Figure 1: NIHSS score(decrease)

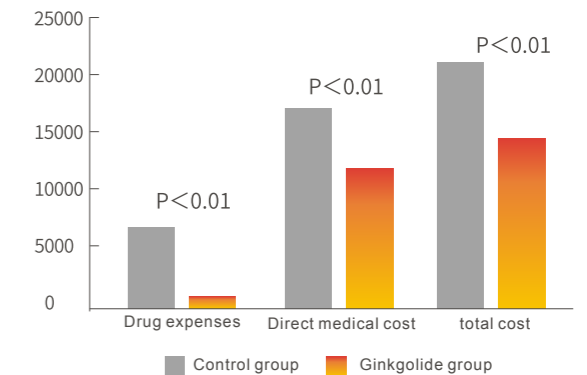


Control group: Butylphthalide sodium chloride injection (100 ml bid) + aspirin enteric-coated tablets in 56 patients.
Ginkgolide group: Ginkgolide Injection (10 mlqd) + aspirin enteric-coated tablets in 106 patients.

Conclusion: It can be known from Figure 1, the NIHSS of patients in the ginkgolide group on days 7 and 14 after treatment was significantly better than that of the control group ($P < 0.05$).

It can be known from Figure 2, the total cost (including drug expenses and direct medical costs) of ginkgolide for 14 days were significantly lower than those of the control group ($P < 0.01$).

Figure 2: Cost comparison of the two options (RMB) (14 days of treatment)



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