Seminar on Research and Development of Chinese medicines 2014
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# 循證醫學临床評價中醫藥治療中風現狀及中醫诊断治療研究的新方向

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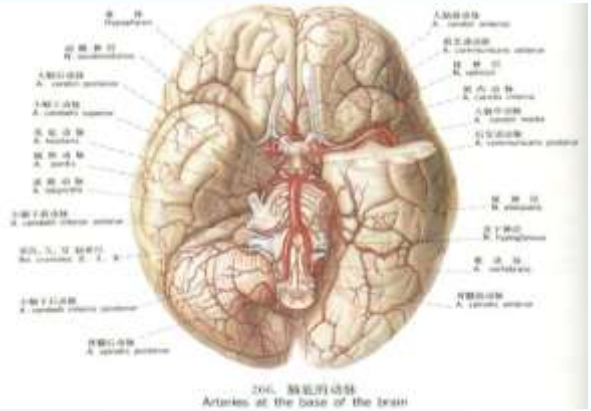
# Stroke and Aging 中風與老年病

- **Stroke is aging related diseases. Stroke becomes the secondary cause of death in human diseases worldwide and the first cause in China.**



# 一组全球数字：

- 每2秒钟就有1人发生脑卒中。
- 每6秒钟就有1人因为脑卒中而致残。
- 每6秒钟就有1人因为脑卒中而死亡。
- 每6人中就有1人一生中会罹患脑卒中。

# Epidemiology

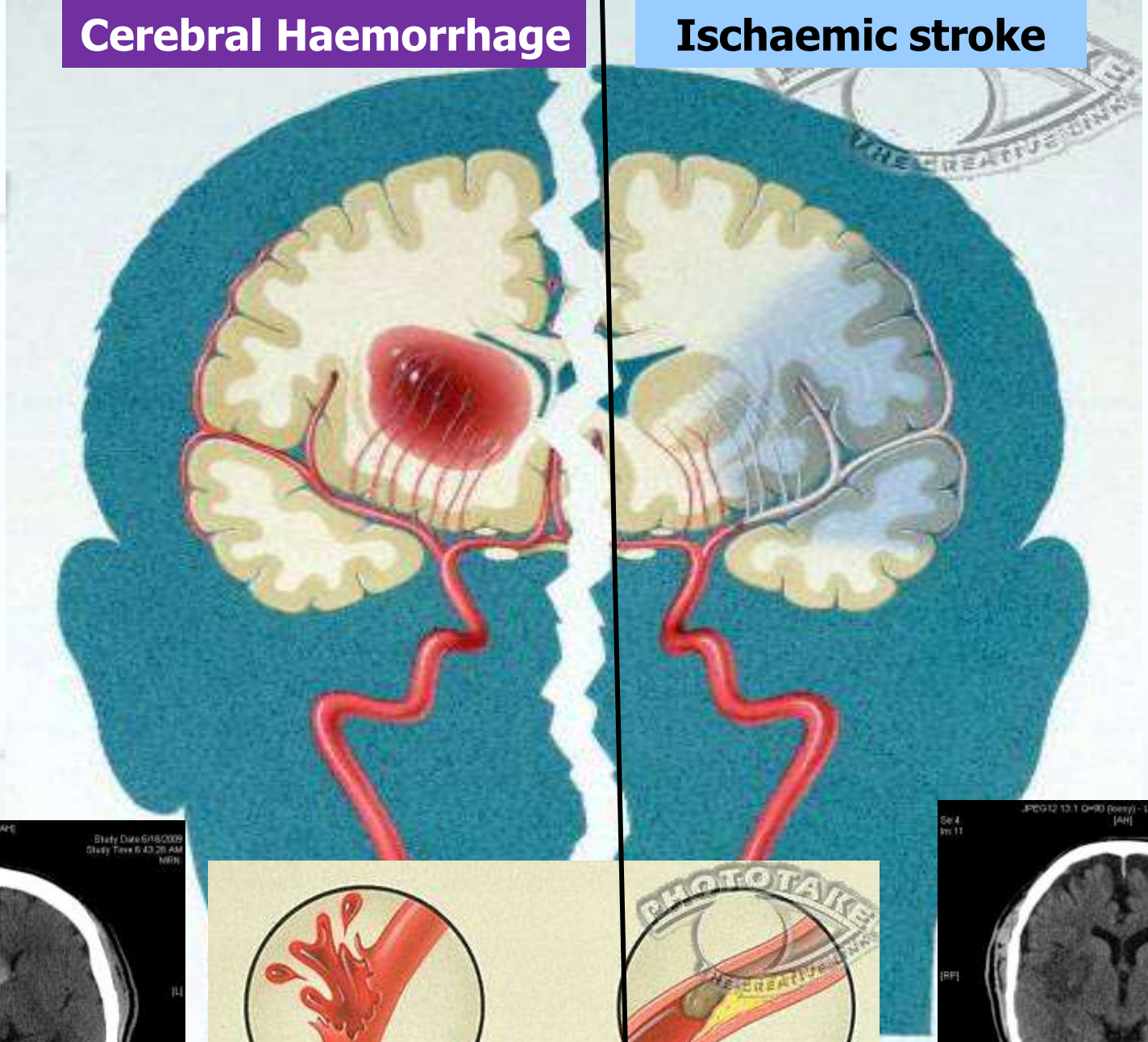
| | Western (USA) | HK |
|---|---|---|
| prevalence | 780000 /yr<br>(600000 new , 180000 recurrent) | 16000/yr |
| Type | 87% ischemic, 10% ICH, 3% SAH | 70% ischemic ,30% ICH/SAH |
| Mortality<br>(1yr mortality 20-25%)<br>(overall mortality 30%) | 273000/yr<br>(3rd leading cause of death) | 3500/yr<br>HK - 3rd leading cause of death<br>China – 1nd cause of death |
| Financial burden | Cost $ 65.5 billion | |
| Residual Disability | >50% | >50% |
| Practice | | China<br>66% Chinese doctor apply on stroke<br>63% believe to be effective |
| | | |

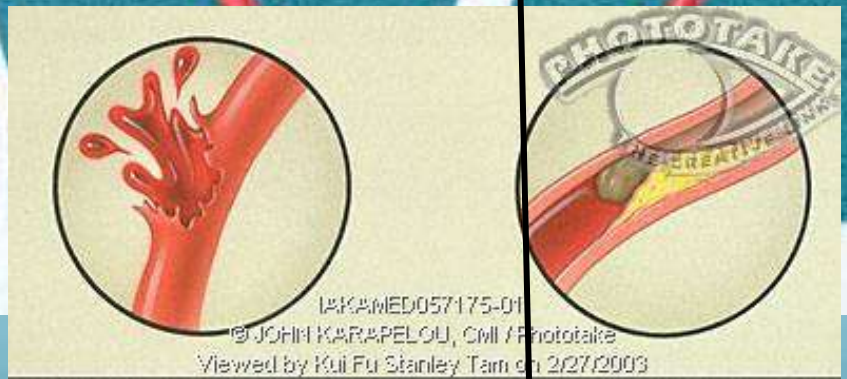
# 中風的診斷和治療現狀

# Current Progress of Diagnosis and Treatment for Stroke

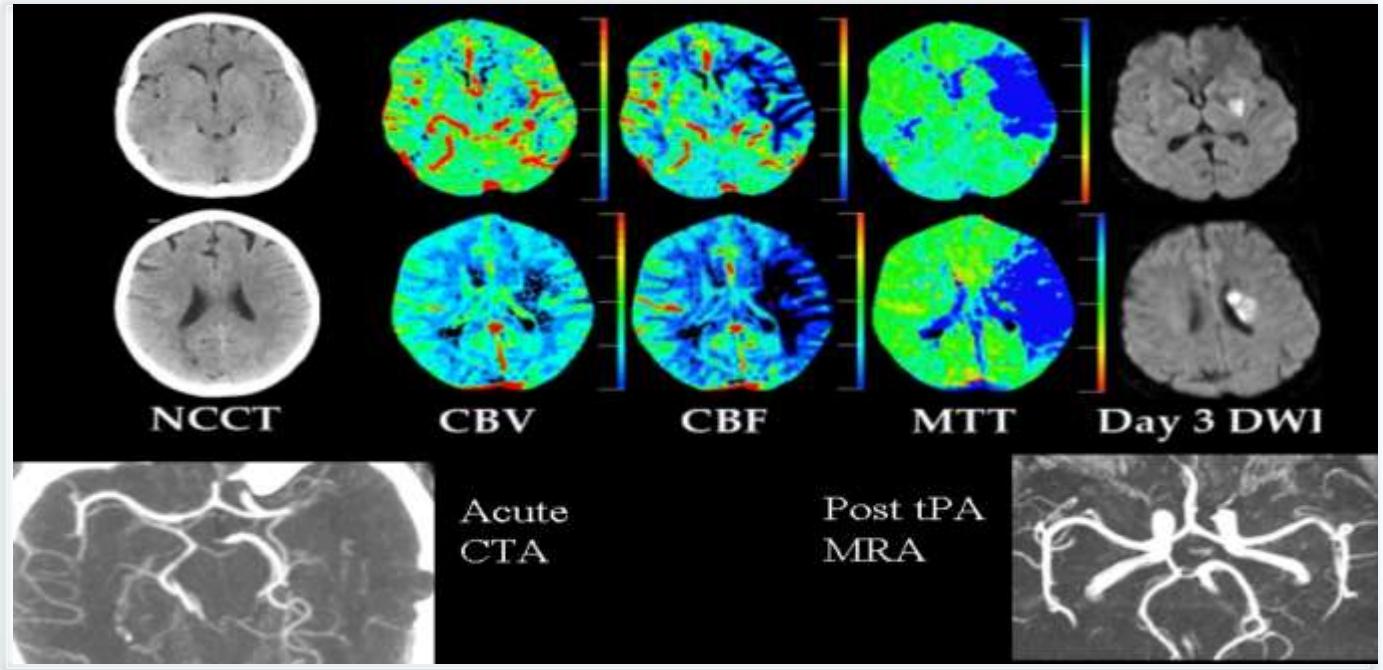
# Cerebral Haemorrhage

# Ischaemic stroke



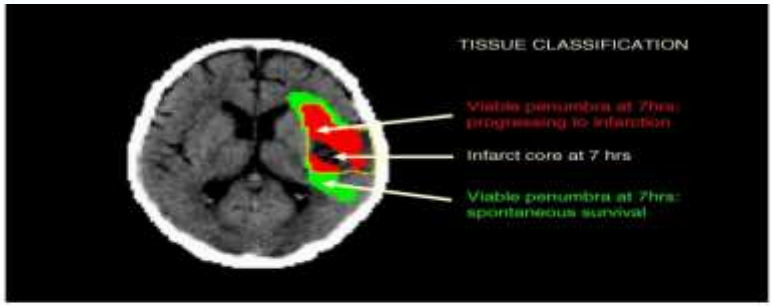



# The penumbra on CT perfusion

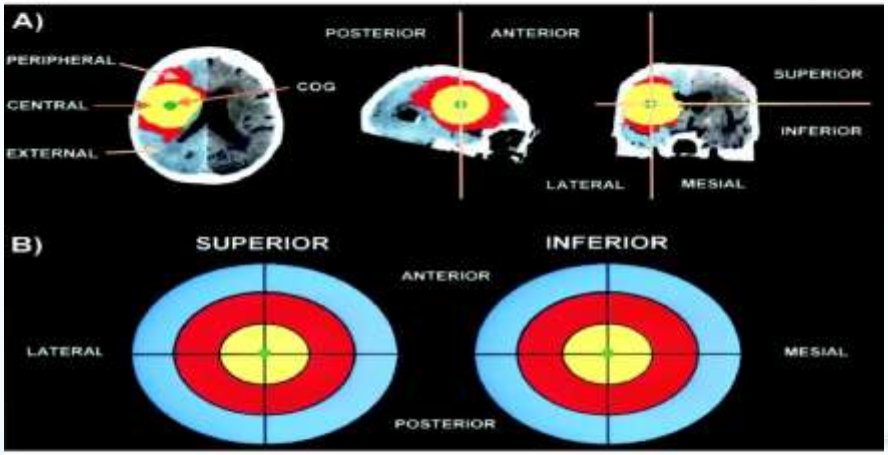



**Patient imaged with multimodal CT at 3.5 hours after stroke. M1 occlusion on CT angiography (CTA) (lower left). Small area of reduced cerebral blood volume (CBV) in lentiform nucleus and deep white matter but surrounded by much larger areas of reduced cerebral blood flow (CBF)/prolonged mean transit time (MTT) consistent with ischemic penumbra. Minimal change seen on non-contrast CT (NCCT). Patient treated with intravenous (IV) thrombolysis and had major early neurologic improvement, complete recanalisation on follow-up magnetic resonance angiography (MRA) (lower right), and only a small amount of infarction on follow-up diffusion-weighted imaging (DWI) (corresponding to pre-treatment areas of reduced CBV).**

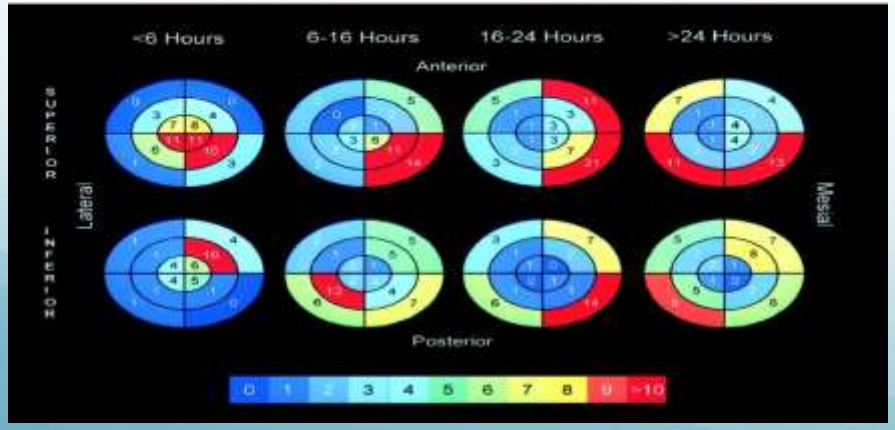
# The penumbra on PET/CT




Top: 18F-fluoromisonidazole (FMISO) PET scan performed 7 hours after stroke onset. The PET scan is co-registered to the delayed CT scan outlining final infarct at 7 days. At 7 hours after stroke onset, a significant volume of penumbral tissue that is potentially viable is observed surrounding the infarct core.



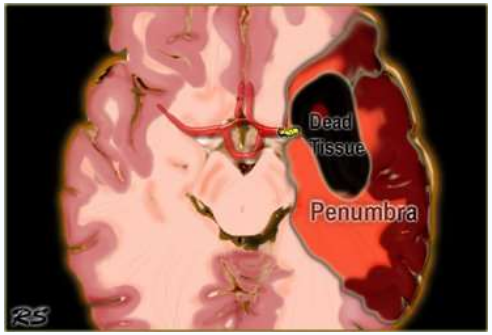

Middle: Construction of the penumbragram. Central (yellow), peripheral (red), and external (blue) zones of the infarcted volume are shown. In the penumbragram, superior and inferior halves of the infarcted volume are defined by the horizontal plane. The inner, middle, and outer circles represent the central, peripheral, and external zones.




Lowest: Temporal evolution of the penumbragram. Composite penumbragram for each time epoch (< 6, 6-16, 16-24, and 24-48 hours) after stroke onset are shown. The number in each region refers to the percentage of hypoxic volume. Higher volume of hypoxic tissue is observed in the central region within 6 hours.

Ebinger M,et al. J Clin Neurosci. 2009 Feb;16(2):178-87

# 1996年美国FDA批准tPA治疗急性缺血性脑卒中



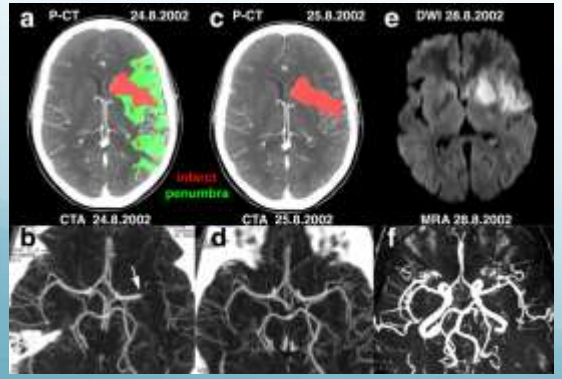

纤溶酶原

tPA

纤溶酶

血栓 脑动脉

挽救缺血脑组织



# tPA溶栓治療腦卒中:兩難選擇


- 經**tPA**及時治療的腦卒中病人，致殘率降低**30%**。

- 嚴重腦出血風險增加**10**倍
- 嚴重腦出血的死亡率高達**61%**
- 迄今無法準確預測腦出血風險

# 神經保護藥：可望而不可及。

- >1000個化合物在動物卒中模型上被證明治療卒中有效
- 114個化合物進入了臨床實驗
- 0個化合物有效

**Neuroprotection: the end of an era? *(Lancet 2006)***

**手術治療對出血性中風的療效也不肯定**

(A large RCT 1033 patients from 83 centers in 27 countries failed to show a benefit of surgery over conservative treatment in acute ICH. Mendelow AD, et al. Lancet. 2005;365(9457):387-397)

# 中醫藥的優勢、挑戰和機遇

- 優勢

. ”基於特定靶點發展新藥“的模式所產生的藥物對於中風後多信號系統紊亂無效。中醫藥基於幾千年[人體試驗]形成的多成分多靶點的治療方案

- 挑戰

中藥質控。

辨證施治多樣性和個體性與西方科學系統科研基本原則不一致。

- 機遇

現代分析化學、系統生物學、代謝組學與生物信息學等技術的發展給闡明中醫藥的治療原理帶來希望。

# 循證醫學評價中藥和針灸治療中風的療效現狀

- **Whether Traditional Chinese Herbal Medicine can Help the Rehabilitation in post-Stroke Patients ?**

# 對中醫藥治療中風的系統評價

## Meta-Analysis of Traditional Chinese Patent Medicine for Ischemic Stroke

Bo Wu, MD, PhD; Ming Liu, MD; Hua Liu, MD; Wei Li, MD; Song Tan, MD, PhD; Shihong Zhang, MD; Yuan Fang, MD

***Background and Purpose***—A large number of traditional Chinese patent medicine (TCPM) are widely used for ischemic stroke in China. The aim of this study was to systematically review the existing clinical evidence on TCPM for ischemic stroke.

***Methods***—We identified all TCPM that were listed in the Chinese National Essential Drug list of 2004 and those commonly used TCPM in current clinical practice for ischemic stroke. Fifty-nine TCPM were identified for further evaluation. We applied Cochrane systematic review methods. We searched for reports of randomized controlled trials and controlled clinical trials on any of the 59 TCPM for ischemic stroke comparing one TCPM with control. Primary outcomes included death or dependency at the end of follow-up (at least 3 months) and adverse events. Effects on neurological impairments were a secondary outcome.

***Results***—One-hundred ninety-one trials (19 338 patients) on 22 TCPM were available and included, of which 120 were definite or possible randomized controlled trials and 71 were controlled clinical trials. The methodological quality of included trials was generally "poor." Few trials reported methods of randomization. Three trials were randomized, double blind, and placebo-controlled. Primary outcomes: one trial on Puerarin and one trial on Shenmai injection assessed death or dependency at the end of long-term follow-up (at least 3 months) and found no statistically significant difference between 2 groups. The reported adverse events including allergic reaction, headache, nausea, diarrhea, bellyache, blood pressure change, and subcutaneous ecchymosis. Most of the adverse events were not severe. Secondary outcomes: analysis of the secondary outcome, "marked improvement in neurological deficit," showed apparent benefits of about the same magnitude for all the TCPM studied. Of the 22 TCPM, 8 drugs (Milk vetch, Mailuoning, Ginkgo biloba, Ligustrazine, Danshen agents, Xuesetong, Puerarin, and Acanthopanax) had relatively more studies and patient numbers.

***Conclusions***—There was insufficient good quality evidence on the effects of TCPM in ischemic stroke on the primary outcome (death or dependency). We considered the apparent benefit on neurological impairment was as likely to be attributable to bias from poor methodology as to a real treatment effect. However, because the agents assessed appeared potentially beneficial and nontoxic, further randomized controlled trials are justified. Eight drugs could be further research priorities. (***Stroke*. 2007;38:1973-1979.)**

**Key Words:** ischemic stroke ■ meta-analysis ■ systematic review ■ traditional Chinese patent medicine

No sufficient evidence supporting the clinical efficacies

Poor designs in methodologies

Biases of evaluation

***Stroke 2007***

- 研究(中風 > 十日)
- 針炙 + 中藥
- 大部分中國文獻
- 不可能作出結論
- 研究質素參差

# Complex Traditional Chinese Medicine for Poststroke Motor Dysfunction

## A Systematic Review

Zhang Junhua, MD; Francesca Menniti-Ippolito, MSc; Gao Xiumei, MD; Fabio Firenzuoli, MD; Zhang Boli, MSc; Marco Massari, MSc; Shang Hongcai, MD; Huang Yuhong, PhD; Rita Ferrelli, MD; Hu Limin, MD; Alice Fauci, MA; Ranieri Guerra, MD; Roberto Raschetti, MSc

***Background and Purpose***—For its current dimensions, stroke represents the world's primary health challenge. In China stroke is the second most common cause of death. Traditional Chinese Medicine (TCM) has for many centuries been used, and it is still widely used today in countries of south and east Asia for the treatment of people with stroke. The objective of this systematic review was to evaluate whether complex Traditional Chinese Medicine (cTCM) improves poststroke motor recovery. In particular, we defined cTCM as intervention that included at least acupuncture and Chinese herbal medicine.

***Methods***—An extensive search including PubMed, EMBASE, CBM, and the Cochrane Library was performed up to December 2007. Randomized clinical trials (RCTs) about cTCM for motor dysfunction of poststroke were searched irrespective of any language. The quality of each trial was assessed according to the Cochrane Reviewers' Handbook 4.2.6.

***Results***—After selection of 11 234 articles, 34 RCTs and quasi-RCTs were included. All these trials were conducted in China and published on Chinese journals. All trials but one reported results in favor of cTCM treatments suggesting a strong publication bias. Because of the significant clinical and methodological heterogeneity, no meta-analysis was performed and thus no cumulative result was obtained pooling data of RCTs.

***Conclusions***—What appears from this systematic review is that scant data are available to evaluate efficacy of cTCM for poststroke motor dysfunction. Most of the primary studies available for this review were inadequately designed trials characterized by unknown dropout rates and definitional vagueness in outcomes measures. None of the studies approached important end points like death, survival times, rate of dependency, reduction in length of stay in hospital, etc. The key to lead to evidence-based practices is establishing a consensus on standardized relevant outcome measures and then designing and conducting appropriate RCTs that adopt those standards. (***Stroke***. **2009;40:2797-2804.**)

**Key Words:** traditional Chinese medicine ■ systematic review ■ stroke ■ rehabilitation

***Stroke 2009***

- >八成研究(中風一個月內)
- 可能有效
- 研究質素參差

## Comments, Opinions, and Reviews

# Acupuncture in Poststroke Rehabilitation

## A Systematic Review and Meta-Analysis of Randomized Trials

Ping Wu, MD, MSc; Edward Mills, MSc, PhD; David Moher, MSc, PhD; Dugald Seely, ND, MSc

***Background and Purpose***—Acupuncture is a low-risk treatment with purported claims of effectiveness for poststroke rehabilitation. To comprehensively assess the efficacy of acupuncture in poststroke rehabilitation, we conducted a systematic review and meta-analysis of all randomized clinical trials of acupuncture for poststroke rehabilitation.

***Methods***—We searched 7 English and 2 Chinese databases from inception to September 2009. Eligible studies included randomized clinical trials that evaluated the clinical efficacy of acupuncture in adult patients with disability after stroke. We extracted data on trial quality, protocol, and outcomes assessed. A summary OR was calculated based on pooled dichotomous results. $I^2$ was used to infer heterogeneity and we conducted metaregression to determine if specific covariates explained heterogeneity.

***Results***—Thirty-five articles written in Chinese and 21 articles written in English were included. The overall quality of the studies was "fair" and most studies were small (median n=86; range, 16 to 241). The majority (80%) of the studies reported a significant benefit from acupuncture; however, there was some evidence of publication bias. In 38 trials, data were available for meta-analysis and metaregression, yielding an OR in favor of acupuncture compared with controls (OR=4.33, 95% CI: 3.09 to 6.08; $I^2$=72.4%). Randomization, modes of delivery, method of control, study source country, and reporting of randomization may explain some of the heterogeneity observed between the studies.

***Conclusions***—Randomized clinical trials demonstrate that acupuncture may be effective in the treatment of poststroke rehabilitation. Poor study quality and the possibility of publication bias hinder the strength of this recommendation and argue for a large, transparent, well-conducted randomized clinical trial to support this claim and implement changes to clinical practice. (***Stroke*. 2010;41:e171-e179.**)

**Key Words:** acupuncture ■ cerebral infarct ■ cerebrovascular disease ■ meta-analysis ■ metaregression ■ systematic review ■ therapy

***Stroke 2010***

# 補陽還五湯 清代王清任《醫林改錯》

- 組方:

*Astragalus membranaceus* 黃耆 120g, *Angelica sinensis* 當歸 6g

*Paeonia lactiflora* 赤芍 4.5g, *Ligusticum chuanxiong* 川芎 3 g

*Carthamus tinctorius* 地龍 3g , *Prunus persica* 桃仁 3g

*Lumbricus* 红花 3g

- 功效：補中益氣，活血通經

為益氣活血的代表性的名方，其配伍在中醫傳統名方中相當獨特。 重用黃耆為君藥，其餘活血通絡的藥物為臣藥或佐使之藥。

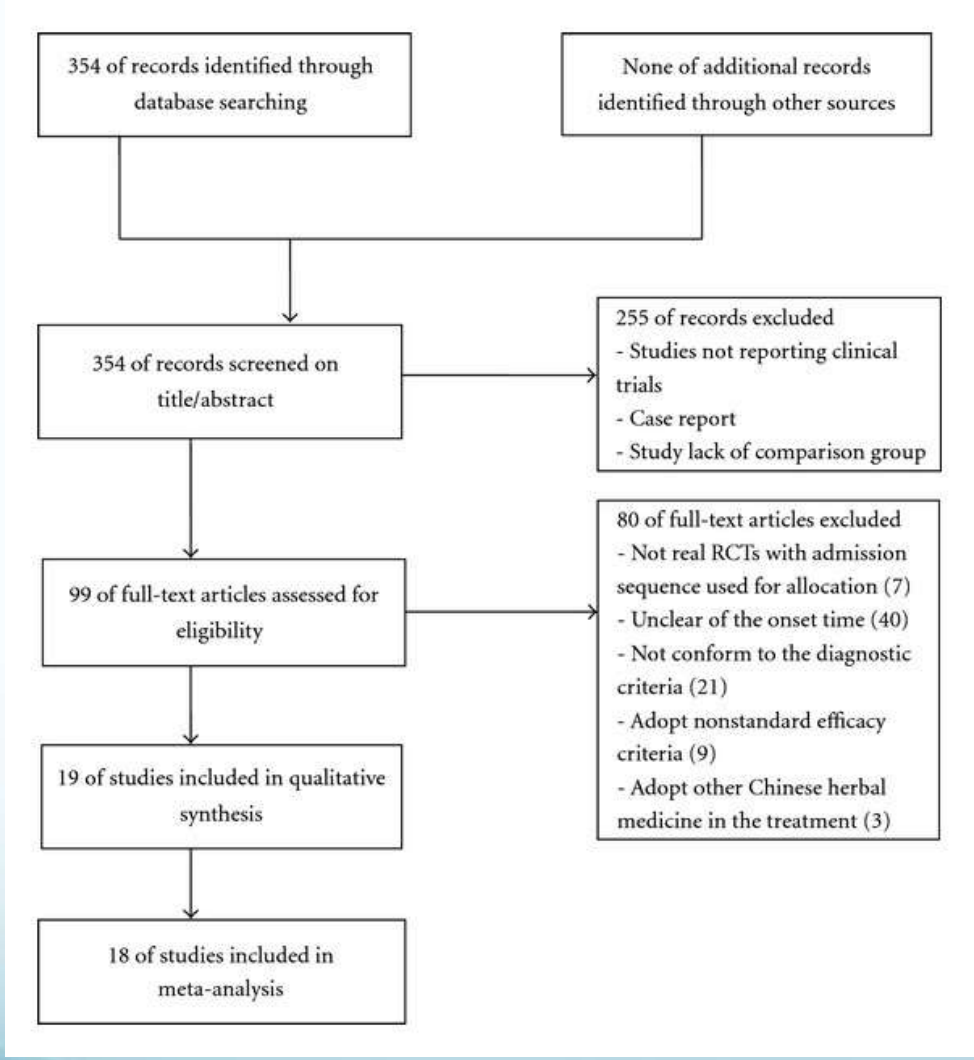
- 適應症：用于治療氣虛血瘀之中風後遺症，出現口眼歪斜，半身不遂，語言不利等症狀。

《醫林改錯》：“此方治半身不遂、口眼歪斜、語言蹇澀、口角流涎、大便干燥、小便頻數、遺尿不禁。”

# 我們的实验研究結論

- 應用現代系統生物學、分子生物學、分子成像等技術和方法闡明的補陽還五湯治療缺血性中風後遺症的機制
- 對該方的促進神經再生作用系統研究，證明該方能調控多種神經再生相關的細胞信號，並促進中風後神經功能的修復
- 臨床治療中風是否有效？

# 集萃分析方法評價該方臨床療效




Hao CZ, Wu F, Shen JG, et al. Evid Based Complement Alternat Med. 2012; 2012: 630124.

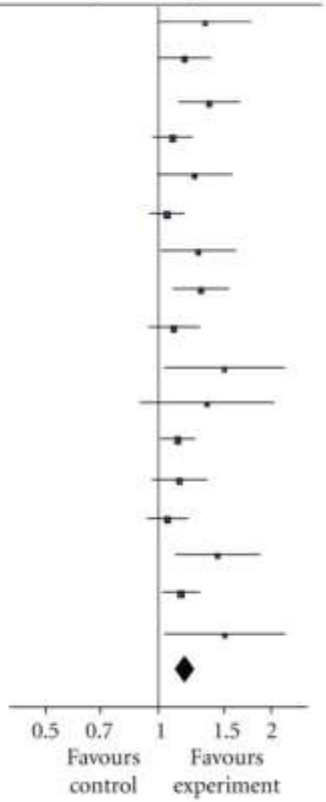
# Meta-analyses of the total effective rate of BHD therapy for acute ischemic stroke

# 集萃分析發現該方臨床治療中風促神經功能改善有效

| Study or subgroup | Experimental | | Control | | Weight | Risk ratio | Risk ratio |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | M-H, random, 95% CI | M-H, random, 95% CI |
| Chen, 2007 [32] | 28 | 32 | 21 | 32 | 3.0% | 1.33 [1.00, 1.77] | |
| Cui et al., 2005 [34] | 49 | 50 | 25 | 30 | 6.6% | 1.18 [1.00, 1.39] | |
| Fang et al., 2005 [27] | 58 | 65 | 47 | 72 | 5.5% | 1.37 [1.13, 1.65] | |
| Guo, 2009 [25] | 56 | 57 | 27 | 30 | 9.1% | 1.09 [0.96, 1.24] | |
| Jia et al., 2010 [26] | 30 | 32 | 21 | 28 | 4.1% | 1.25 [0.99, 1.58] | |
| Kang, 2006 [30] | 35 | 36 | 35 | 38 | 10.4% | 1.06 [0.95, 1.18] | |
| Lin, 2008 [31] | 30 | 32 | 22 | 30 | 4.0% | 1.28 [1.01, 1.61] | |
| Liu, 2010 [35] | 52 | 55 | 40 | 55 | 6.2% | 1.30 [1.09, 1.55] | |
| Lv, 2009 [39] | 33 | 35 | 30 | 35 | 7.0% | 1.10 [0.94, 1.29] | |
| Run, 2001 [37] | 21 | 24 | 14 | 24 | 1.8% | 1.50 [1.04, 2.17] | |
| Shi and Zhang, 1995 [36] | 17 | 21 | 12 | 20 | 1.5% | 1.35 [0.89, 2.04] | |
| Wang and Yu, 2005 [38] | 62 | 64 | 55 | 64 | 10.4% | 1.13 [1.01, 1.26] | |
| Wu and Luo, 2011 [23] | 33 | 35 | 29 | 35 | 6.3% | 1.14 [0.96, 1.35] | |
| Yan and Mei, 2004 [33] | 55 | 60 | 52 | 60 | 9.1% | 1.06 [0.93, 1.20] | |
| Zhang, 2004 [24] | 36 | 40 | 25 | 40 | 3.4% | 1.44 [1.11, 1.87] | |
| Zhang et al., 2010 [12] | 77 | 82 | 67 | 82 | 9.7% | 1.15 [1.02, 1.29] | |
| Zheng et al., 2004 [40] | 24 | 27 | 13 | 22 | 1.8% | 1.50 [1.04, 2.18] | |
| **Total (95% CI)** | | **747** | | **697** | **100.0%** | **1.18 [1.12, 1.24]** | |
| Total events | 696 | | 535 | | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 24.82$, df = 16 ($P = 0.07$); $I^2 = 36\%$

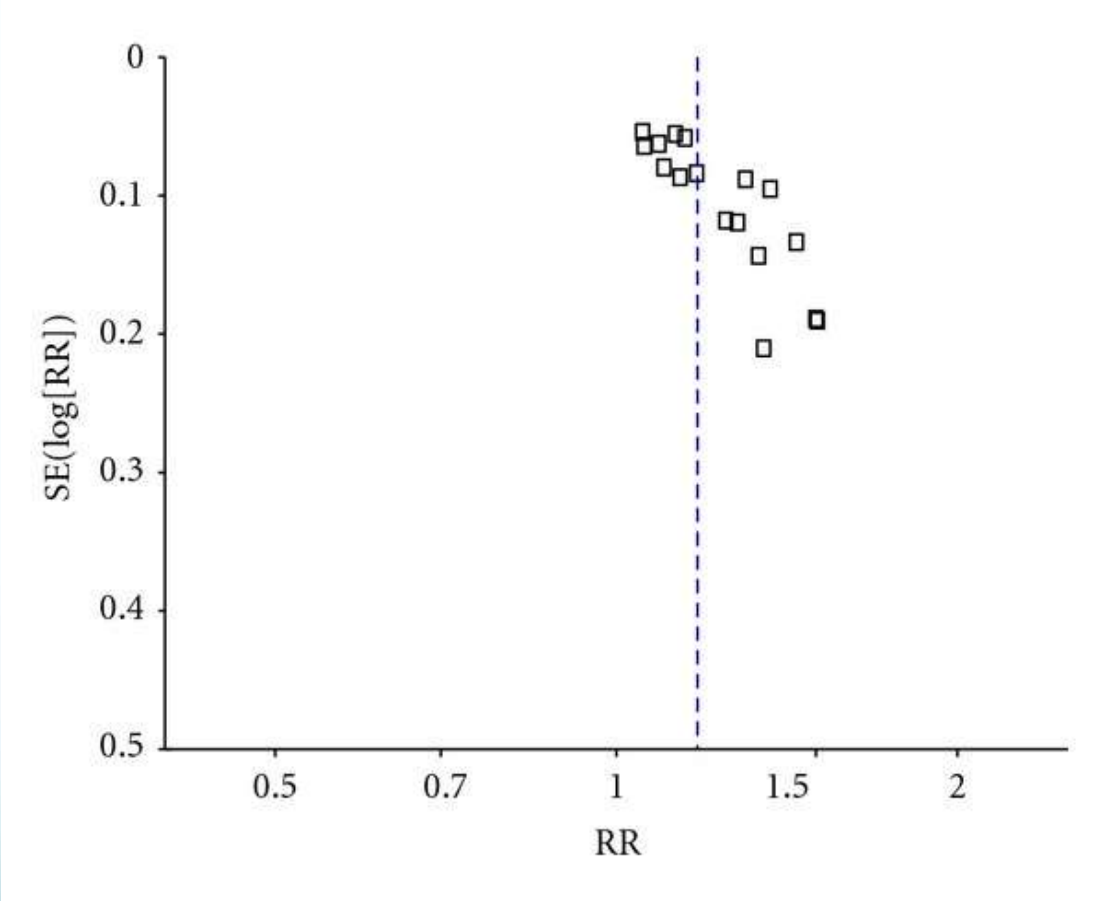
Test for overall effect: $Z = 6.02$ ($P < 0.00001$)




Hao CZ, Wu F, Shen JG, et al. Evid Based Complement Alternat Med. 2012; 2012: 630124.

# F集萃分析方法顯示臨床療效評價存在出版偏見

# Funnel plot of the total effective rate of BHD therapy for acute ischemic stroke



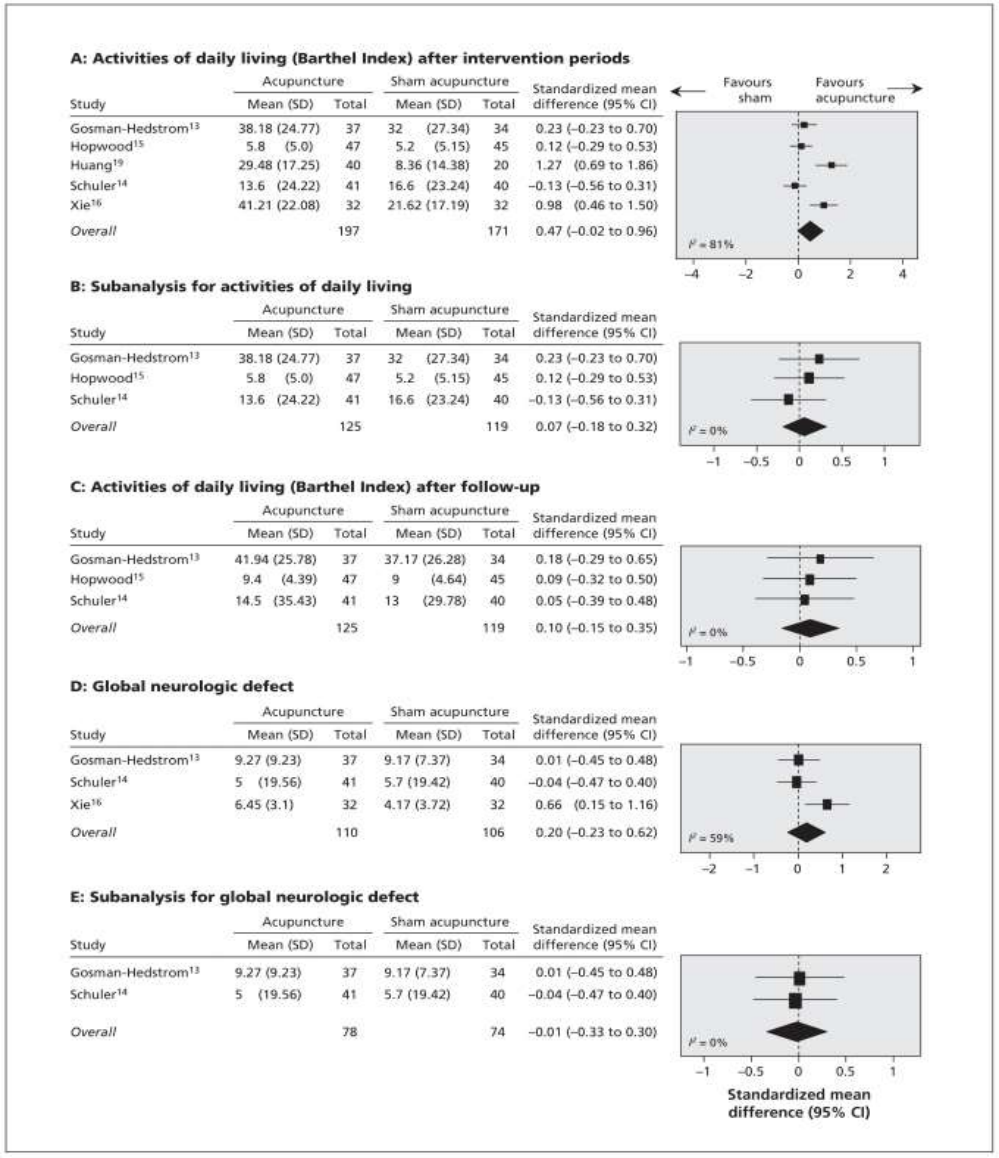

Hao CZ, Wu F, Shen JG, et al. Evid Based Complement Alternat Med. 2012; 2012: 630124.

隨機對照臨床試驗評價針刺治療是否對中風後神經康復有效?

**Whether randomized clinical trials (RCT) support that Acupuncture Treatment can help the rehabilitation of post-stroke patients?**

# Results did not favor Acupuncture Treatment

## 針刺治療對中風後神經康復無效的證據



**A: Activities of daily living (Barthel Index) after intervention periods**

| Study | Acupuncture Mean (SD) | Acupuncture Total | Sham acupuncture Mean (SD) | Sham acupuncture Total | Standardized mean difference (95% CI) |
|---|---|---|---|---|---|
| Gosman-Hedstrom[13] | 38.18 (24.77) | 37 | 32 (27.34) | 34 | 0.23 (–0.23 to 0.70) |
| Hopwood[15] | 5.8 (5.0) | 47 | 5.2 (5.15) | 45 | 0.12 (–0.29 to 0.53) |
| Huang[19] | 29.48 (17.25) | 40 | 8.36 (14.38) | 20 | 1.27 (0.69 to 1.86) |
| Schuler[14] | 13.6 (24.22) | 41 | 16.6 (23.24) | 40 | –0.13 (–0.56 to 0.31) |
| Xie[16] | 41.21 (22.08) | 32 | 21.62 (17.19) | 32 | 0.98 (0.46 to 1.50) |
| *Overall* | | 197 | | 171 | 0.47 (–0.02 to 0.96) |

**B: Subanalysis for activities of daily living**

| Study | Acupuncture Mean (SD) | Acupuncture Total | Sham acupuncture Mean (SD) | Sham acupuncture Total | Standardized mean difference (95% CI) |
|---|---|---|---|---|---|
| Gosman-Hedstrom[13] | 38.18 (24.77) | 37 | 32 (27.34) | 34 | 0.23 (–0.23 to 0.70) |
| Hopwood[15] | 5.8 (5.0) | 47 | 5.2 (5.15) | 45 | 0.12 (–0.29 to 0.53) |
| Schuler[14] | 13.6 (24.22) | 41 | 16.6 (23.24) | 40 | –0.13 (–0.56 to 0.31) |
| *Overall* | | 125 | | 119 | 0.07 (–0.18 to 0.32) |

**C: Activities of daily living (Barthel Index) after follow-up**

| Study | Acupuncture Mean (SD) | Acupuncture Total | Sham acupuncture Mean (SD) | Sham acupuncture Total | Standardized mean difference (95% CI) |
|---|---|---|---|---|---|
| Gosman-Hedstrom[13] | 41.94 (25.78) | 37 | 37.17 (26.28) | 34 | 0.18 (–0.29 to 0.65) |
| Hopwood[15] | 9.4 (4.39) | 47 | 9 (4.64) | 45 | 0.09 (–0.32 to 0.50) |
| Schuler[14] | 14.5 (35.43) | 41 | 13 (29.78) | 40 | 0.05 (–0.39 to 0.48) |
| *Overall* | | 125 | | 119 | 0.10 (–0.15 to 0.35) |

**D: Global neurologic defect**

| Study | Acupuncture Mean (SD) | Acupuncture Total | Sham acupuncture Mean (SD) | Sham acupuncture Total | Standardized mean difference (95% CI) |
|---|---|---|---|---|---|
| Gosman-Hedstrom[13] | 9.27 (9.23) | 37 | 9.17 (7.37) | 34 | 0.01 (–0.45 to 0.48) |
| Schuler[14] | 5 (19.56) | 41 | 5.7 (19.42) | 40 | –0.04 (–0.47 to 0.40) |
| Xie[16] | 6.45 (3.1) | 32 | 4.17 (3.72) | 32 | 0.66 (0.15 to 1.16) |
| *Overall* | | 110 | | 106 | 0.20 (–0.23 to 0.62) |

**E: Subanalysis for global neurologic defect**

| Study | Acupuncture Mean (SD) | Acupuncture Total | Sham acupuncture Mean (SD) | Sham acupuncture Total | Standardized mean difference (95% CI) |
|---|---|---|---|---|---|
| Gosman-Hedstrom[13] | 9.27 (9.23) | 37 | 9.17 (7.37) | 34 | 0.01 (–0.45 to 0.48) |
| Schuler[14] | 5 (19.56) | 41 | 5.7 (19.42) | 40 | –0.04 (–0.47 to 0.40) |
| *Overall* | | 78 | | 74 | –0.01 (–0.33 to 0.30) |



Ten of 664 relevant studies met inclusion criteria. For acute and subacute stages after stroke, seven trials were included. A meta-analysis of the five studies revealed that assessed functionality did not show a significant difference in favor of acupuncture, with high heterogeneity

**Kong JC, Lee MS, Shin BC, Song YS, Ernst E.**
**Acupuncture for functional recovery after stroke: a systematic review of sham-controlled randomized clinical trials.**
**CMAJ. 2010 Nov 9;182(16):1723-9. Epub 2010 Sep 27.**

# Results Favor Acupuncture Treatment
# 支持針刺治療對中風後神經康復有效的證據

.

- Thirty-five articles written in Chinese and 21 articles written in English were included. The overall quality of the studies was "fair" and most studies were small (median n=86; range, 16 to 241). The majority (80%) of the studies reported a significant benefit from acupuncture; however, there was some evidence of publication bias. In 38 trials, data were available for meta-analysis and metaregression, yielding an OR in favor of acupuncture compared with controls (OR=4.33, 95% CI: 3.09 to 6.08; I2=72.4%). Randomization, modes of delivery, method of control, study source country, and reporting of randomization may explain some of the heterogeneity observed between the studies.

- CONCLUSIONS: Acupuncture may be effective in the treatment of poststroke rehabilitation. Poor study quality and the possibility of publication bias hinder the strength of this recommendation, and argue for a large, transparent, well-conducted RCT to support this claim and implement changes to clinical practice.

Wu P, Mills E, Moher D, Seely D. Acupuncture in poststroke rehabilitation: a systematic review and meta-analysis of randomized trials. Stoke. 2010 Apr;41(4):e171-9.

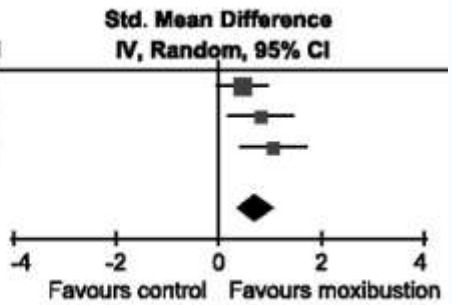
# 集萃分析隨機對照臨床試驗評價艾灸治療是否對中風後神經康復有效?
# Meta-analysis of moxibustion for stroke

**A, Motor function. B, Activities of daily living.**

A

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chen 2008 | 16.29 | 9.71 | 32 | 11.7 | 9.91 | 30 | 45.1% | 0.46 [-0.04, 0.97] |
| Choi 2003a | 13.6 | 7.5 | 20 | 8.4 | 4.5 | 20 | 28.2% | 0.82 [0.18, 1.47] |
| Choi 2003b | 16.5 | 9 | 20 | 8 | 6.5 | 20 | 26.7% | 1.06 [0.39, 1.73] |
| **Total (95% CI)** | | | **72** | | | **70** | **100.0%** | **0.72 [0.37, 1.08]** |

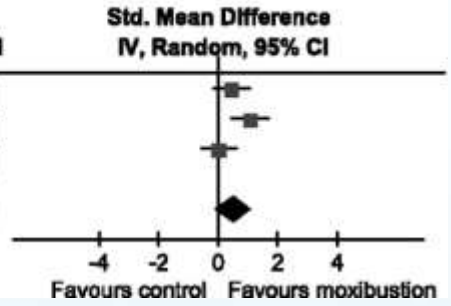
Heterogeneity: Tau² = 0.01; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 4.03 (P < 0.0001)




B

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Choi 2003a | 2.2 | 3.7 | 20 | 0.9 | 1.6 | 20 | 33.5% | 0.45 [-0.18, 1.08] |
| Lee 2008 | 24.2 | 5.9 | 21 | 18.57 | 4.2 | 21 | 32.6% | 1.08 [0.43, 1.73] |
| Yun 2007 | 4.75 | 26.04 | 20 | 3.95 | 26.55 | 20 | 33.9% | 0.03 [-0.59, 0.65] |
| **Total (95% CI)** | | | **61** | | | **61** | **100.0%** | **0.51 [-0.08, 1.10]** |

Heterogeneity: Tau² = 0.17; Chi² = 5.27, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 1.69 (P = 0.09)




*RESULTS:* Nine randomized clinical trials met inclusion criteria. Three RCT reported favorable effects of moxibustion plus standard care on motor function versus standard care alone (N=142; standardized mean difference=0.72; 95% confidence interval, 0.37 to 1.08; P<0.0001). Three RCT compared the effects of moxibustion on activities of daily living alone but failed to show favorable effects of moxibustion. Limited effectiveness of moxibustion was found as an adjunct to standard care in stroke rehabilitation.

# 集萃分析隨機對照臨床試驗評價頭針治療是否對中風後神經康復有效?

# Whether Scalp Acupuncture treatment can help the rehabilitation of post-stroke patients?


**References:**

1. **Wang Y, Shen JG*, Wang XM, Fu DL, Chen CY, Lu LY, Lu L, Xie CL, Fang JQ, Zheng GQ. Scalp Acupuncture for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Evidence-based Complementary and Alternative Medicine 2012, Article ID.* 480950**
2. **Zheng GQ, Zhao ZM, Wang Y, Gu Y, Li Y, Chen XM, Fu SP, Shen JG*. Meta-analysis of scalp acupuncture for acute hypertensive intracerebral hemorrhage. *J Altern Complement Med.* 2011; 17(4):293-299.**

# Scalp acupuncture could reduce rapidly neurological dysfunction in spontaneously hypertensive stroke –prone (SHR-SP) rats

Day 0 (Stroke onset)
Grade 4

Day 1
Grade 4

Day 2
Grade 3

Day 3
Grade 2

Day 4
Grade 0

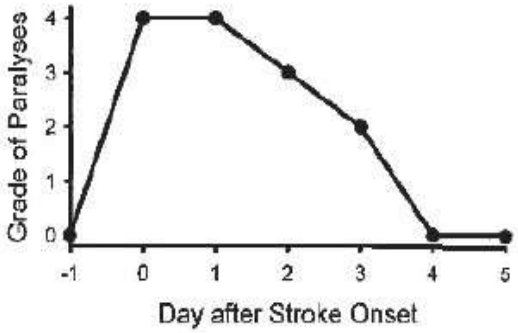



**Figure 1** Photographic pictures taken during 4 days after stroke onset demonstrating the scalp acupuncture effect on paralyses appearing in a rat after suffering a stroke. Scalp acupuncture was treated for 10 min each day. The graph shows a plot of the grade of paralyses of this rat during the 5 days after the stroke onset.

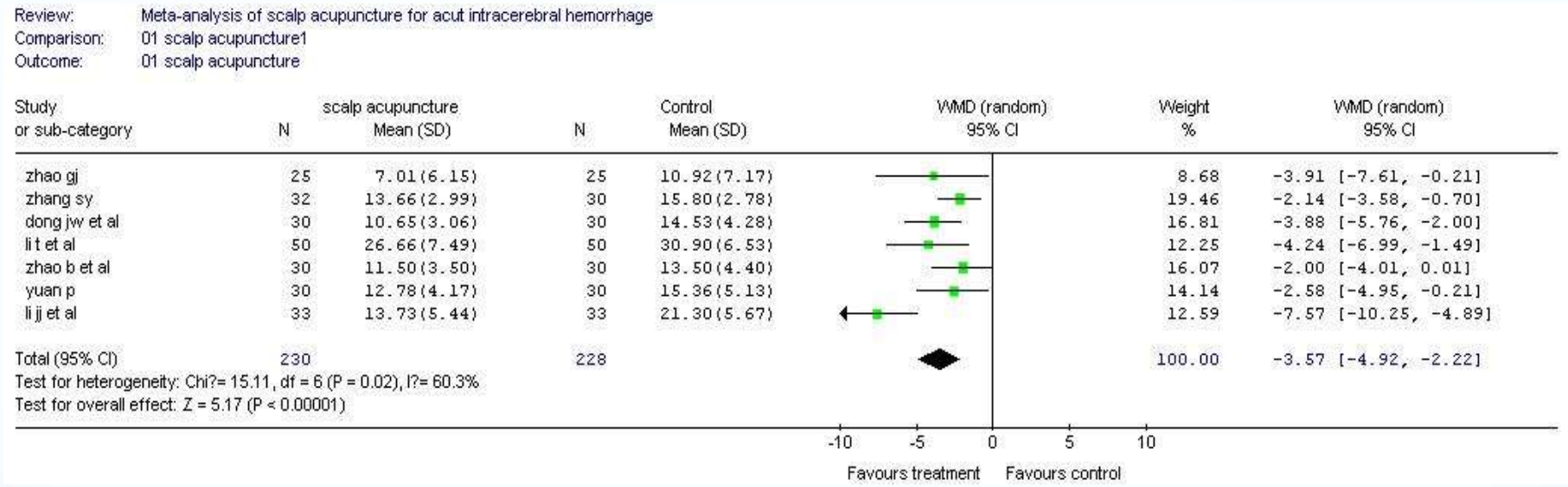
( Inoue et al; Scalp acupuncture effects of stroke studied with magnetic resonance imaging: different actions in the two stroke model rats. *Acupunct Med* 2009;27:155–162)

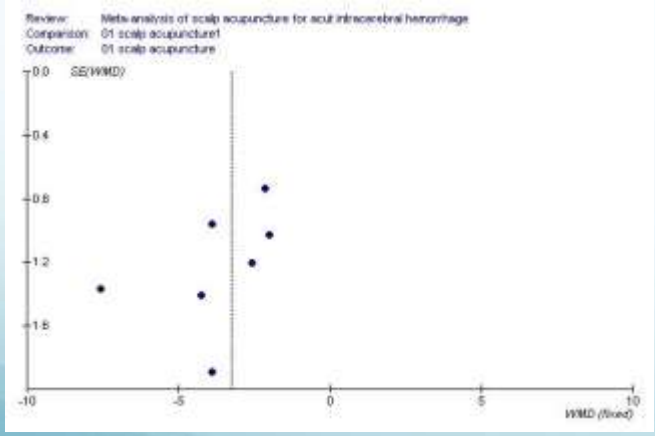
# 集萃分析頭針治療是否對出血性中風神經康復有效?
# Meta-Analysis of Scalp Acupuncture for Acute Hypertensive Intracerebral Hemorrhage (ICH)

- *Methods:* Seven independent trials (230 patients) were included in this study. All trials described the methods of randomization in which four trials had adequate concealment of randomization at the level of grade A, but no trial included sham acupuncture as a control group.
- The primary outcome measures were death or dependency at the end of long-term follow-up (at least 3 months) and adverse events.
- The secondary outcome measure was neurological deficit improvement at the end of the treatment. The criteria of neurological deficit score were adopted based on the Modified Edinburgh-Scandinavian Stroke Scores.

Zheng GQ, Zhao ZM, Wang Y, Gu Y, Li Y, Chen XM, Fu SP, Shen JG,. *Journal of Alternative and Complementary Medicine* 17(4):293-299, 2011

# Neurological deficit improvement in hemorrhage stroke patients after SA therapy




***Conclusions:*** **No evidence is available whether SA therapy can be used to treat acute ICH according to the primary outcome measure. However, the SA therapy appears to be able to improve neurological deficit in the acute hypertensive ICH patients.**

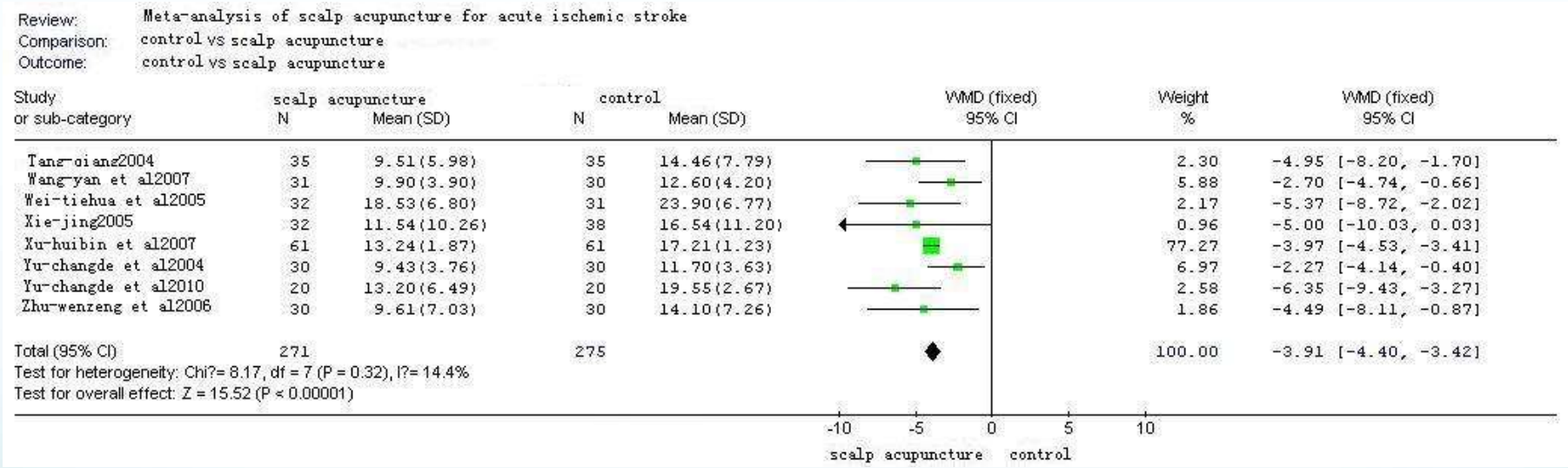
Funnel plot of publication bias analysis

Zheng GQ, Shen JG, et al. JACM 2011

# 集萃分析評價頭針治療是否對缺血性中風後神經康復有效?

# Meta-Analysis for Scalp Acupuncture on Acute Ischemic Stroke

**Group I with homogeneous clinical characteristics**




神经功能缺损评分，8篇文献具有同质性（$\chi^2$=8.17，P=0.32>0.05）,与对照组相比，头针可显著降低治疗后脑梗死患者神经功能缺损评分（z=15.52，P<0.01）。

**Neurological deficit scores were improved by the SA treatment**

# 集萃分析是否為臨床療效評價的金標準?
# Whether Meta analysis is a "golden standard' " in the evaluations of clinical trials?

A. 由於研究對象的異質性, 出現錯誤結論的機會高

As the observing population, evaluation methods and the criteria of sample selections and justifying clinical efficacies and others in original clinical trials are heterogeneous, there are high risks to get wrong conclusions.

B. 評價者的主觀偏見往往左右病例觀察的選擇

The bias from the reviewers in selections of the literature into the systematic reviews impact on the conclusion of the results.

# A meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized controlled trials.

- PATIENTS: 135,967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d).

- DATA SOURCES: PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Clinical Trials Database and review of citations of published reviews and meta-analyses.

- DATA SYNTHESIS: 9 of 11 trials testing high-dosage vitamin E (> or =400 IU/d) showed increased risk (risk difference > 0) for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10,000 persons (95% CI, 3 to 74 per 10,000 persons; P = 0.035). For low-dosage vitamin E trials, the risk difference was -16 per 10,000 persons (CI, -41 to 10 per 10,000 persons; P > 0.2). A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.

- LIMITATIONS: High-dosage (> or =400 IU/d) trials were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult.

- **CONCLUSION: High-dosage (> or =400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.**

Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. **Meta-analysis:** high-dosage **vitamin E** supplementation may increase all-cause mortality. Ann Intern Med. **2005** Jan 4;142(1):37-46.

# Comments and Suggestions:

Comments

- Ann Intern Med. 2005 Jan 4;142(1):75-6. ; Ann Intern Med. 2005 Jul 19;143(2):155; author reply 156-8.
- J Fam Pract. 2005 Mar;54(3):199-200. ; Evid Based Nurs. 2005 Jul;8(3):82.
- ACP J Club. 2005 Jul-Aug;143(1):1. ; Ann Intern Med. 2005 Jul 19;143(2):143-5. Ann Intern Med. 2005 Jul 19;143(2):150-1; author reply 156-8.
- Ann Intern Med. 2005 Jul 19;143(2):151; author reply 156-8. ; Ann Intern Med. 2005 Jul 19;143(2):151-2; author reply 156-8.
- Ann Intern Med. 2005 Jul 19;143(2):152; author reply 156-8. ; Ann Intern Med. 2005 Jul 19;143(2):152-3; author reply 156-8.
- Ann Intern Med. 2005 Jul 19;143(2):153; author reply 156-8. ; Ann Intern Med. 2005 Jul 19;143(2):153-4; author reply 156-8.
- Ann Intern Med. 2005 Jul 19;143(2):154; author reply 156-8. ; Ann Intern Med. 2005 Jul 19;143(2):155; author reply 156-8.
- Ann Intern Med. 2005 Jul 19;143(2):155-6; author reply 156-8.

Summary for patients in: Ann Intern Med. 2005 Jan 4;142(1):I40.

**Following meta-analysis:**


Hayden KM, Welsh-Bohmer KA, Wengreen HJ, Zandi PP, Lyketsos CG, Breitner JC; Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med*. 2007 Feb;120(2):180-4.

Wright ME, Lawson KA, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr*. 2006 Nov;84(5):1200-7.

# 目前集萃分析評價中醫藥臨床研究存在的主要問題
# Major shortcoming in meta analysis on TCM clinical trials

- **臨床研究設計質量問題**

  Poor qualities in the designed “RCT” clinical trials

- **臨床研究的選擇存在偏見**

  Publication bias exists in both clinical trials themselves and meta-analysis on these clinical trials.

# 提高中醫藥臨床研究質量和集萃分析可靠性的建議

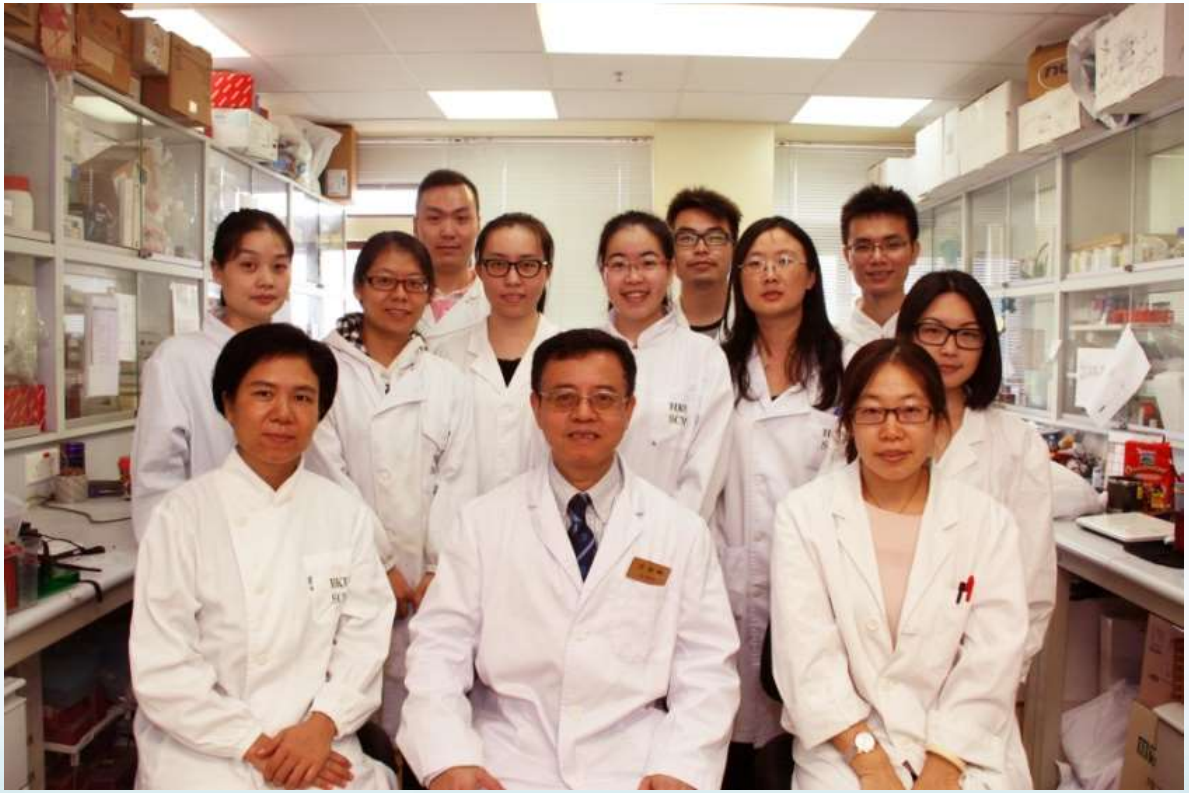
- 嚴謹的臨床實驗是獲得正確結論的前提
- **Well designed "RCT" Trials are essential for evaluations of Chinese herbal medicine and acupuncture treatment.**
- 中醫藥的研究應當遵循中醫藥理論的基礎
- **Clinical trials should be conducted with the grounds of TCM theory and practices. The RCT studies on a TCM therapeutic approach without the instruction of TCM theory may include the patients with particular TCM clinical types who should not use the formula or acupoints although those patients are diagnosed as stroke. Thus, the systemic errors will bring artifacts into the studies**
- 應當高度重視研究對象的同質性的問題
- **The evaluations on the effects of "so called" herbal medicine, acupuncture or moxibustion with meta-analysis are not scientific and conclusive if without considering the particular acupoints and herbs or formula involved. With the diverse therapies and heterogeneity of research topics in a single meta-analysis, the studies can be view as the studies on the effects of western medicine instead of a particular therapy. How conclusive results can be obtained?**

# 中醫诊断治療研究學術發展的方向

- 基於當代臨床疾病變化的新趨勢探討中醫藥诊断治療的新規律
- 基於臨床流行病學的方法結合探討中醫理論的共同規律
- 標準化和規範化是中醫藥發展的必然趨勢
- 結合現代科學的理論和實踐是中醫藥走向世界走向未來的重要途徑

# *Acknowledgements*

My Team Member



# The 8th Pong Ding Yuen International Symposium on Traditional Chinese Medicine cum The 2nd International Chinese Symposium on Free Radical Research & The 6th Symposium for Three Districts of Cross-straits on Free Radical Research

# 第八屆龐鼎元國際中醫藥研討會暨第二屆世界華人自由基生物學與自由基醫學學術大會及第六屆海峽兩岸三地自由基生物學與自由基醫學研討會

**Theme** 主題:

## Free Radical, Chinese Medicine and Translational Medicine

## 自由基、中醫藥與轉化醫學

會議時間：2014年11月14-16日(星期五至日)

會議地點：香港薄扶林沙宣道21號香港大學李嘉誠醫學院
蒙民偉樓地下鐘江海會議中心演講廳

預計參加人數：300-400人

對象：相關領域的學者、專業人士及學生

語言: 英語/普通話

**www.scm.hku.hk/pdy2014**