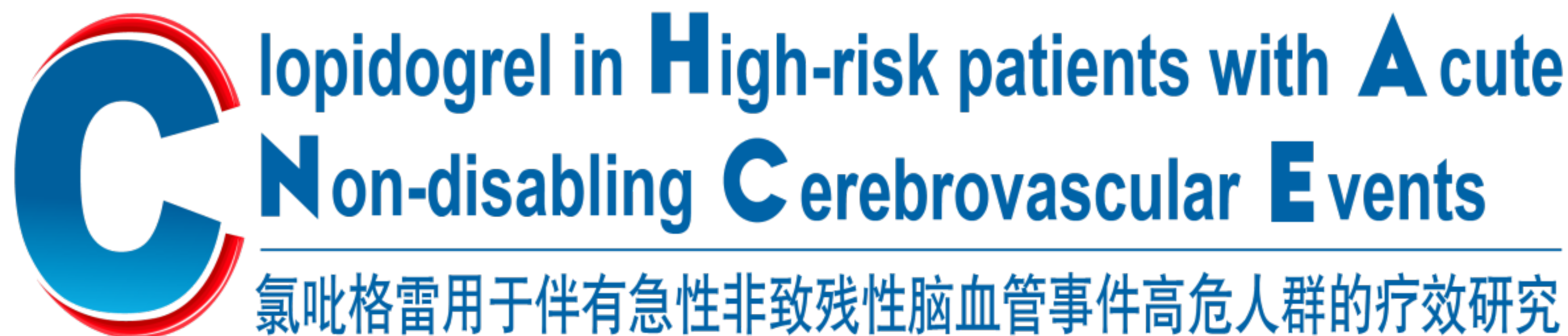

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Disclosures

CHANCE

- **Conflict of interest disclosures:**
    - No Disclosures
- **Funding**
    - The CHANCE trial is funded by the Minister of Science and Technology of the People's Republic of China. The grant no. is 2008ZX09312-008.
- **Identifier NCT00979589** （www.clinicaltrials.gov）

Minor ischemic stroke are common

	TIA	Minor Stroke	Major Stroke
Hospital-based Cohort CNSR n=11384 2007-2008 China	9%	29%	62%
Hospital-based Cohort ASTRAL n=2210 2003-2008 Lausanne, Switzerland	26%	30%	44%

Stroke. 2010;41:2491-2498

Short-term Prognosis After TIA /Minor Stroke

Risk of stroke (%)

25
20
15
10
5
0

Minor stroke
TIA

Log rank P=0.8

0 30 60 90

Days

Several cohort studies have shown that early (3 months) risk of stroke following index TIA and minor ischemic stroke is much higher than previously thought, even in patients treated with aspirin, the current standard of care.

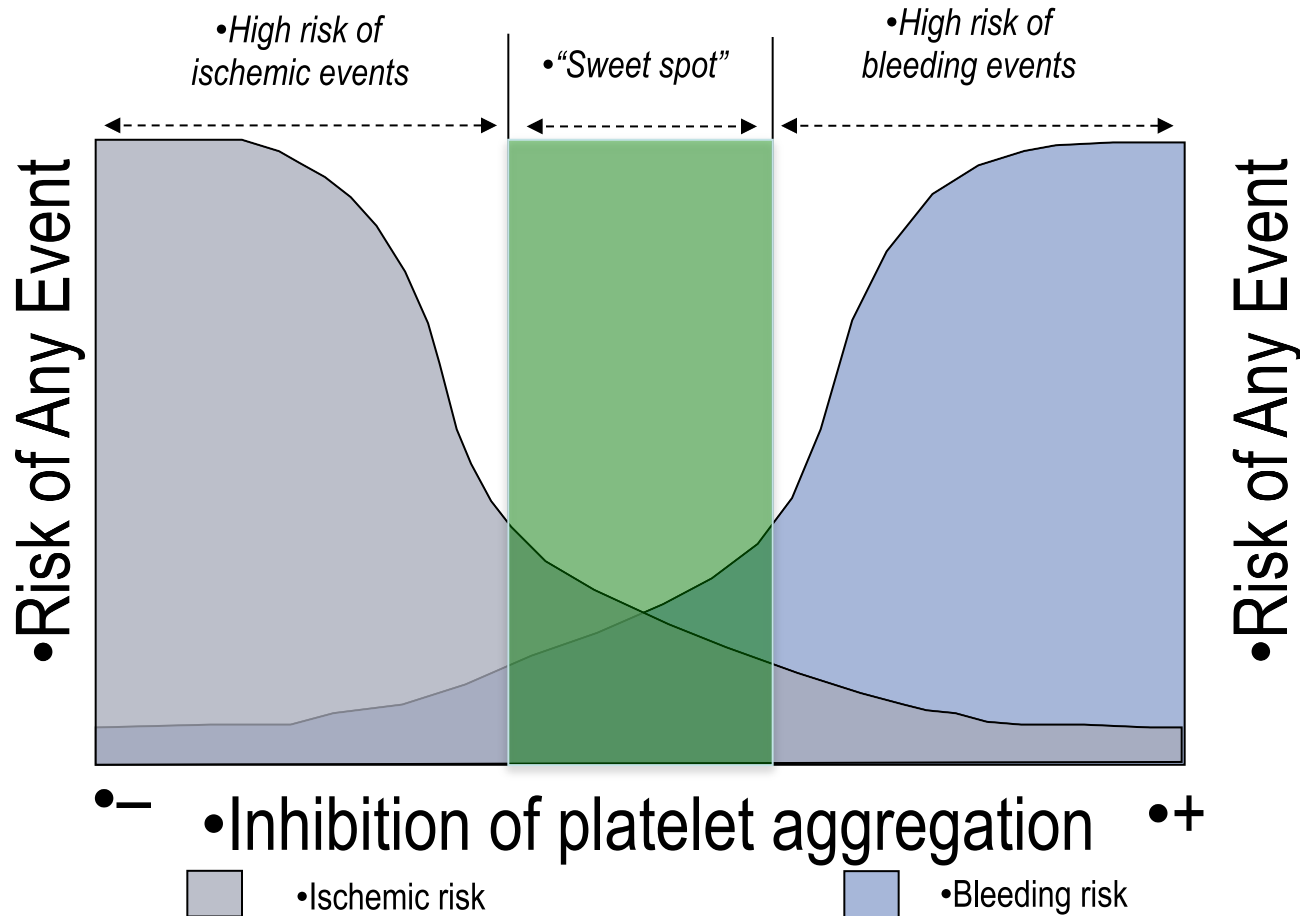
•**Coull A J et al. BMJ 2004;328:326**

clopidogrel+ASA

It might be benefit with early intervention

High risk of Minor stroke/TIA, low risk for bleeding

PLATELET INHIBITION RELATED TO THE RISK OF ISCHEMIC AND BLEEDING EVENTS



•Ferreiro JL et al. *Thromb Haemost.* 2010;103:1-8.

PERFECT SWEET SPOT?

- MATCH and SPS3 trials did not study the acute high-risk period after stroke, they included some with strokes of moderate severity, and they included few if any patients with TIA
- Focus on early intervention in high-risk for thrombosis, low-risk for bleeding
- Acute TIA and Minor stroke population = sweet spot?

CHANCE Rationale

CHANCE

- Treat TIA and minor stroke as acute condition
  - Begin treatment rapidly (within 24 hours)
- Choose an aggressive therapy that is likely to be effective regardless of underlying cause
  - Clopidogrel, on background of aspirin
- Select an outcome that reflects major potential benefits
  - Stroke
  - Composite of stroke, MI, and vascular death
  - 90 day follow-up

Primary objective of the CHANCE trial

- To assess the efficacy of a 3-month regimen of clopidogrel-aspirin (300 mg load followed by 75 mg/day) vs. aspirin alone on reducing the 3-month risk of new stroke (ischemic or hemorrhagic) when initiated within 24 hours of symptom onset in patients with high-risk TIA or minor stroke.

Study Design and Flow

Group 1

Clopidogrel 300mg	Clopidogrel 75mg from Day 2 to 3 months	
ASA 75–300mg*	ASA 75mg from D2 to D21	Placebo ASA from D21 to 3 months

Day 1

Day 2

D21

M3

Patients with TIA or minor stroke

R

(Within 24 hours of symptoms onset)

Day 21 Visit (21 ±2 Days)

3 Month Visit or final visit (90 ±7 Days)

D21

M3

Selection (inclusion + exclusion criteria verified) + informed consent signed

Day 1

Day 2

Group 2

ASA 75–300mg*	ASA 75mg from Day 2 to 3 months
Placebo clopidogrel 300mg	Placebo clopidogrel 75mg from Day 2 to 3 months

•Am Heart J. 2010 ;160:380-386

Key Inclusion Criteria

- Age ≥ 40 years;
- Either:
  - Non-disabling ischemic stroke (NIHSS≤3), or
  - TIA with moderate-to-high risk of stroke recurrence ($ABCD^2$ score ≥ 4).
- Study drug can be given within 24 h of symptom onset.
- Informed consent signed.

Efficacy Evaluation

CHANCE

Primary Efficacy Endpoint

- 3-month new stroke (ischemic or hemorrhagic)

Secondary Efficacy Endpoint

- 3 months new clinical vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death)

Safety Evaluation

CHANCE

1. Severe and moderate bleeding event (GUSTO definition)
   1. fatal bleeding and symptomatic intracranial hemorrhage
   2. incidence of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months
2. Intracranial hemorrhage
3. total mortality
4. Adverse events/severe adverse events (AE/ SAE)

Trial profile

41561 stroke or TIA patients screened

→ 35391 excluded

5170 randomised

Aspirin and placebo	Clopidogrel and aspirin
2586 received aspirin and placebo analysis by intention to treat	2584 received clopidogrel and aspirin analysis by intention to treat
8 enrolled inappropriately 3 age<40y 3 TIA and ABCD2<4 2 >24h from onset	10 enrolled inappropriately 2 age<40y 4 TIA and ABCD2<4 1 mRS>2 before onset 3 >24h from onset
146 discontinued 16 lost to follow up 21 had surgery 58 had adverse events 51 owning to other cause 7 died of cause other than stroke	165 discontinued 20 lost to follow up 19 had surgery 63 had adverse events 63 owning to other cause 7 died of cause other than stroke
2425 Included in per-protocol analysis	2402 Included in per-protocol analysis

N Engl J Med. 2013 Jul 4;369(1):11-9

Baseline Characters

Characteristics	Aspirin (N=2586)	Clopidogrel-Aspirin (N=2584)
Age - y	62 (54-71)	63 (55-72)
Female sex ,n (%)	898 (34.7)	852 (33.0)
Qualifying event ,n (%)		
TIA ,n (%)	728 (28.2)	717 (27.8)
Minor stroke ,n (%)	1858 (71.8)	1867 (72.2)
Qualifying TIA baseline $ABCD^2$score	4 (4-5)	4 (4-5)
Time to randomization – hr	13	13
Time to randomization ,n (%)		
< 12h ,n (%)	1280 (49.5)	1293 (50.0)
>= 12h ,n (%)	1306 (50.5)	1291 (50.0)

for any variable

Primary outcome: stroke

CHANCE

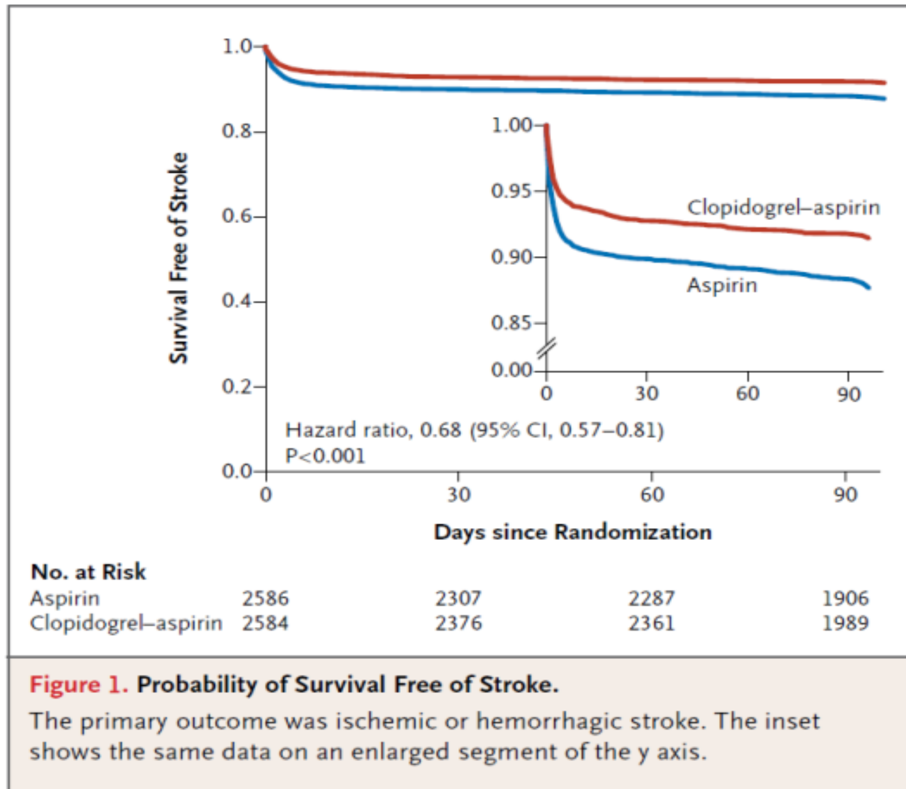


Figure 1. Probability of Survival Free of Stroke.
The primary outcome was ischemic or hemorrhagic stroke. The inset shows the same data on an enlarged segment of the y axis.

Subgroup	No. of Patients	Aspirin	Clopidogrel–Aspirin	Hazard Ratio (95% CI)	P Value
		no. of events (%)			
Overall	5170	303 (11.7)	212 (8.2)	0.68 (0.57–0.81)	
Age					0.84
<65 yr	3029	164 (10.7)	110 (7.4)	0.67 (0.52–0.85)	
≥65 yr	2141	139 (13.2)	102 (9.4)	0.70 (0.54–0.90)	
Sex					0.37
Male	3420	190 (11.3)	130 (7.5)	0.65 (0.52–0.81)	
Female	1750	113 (12.6)	82 (9.6)	0.79 (0.59–1.05)	
Index event					0.91
Minor stroke	3725	223 (12.0)	159 (8.5)	0.69 (0.56–0.84)	
TIA	1445	80 (11.0)	53 (7.4)	0.65 (0.45–0.93)	
$ABCD^2$ score					0.47
4	747	33 (8.8)	27 (7.3)	0.69 (0.40–1.19)	
>4	698	47 (13.4)	26 (7.5)	0.60 (0.36–1.00)	
Previous stroke					0.49
Yes	1033	54 (10.4)	42 (8.1)	0.80 (0.52–1.21)	
No	4137	249 (12.0)	170 (8.2)	0.66 (0.55–0.81)	
Previous TIA					0.34
Yes	174	13 (16.2)	7 (7.4)	0.47 (0.15–1.44)	
No	4996	290 (11.6)	205 (8.2)	0.69 (0.58–0.83)	
History of hypertension					0.69
Yes	3399	220 (13.1)	158 (9.2)	0.70 (0.57–0.85)	
No	1771	83 (9.2)	54 (6.2)	0.63 (0.44–0.89)	
Previous diabetes					0.69
Yes	1093	74 (13.6)	56 (10.2)	0.75 (0.52–1.07)	
No	4077	229 (11.2)	156 (7.7)	0.67 (0.54–0.82)	
Systolic pressure					0.25
≥140 mm Hg	3790	250 (13.2)	165 (8.7)	0.65 (0.53–0.79)	
<140 mm Hg	1376	53 (7.6)	46 (6.7)	0.84 (0.56–1.26)	
Time to randomization					0.36
<12 hr	2573	162 (12.7)	125 (9.7)	0.73 (0.58–0.93)	
≥12 hr	2597	141 (10.8)	87 (6.7)	0.62 (0.47–0.81)	
Aspirin taken within 24 hr					0.91
Yes	597	38 (12.3)	26 (9.0)	0.66 (0.47–1.11)	
No	4573	265 (11.6)	186 (8.1)	0.68 (0.56–0.82)	

0.1 0.3 0.5 1.0 2.0

Clopidogrel–Aspirin Better / Aspirin Better

Figure 2. Hazard Ratio for the Primary Outcome in Prespecified Subgroups.

Combination of clopidogrel and aspirin for patients with TIA or minor stroke：

✓ **reduce the risk of stroke in the first 90 day (HR 0.68, 95%CI 0.57-0.81)**

✓ **not increase the risk of hemorrhage**

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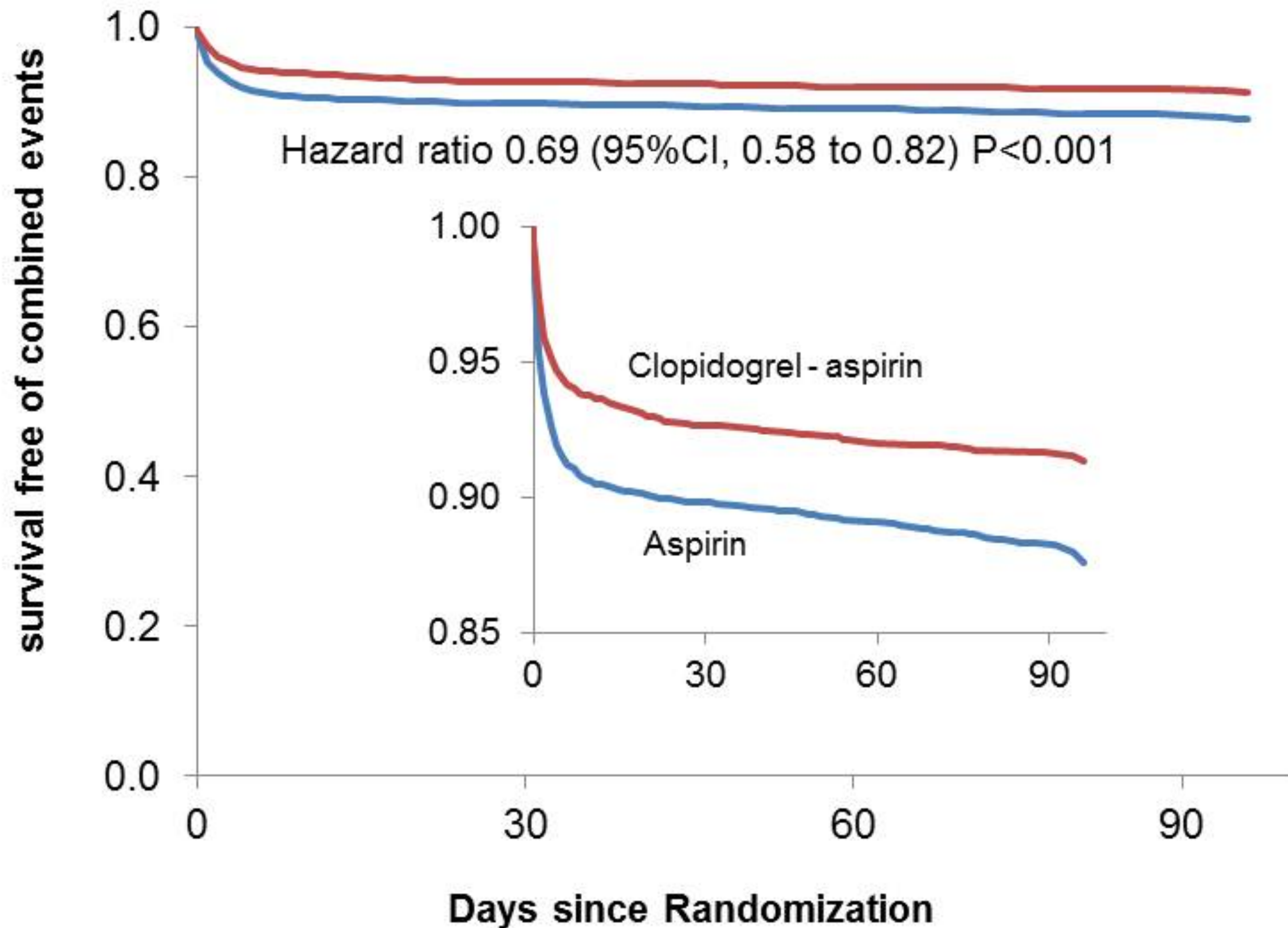
Secondary combined outcome

CHANCE



•The secondary combined outcome was stroke, myocardial infarction, or death from cardiovascular causes

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Early Dual versus Mono Antiplatelet Therapy for Acute Non-Cardioembolic Ischemic Stroke or Transient Ischemic Attack: An Updated Systematic Review and Meta-Analysis

Ka Sing Lawrence Wong, Yilong Wang, Xinyi Leng, Chen Mao, Jinling Tang, Philip M. W. Bath, Hugh S. Markus, Philip B. Gorelick, Liping Liu, Wenhua Lin and Yongjun Wang

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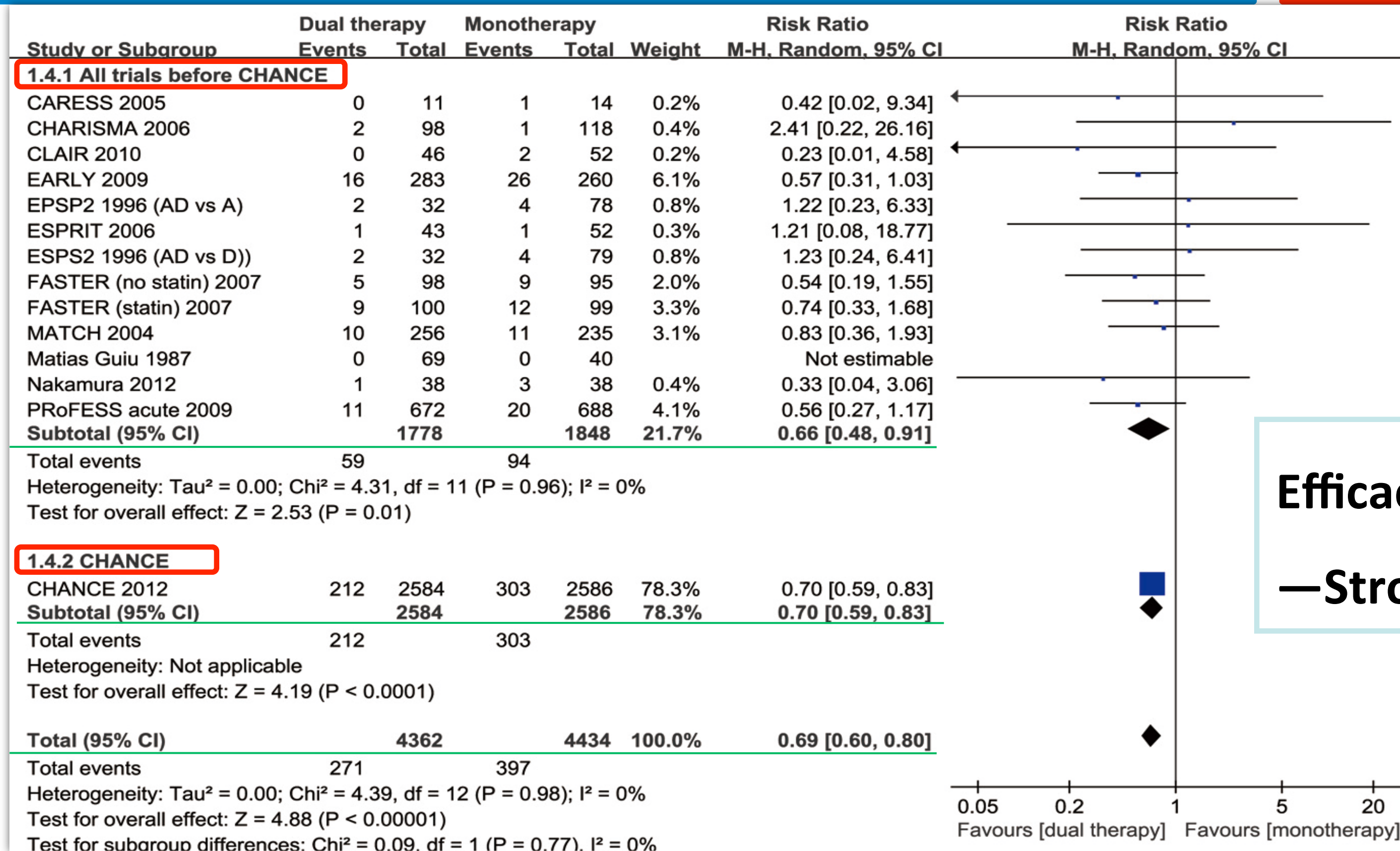
Updated systematic review

- 14 RCTs (9,012 patients) included

Dual therapy	Mono therapy	No. of RCTs	No. of patients
Aspirin + Clopidogrel	Aspirin	5	5,901
Aspirin + Clopidogrel	Clopidogrel	1	491
Aspirin + Dipyridamole	Aspirin	5	964
Aspirin + Dipyridamole	Dipyridamole	2	220
Aspirin + Dipyridamole	Clopidogrel	1	1,360
Aspirin + Cilostazol	Aspirin	1	76

Circulation. published online September 12, 2013

CHANCE and all trials before CHANCE



Study or Subgroup	Dual therapy Events	Dual therapy Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 All trials before CHANCE						
CARESS 2005	0	11	1	14	0.2%	0.42 [0.02, 9.34]
CHARISMA 2006	2	98	1	118	0.4%	2.41 [0.22, 26.16]
CLAIR 2010	0	46	2	52	0.2%	0.23 [0.01, 4.58]
EARLY 2009	16	283	26	260	6.1%	0.57 [0.31, 1.03]
EPSP2 1996 (AD vs A)	2	32	4	78	0.8%	1.22 [0.23, 6.33]
ESPRIT 2006	1	43	1	52	0.3%	1.21 [0.08, 18.77]
ESPS2 1996 (AD vs D))	2	32	4	79	0.8%	1.23 [0.24, 6.41]
FASTER (no statin) 2007	5	98	9	95	2.0%	0.54 [0.19, 1.55]
FASTER (statin) 2007	9	100	12	99	3.3%	0.74 [0.33, 1.68]
MATCH 2004	10	256	11	235	3.1%	0.83 [0.36, 1.93]
Matias Guiu 1987	0	69	0	40		Not estimable
Nakamura 2012	1	38	3	38	0.4%	0.33 [0.04, 3.06]
PRoFESS acute 2009	11	672	20	688	4.1%	0.56 [0.27, 1.17]
Subtotal (95% CI)		**1778**		**1848**	**21.7%**	**0.66 [0.48, 0.91]**
Total events	59		94			
Heterogeneity: Tau² = 0.00; Chi² = 4.31, df = 11 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.53 (P = 0.01)						
1.4.2 CHANCE						
CHANCE 2012	212	2584	303	2586	78.3%	0.70 [0.59, 0.83]
Subtotal (95% CI)		**2584**		**2586**	**78.3%**	**0.70 [0.59, 0.83]**
Total events	212		303			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.19 (P < 0.0001)						
Total (95% CI)		**4362**		**4434**	**100.0%**	**0.69 [0.60, 0.80]**
Total events	271		397			
Heterogeneity: Tau² = 0.00; Chi² = 4.39, df = 12 (P = 0.98); I² = 0%						
Test for overall effect: Z = 4.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						

Efficacy outcome

—Stroke recurrence

Figure. The overall effect with the addition of CHANCE was consistent with the estimate from all previous trials, but the 95% CI became narrower (0.60-0.80 versus 0.48-0.91).

CHANCE and all trials before CHANCE

Study or Subgroup	Dual therapy Events	Dual therapy Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 All trials before CHANCE						
CARESS 2005	0	11	0	14		Not estimable
CHARISMA 2006	1	98	0	118	4.2%	3.61 [0.15, 87.54]
CLAIR 2010	0	46	0	52		Not estimable
EARLY 2009	1	283	1	260	5.6%	0.92 [0.06, 14.61]
ESPRIT 2006	0	43	0	52		Not estimable
FASTER (no statin) 2007	1	98	0	95	4.2%	2.91 [0.12, 70.54]
FASTER (statin) 2007	2	100	0	99	4.7%	4.95 [0.24, 101.82]
MATCH 2004	4	256	1	235	8.9%	3.67 [0.41, 32.62]
Nakamura 2012	0	38	1	38	4.2%	0.33 [0.01, 7.93]
PRoFESS acute 2009	6	672	4	688	26.8%	1.54 [0.44, 5.42]
Subtotal (95% CI)		**1645**		**1651**	**58.5%**	**1.83 [0.78, 4.28]**
Total events	15		7			
Heterogeneity: Tau² = 0.00; Chi² = 2.49, df = 6 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
1.6.2 CHANCE						
CHANCE 2012	7	2584	8	2586	41.5%	0.88 [0.32, 2.41]
Subtotal (95% CI)		**2584**		**2586**	**41.5%**	**0.88 [0.32, 2.41]**
Total events	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**4229**		**4237**	**100.0%**	**1.35 [0.70, 2.59]**
Total events	22		15			
Heterogeneity: Tau² = 0.00; Chi² = 3.69, df = 7 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 1.18, df = 1 (P = 0.28), I² = 15.5%						

Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours [dual therapy] Favours [monotherapy]

Safety outcome

—Major bleeding

Figure. Effects of dual versus mono antiplatelet therapy on risk of major bleeding: all trials before CHANCE, CHANCE, and the updated overall effects.

Sub-group analysis

- Effect of Clopidogrel plus Aspirin versus Aspirin Alone in patients with Intracranial arterial stenosis

·45 sites, 1500 patients screening

525 patients with Intracranial arterial stenosis

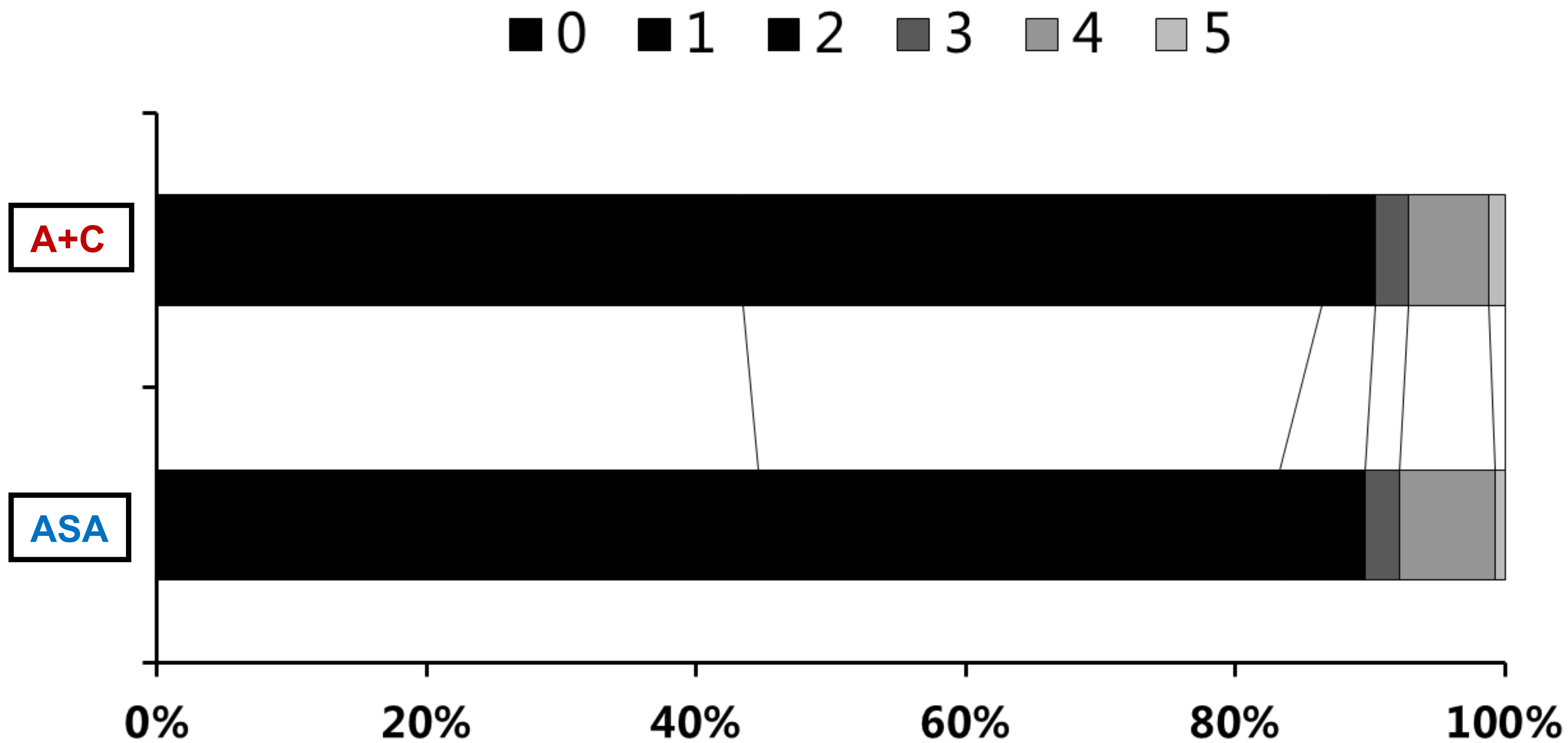
Stenosis ≥50% : ICA/VA/MCA/BAS

Baseline

	All	Placebo plus Aspirin（n=255）	Clopidogrel plus Aspirin（n=270）	P_value
Age, mean±SD, year	65.23(57.53-72.65)	65.57(57.98-72.7)	64.97(57.39-72.65)	0.7642
Female, n (%)	335 (63.81%)	169 (62.59%)	166 (65.10%)	0.5505
BMI at admission, median (IQR), kg/m2	24.57±3.35	24.55±3.36	24.59±3.35	0.8766
Previous stroke or TIA, n (%)	116 (22.1%)	56 (20.74%)	60 (23.53%)	0.4415
Previous TIA, n (%)	23 (4.38%)	15 (5.56%)	8 (3.14%)	0.176
myocardial infarction,n (%)	13 (2.48%)	5 (1.85%)	8 (3.14%)	0.3435
Angina,n (%)	14 (2.67%)	6 (2.22%)	8 (3.14%)	0.5154
heart failure, n (%)	11 (2.1%)	7 (2.59%)	4 (1.57%)	0.4129
Atrial fibrillation / atrial flutter,n (%)	10 (1.9%)	6 (2.22%)	4 (1.57%)	0.584
Dyslipidemia, n (%)	64 (12.19%)	36 (13.33%)	28 (10.98%)	0.4102
Current or previous smoking, n (%)	215 (40.95%)	101 (37.41%)	114 (44.71%)	0.0892
Heavy alcohol, n (%)	160 (30.48%)	77 (28.52%)	83 (32.55%)	0.316
Hypertension, n (%)	354 (67.43%)	173 (64.07%)	181 (70.98%)	0.0915
Diabetes mellitus, n (%)	133 (25.33%)	63 (23.33%)	70 (27.45%)	0.2783
SBP- mm Hg	150(140-168)	150.5(140-170)	150(140-165)	0.295
DBP- mm Hg	88(80-96)	88.5(80-99)	86(80-95)	0.1936
HR- n/min	76(70-80)	76(70-80)	76(70-80)	0.5878
mRS score before symptom onset				
0	433 (82.48%)	229 (84.81%)	204 (80.00%)	0.1004
1	76 (14.48%)	31 (11.48%)	45 (17.65%)	
2	16 (3.05%)	10 (3.70%)	6 (2.35%)	
minor stroke,n (%)	398 (75.81%)	205 (75.93%)	193 (75.69%)	0.9489
TIA,n (%)	127 (24.19%)	65 (24.07%)	62 (24.31%)	

Stroke recurrence

90d mRS



Conclusions

- TIA and minor ischemic stroke are a treatable emergency
  - Clopidogrel with a 300 mg load plus aspirin reduces subsequent stroke risk compared to aspirin alone.
  - Clopidogrel-aspirin is safe in this setting with no increase in bleeding.
  - Can be coding for ICADs.

- Even more aggressive interventions after acute TIA and minor stroke may be indicated but require clinical trials.

Thank you for your attention