Acute therapy and long term prevention: should it be different for small vessel disease?

Geoffrey A Donnan

The Florey Institute of Neuroscience & Mental Health
Melbourne, Australia

Email: geoffrey.donnan@florey.edu.au

WCN teaching course 2015

THE FLOREY

Disclosures

I have received honoraria from:

- Boehringer Ingelheim
- Sanofi Aventis
- MSD
- Pfizer
- Bayer

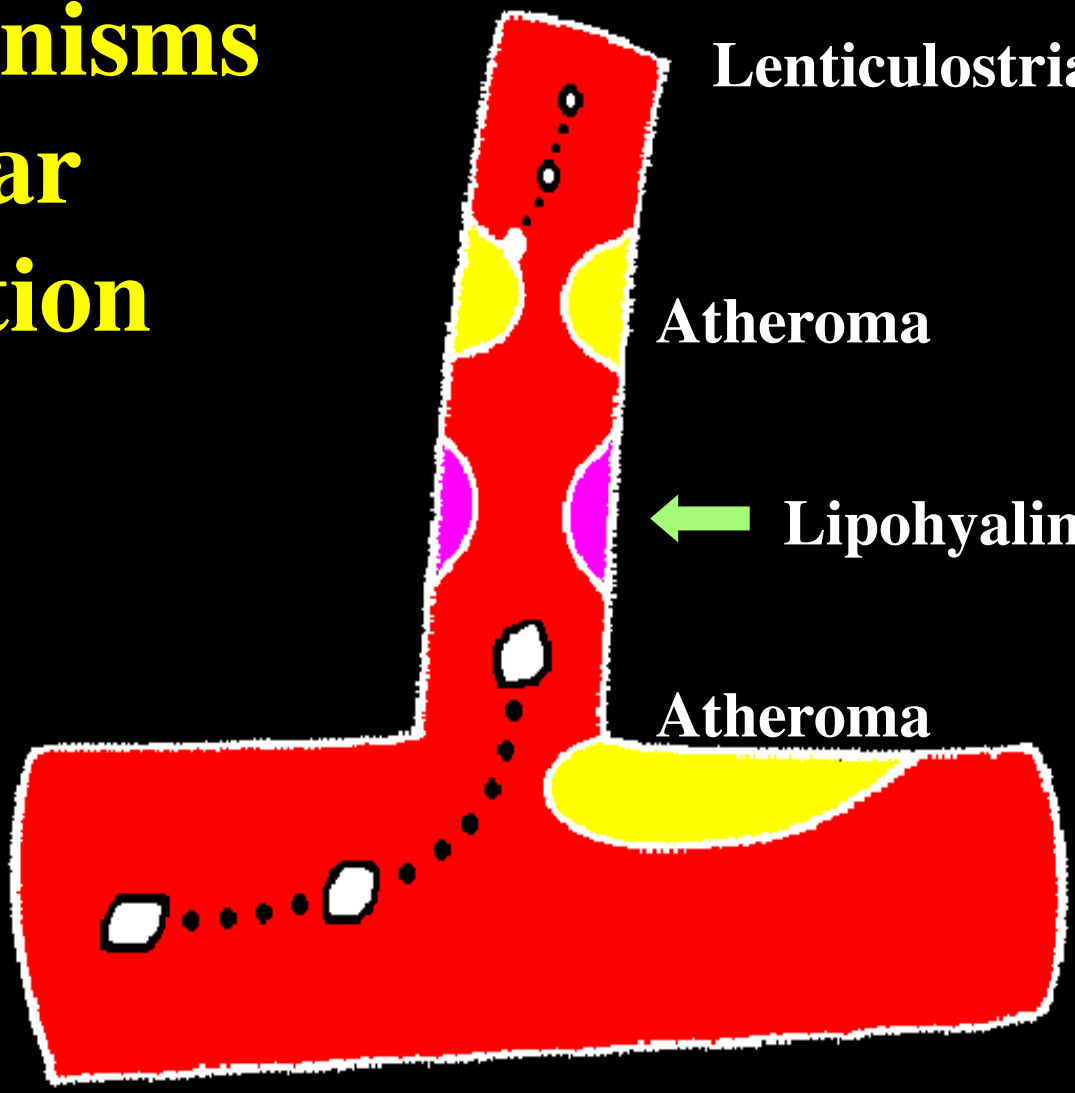
Learning objectives

1. Gain an understanding of the pathogenesis of small vessel disease
2. The risks/benefits for lacunar stroke with
    - acute interventions
    - early secondary prevention
    - late secondary prevention

Therapy for small vessel disease?

1. Background
2. Acute therapies
3. Early secondary prevention
4. Long term secondary prevention

Mechanisms Lacunar Infarction



National Stroke Research Institute

What has been the concern about therapy and small vessel disease?

- Lipohyalinosis as lacunar mechanism
- Small vessels block or burst
- Concern about bleeding with therapy
- Aspirin in 1978
- Then thrombolytics
- Other antiplatelet agents

NINDS Trial 1995

Table 5. Outcome at Three Months According to the Classification of the Stroke Subtype at Base Line.

STROKE SUBTYPE*	t-PA		PLACEBO	
	NO. OF PATIENTS	% WITH FAVORABLE OUTCOME†	NO. OF PATIENTS	% WITH FAVORABLE OUTCOME†
Small-vessel occlusive	51		30	
Barthel index		75		50
Modified Rankin scale		63		40
Glasgow outcome scale		63		43
NIHSS		47		33
Large-vessel occlusive	117		135	
Barthel index		49		36
Modified Rankin scale		40		22
Glasgow outcome scale		45		28
NIHSS		33		18
Cardioembolic	136		137	
Barthel index		46		37
Modified Rankin scale		38		28
Glasgow outcome scale		39		31
NIHSS		29		20

The burden of recurrent stroke

- Represent 25-30% of all strokes
- About 20% due to small vessel disease
- May reduce this by 25%

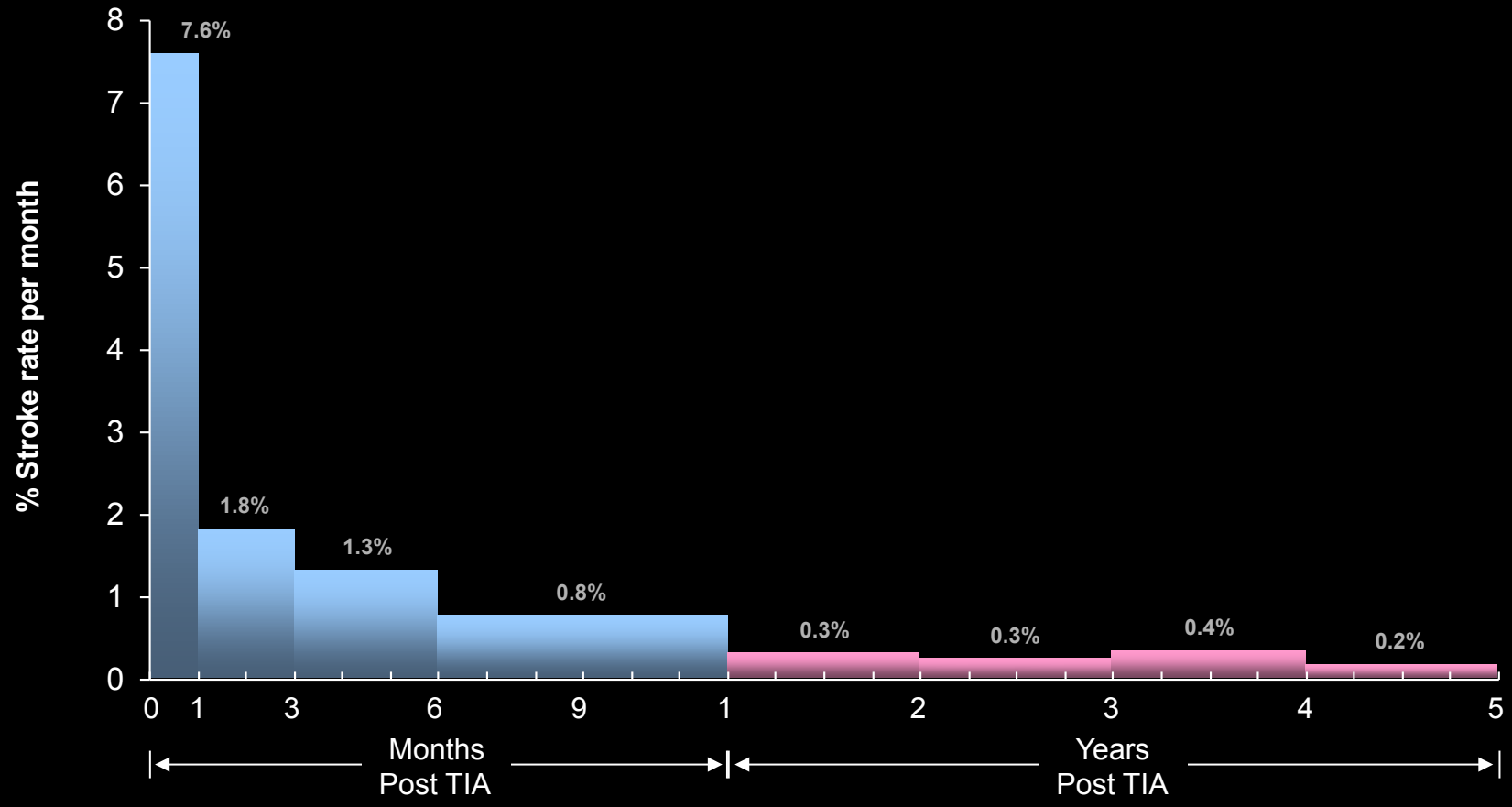
Transient Ischaemic Attacks

Stroke risk

- Early data suggested 5-7 % per year
- Whisnant emphasized early vs late risk
- Wiebers quantified risk TIA/RIND

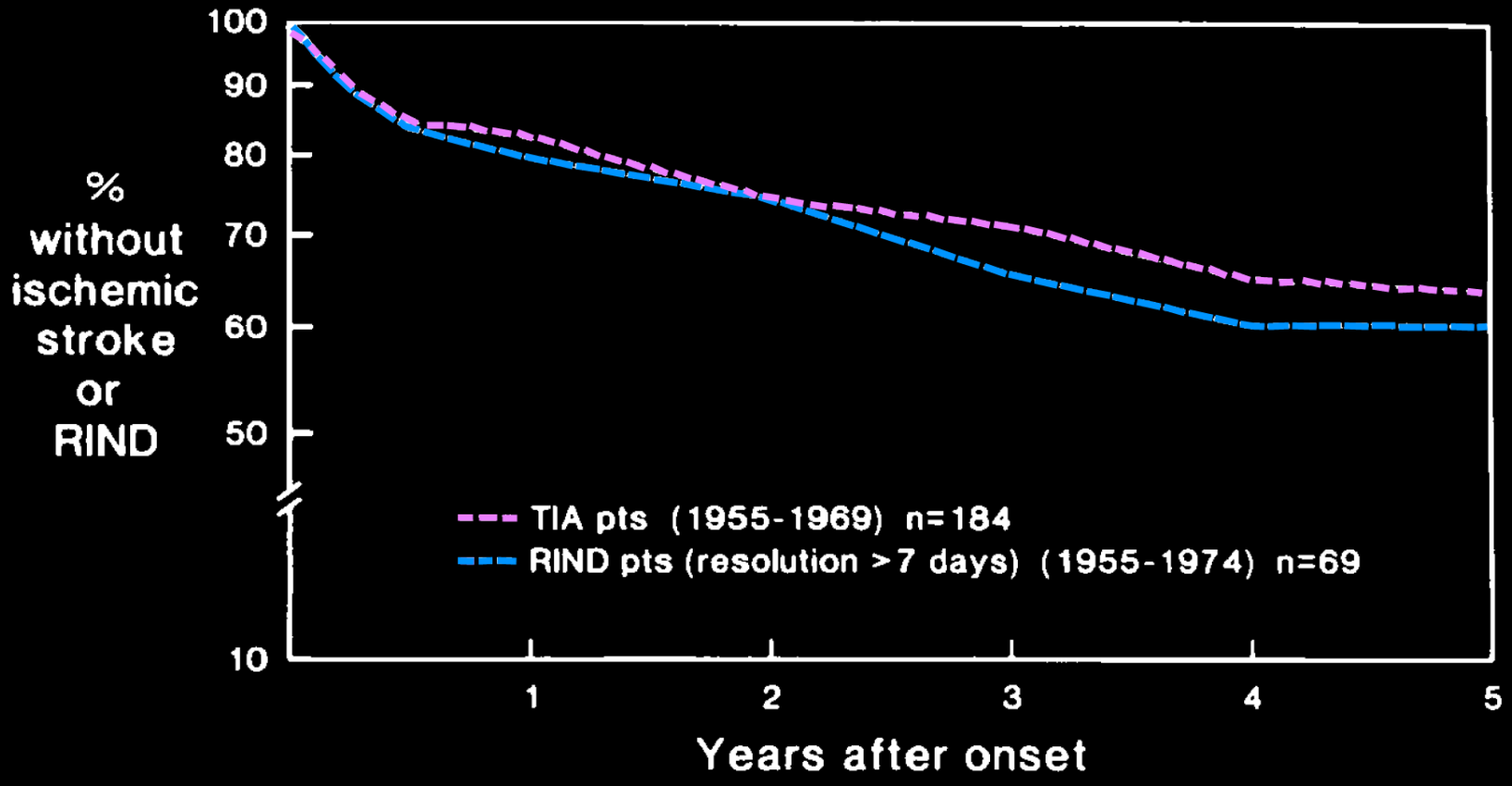
continuity

Stroke rate per month after TIA



Whisnant et al, Mayo Clin Proc 48:194-8, 1973.

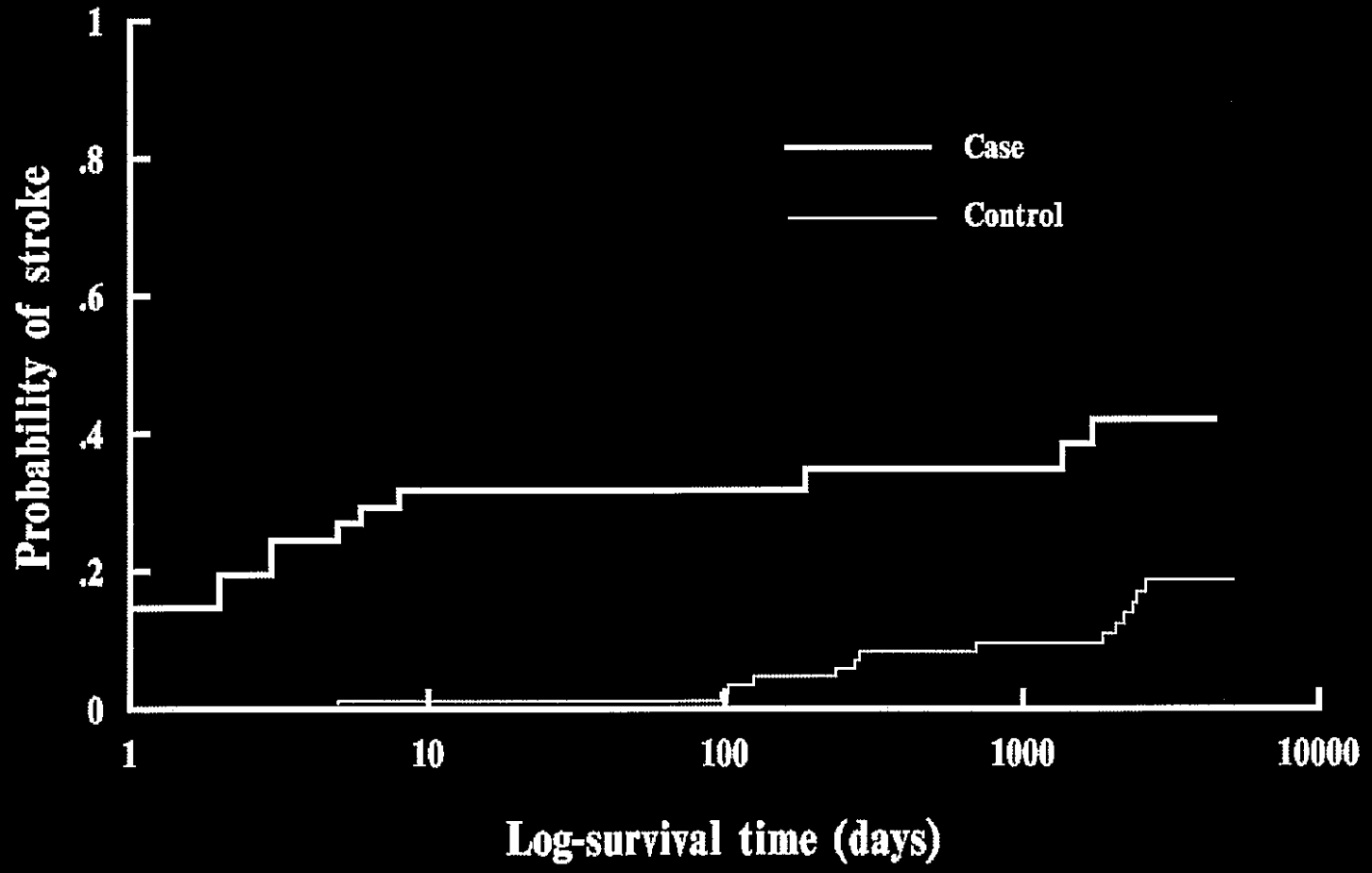
Comparison of probability of survival free of subsequent ischemic stroke or RIND among patients with initial RIND, TIA, and ischemic stroke



National Stroke Research Institute

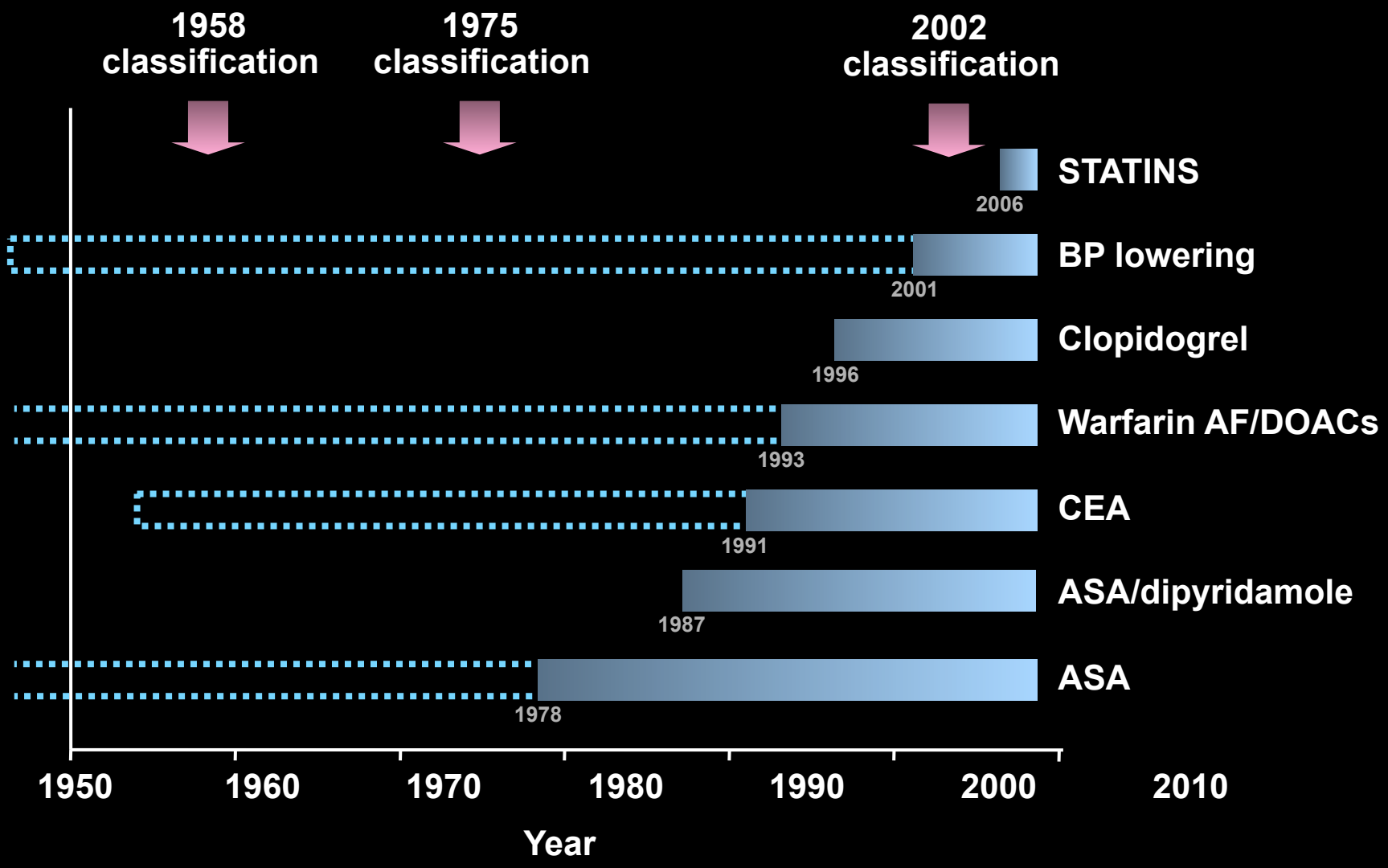
Wiebers DO, et al., Neurology 32:459-65, 1982.

The probability of stroke among 41 patients with the Capsular Warning Syndrome compared to 85 controls

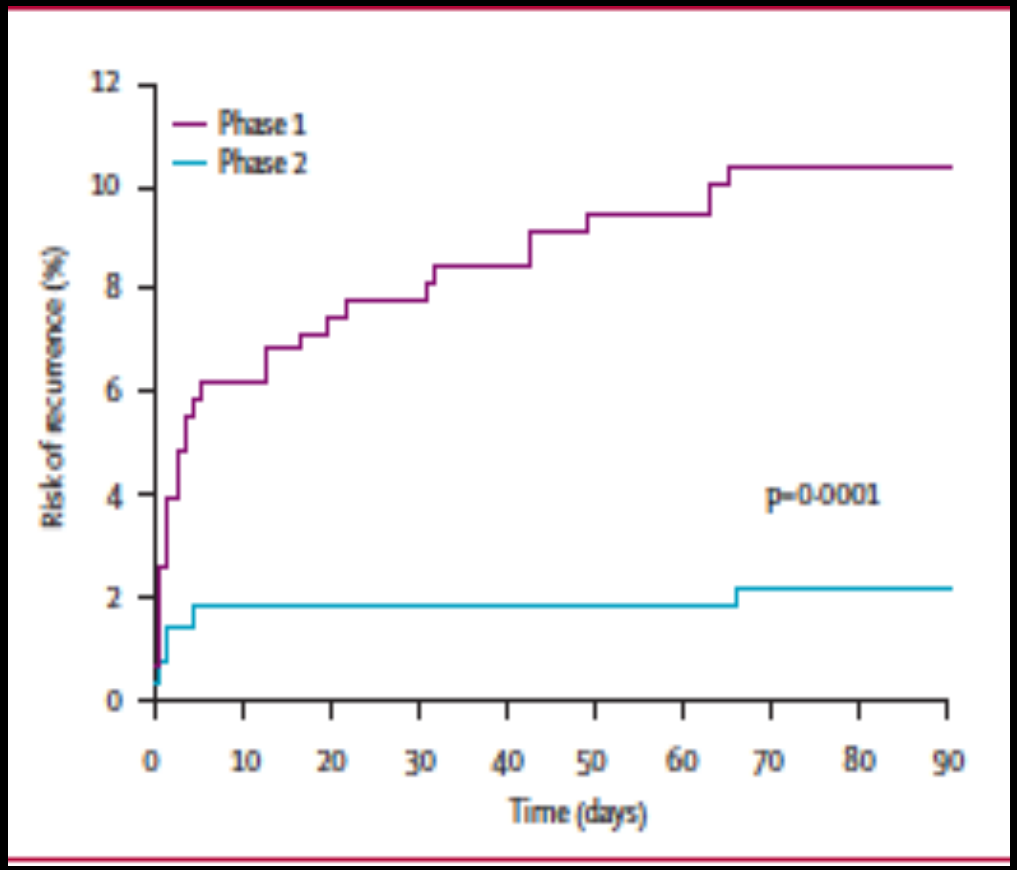


Donnan GA, et al. Cerebrovasc Dis 457, 1995.

Secondary Stroke Prevention



EXPRESS Study: pre and post aggressive TIA managem



58% relative risk reduction in stroke recurrence

Rothwell P et al, Lancet 370:1432-42,2007

FASTER: Primary outcomes

	Risk difference (95% CI)	Risk ratio (95% CI)	p
Primary efficacy outcomes			
Clopidogrel vs placebo			
At the margins	−3·8% (−9·4 to 1·9)	0·7 (0·3–1·2)	0·19
Inside the table	−4·4% (−11·7 to 3·0)	0·5 (0·2–1·5)	0·24
Simvastatin vs placebo			
At the margins	3·3% (−2·3 to 8·9)	1·5 (0·8–2·8)	0·25
Inside the table	2·6% (−6·1 to 11·4)	1·3 (0·6–2·9)	0·55

Kennedy J et al, Lancet Neurology, 6:961-9,2007

FASTER: Bleeding risk

	n (%)		Risk difference (95% CI)	p*
	No clopidogrel (n=194)	Clopidogrel (n=198)		
Intracranial haemorrhage	0	2 (1·0%)	1% (−0·4 to 2·4)	0·5
Extracranial haemorrhage				
Severe	0	1 (0·5%)	0·5% (−0·5 to 1·5)	1·0
Moderate	0	2 (1·0%)	1% (−0·4 to 2·4)	0·5
Mild	0	1 (0·5%)	0·5% (−0·5 to 1·5)	1·0
Total symptomatic	0	6 (3·0%)	3·0% (0·6 to 5·4)	0·03
Total asymptomatic	27 (13·9%)	61 (30·8%)	16·9% (8·8 to 25·0)	0·0001

*Fisher's exact test. 94 patients had 124 bleeding events. One patient had two mild events and one severe extracranial bleeding event and was classified as severe for the purposes of the analysis. The other events were all asymptomatic and if a patient had more than one asymptomatic event it was classified as a single event.

Table 7: Site and severity of bleeding outcomes

Kennedy J et al, Lancet Neurology, 6:961-9,2007

POINT PROTOCOL

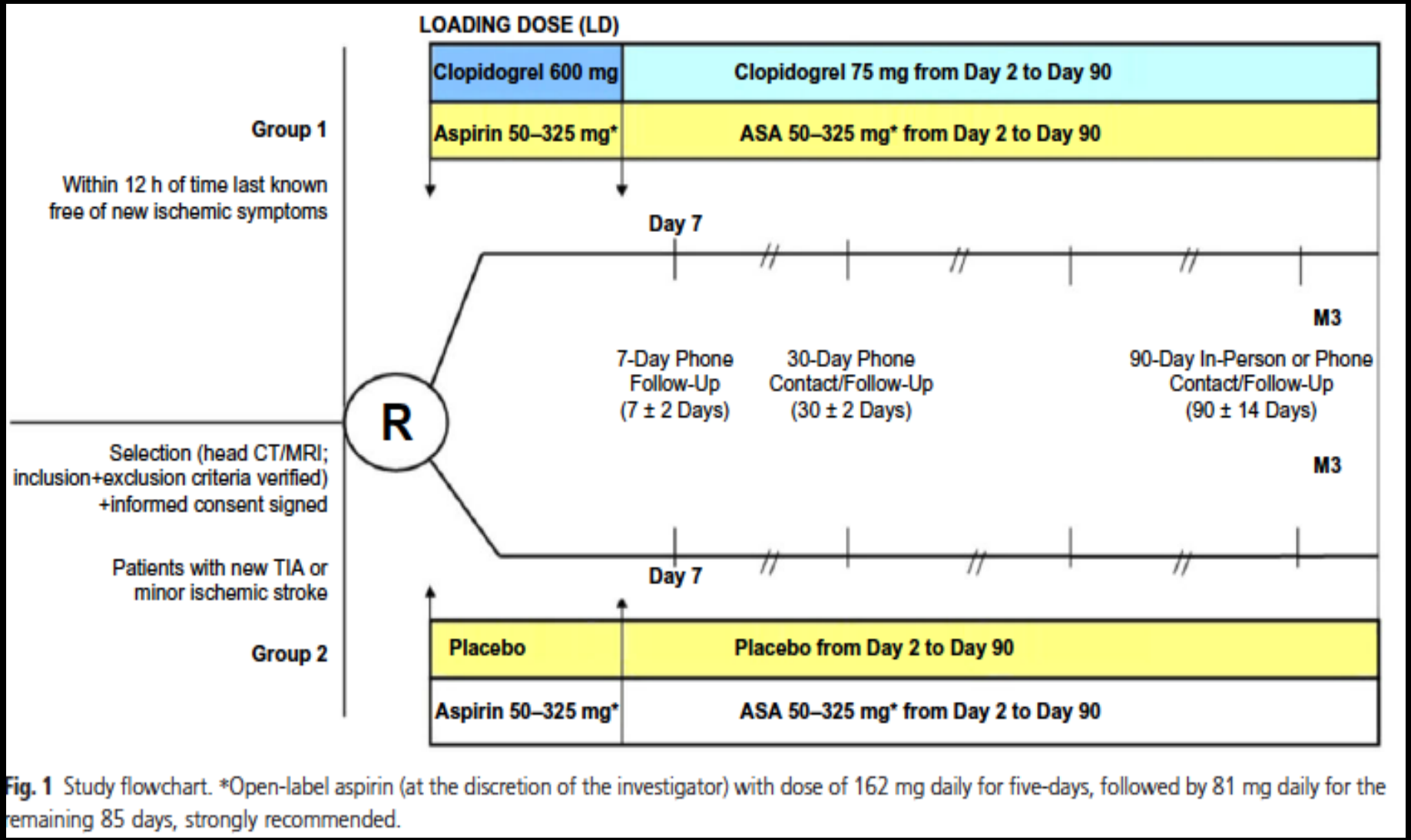
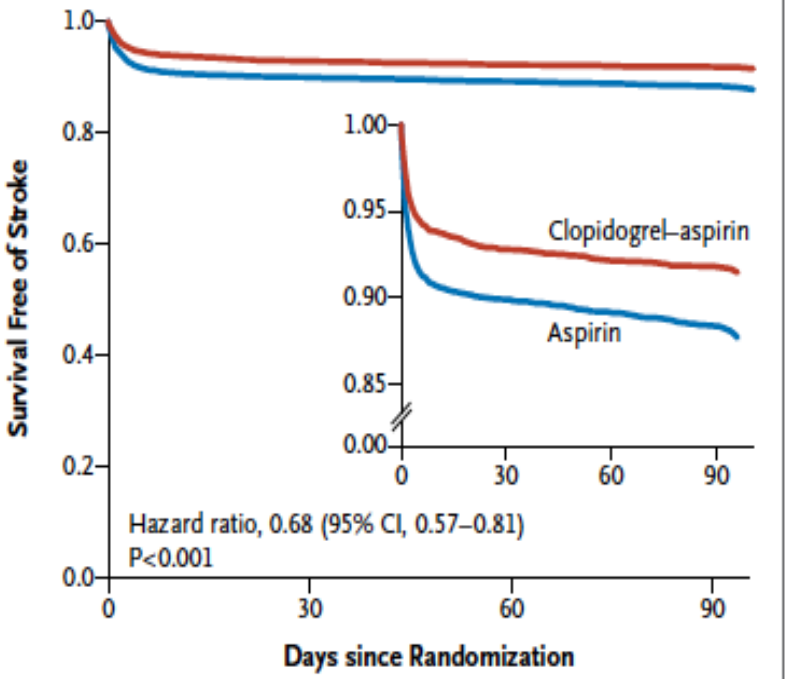


Fig. 1 Study flowchart. *Open-label aspirin (at the discretion of the investigator) with dose of 162 mg daily for five-days, followed by 81 mg daily for the remaining 85 days, strongly recommended.

International Journal of Stroke; 8:479-83,20

CHANCE



No. at Risk

Aspirin	2586	2307	2287	1906
Clopidogrel–aspirin	2584	2376	2361	1989

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.

Wang J et al, NEJM, 369:11-19,2013

CHANCE

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event *no.*	Event Rate %	Patients with Event *no.*	Event Rate %		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36

Wang J et al, NEJM, 369:11-19,2013

Long term secondary stroke prevention: Small vessel disease

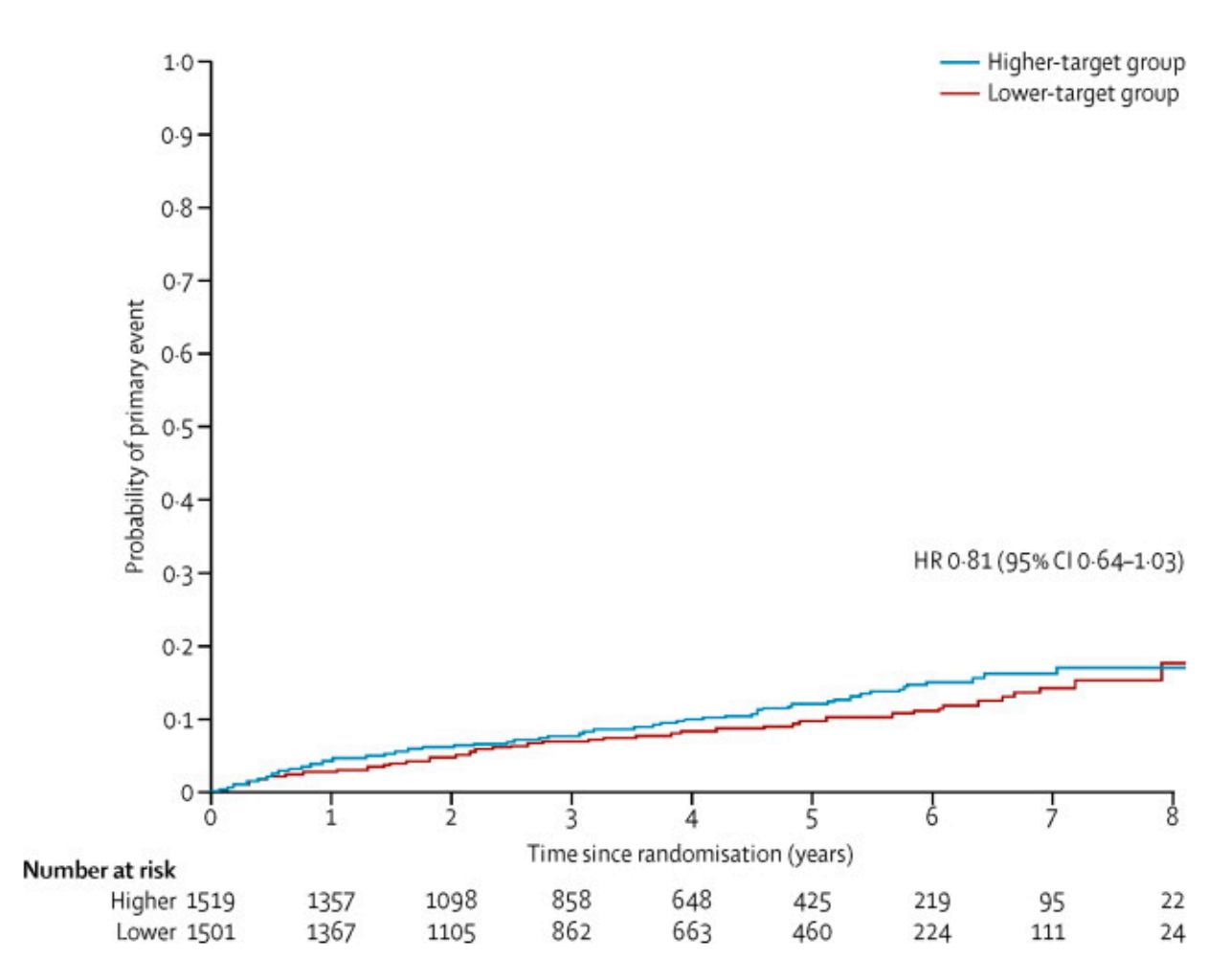
Points of contention:

Blood Pressure Lowering

Dual Antiplatelet therapy

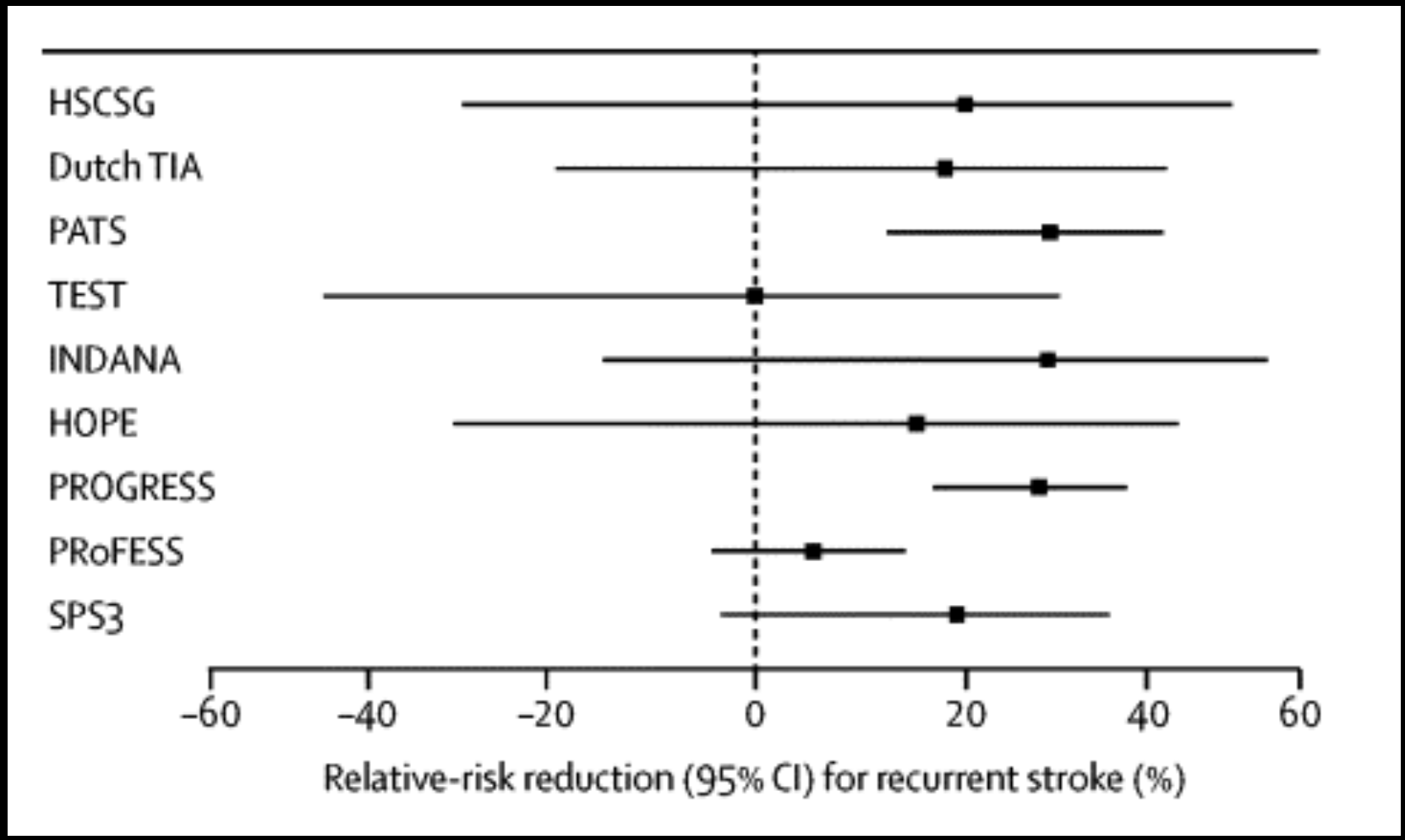
SPS 3: BLOOD PRESSURE LOWERING

Probability of patients experiencing a primary event by time after randomisation



Lancet 2013; 382: 507-15

RCTs for BP lowering: secondary stroke prevention



Lancet 2013; 382: 507-15

MATCH

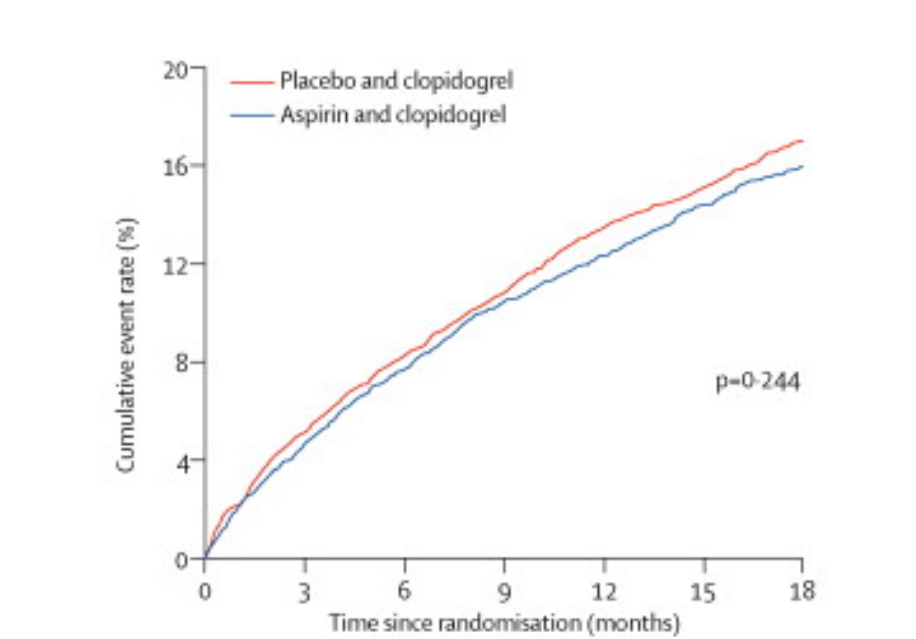
Baseline characteristics

	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)
Mean (SD) age (years)	66·5 (9·9)	66·1 (9·9)
Women	1415 (37%)	1406 (37%)
TOAST classification*		
Cardioembolism	61 (2%)	76 (3%)
Large-artery atherosclerosis	1019 (34%)	1020 (34%)
Small-vessel occlusion	1590 (53%)	1558 (52%)
Stroke of other determined cause	33 (1%)	36 (1%)
Undetermined cause	287 (10%)	304 (10%)

Lancet 2004; 364: 331-37

MATCH

Kaplan-Meier curves for cumulative rates of primary endpoint events

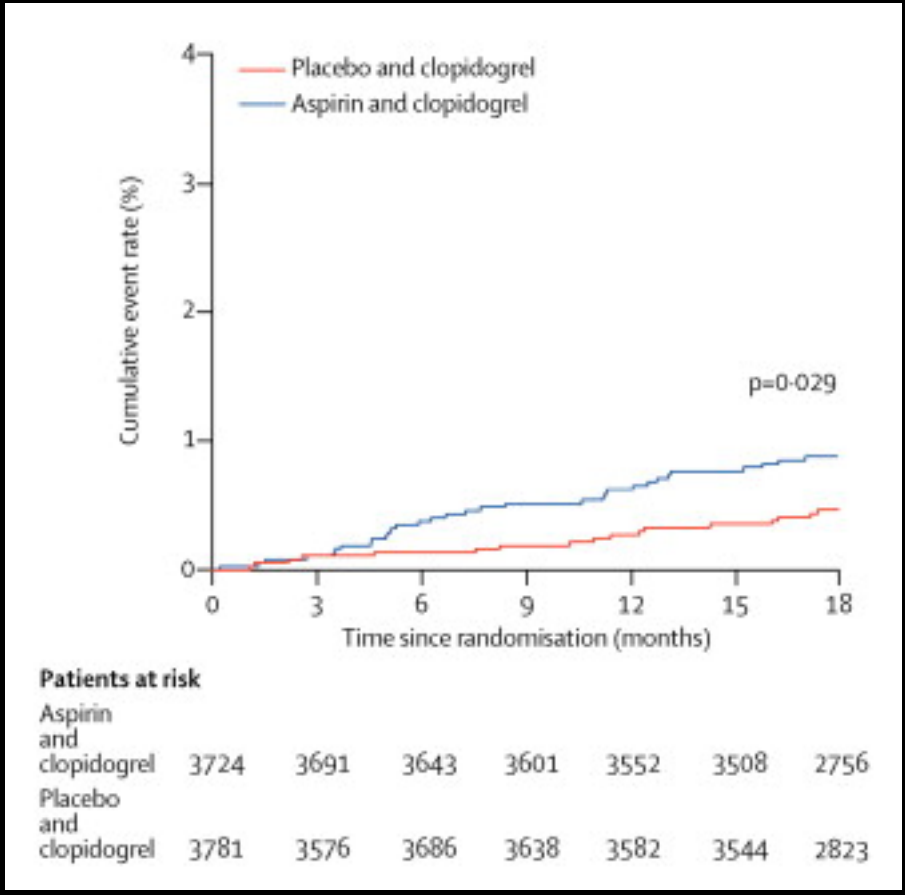


Patients at risk

Aspirin and clopidogrel	3797	3576	3440	3321	3229	3130	2441
Placebo and clopidogrel	3802	3576	3439	3326	3200	3119	2446

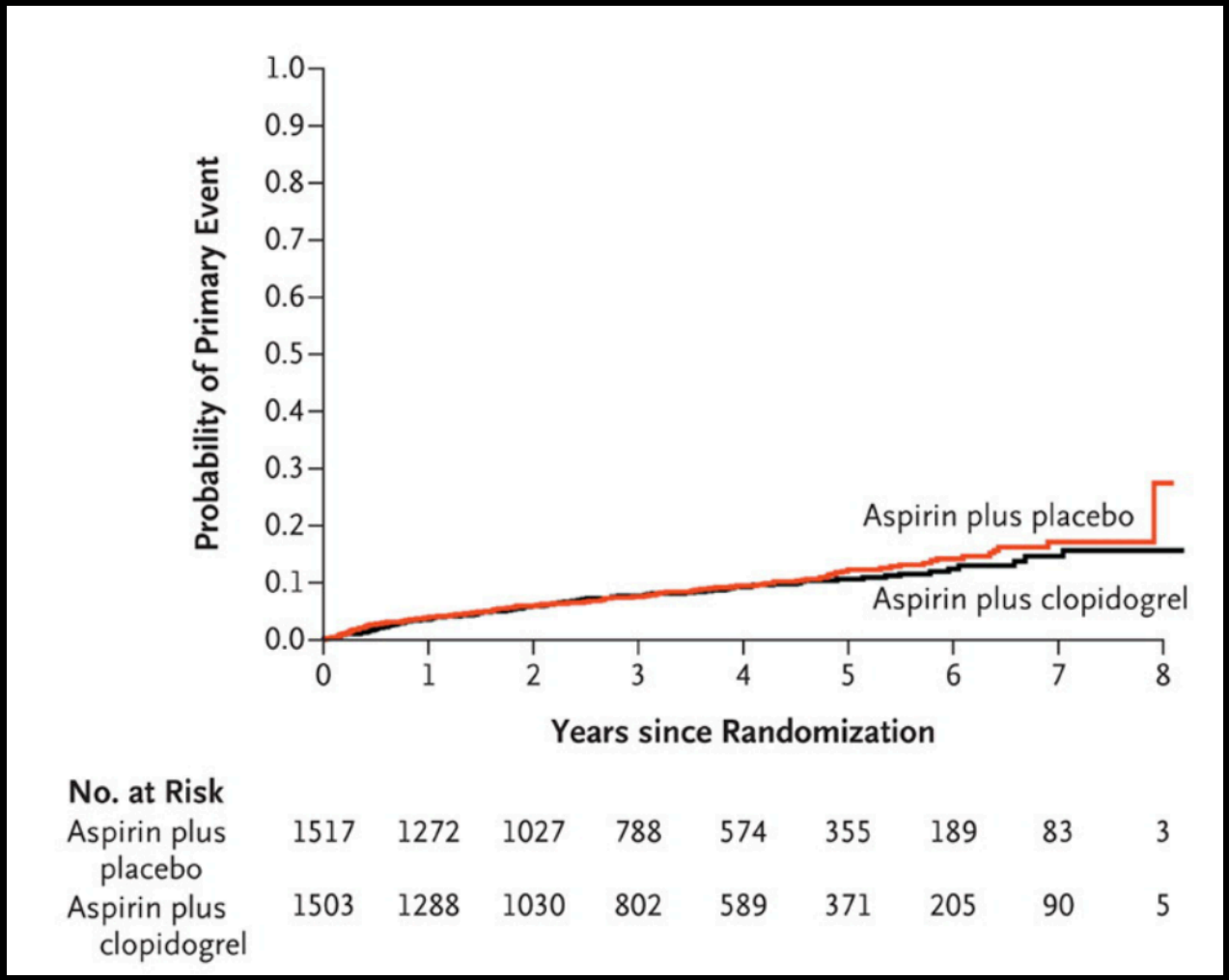
Lancet 2004; 364: 331-37

MATCH Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage



Lancet 2004; 364: 331-37

SPS3 Probability of the Primary Outcome



No. at Risk									
Aspirin plus placebo	1517	1272	1027	788	574	355	189	83	3
Aspirin plus clopidogrel	1503	1288	1030	802	589	371	205	90	5

N Engl J Med 2012;367:817-825

SPS3

Table 3. Safety Outcomes.*

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	*rate (%/yr)*	*no.*	*rate (%/yr)*		
All major hemorrhages	56	1.1	105	2.1	1.97 (1.41–2.71)	<0.001
Intracranial hemorrhages†	15*	0.28	22	0.42	1.52 (0.79–2.93)	0.21
Intracerebral	8	0.15	15	0.28	1.92 (0.82–4.54)	0.14
Subdural or epidural	6	0.11	7	0.13	1.23 (0.41–3.64)	0.72
Other	4	0.07	2	0.04	0.53 (0.10–2.89)	0.46
Extracranial bleeding	42	0.79	87	1.7	2.15 (1.49–3.11)	<0.001
Gastrointestinal‡	28	0.52	58	1.1	2.14 (1.36–3.36)	<0.001
Fatal hemorrhages	4	0.07	9	0.17	2.29 (0.70–7.42)	0.17
Intracranial	4	0.07	7	0.13	1.78 (0.52–6.07)	0.36
Extracranial	0	0	2	0.04	—	—

The SPS3 Investigators. N Engl J Med 2012;367:817-825

Summary: Key messages

1. Lacunar stroke pathophysiologicaly distinct
2. Lipohyalinosis is a less common cause
3. Thrombolysis: benefits/risk similar to other strokes
4. Early secondary prevention, benefits/risk poorly studied but also similar

Summary: key messages

5. For late secondary prevention strategies, most beneficial with little risk, although poorly studied with the exception of blood pressure lowering

6. For dual antiplatelet therapy of aspirin plus clopidogrel, risk of bleeding outweighs benefit

References

1. C M Fisher, Acta Neuropath, Berlin 12:1-45, 196
2. C M Fisher et al., Neurology 21:900-905, 1971
3. GA Donnan et al. Lacunar and other subcortical infarctions. Oxford University Press, Editions 1 and 2.
4. NINDS trial, NEJM. 1995,
5. Whisnant et al, Mayo Clin Proc 48:194-8, 1973
6. Wiebers DO, et al., Neurology 32:459-65, 1982.
7. Donnan GA, et al. Cerebrovasc Dis 457, 1995.
8. Rothwell P et al, Lancet 370:1432-42,2007
9. Kennedy J et al, Lancet Neurology, 6:961-9,2007
10. Johnston C et al International Journal of Stroke; 8:479-83,2013
11. Wang J et al, NEJM, 369:11-19,2013
12. SPS3 Lancet 2013; 382: 507-15
13. The SPS3 Investigators. N Engl J Med 2012;367:817-825
14 .MATCH Lancet 2004; 364: 331-37