Recent Treatment Strategies in Stroke

Hans-Christoph Diener

Essen

Conflict of Interest Statement

The speaker or his institution received financial support from the following bodies or companies:

- German Research Council
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- German Ministry of Science and Technology
- European Union
- Bertelsmann Foundation
- Heinz-Nixdorf Foundation

- Allergan
- Brainsgate
- Covidien
- Corimmun

- Yamanouchi
- Novo Nordisk
- Novartis
- Neurobiological Technologies
- MindFrame
- Fresenius
- CoAxia
- Abbott
- Novartis
- Schering
- Janssen-Cilag
- SanofiAventis
- MSD
- Astra-Zeneca
- GlaxoSmithKline
- Pfizer

- Paion
- Solvay
- Schering Plough
- Medtronic
- Lundbeck
- Syngis
- Tacrelis
- Boehringer Ingelheim
- D-Pharm
- BMS
- Bayer
- Wyeth
- Knoll
- Servier
- EV3

General Management in Acute Stroke

Benefit of Stroke Units

Stroke Unit: 4936 Patients versus conventional ward: 6636 Pat..

274 ^Hospitals, 2 year follow-up

Rankin > 2: <u>53% vs. 62%</u>; OR 0,81 (0,72-0,91)

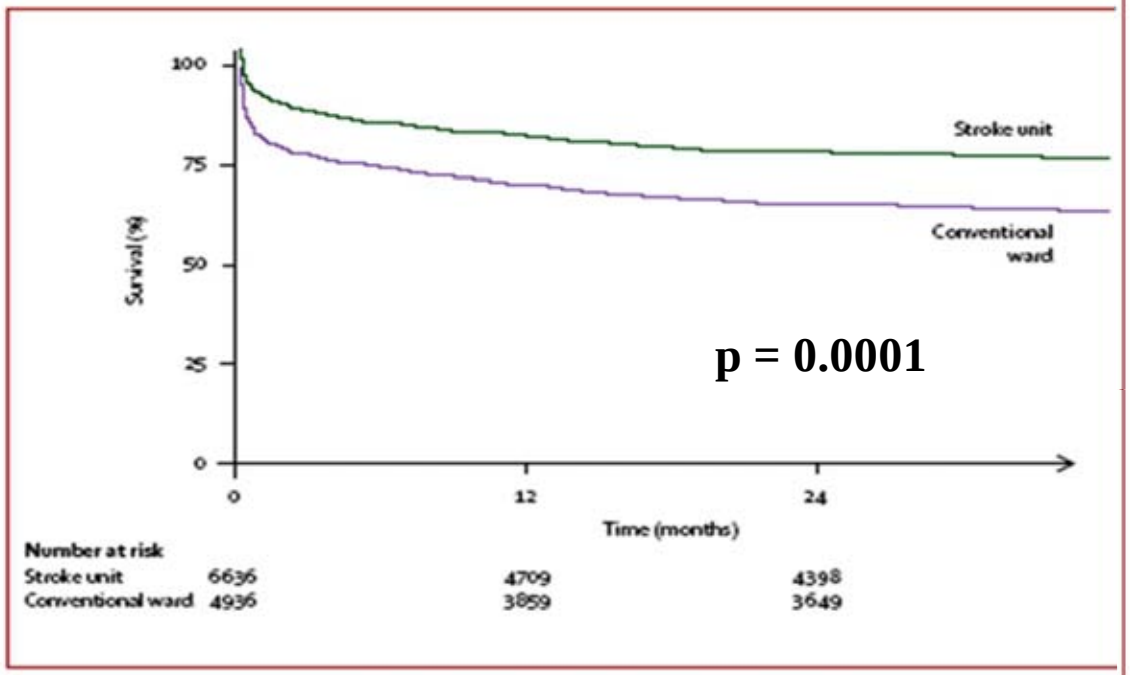


Figure 2: Survival curves for patients admitted to stroke unit or conventional ward

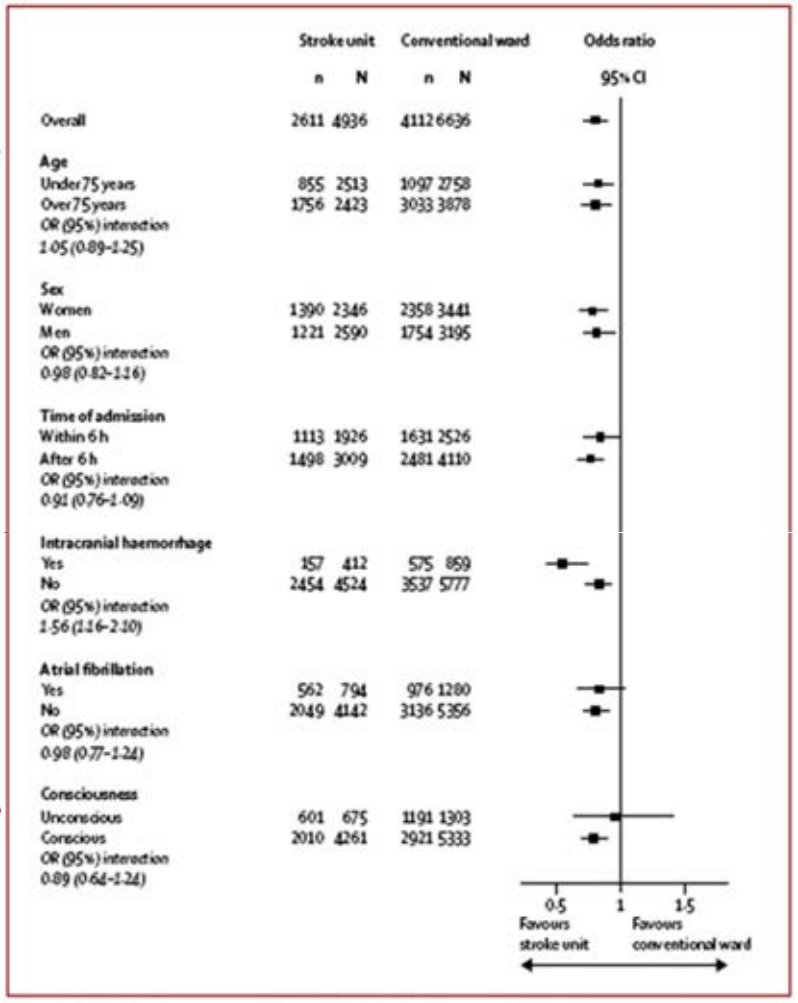
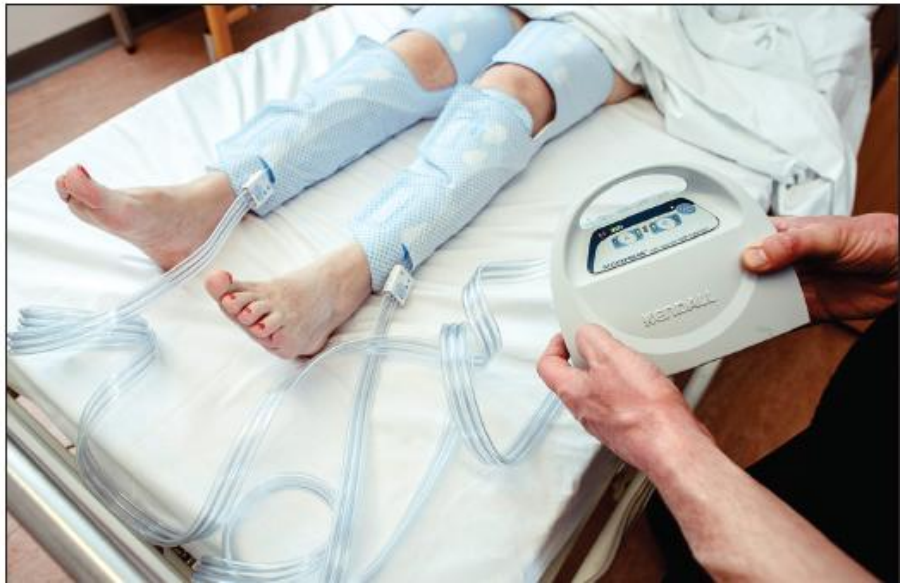


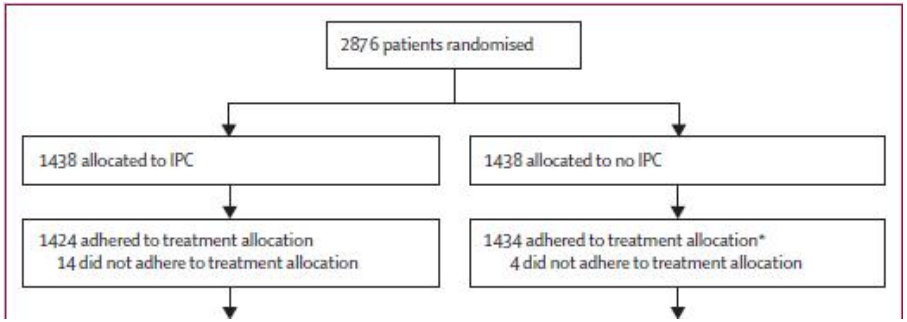
Figure 3: Effect of stroke unit care on death or disability by patient subgroups
Data adjusted for patient characteristics and clustered at the hospital level.

Lancet 2007;369:299-305

Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial

*CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration**





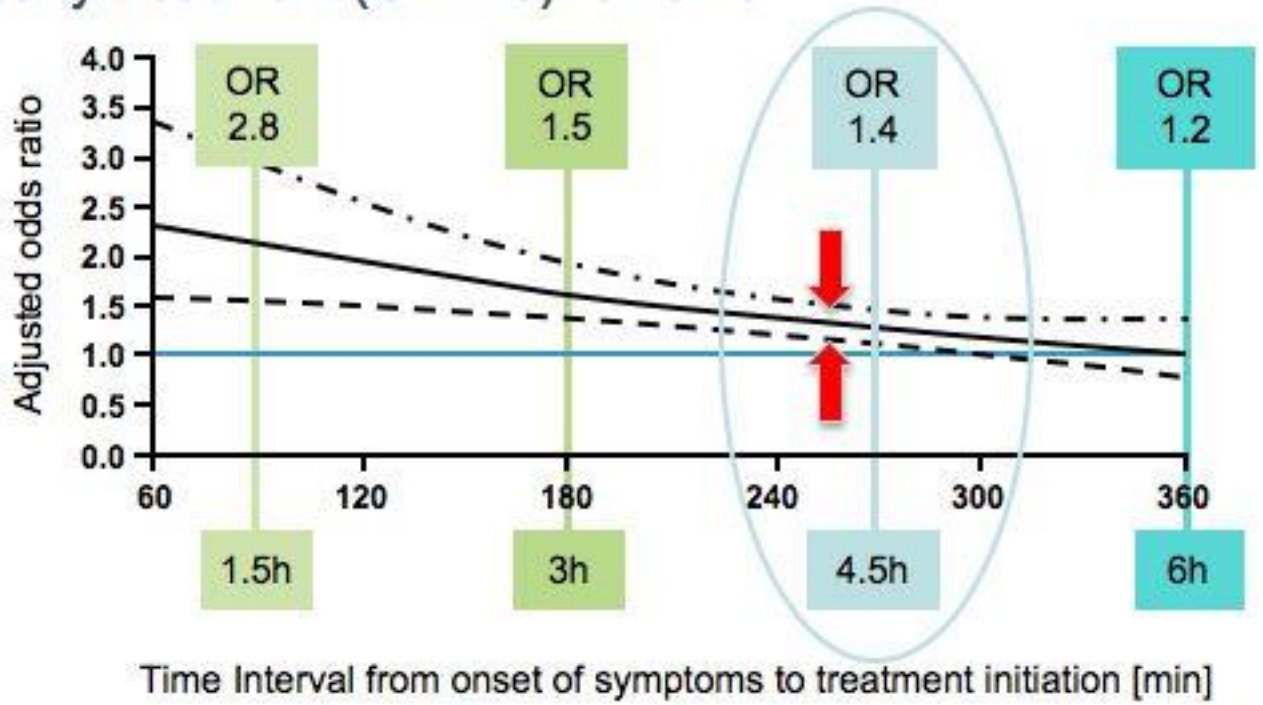
CLOTS Primary Outcome

	IPC (n=1438)	No IPC (n=1438)	Absolute risk difference (95% CI)	Risk ratio (95% CI)*	Odds ratio (95% CI)	p value
Primary outcome						
Primary outcome (proximal DVT)	122 (8·5%)	174 (12·1%)	−3·6 (−5·8 to −1·4)			
Alive and free of primary outcome	1145 (79·6%)	1071 (74·5%)				
Died before any primary outcome	147 (10·2%)	176 (12·2%)				
Missing	24 (1·7%)	17 (1·2%)				
Unadjusted (dead and missing patients excluded)	122/1267 (9·6%)	174/1245 (14·0%)	−4·3 (−6·9 to −1·8)	0·69 (0·55 to 0·86)	0·66 (0·51 to 0·84)	0·001
Primary analysis–adjusted (dead and missing patients excluded)				0·68 (0·54 to 0·85)	0·65 (0·51 to 0·84)	0·001
Unadjusted (dead patients included with DVT and missing patients included with no DVT)	269/1438 (18·7%)	350/1438 (24·3%)	−5·6 (−8·6 to −2·6)	0·77 (0·67 to 0·89)	0·71 (0·59 to 0·85)	0·00023
Adjusted (dead patients included with DVT and missing patients included with no DVT)				0·75 (0·64 to 0·88)	0·71 (0·60 to 0·86)	0·00021

i.v. Thrombolysis

Early Treatment Remains Essential

- The effect size (OR 1.4) in the 3-4.5h is confirmed by ECASS III, and the confidence intervals will significantly narrow in the new pooled analysis, however, the differnce in effect size compared with early treatment (OR 2.8) remains



OR, odds ratio

Hacke et al. Lancet 2004; 363: 768–74

Time is brain!

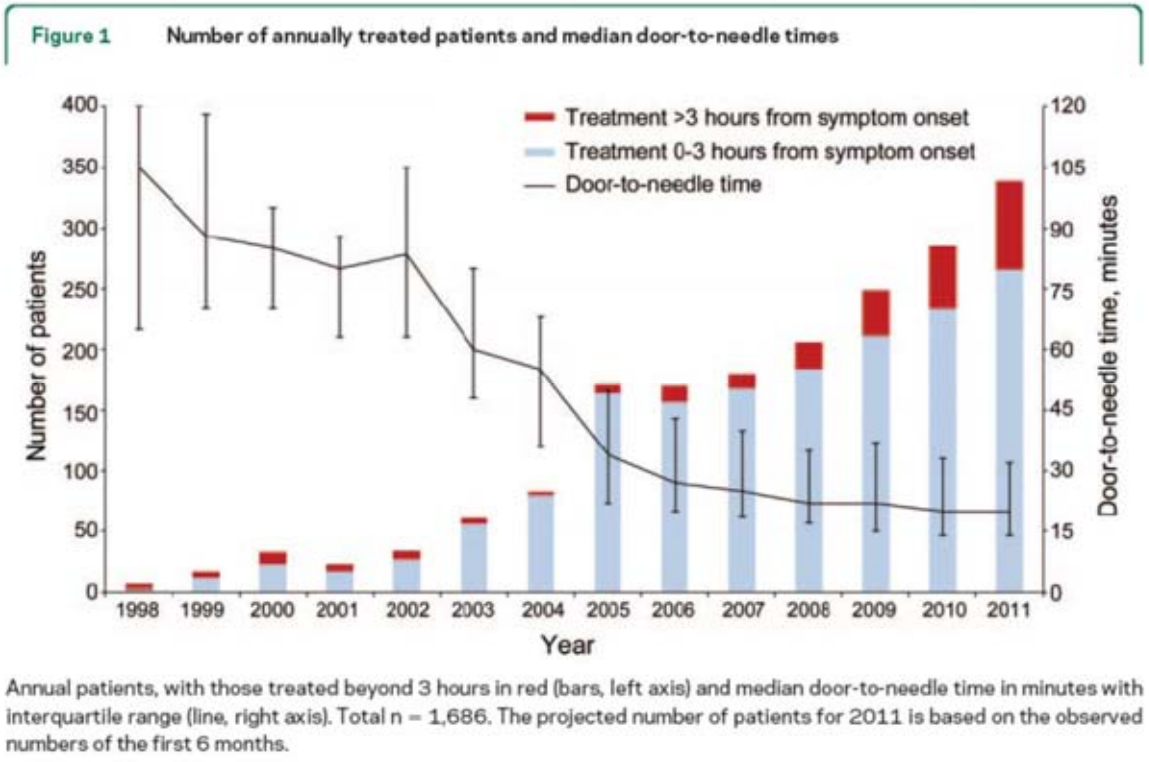
Reducing in-hospital delay to 20 minutes in stroke thrombolysis

Meretoja 2012 Neurology

Thrombolysis registry Helsinki

1998-2011

N=1860



Annual patients, with those treated beyond 3 hours in red (bars, left axis) and median door-to-needle time in minutes with interquartile range (line, right axis). Total n = 1,686. The projected number of patients for 2011 is based on the observed numbers of the first 6 months.

Meretoja 2012 Neurology

Table 1 Twelve measures to reduce treatment delays

Measure	Description	Year
EMS involvement	Education of dispatchers and EMS personnel, stroke high-priority dispatch	1998
Hospital prenotification	EMS contacts stroke physician directly via mobile phone	2001
Alarm and preorder of tests	Laboratory and CT computer-ordered and alarmed at prenotification	2001
No-delay CT interpretation	Stroke physician interprets the CT scan, not waiting for formal radiology report	2001
Premixing of tPA	With highly suspect thrombolysis candidates, tPA premixed prior to patient arrival	2002
Delivery of tPA on CT table	Bolus administered on CT table	2002
CT relocated to ER	Patient transfers of several hundred meters, including elevators, were no longer needed	2003
CT priority and CT transfer	CT emptied prior to patient arrival, and patient transferred straight onto CT table, not ER bed	2004
Rapid neurologic evaluation	Patient is examined upon arrival, on CT table	2004
Preacquisition of history	Statewide electronic patient records and eyewitness interview before/during transportation	2005
Point-of-care INR	Laboratory personnel draw blood while patient on CT table, and perform instant POC INR	2005
Reduced imaging	While all patients have a CT, advanced imaging reserved for unclear cases only	2005

Abbreviations: EMS = emergency medical service; ER = emergency room; INR = international normalized ratio; POC = point-of-care; tPA = tissue plasminogen activator.

Time to Treatment With Intravenous Tissue Plasminogen Activator and Outcome From Acute Ischemic Stroke

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Gregg C. Fonarow, MD
Eric E. Smith, MD, MPH
Mathew J. Reeves, PhD
Maria V. Grau-Sepulveda, MD, MPH
Wenqin Pan, PhD
DaiWai M. Olson, PhD
Adrian F. Hernandez, MD, MHS
Eric D. Peterson, MD, MPH
Lee H. Schwamm, MD

Importance Randomized clinical trials suggest the benefit of intravenous tissue-type plasminogen activator (tPA) in acute ischemic stroke is time dependent. However, modest sample sizes have limited characterization of the extent to which onset to treatment (OTT) time influences outcome; and the generalizability of findings to clinical practice is uncertain.

Objective To evaluate the degree to which OTT time is associated with outcome among patients with acute ischemic stroke treated with intraveneous tPA.

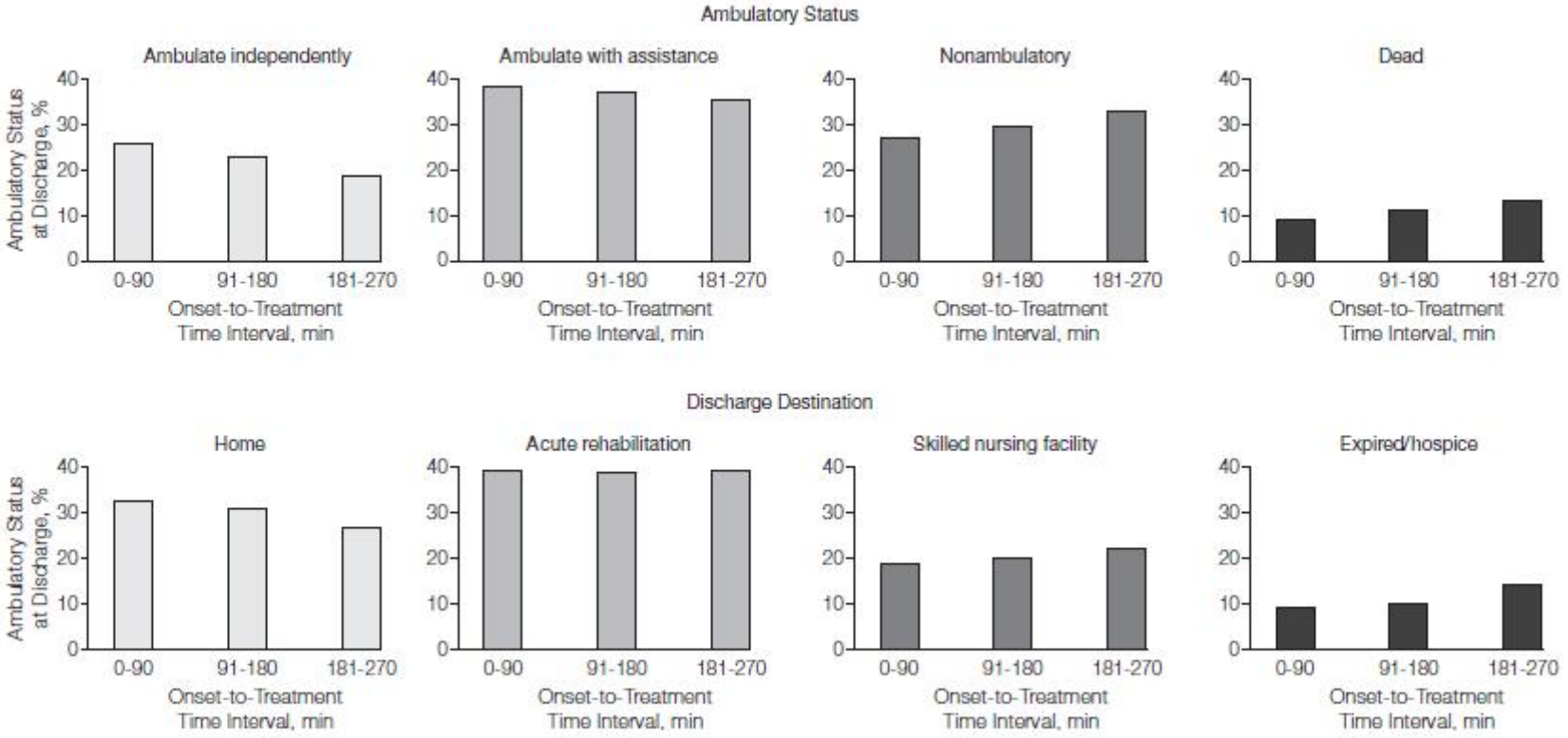
Design, Setting, and Patients Data were analyzed from 58 353 patients with acute ischemic stroke treated with tPA within 4.5 hours of symptom onset in 1395 hospitals participating in the Get With The Guidelines-Stroke Program, April 2003 to March 2012.

Main Outcomes and Measures Relationship between OTT time and in-hospital mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination.

Results Among the 58 353 tPA-treated patients, median age was 72 years, 50.3%

INTRAVENOUS (IV) TISSUE-TYPE PLASMINOGEN ACTIVATOR (tPA) is a treat

Figure 2. Ordinal Outcomes for Onset-to-Treatment Time Windows for Ambulatory Status at Discharge and Discharge Destination, Adjusted for Baseline Covariates



There were 5404 patients in the 0- to 90-minute time window, 45 029 in the 91- to 180-minute segment, and 7920 in the 181- to 270-minute time window. SNF indicates skilled nursing facility.

The third international stroke trial (IST-3) main results: primary and secondary outcomes among 3035 patients

The IST3 Collaborative Group - 156 hospitals in UK, Poland, Italy, Sweden, Norway, Australia, Portugal, Belgium, Austria, Switzerland, Canada, Mexico

Available online at
www.thelancet.com

MRC Medical Research Council

IST-3 Thrombolysis

Main features of IST - 3

Randomised, open study i.v. rt-PA vs control

Target: 3100 acute ischaemic stroke < 6h

Randomised by phone or internet:

Key prognostic factors balanced

Imaging CT or MR

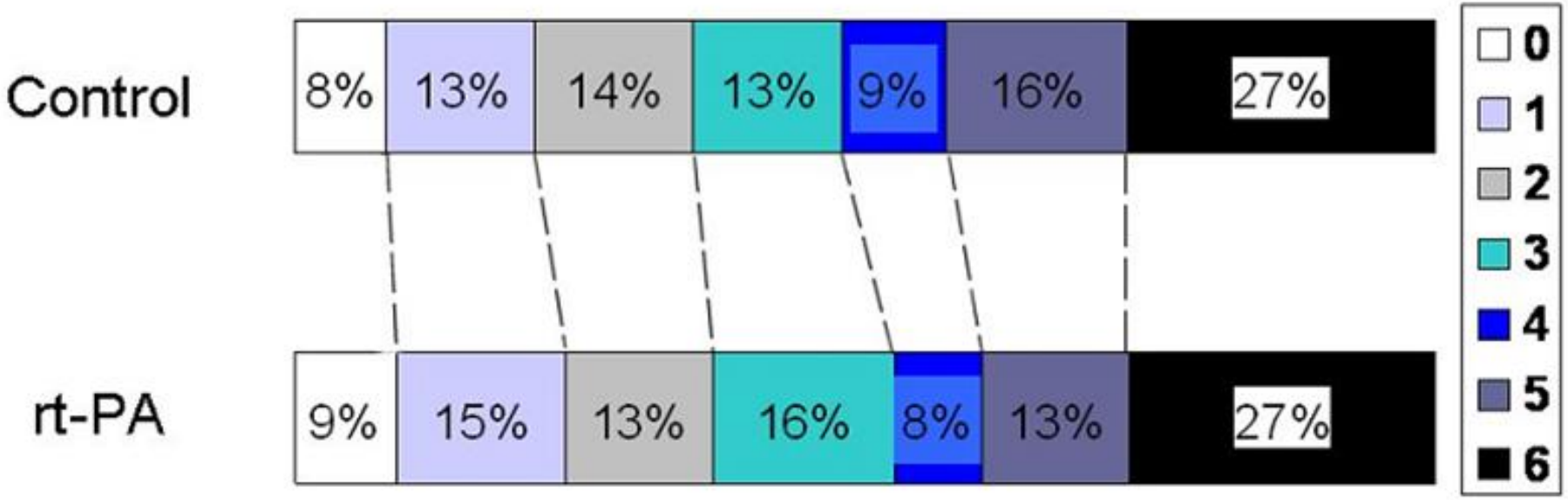
Oxford Handicap Scale (OHS) at 6 months

Primary outcome: % 'alive and independent' (OHS 0-2)

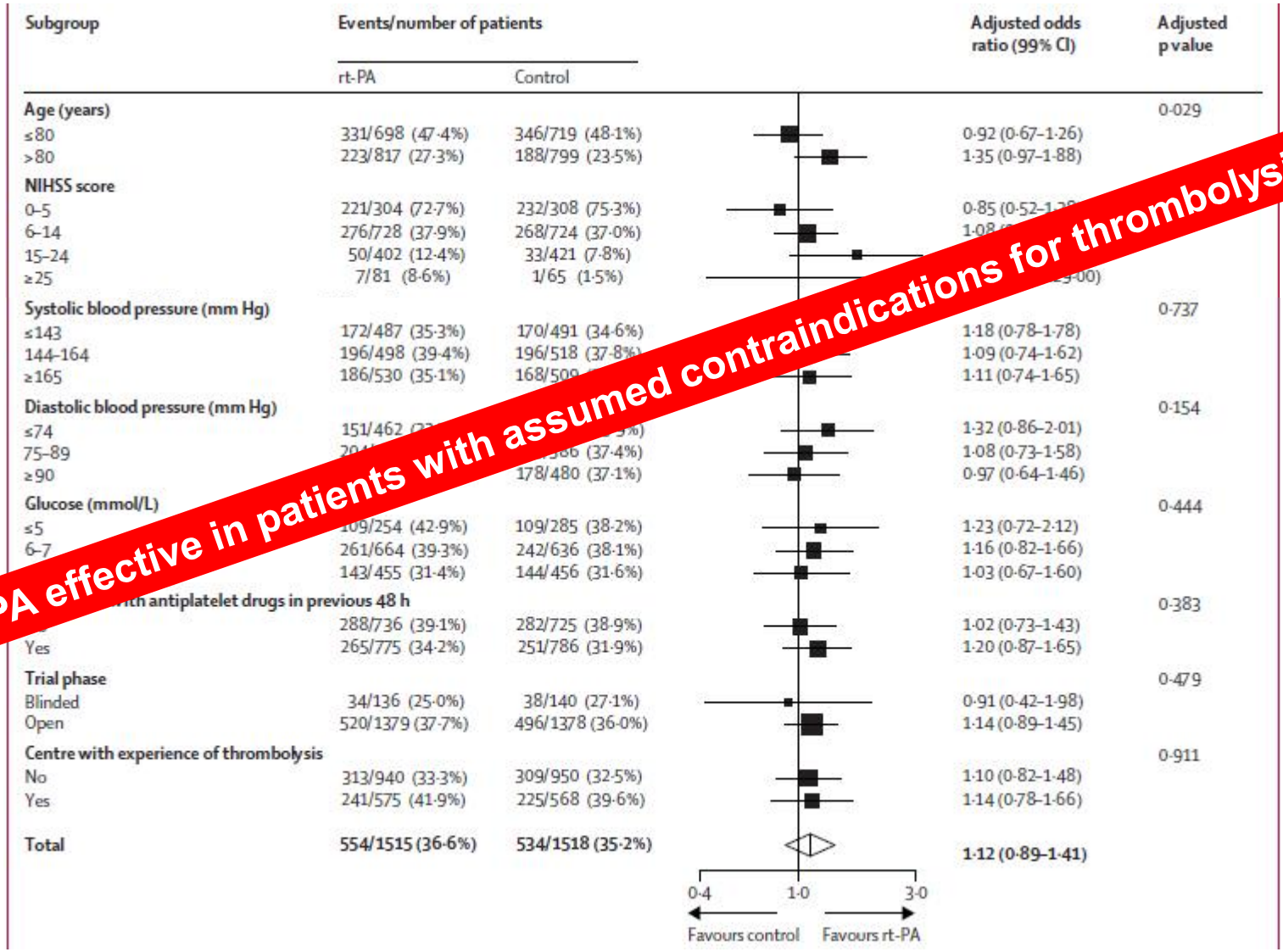
Secondary: ordinal 'shift' analysis of OHS[1]

1. Analysis plan. *Int J Stroke. 2012;7:186-7*

Ordinal analysis 6 month OHS



Favourable shift; adjusted common odds ratio 1·27 (95% CI 1·10- 1·47), p=0·001
or, the odds of surviving with less disability were 27% greater for patients treated with rt-PA



rt-PA effective in patients with assumed contraindications for thrombolysis

At six months, for every 1000 patients treated with rt-PA

All ages 0-6 hrs

- 14 more alive and independent (NS)
- **29** more ‘favourable outcome’ (p=0·018)
- Favourable shift in OHS (p=0.001)
- No difference in deaths

In patients > 80 years 0-6hrs

- **38** more alive and independent

In patients all ages < 3hrs

- **80** more alive and independent

Bleeding risk with systemic thrombolysis in patients on warfarin (INR? 1.7)?

Data from Get-With-The-Guidelines Registry USA

23,437 patients; 1,802 on warfarin (INR?”1.7)

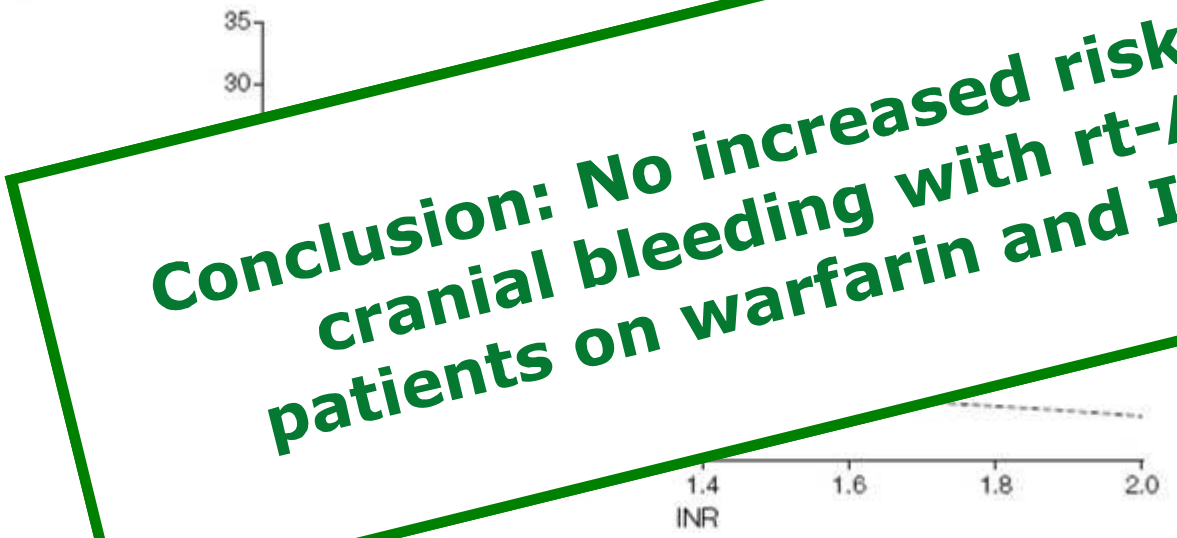
Table 3. Primary and Secondary Outcomes Measures According to Preadmission Warfarin Use

Outcome	No. of Events/Total No. of Patients (%)		OR (95% CI)		*P* Value
	Preadmission Warfarin Use	No Preadmission Warfarin Use	Unadjusted	Adjusted	
Symptomatic intracranial hemorrhage	102/1802 (5.7)	1005/21 635 (4.6)	1.22 (0.99-1.51)	1.01 (0.82-1.25)[a]	.94
Life-threatening or serious systemic hemorrhage	16/1802 (0.9)	199/21 635 (0.9)	0.99 (0.62-1.56)	0.78 (0.49-1.24)[a]	.29
Any tPA complication[b]	191/1802 (10.6)	1824/21 635 (8.4)	1.29 (1.10-1.52)	1.09 (0.93-1.29)[a]	.30

Risks of Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Receiving Warfarin and Treated With Intravenous Tissue Plasminogen Activator

Bleeding risk with systemic thrombolysis in patients on warfarin (INR?≥1.7)?

Figure 2. Relationship Between International Normalized Ratio and Risk of S
Intracranial Hemorrhage in Warfarin-Treated Patients (Baseline INR



Solid li ates risk of symptomatic intracranial hemorrhage (sICH); dashed lines, 95% confidence intervals. Logistic regression modeling was conducted to examine the relationship between international normalized ratio (INR) and binary outcome of sICH. The Stone and Koo additive spline method was fitted to generate the plot; adequacy of linearity was tested using likelihood ratio statistic by comparing the linear and nonlinear logistic models.

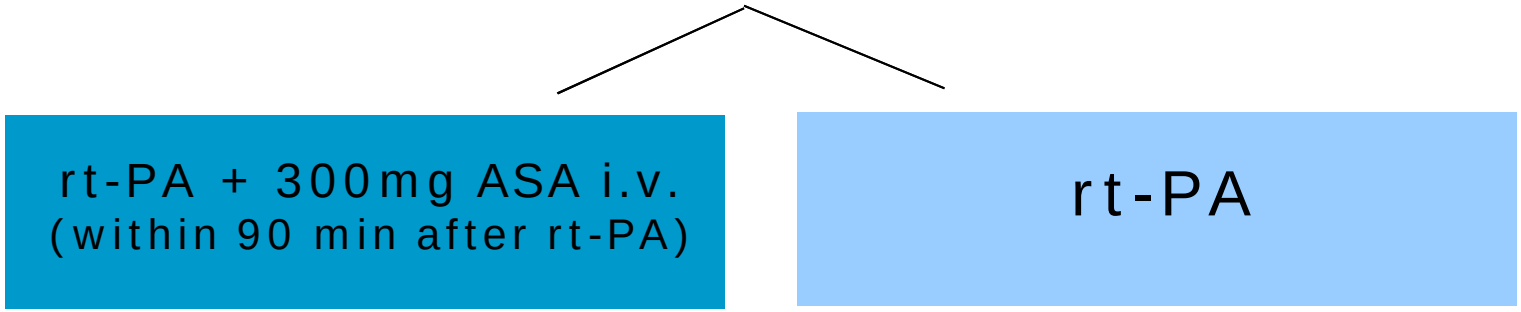
Conclusion: No increased risk of intracranial bleeding with rt-AP in patients on warfarin and INR≤1.7

Xian 2012 JAMA

Early Aspirin Therapy after iv Thrombolysis?

Rationale: Prevention of early re-occlusion after rt-PA thrombolysis

Multicentre, open, RCT, n=642



Oral aspirin after 24 hours

Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial

Sanne M Zinkstok, Yvo B Roos, on behalf of the ARTIS investigators

Early Aspirin Therapy after iv Thrombolysis?

Study terminated prematurely by DSMB

Conclusion: early i.v. aspirin after thrombolysis not recommended

No benefit in outcome

Higher bleeding risk with iv aspirin (RR 2.74 p=0.04)

ECASS4 Protocol

Inclusion criteria

- Patients presenting with acute ischemic stroke
- Given informed consent
- Patient's age is ?18 years
- Treatment onset within ?4.5 – 9 hours after stroke onset
- Patients who wake up with stroke may be included if neurological and other exclusion criteria are fulfilled.
- NIHSS score of 4 to 26 with clinical signs of hemispheric infarction
- Penumbral imaging via centralized software system (e.g. RAPID-system)

NB! Based on protocol version 4.4, dated 03.04.2012

- I.A. thrombolysis
- Thrombectomy

Intra-arterial lysis and mechanical recanalization

IV-thrombolysis <4.5 h is the gold standard

Intra-arterial thrombolysis:

- Only one RCT (PROACT II; 1992): treatment not approved

Recanalization

  - Approved without proof of clinical benefit
  - Approved for opening vessels, not for treating stroke
  - At present no RCT against iv thrombolyis
-

IMS 3 – ~900 patients
Phase III, multicentre, randomised

Bridging IV/IA versus IV rt-PA, time window <3h

NIHSS ?10

2:1 randomisation

IA rt-PA or EKOS or MER… indow <5h

Primary efficacy

- mRS 0…

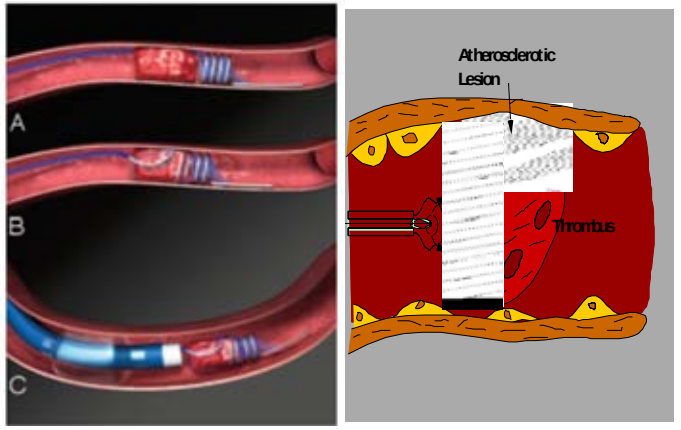
Pri…y endpoint:

- Mortality 3 mo und sICH <36h

Initiated 2006

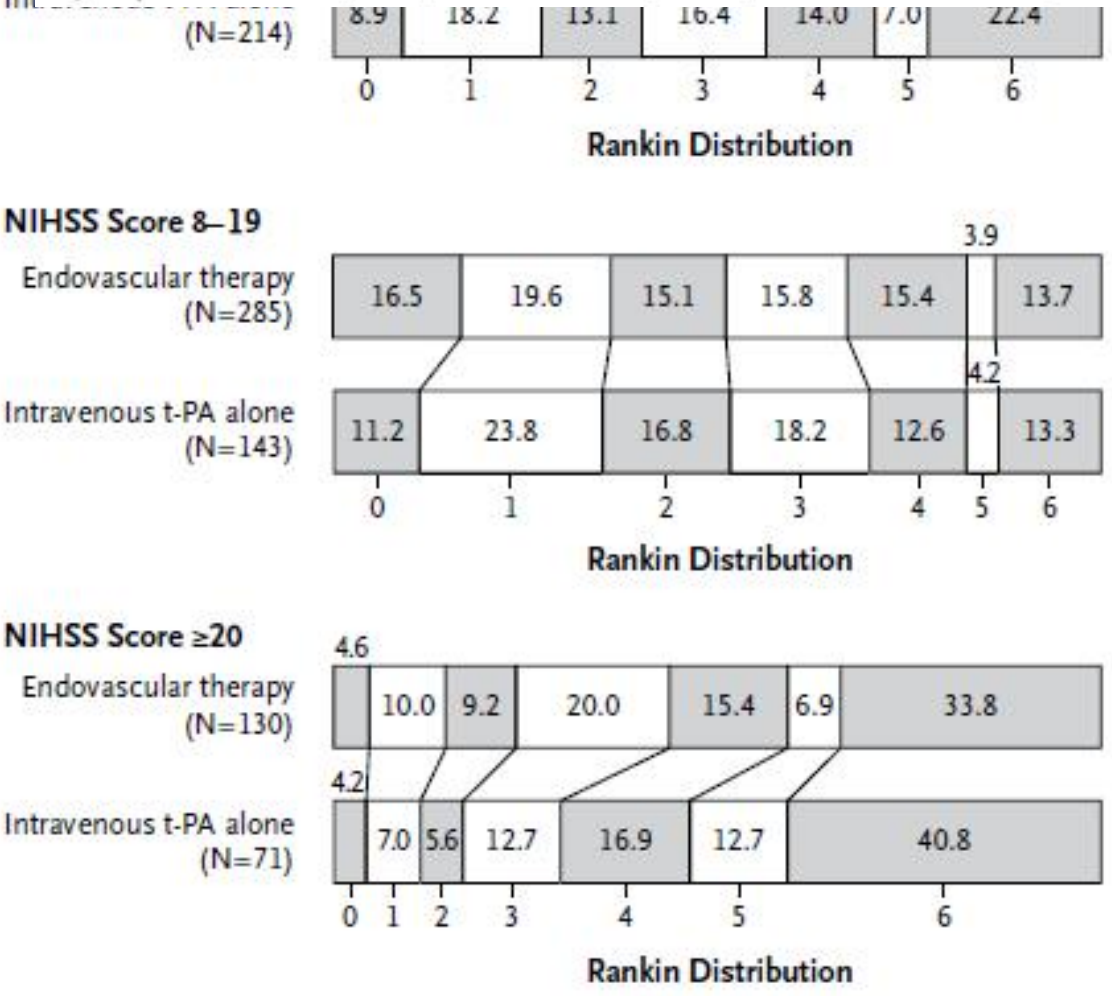
Later added: MERCI, Penumbra

Study terminated for „futility“



Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

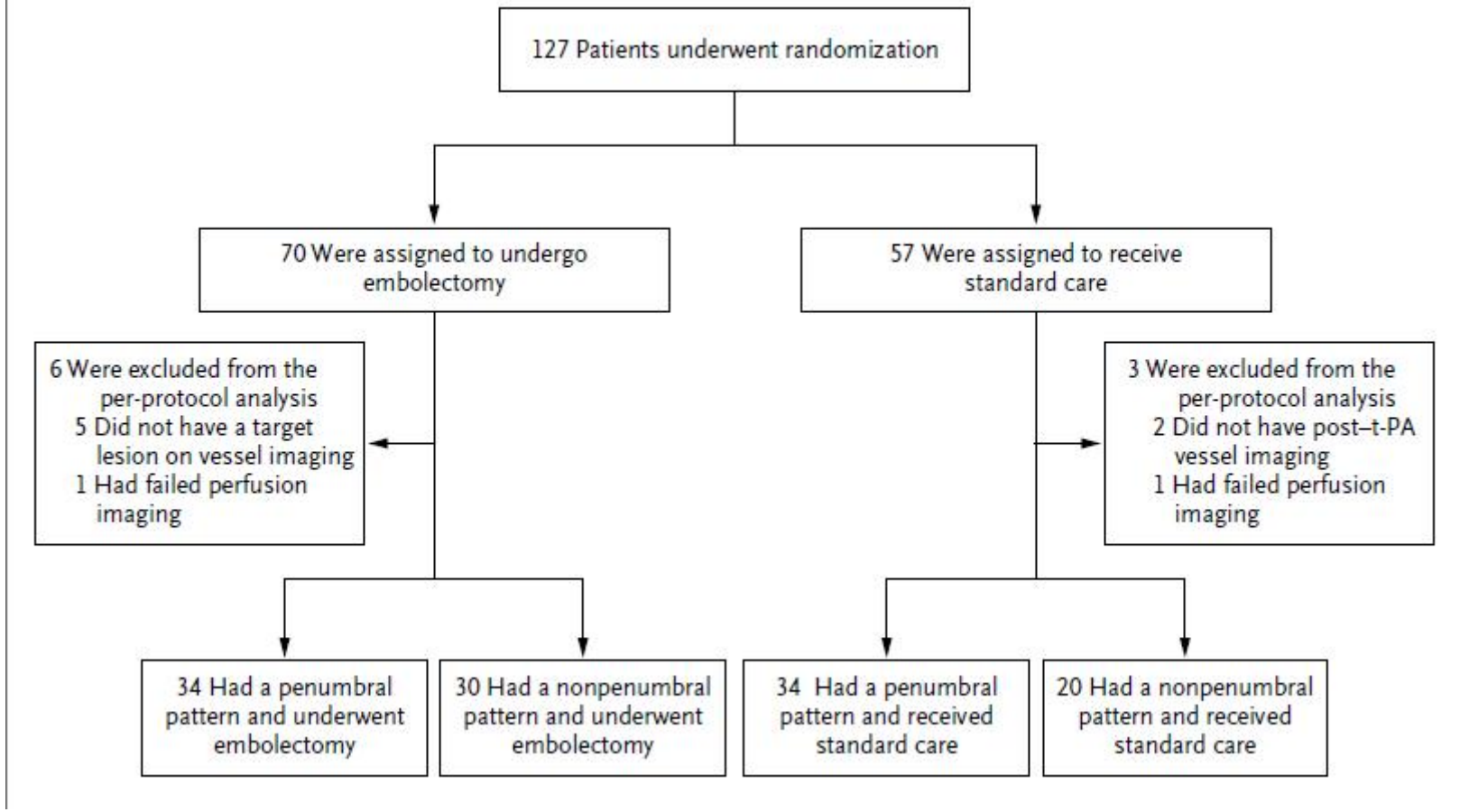
Joseph P. Broderick, M.D., Yuko Y. Palesch, Ph.D., Andrew M. Demchuk, M.D.,

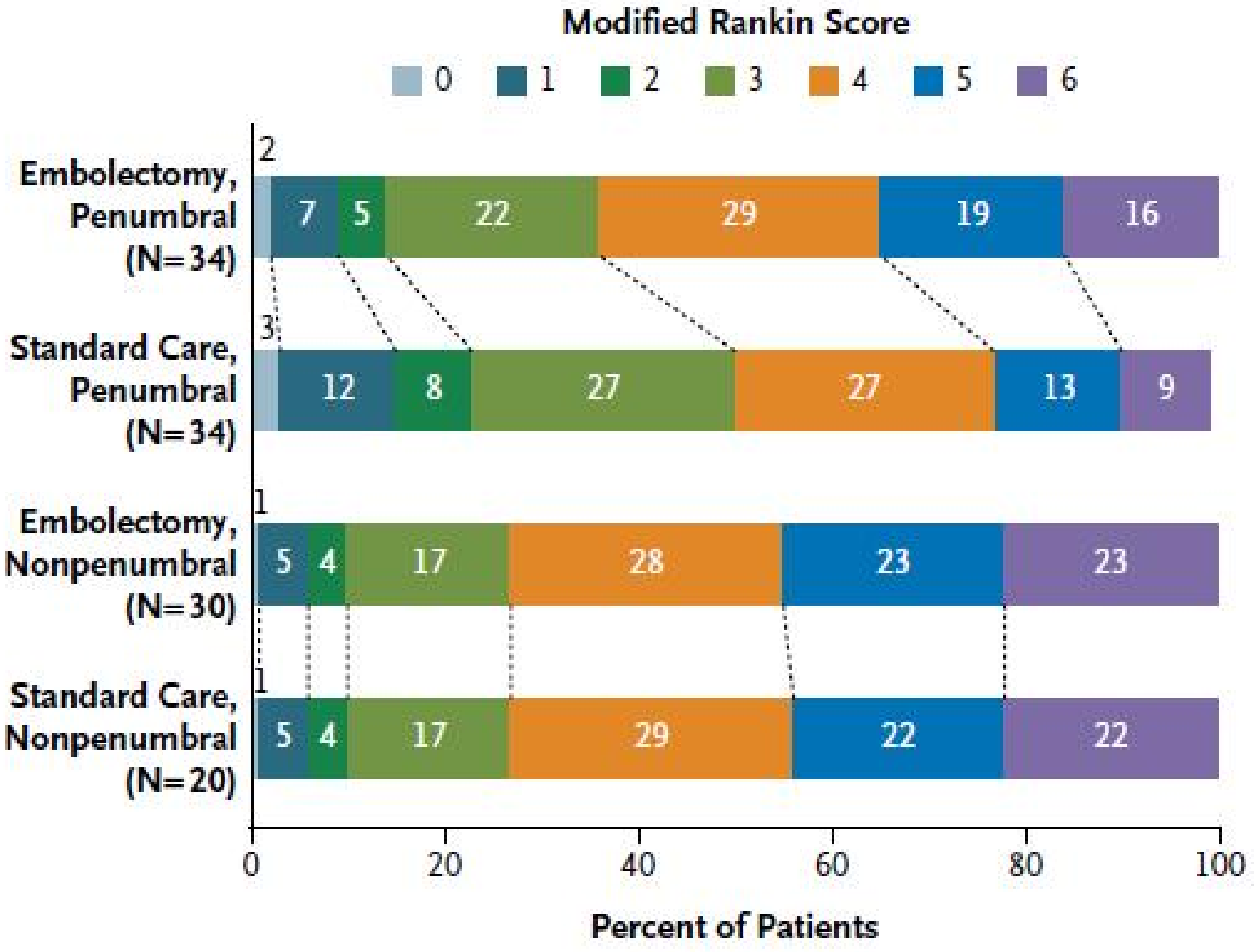


ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H.,
Jeffry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D.,




Modified Rankin Score
0
1
2
3
4
5
6
Embolectomy, Penumbral (N=34)
2
7
5
22
29
19
16
Standard Care, Penumbral (N=34)
3
12
8
27
27
13
9
Embolectomy, Nonpenumbral (N=30)
1
5
4
17
28
23
23
Standard Care, Nonpenumbral (N=20)
1
5
4
17
29
22
22
0
20
40
60
80
100
Percent of Patients

Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Endovascular Treatment (N=181)	Intravenous t-PA (N=181)
Age — yr	66±11	67±11
Male sex — no. (%)	106 (59)	103 (57)
Weight — kg	75±14	75±13
Blood pressure — mm Hg		
Systolic	155±26	150±23
Diastolic	84±12	83±12
NIHSS score†		
Median (interquartile range)	13 (9–17)	13 (9–18)
Range	2–26	3–24

Results

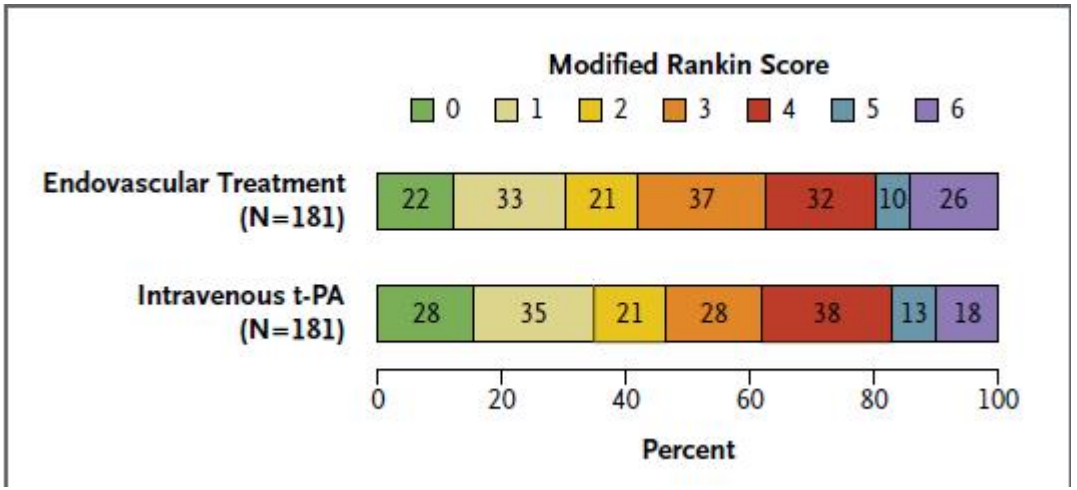


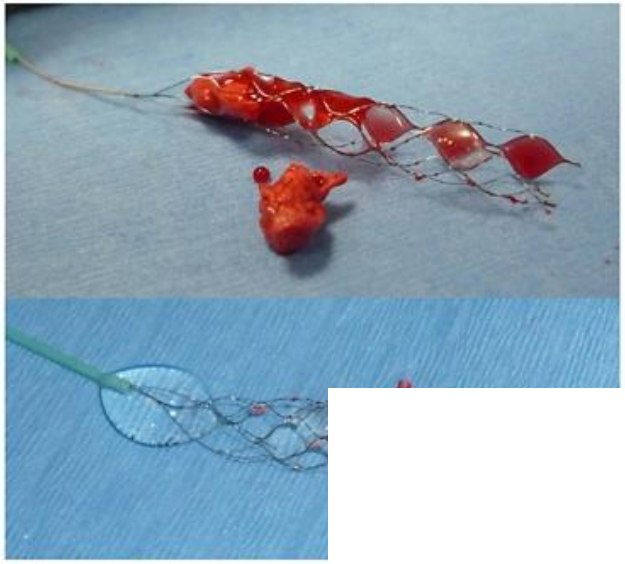
Table 2. Secondary Outcomes at Day 7.*

Outcome	Endovascular Treatment (N=181)	Intravenous t-PA (N=181)	P Value
NIHSS score ≤6 — no. of patients (%)†	97 (54)	100 (55)	0.89
Neurologic deterioration — no. of patients (%)‡	16 (9)	12 (7)	0.39
Death — no. of patients (%)	14 (8)	11 (6)	0.53
Symptomatic intracranial hemorrhage — no. of patients (%)	10 (6)	10 (6)	0.99
Nonfatal	6	9	
Fatal	4	1	

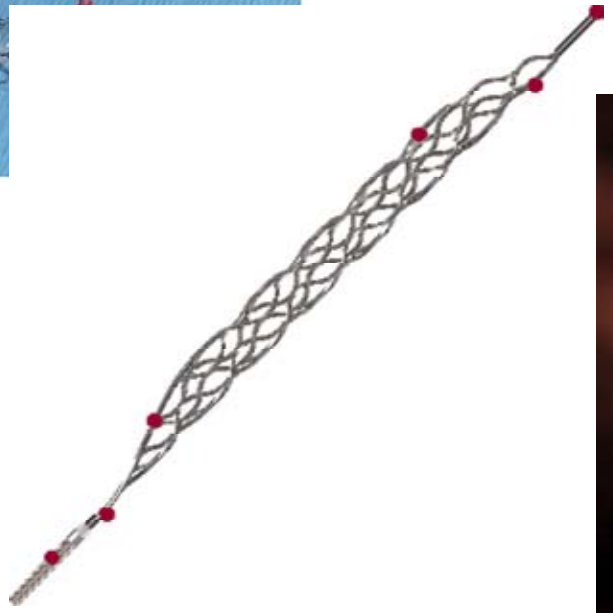
Conclusions

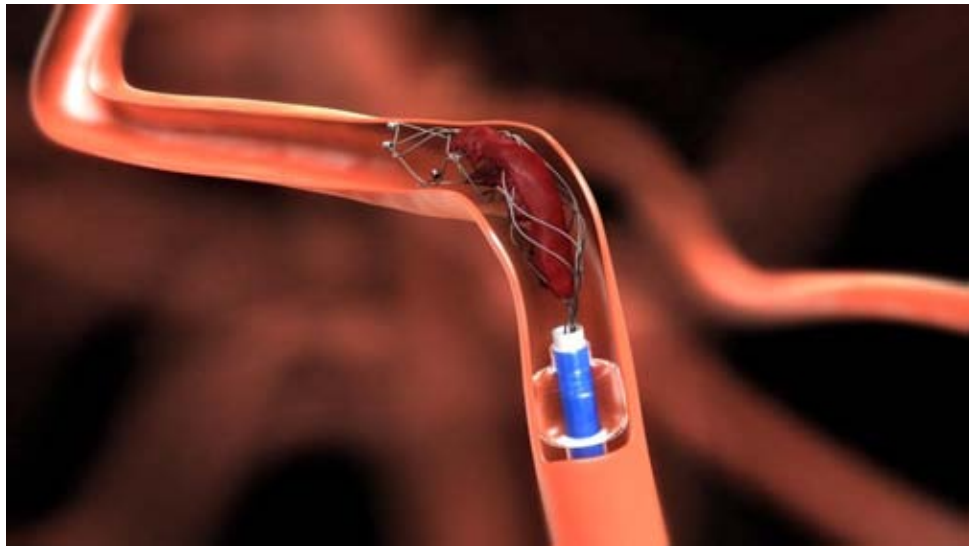
- 3 negative studies for rt-PA plus thrombectomy or i.a. thrombolysis versus rt-PA
- Studies lasted for many years
- Time interval until intervention too long
- Outdated devices with poor recanalization rates

The future is Solitaire, Trevo, ReVive, IRIIS …



MINDFRAME CAPTURE™





Thrombectomy: Planned studies

With the newest generation of devices we are ready to go

Running or planned controlled trials

- TREVO
- RIVER I-III
- SWIFT-Prime
- Penumbra

Pooled analysis planned and agreed

Final conclusions

IV thrombolysis is the gold standard

IAT with or without device is a valuable option

- Patients should be included in randomised trials
- Off-label use in life threatening conditions (basilar thrombosis)

IAT +/- device possible more effective despite:

- Longer time interval
- Stroke severity

Intervention is most effective:

- early
- fast
- without intubation (if possible)
- On top of IV rt-PA

New study protocols:

- Define bridging
- Number of attempts/multiple devices

Therapy of Acute Stroke: Conclusions

Thrombolysis

- Longer time window
- Fewer contraindications

Thrombectomy

- Randomized trials starting or ongoing

Other approaches

- Near infrared laser (NEST)(terminated for futility)
- Stimulation of spheno-palatine ganglion
- Augmentation of cerebral blood flow (SENTIS)

Neuroprotection

- Hypothermia
- >140 negative trials with medical therapy

Hemicraniectomy in malignant MCA infarction

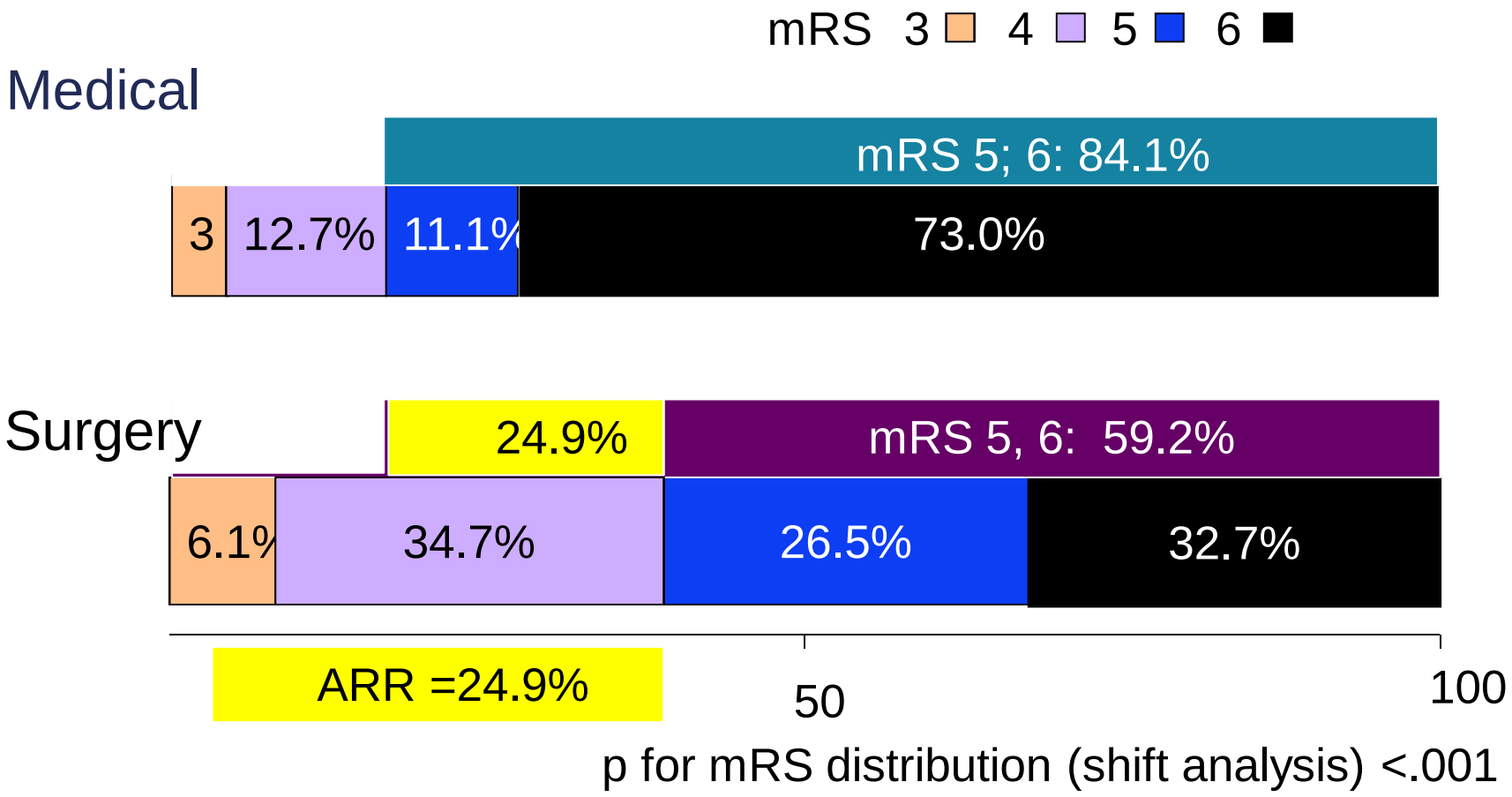
Should only patients below the age of 60 years be operated?

DESTINY II: Study design

- Inclusion criteria
  - Age 61 years or older
  - NIH Stroke Scale score > 15 (dominant hemispheric infarction) or > 20 (non-dominant hemispheric infarction), level of consciousness (loc) >0 (loc≥1)
  - complete or subtotal infarction of the MCA territory, at least partially including the basal ganglia +/- ACA and/or PCA infarction
  - possibility to start treatment <48 hours after symptom onset and within 6 hours after randomisation

DESTINY II: Results

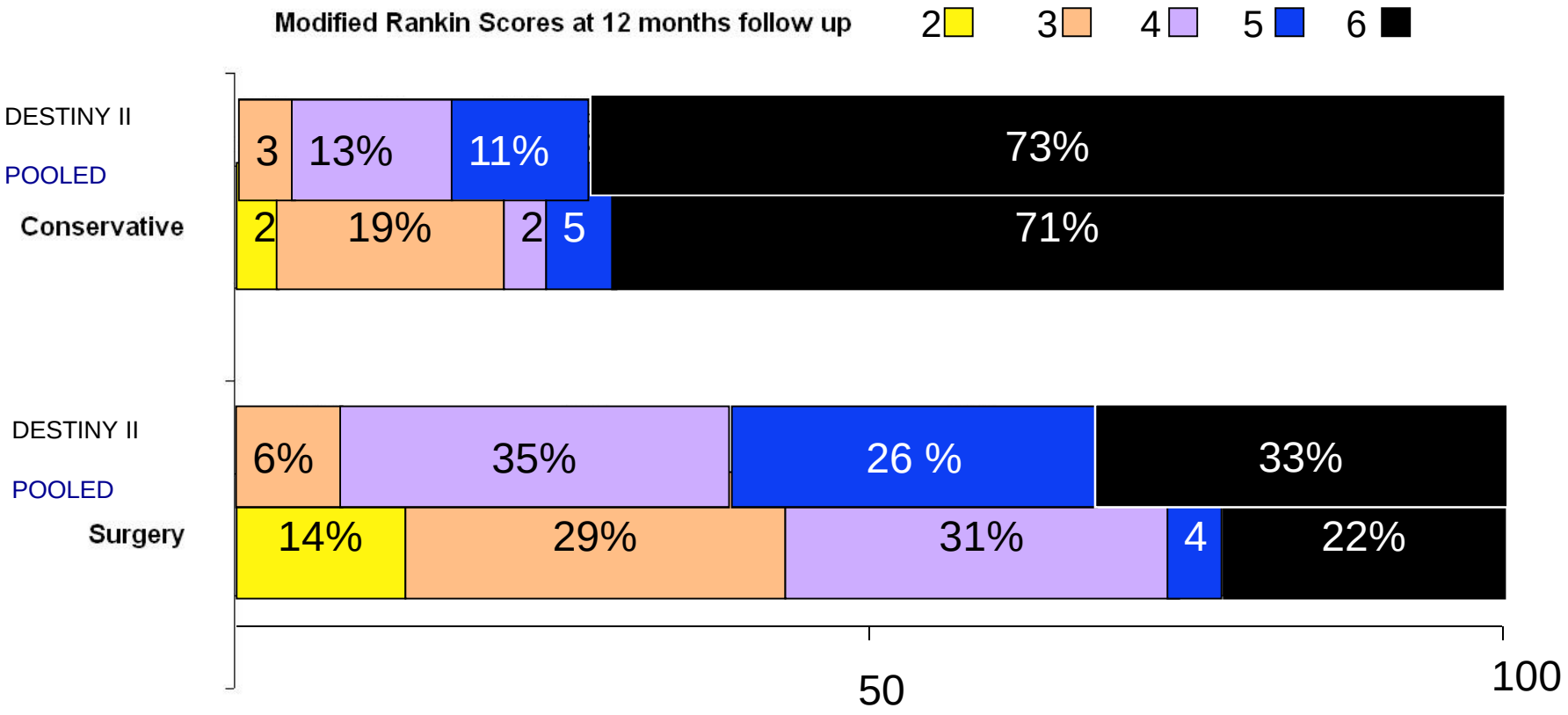
- Outcome



p for mRS distribution (shift analysis) <.001

DESTINY II: Comparison with patients <60 years

Pooled Analysis: Vahedi et al Lancet Neurol 2007



Compared with the pooled analysis, mortality rates are comparable but the number of patients with a mRS 5 outcome in the surgical arm is higher. These are 6 months outcome figures, not 12 months like in the pooled analysis

Secondary Stroke Prevention 2013

Hans-Christoph Diener
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Secondary Stroke Prevention

- Antiplatelet drugs
- Anticoagulation
- Patent foramen ovale (PFO)
- Carotid stenosis
- Intracranial stenosis

Secondary Stroke Prevention

- **Antiplatelet drugs**
- Anticoagulation
- Patent foramen ovale (PFO)
- Carotid stenosis
- Intracranial stenosis

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

The efficacy and safety of aspirin plus dipyridamole versus aspirin in secondary prevention following TIA or stroke: A meta-analysis of randomized controlled trials

Xia Li [a], Guoyu Zhou [b], Xueying Zhou [c], Shengnian Zhou [b,d,*]

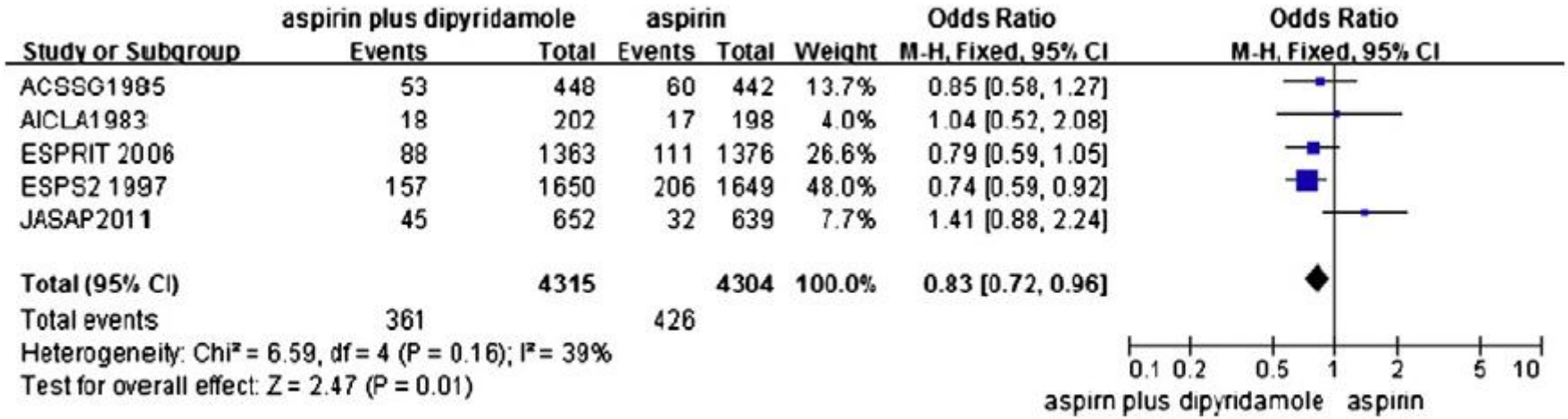
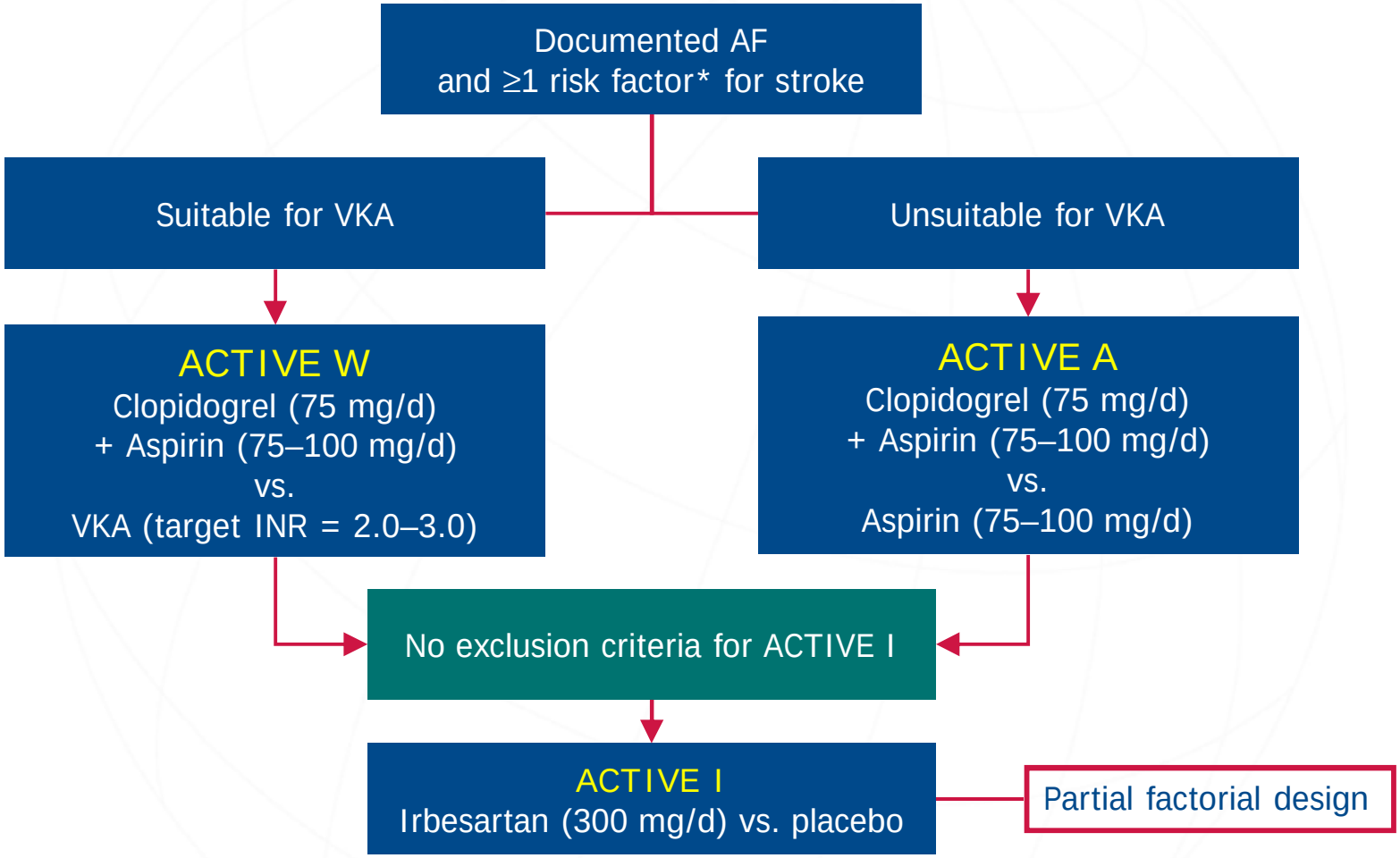


Fig. 2. The effect of aspirin plus dipyrimadole therapy on stroke (fatal and nonfatal).

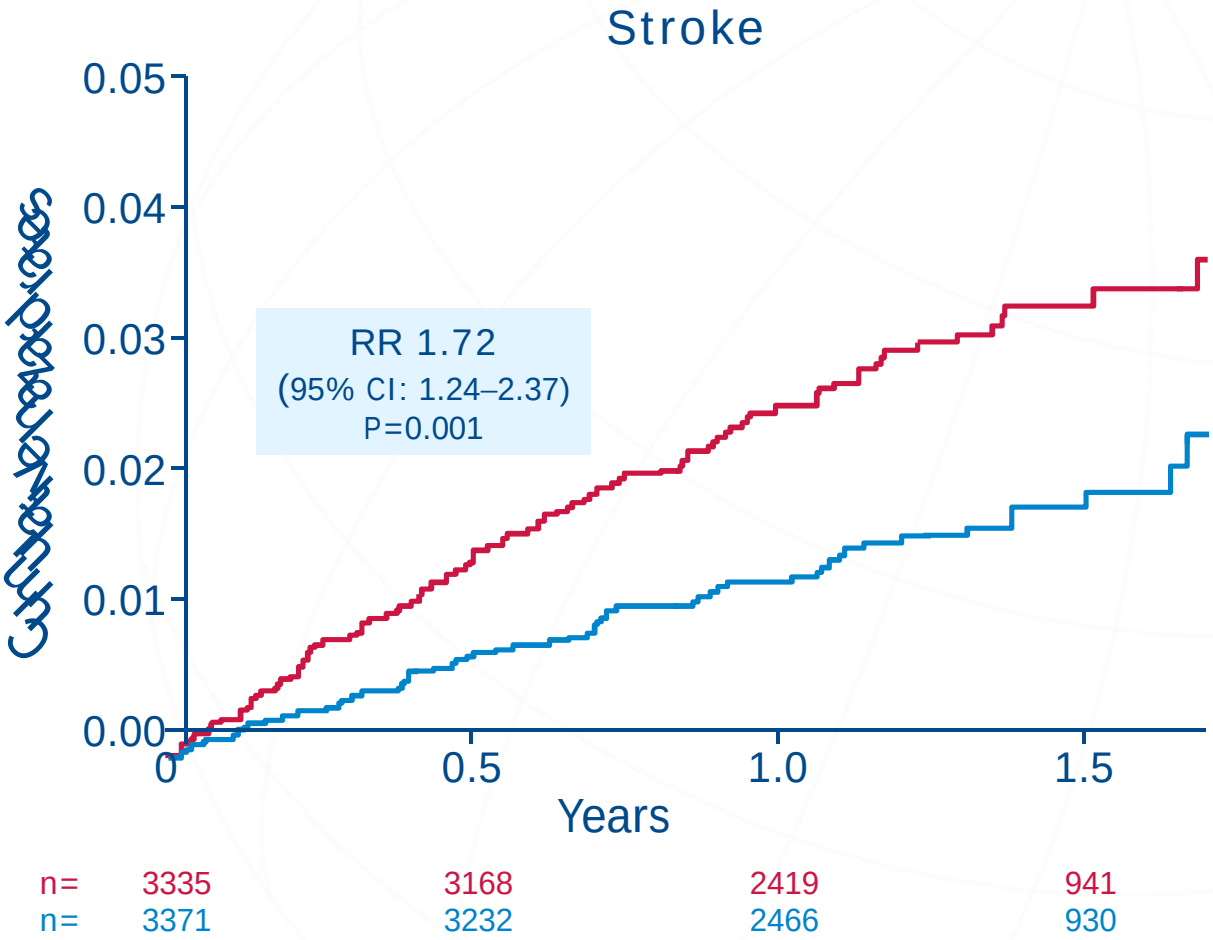
ACTIVE trials: dual antiplatelet therapy for stroke prevention in AF



*Risk factors: age ≥75 years; hypertension, prior stroke/transient ischaemic attack; left ventricular ejection fraction <45; peripheral arterial disease; age 55–74 years plus coronary artery disease or diabetes;
INR = international normalized ratio; VKA = vitamin K antagonist

Connolly SJ et al. Am Heart J 2006;151:1187–1193

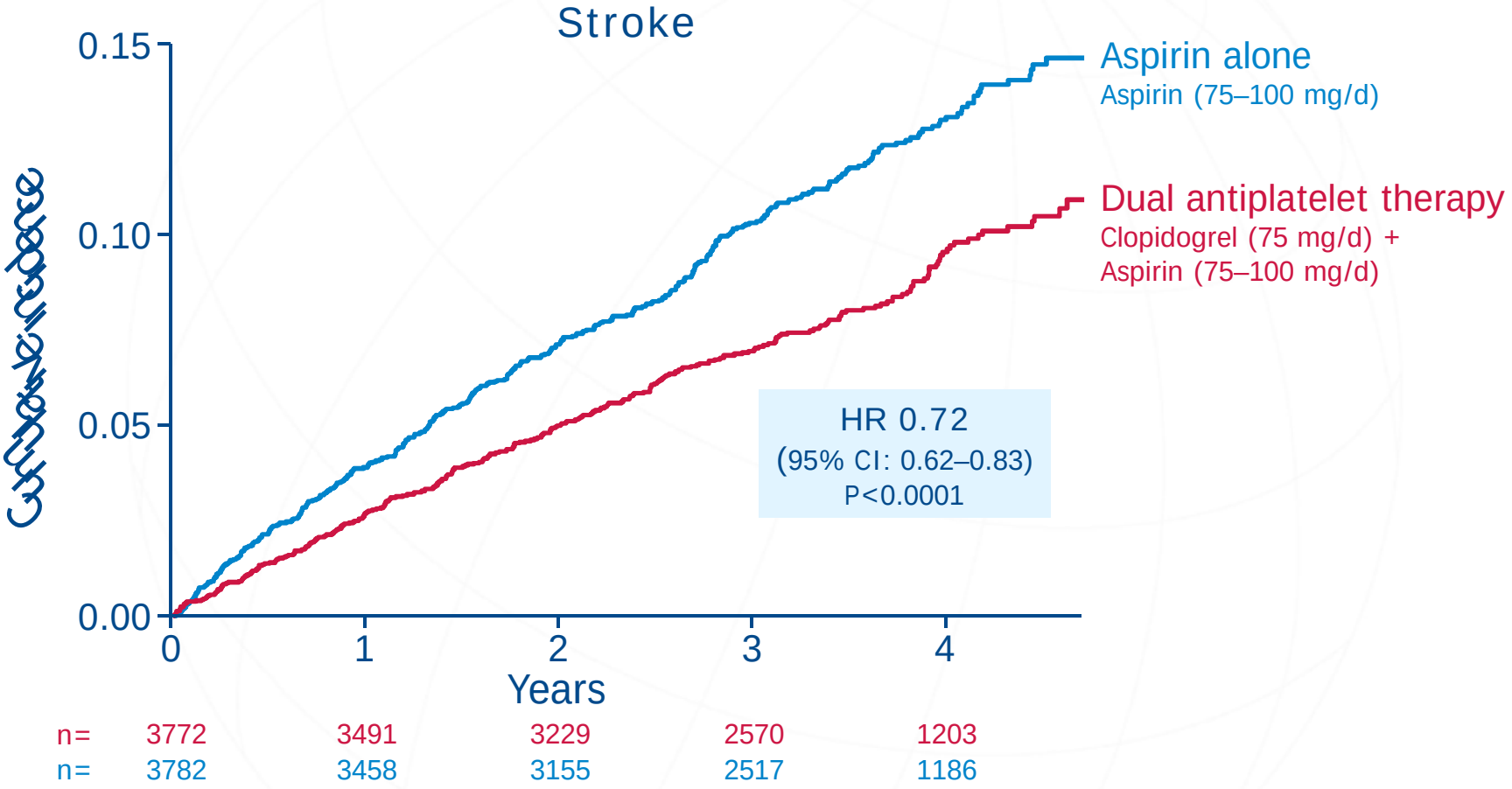
ACTIVE W: dual antiplatelet therapy inferior to oral anticoagulation for stroke prevention in AF



INR = international normalized ratio; RR = relative risk; VKA = vitamin K antagonist

ACTIVE Investigators. Lancet 2006;151:1903–12

ACTIVE A: dual antiplatelet therapy superior to Aspirin alone for stroke prevention in AF



Reasons for considering patients inappropriate for vitamin K antagonist included specific risk of bleeding (22.9%), physician's judgement in absence of specific bleeding risk (49.7%) and patient preference alone (26.0%); HR = hazard ratio

ACTIVE Investigators. N Engl J Med 2009;360:2066–78

ACTIVE A: greater bleeding risk with dual antiplatelet therapy compared with Aspirin alone

Bleeding	Clopidogrel & Aspirin (n=3772) Events		Aspirin alone (n=3782) Events		RR (95% CI)	P value
	(n)	(%/yr)	(n)	(%/yr)		
Major bleeding	251	2.0	162	1.3	1.57 (1.29–1.92)	<0.001
Severe	190	1.5	122	1.0	1.57 (1.25–1.98)	<0.001
Fatal	42	0.3	27	0.2	1.56 (0.96–2.53)	0.07
Minor bleeding	408	3.5	175	1.4	2.42 (2.03–2.89)	<0.001
Any bleeding	1014	9.7	651	5.7	1.68 (1.52–1.85)	<0.001
Site of major bleeding*						
Gastrointestinal	132	1.1	68	0.5	1.96 (1.46–2.63)	<0.001
Gastrointestinal, with transfusion	117	0.9	61	0.5	1.93 (1.42–2.63)	<0.001
Intracranial	54	0.4	29	0.2	1.87 (1.19–2.94)	0.006
Extracranial	200	1.6	134	1.1	1.51 (1.21–1.88)	<0.001

Dosing: clopidogrel 75 mg/day; Aspirin 75–100 mg/day; *Four patients had both intracranial and extracranial bleeding; RR = relative risk

ACTIVE Investigators. N Engl J Med 2009;360:2066–78

Conclusions: Antiplatelet therapy in patients with atrial fibrillation

In patients with Afib and stable coronary heart disease the addition of aspirin to anticoagulation has no benefit and increases bleeding risk

Aspirin plus clopidogrel is inferior to warfarin in patients with atrial fibrillation

Aspirin plus clopidogrel is superior to aspirin monotherapy in patients with atrial fibrillation but carries a higher risk of major bleeds

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

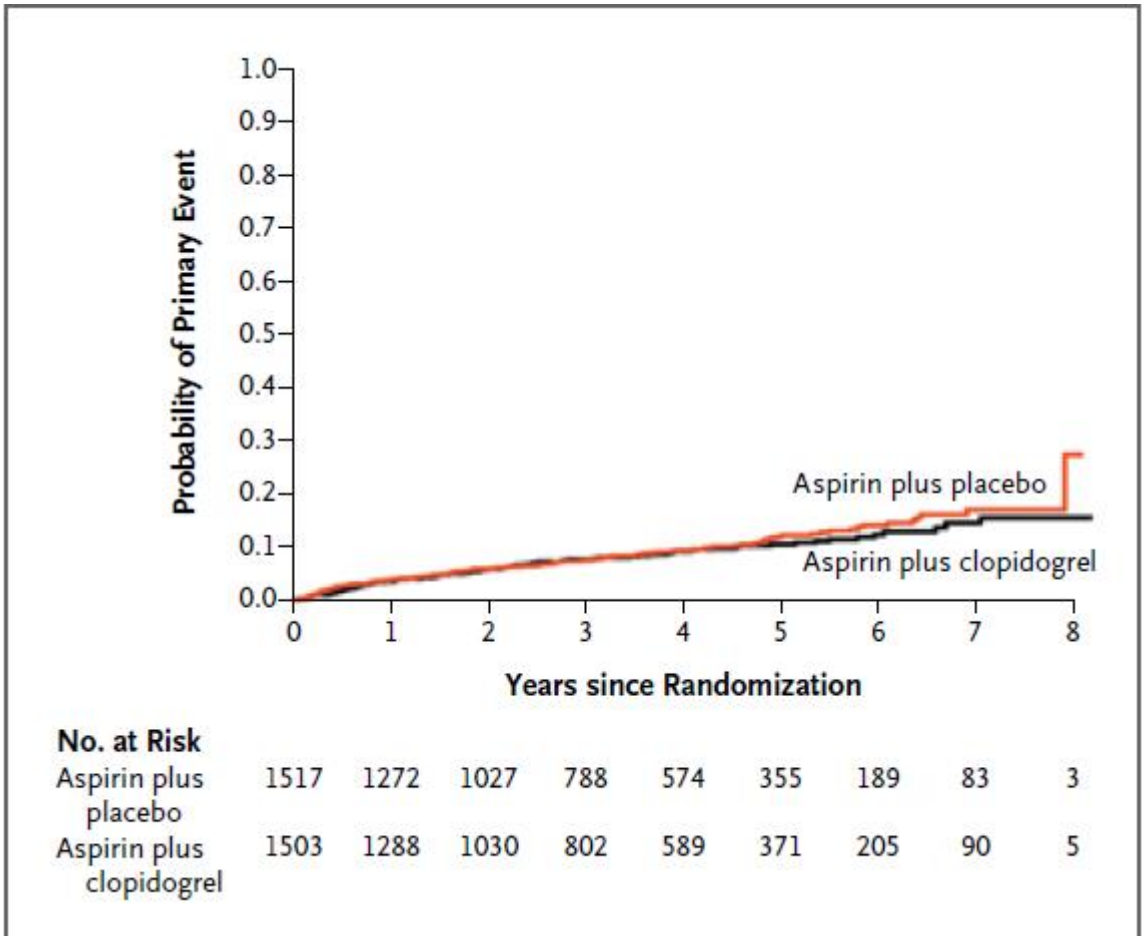


Table 3. Safety Outcomes.*

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	—	—

Conclusions

- Based on MATCH, CHARISMA and SPS3 the combination of clopidogrel plus aspirin is not more effective than clopidogrel or aspirin mono-therapy
- The combination of clopidogrel plus aspirin carries a higher bleeding risk than clopidogrel or aspirin mono-therapy in secondary stroke prevention

Secondary Stroke Prevention

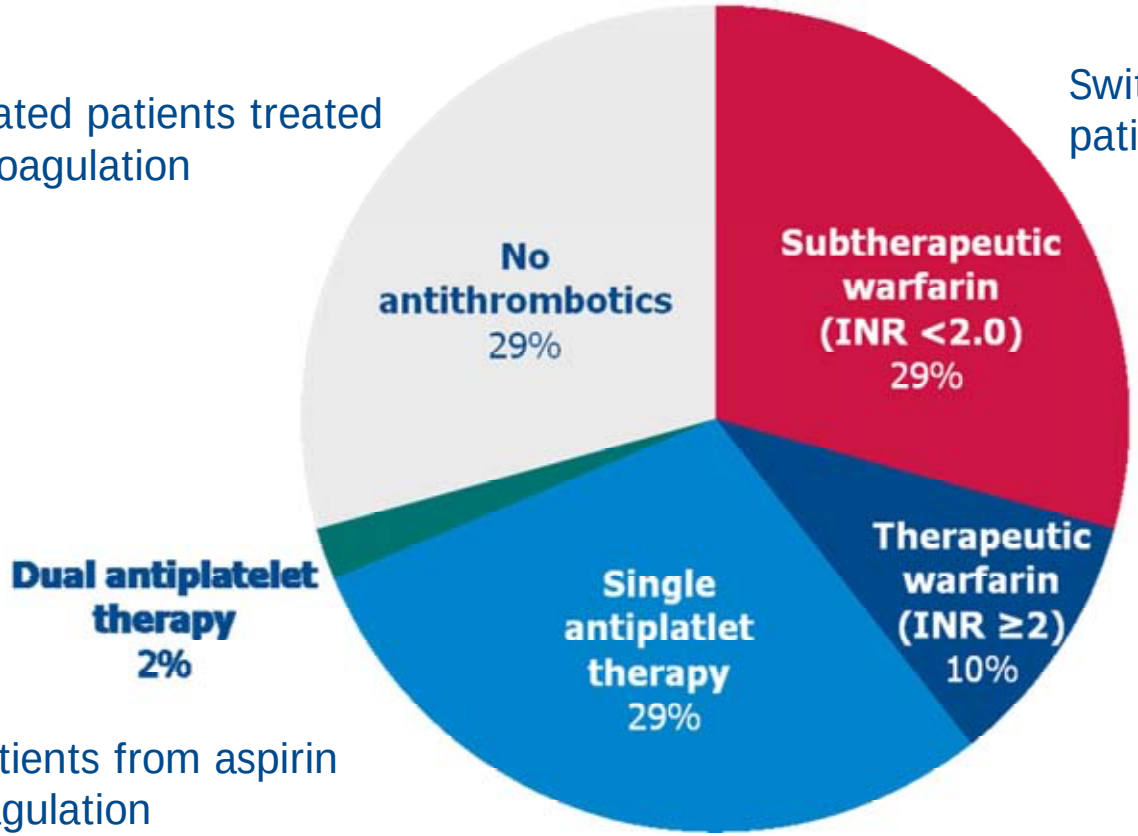
- Antiplatelet drugs
- **Anticoagulation**
- Patent foramen ovale (PFO)
- Carotid stenosis
- Intracranial stenosis

Most ischaemic strokes occur in patients who are suboptimally anticoagulated

Pre-admission medications in high-risk* AF patients admitted for first ischaemic stroke

Get untreated patients treated with anticoagulation

Switch poorly controlled patients on warfarin to NOACs

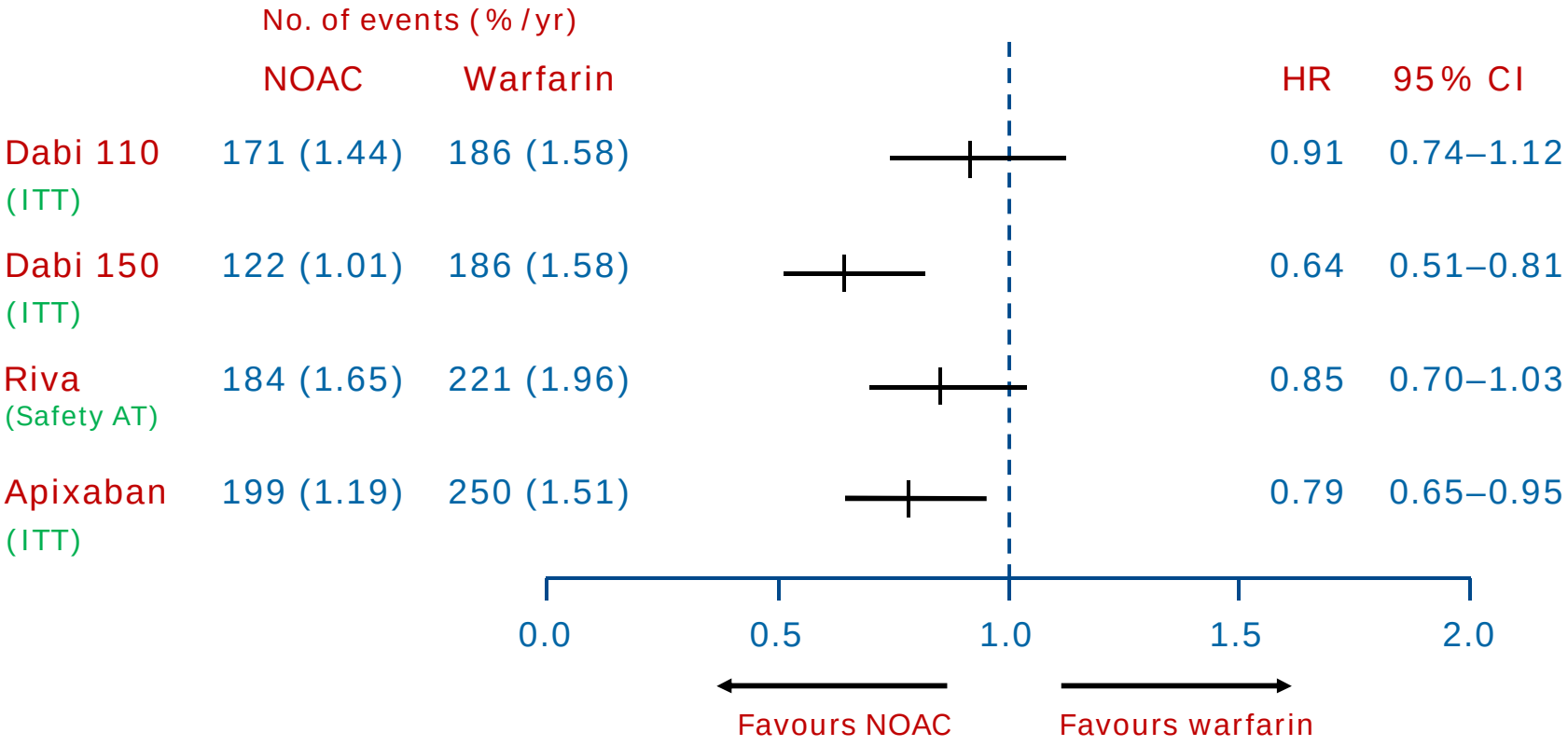


Switch patients from aspirin to anticoagulation

Data from a prospective stroke registry of 597 patients with AF at high risk of stroke (*1 high-risk factor or ?a1 moderate-risk factor according to American College of Chest Physicians guidelines)

Gladstone DJ et al. Stroke 2009;40:235–40

Stroke

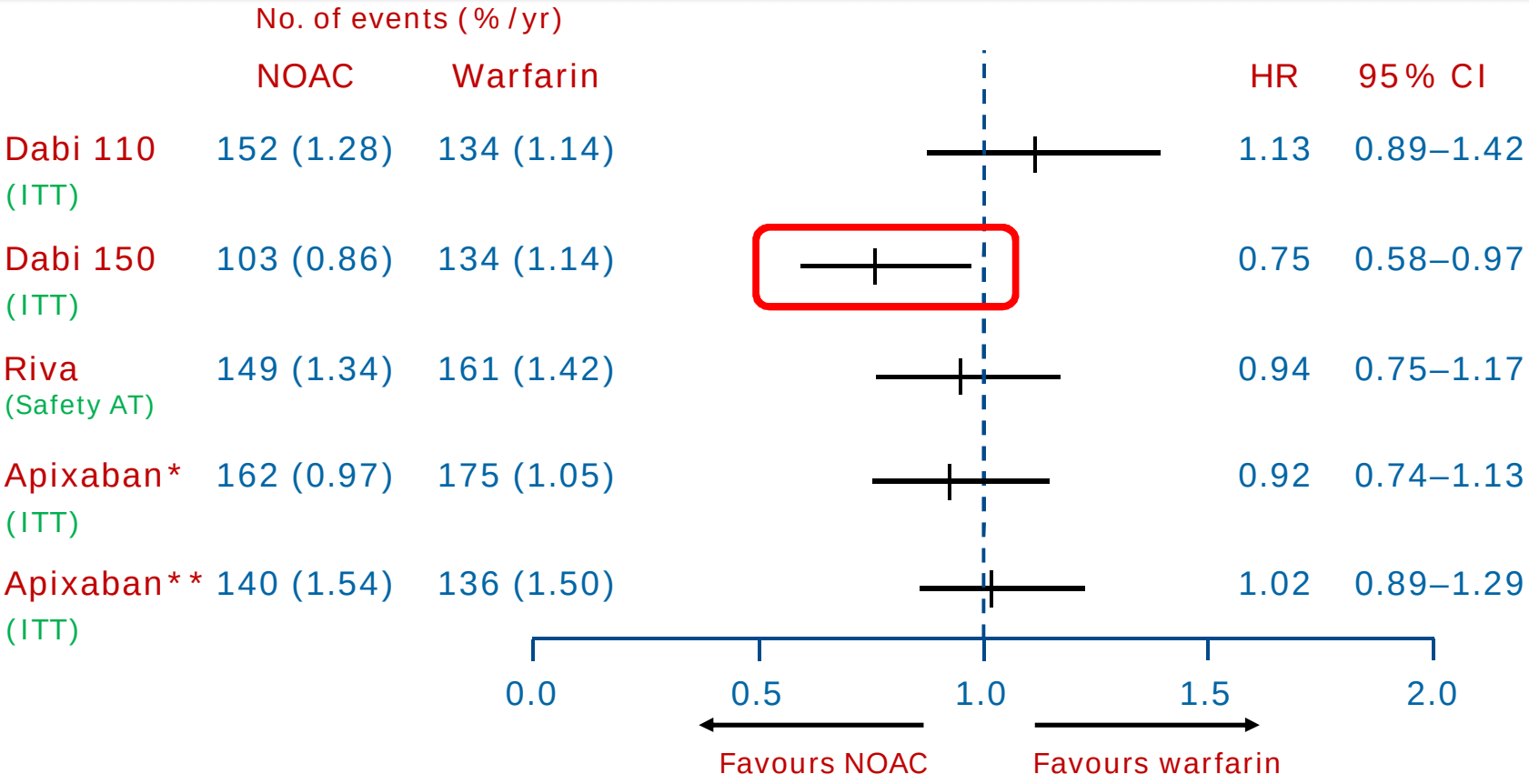


Not head-to-head comparison – for illustrative purposes only – adapted from references 1–4

AT = as treated; CI = confidence interval; Dabi 110/150 = dabigatran 110 mg/150 mg twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant; Riva = rivaroxaban

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92

Ischaemic stroke



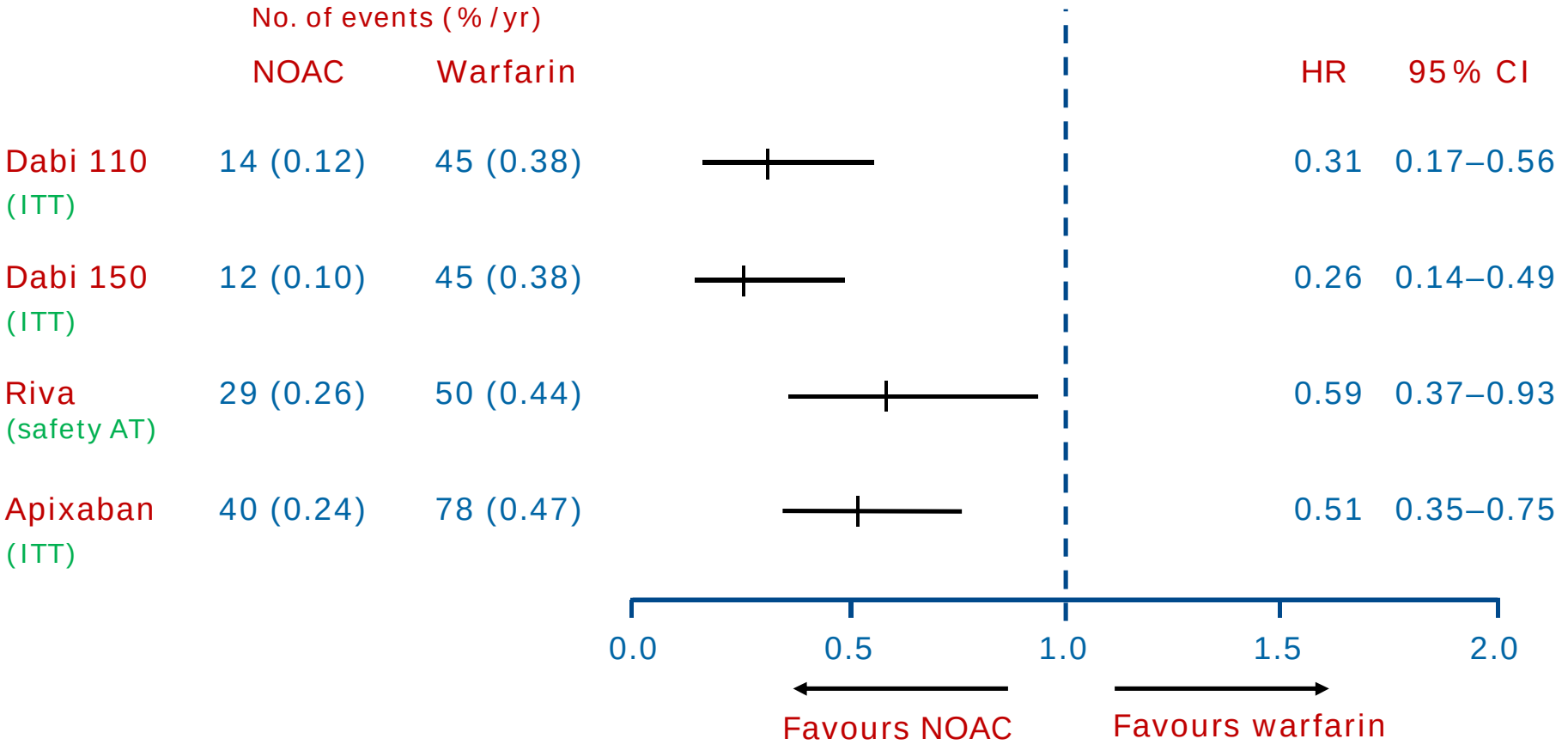
Not head-to-head comparison – for illustrative purposes only – adapted from references 1–5

*Unknown type of stroke occurred in 14 patients in the apixaban group and 21 patients in the warfarin group. Among the patients with ischaemic strokes, haemorrhagic transformation occurred in 12 patients with apixaban and 20 patients with warfarin

** Revised data; re-categorized following original publication

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92;
5. Lopes R et al. Lancet 2012; 380:1749–58

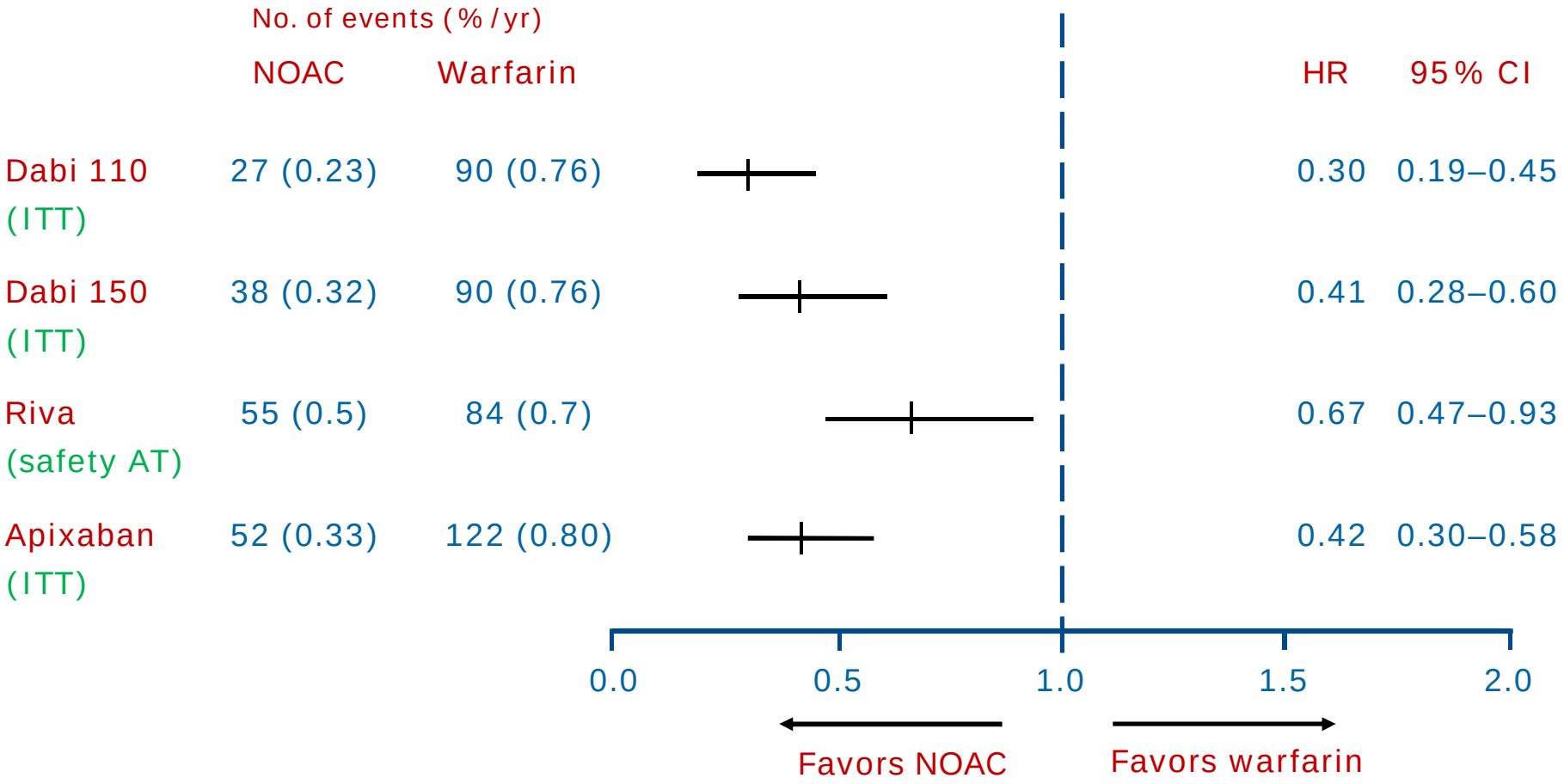
Haemorrhagic stroke



Not head-to-head comparison – for illustrative purpose only – adapted from references 1–4

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92

Intracranial bleeding



Not head-to-head comparison – for illustrative purpose only – adapted from references 1–4

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92

Novel Anticoagulants in Secondary Stroke Prevention in Patients With AF

- TIA or ischemic stroke is the most important risk factor for recurrent stroke in patients with AF[1]
- Only a minority of AF patients with TIA or stroke are anticoagulated at present[2]
- In secondary stroke prevention the NOACs are at least as effective as warfarin or show superior efficacy for stroke risk reduction[3-5]
- NOACs have a lower risk of major bleeds and relevant decrease in the risk of cerebral hemorrhage compared with warfarin[3-5]
- Apixaban is superior to aspirin for stroke risk reduction with comparable bleeding[6]

AF, atrial fibrillation; TIA, transient ischemic attack; NOAC, novel oral anticoagulant.

1. Sacco RL, et al. *Stroke*. 2006;37:577-617; 2. Gladstone DJ, et al. *Stroke.* 2009;40:235-40; 3. Diener HC, et al. Lancet Neurol. 2010;9:1157-63; 4. Hankey G, et al. Lancet Neurol. 2012;11:315-22; 5. Easton JD, et al. *Lancet Neurol* 2012; 11:503-11; 6. Diener HC, et al. *Lancet Neurol.* 2012;11:225-31.

Novel Oral Anticoagulants in Patients With Atrial

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack : A Systematic Review and Meta-Analysis of Randomized Controlled Trials

George Ntaios, Vasileios Papavasileiou, Hans-Christoph Diener, Konstantinos Makaritsis and Patrik Michel

Stroke. published online November 13, 2012;

NOAC, novel oral anticoagulant.

Ntaios G, et al. *Stroke.* 2012

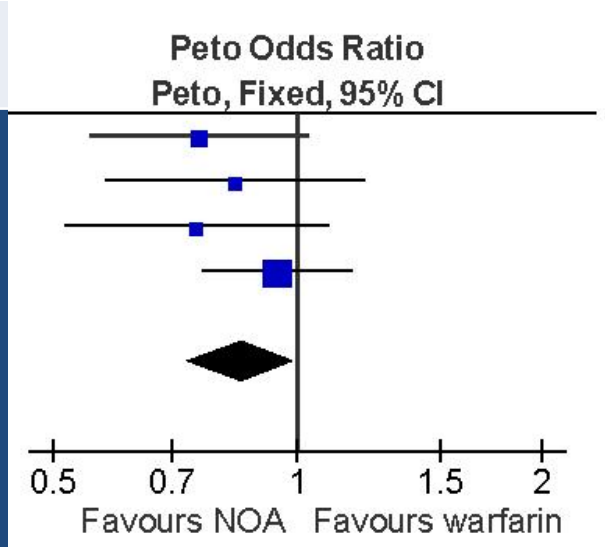
This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.

Effects of Novel Oral Anticoagulants Versus Warfarin on Stroke or Systemic Embolism in Patients With AF and Previous Stroke or TIA (1)

Stroke or Systemic Embolism	NOACs		Warfarin			Peto Odds Ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed (95% CI)
ARISTOTLE	73	1694	98	1742	22.1%	0.76 (0.56–1.03)
RELY 110	55	1195	65	1195	15.5%	0.84 (0.58–1.21)
RELY 150	51	1233	65	1195	15.0%	0.75 (0.52–1.09)
ROCKET-AF	179	3754	187	3714	47.4%	0.94 (0.77–1.17)
Total (95% CI)		7876		7846	100%	0.85 (0.74–0.99)
Total events	358		415			

Heterogeneity: $\chi^2 = 1.93$, $df = 3$ ($P = 0.59$); $I^2 = 0\%$
Test for overall effect: $Z = 2.15$ ($P = 0.03$)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.



AF, atrial fibrillation; TIA, transient ischemic attack; NOAC, novel oral anticoagulant.

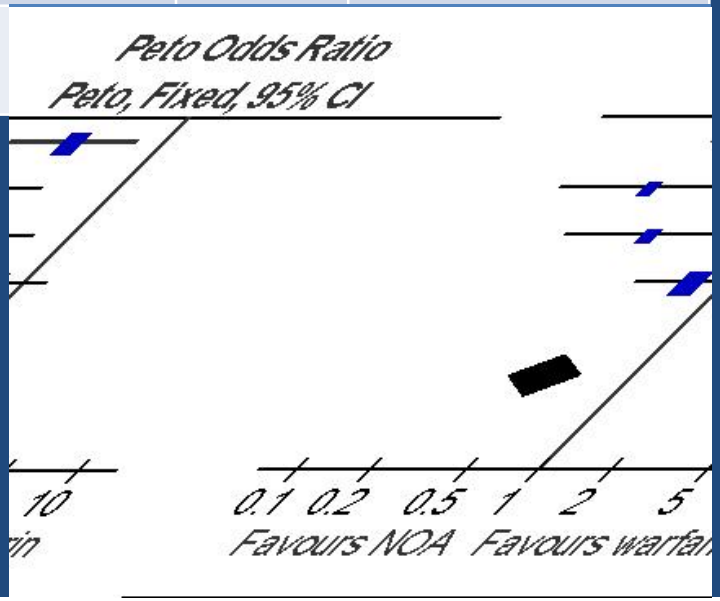
Ntaios G, et al. *Stroke.* In press.

Effects of Novel Oral Anticoagulants Versus Warfarin on Hemorrhagic Stroke in Patients With AF and Previous Stroke or TIA (2)

Hemorrhagic Stroke	NOACs		Warfarin			Peto Odds Ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed (95% CI)
ARISTOTLE	12	1694	31	1742	31.1%	0.42 (0.23–0.77)
RELY 110	2	1195	18	1195	14.5%	0.20 (0.08–0.48)
RELY 150	5	1233	18	1195	16.7%	0.31 (0.14–0.70)
ROCKET-AF	22	3754	30	3714	37.8%	0.73 (0.32–0.62)
Total (95% CI)		7876		7846	100%	0.44 (0.32– 0.62)
Total events	41		97			

Heterogeneity: $\chi^2 = 7.07$, $df = 3$ ($P = 0.07$); $I^2 = 58\%$
Test for overall effect: $Z = 4.79$ ($P < 0.00001$)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.



AF, atrial fibrillation; TIA, transient ischemic attack; NOAC, novel oral anticoagulant.

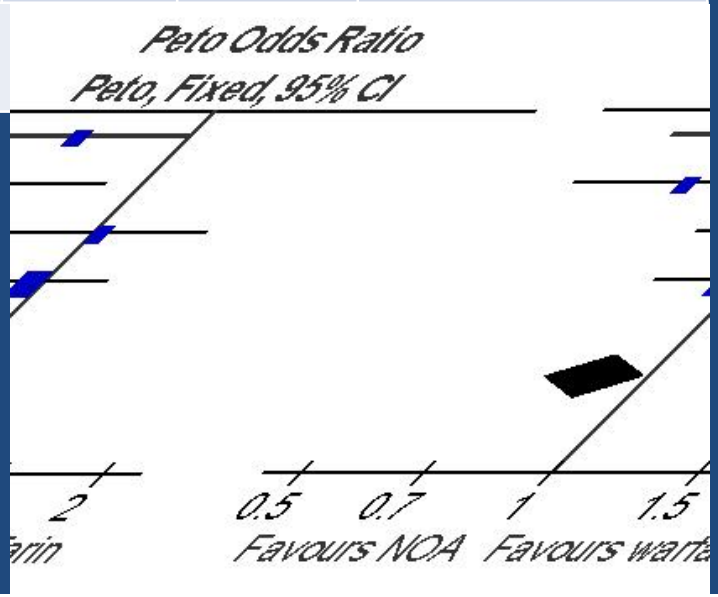
Ntaios G, et al. *Stroke.* In press.

Effects of Novel Oral Anticoagulants Versus Warfarin on Major Bleeding in Patients with AF and Previous Stroke or TIA (3)

Major Bleeding	NOACs		Warfarin			Peto Odds Ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed (95% CI)
ARISTOTLE	77	1694	106	1742	20.4%	0.75 (0.55–0.99)
RELY 110	65	1195	97	1195	17.8%	0.65 (0.48–0.90)
RELY 150	102	1233	97	1195	21.5%	1.02 (0.76–1.36)
ROCKET-AF	178	3754	183	3714	40.4%	0.96 (0.75–0.99)
Total (95% CI)		7876		7846		0.86 (0.75–0.99)
Total events	422		483			

Heterogeneity: $\chi^2 = 6.23$, $df = 3$ ($P = 0.10$); $I^2 = 52\%$
Test for overall effect: $Z = 2.18$ ($P = 0.03$)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.



AF, atrial fibrillation; TIA, transient ischemic attack; NOAC, novel oral anticoagulant.

Ntaios G, et al. *Stroke.* In press.

Meta-analysis: NOACs Versus Warfarin in Secondary Stroke Prevention

Reduction in stroke and systemic embolism

- Odds Ratio 0.85
- Relative risk reduction 14.0%
- Absolute risk reduction 0.7%
- NNT 134

Major bleed

- Odds Ratio 0.86
- Relative risk reduction 13.0%
- Absolute risk reduction 0.8%
- NNT 125

NOAC, novel oral anticoagulant; OR, odds ratio; NNT, number needed to treat.

Ntaios G, et al. *Stroke.* In press. This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available

Final conclusion

- Highest priorities in AF patients
  - Get untreated patients treated with oral anticoagulation
  - Switch patients from aspirin to new oral anticoagulants
  - Switch patients with poor INR control on warfarin to NOACs
- Low priority
  - Switch well controlled patients on warafarin to NOACs

When to Start a NOAC After an Acute Stroke

Stroke severity	Restart dabigatran
TIA	As soon as imaging has excluded a cerebral hemorrhage
Mild stroke	3-5 days after symptom onset
Moderate stroke	5-7 days after stroke onset
Severe stroke	2 weeks after stroke onset

NOAC, novel oral anticoagulant; TIA, transient ischemic attack.

Huisman M, et al. *Thromb Haemost*. doi:10.1160/TH11-10-0718.

Secondary Stroke Prevention

- Antiplatelet drugs
- Anticoagulation
- **Patent foramen ovale (PFO)**
- Carotid stenosis
- Intracranial stenosis

PFO Closure in Cryptogenic Stroke

Background

- Patients aged <60 years with cryptogenic stroke have a higher incidence of patent foramen ovale (PFO) with or without atrial septum aneurysm
- Open observational studies reported a decrease in stroke risk after PFO closure

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

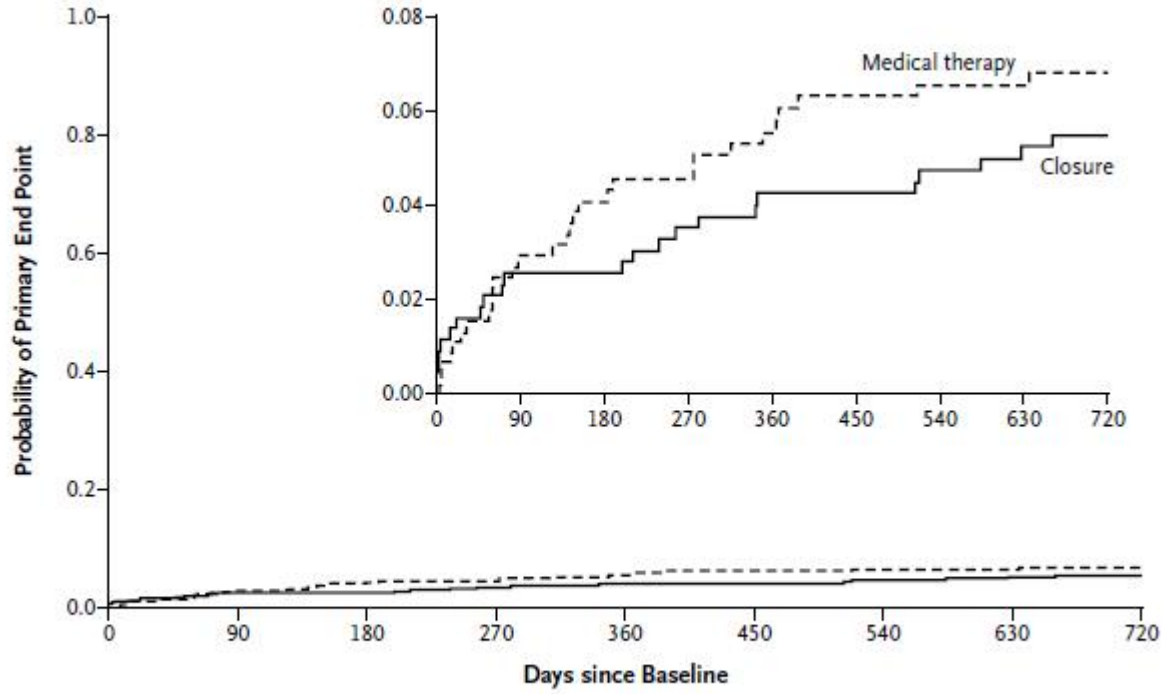
Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

METHODS

We conducted a multicenter, randomized, open-label trial of closure with a percutaneous device, as compared with medical therapy alone, in patients between 18 and 60 years of age who presented with a cryptogenic stroke or transient ischemic attack (TIA) and had a patent foramen ovale. The primary end point was a composite of stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years.

Table 2. Kaplan–Meier Event Rates for Primary End Point at 2 Years.*

End Point	Closure (N=447)	Medical Therapy (N=462)	Hazard Ratio (95% CI)†‡	P Value†
Intention-to-treat population				
Composite end point — no. (%)	23 (5.5)	29 (6.8)	0.78 (0.45–1.35)	0.37
Stroke — no. (%)	12 (2.9)	13 (3.1)	0.90 (0.41–1.98)	0.79
TIA — no. (%)	13 (3.1)	17 (4.1)	0.75 (0.36–1.55)	0.44



No. at Risk

Closure	447	411	406	399	392	389	384	380	254
Medical therapy	462	421	405	388	378	365	359	356	242

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

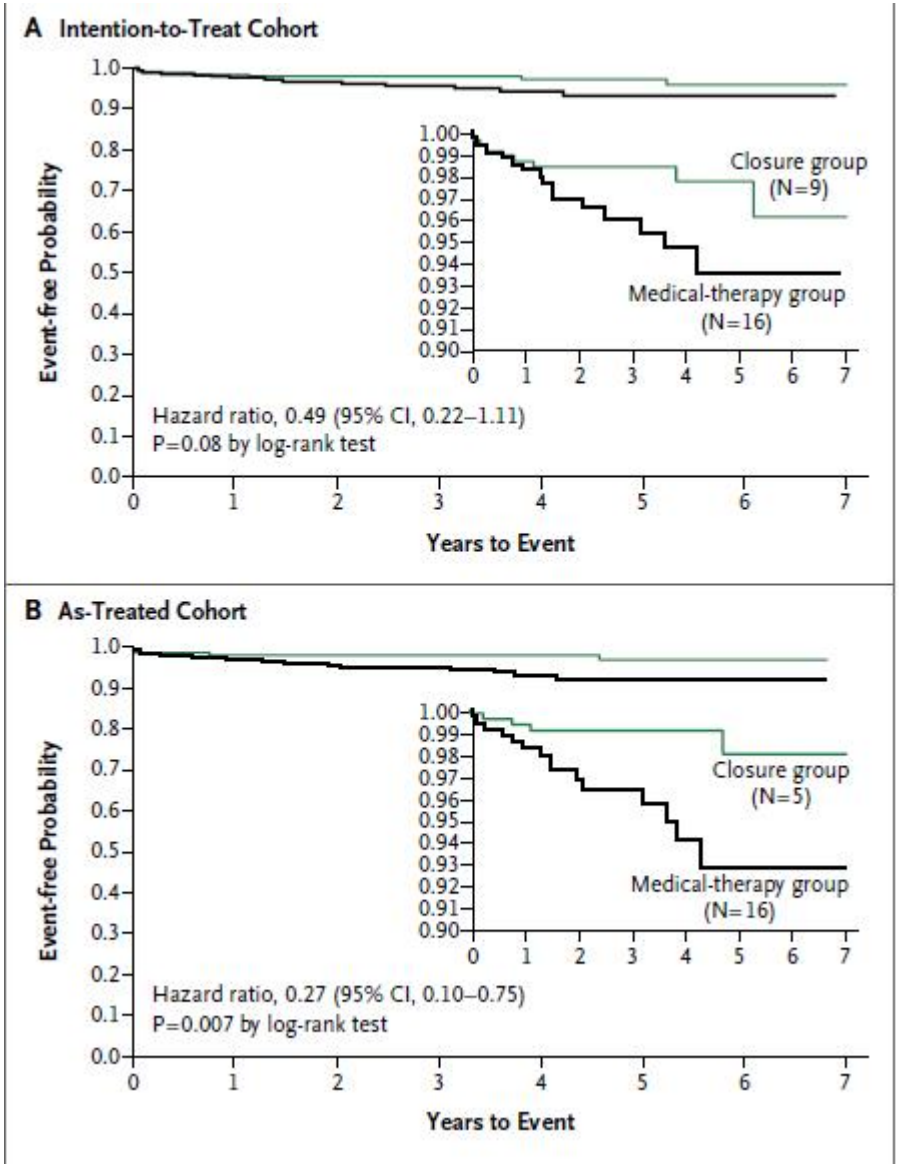
John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

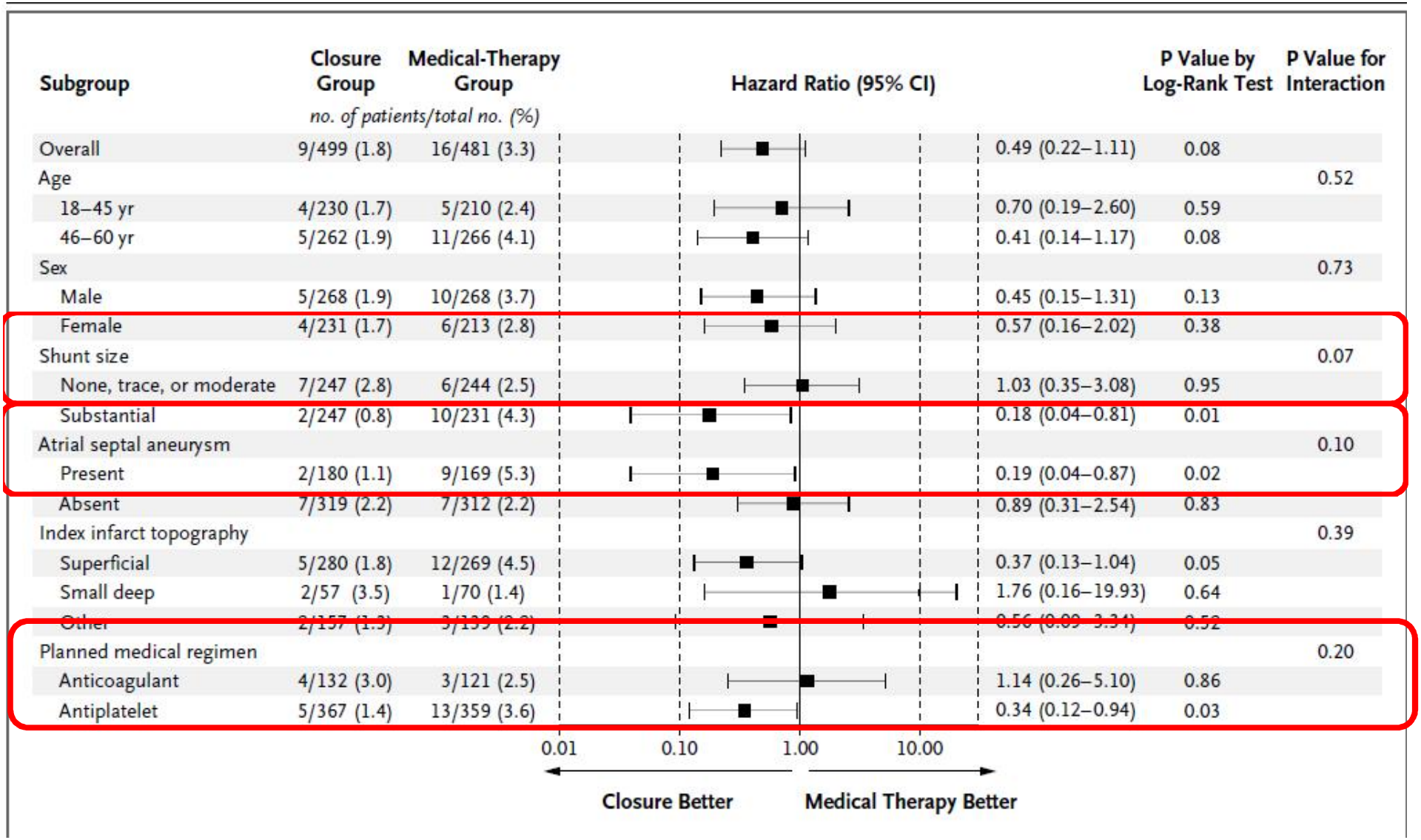
METHODS

In this prospective, multicenter, randomized, event-driven trial, we randomly assigned patients, in a 1:1 ratio, to medical therapy alone or closure of the patent foramen ovale. The primary results of the trial were analyzed when the target of 25 primary end-point events had been observed and adjudicated.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The medical-therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%).


A Intention-to-Treat Cohort
Event-free Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7
Years to Event
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
0 1 2 3 4 5 6 7
Closure group
(N=9)
Medical-therapy group
(N=16)
Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test
B As-Treated Cohort
Event-free Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7
Years to Event
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
0 1 2 3 4 5 6 7
Closure group
(N=5)
Medical-therapy group
(N=16)
Hazard ratio, 0.27 (95% CI, 0.10–0.75)
P=0.007 by log-rank test


Subgroup
Closure Group
Medical-Therapy Group
no. of patients/total no. (%)
Hazard Ratio (95% CI)
P Value by Log-Rank Test
P Value for Interaction
Overall 9/499 (1.8) 16/481 (3.3) 0.49 (0.22–1.11) 0.08
Age 0.52
18–45 yr 4/230 (1.7) 5/210 (2.4) 0.70 (0.19–2.60) 0.59
46–60 yr 5/262 (1.9) 11/266 (4.1) 0.41 (0.14–1.17) 0.08
Sex 0.73
Male 5/268 (1.9) 10/268 (3.7) 0.45 (0.15–1.31) 0.13
Female 4/231 (1.7) 6/213 (2.8) 0.57 (0.16–2.02) 0.38
Shunt size 0.07
None, trace, or moderate 7/247 (2.8) 6/244 (2.5) 1.03 (0.35–3.08) 0.95
Substantial 2/247 (0.8) 10/231 (4.3) 0.18 (0.04–0.81) 0.01
Atrial septal aneurysm 0.10
Present 2/180 (1.1) 9/169 (5.3) 0.19 (0.04–0.87) 0.02
Absent 7/319 (2.2) 7/312 (2.2) 0.89 (0.31–2.54) 0.83
Index infarct topography 0.39
Superficial 5/280 (1.8) 12/269 (4.5) 0.37 (0.13–1.04) 0.05
Small deep 2/57 (3.5) 1/70 (1.4) 1.76 (0.16–19.93) 0.64
Other 2/157 (1.3) 3/139 (2.2) 0.56 (0.09–3.34) 0.52
Planned medical regimen 0.20
Anticoagulant 4/132 (3.0) 3/121 (2.5) 1.14 (0.26–5.10) 0.86
Antiplatelet 5/367 (1.4) 13/359 (3.6) 0.34 (0.12–0.94) 0.03
0.01
0.10
1.00
10.00
Closure Better
Medical Therapy Better

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

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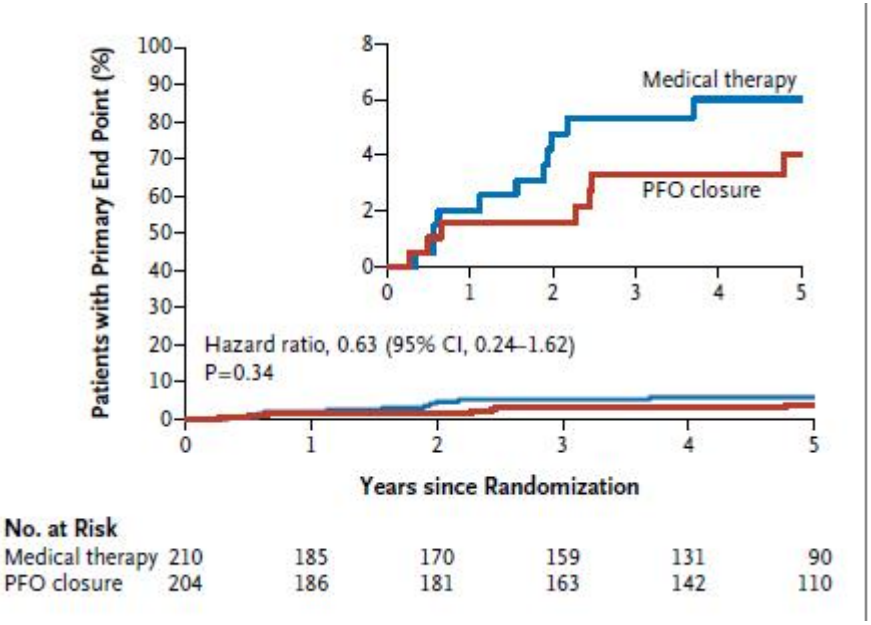
Table 1. Baseline Characteristics of the Patients.*

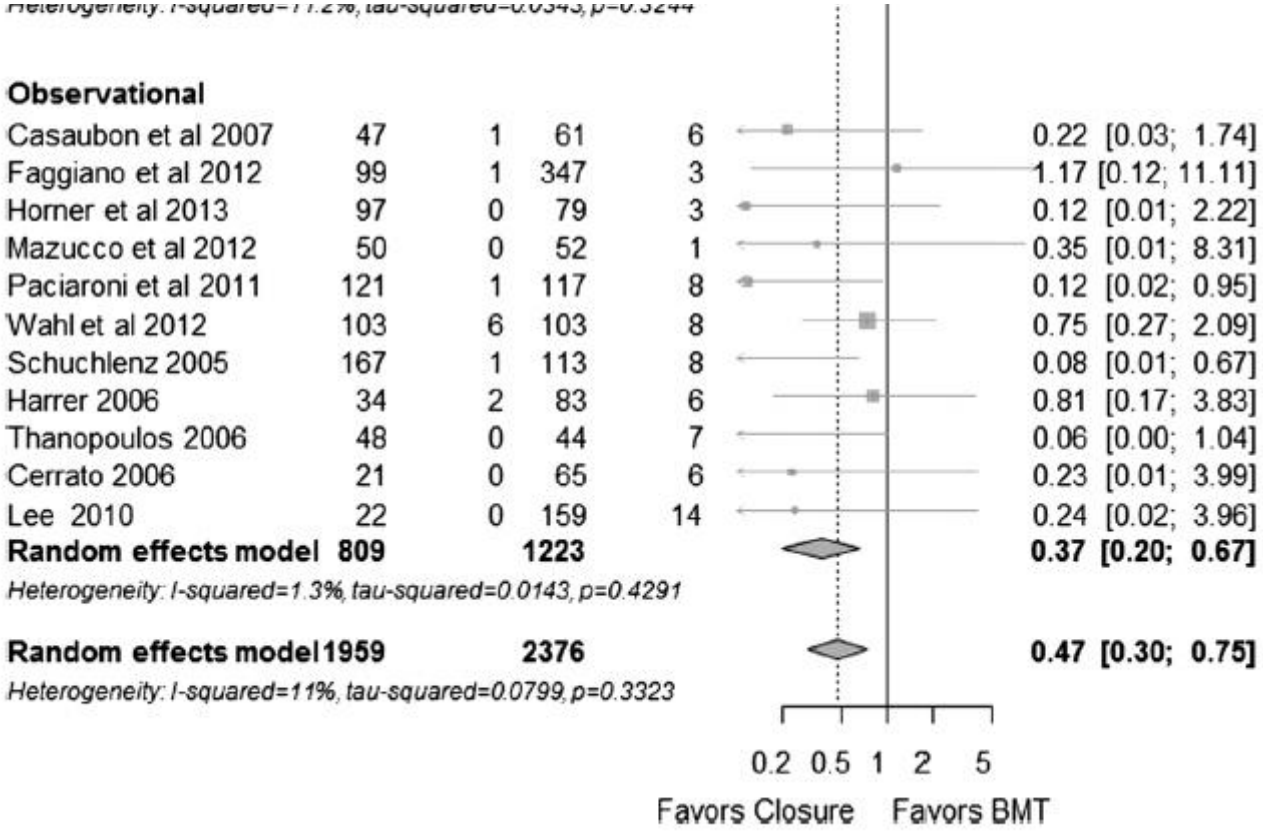
Characteristic	PFO Closure (N=204)	Medical Therapy (N=210)
Age — yr	44.3±10.2	44.6±10.1
Male sex — no. (%)	92 (45.1)	114 (54.3)
Body-mass index†	26.6±5.6	26.3±4.8
Family history of cerebrovascular event — no. (%)	53 (26.0)	40 (19.0)
Current smoker — no. (%)	52 (25.5)	47 (22.4)
Arterial hypertension — no. (%)	49 (24.0)	58 (27.6)
Diabetes mellitus — no. (%)	5 (2.5)	6 (2.9)
Hypercholesterolemia — no. (%)	50 (24.5)	62 (29.5)
Valvular heart disease — no. (%)	8 (3.9)	5 (2.4)
Peripheral vascular disease — no. (%)	3 (1.5)	2 (1.0)
Coronary artery disease — no. (%)	4 (2.0)	4 (1.9)
History of myocardial infarction — no. (%)	3 (1.5)	1 (0.5)
Migraine — no. (%)	47 (23.0)	38 (18.1)
Cerebrovascular index event — no. (%)		
Peripheral embolism	6 (2.9)	5 (2.4)
Transient ischemic attack	33 (16.2)	42 (20.0)
Stroke	165 (80.9)	163 (77.6)



Outcome	PFO Closure (N=204)	Medical Therapy (N=210)	Hazard Ratio or Relative Risk (95% CI)†	P Value
	no. of patients (%)			
Primary composite outcome of death, stroke, TIA, or peripheral embolism	7 (3.4)	11 (5.2)	0.63 (0.24–1.62)	0.34
Death‡	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Cardiovascular	0	0	NA	
Noncardiovascular	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Thromboembolic event				
Stroke§	1 (0.5)	5 (2.4)	0.20 (0.02–1.72)	0.14
TIA	5 (2.5)	7 (3.3)	0.71 (0.23–2.24)	0.56

Stroke prevention by percutaneous closure of patent foramen ovale: a systematic review and meta-analysis

Mathias Wolfrum,[1] Georg M Froehlich,[2] Guido Knapp,[3] Leanne K Casaubon,[4] James J DiNicolantonio,[5] Alexandra J Lansky,[6] Pascal Meier[2,6]



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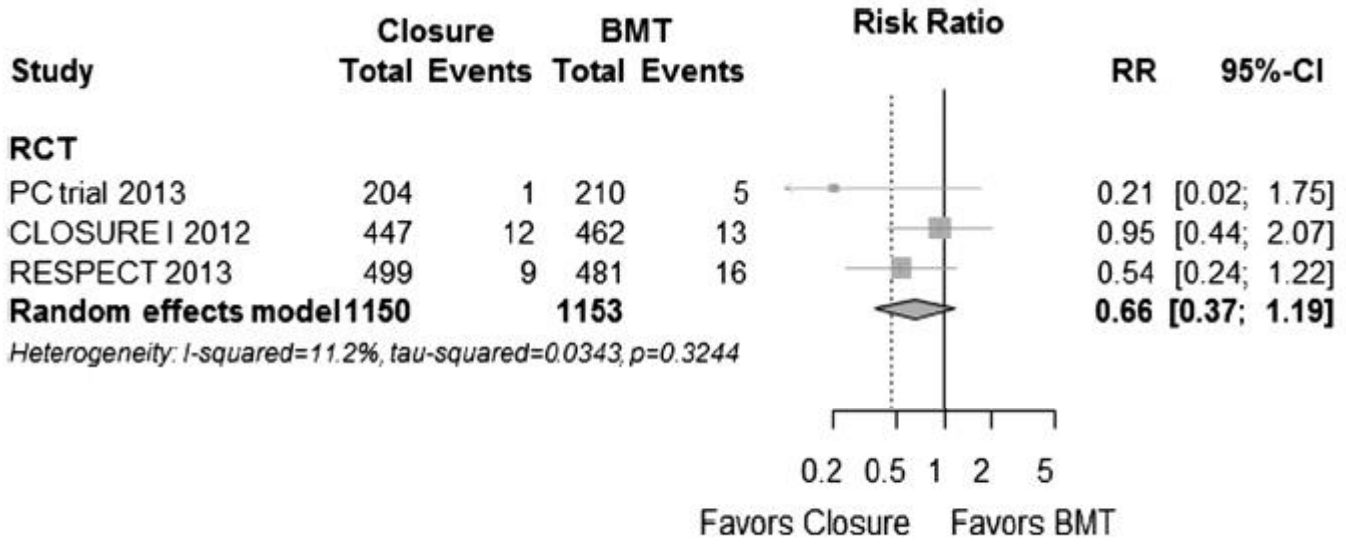


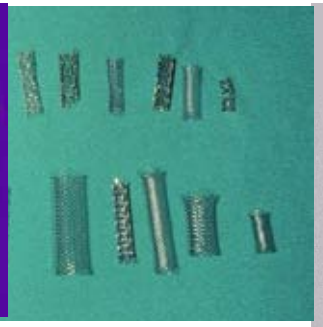
PFO Closure in Patients with Cryptogenic Stroke

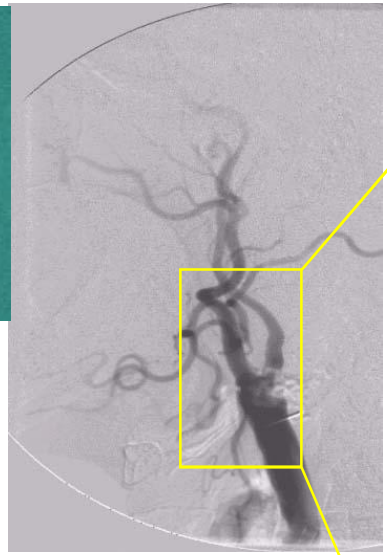
- At present 3 randomised trials without statistically significant benefit
- PFO closure recommended in patients with proven or suspected paradoxical embolism (DVT, pulmonary embolism, Valsalva) or recurrent stroke despite antithrombotic therapy

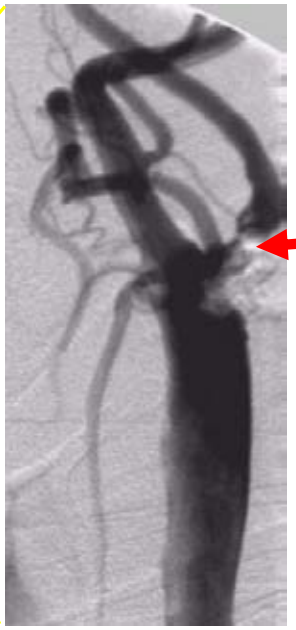
Secondary Stroke Prevention

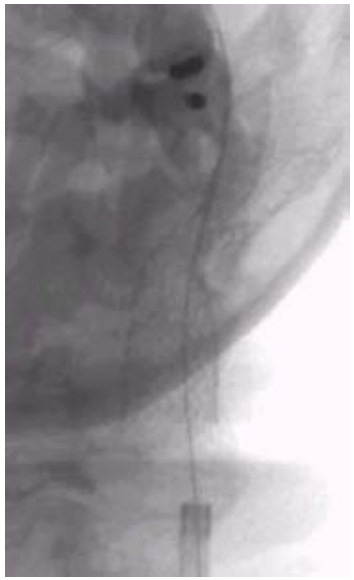
- Patent foramen ovale (PFO)
- Antiplatelet drugs
- Anticoagulation
- **Carotid stenosis**
- Intracranial stenosis

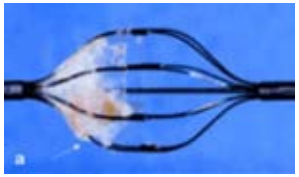
Stenting or Angioplasty in Patients with Carotid Stenosis?

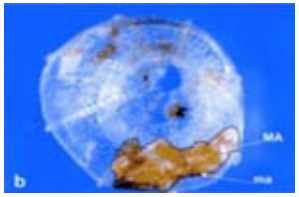




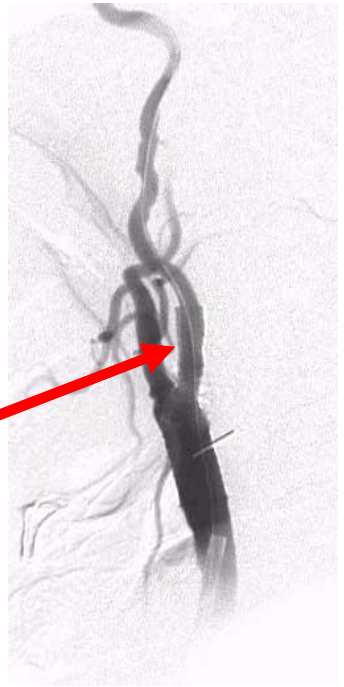








Stent



Conclusions

- Endarterectomy has a lower complication rate than stenting
- Re-stenosis rate similar
- Endarterectomy is preferred in females and patients >70 years
- Protection devices are not protecting
- Complication rate needs to be <6%

Outline

- Patent foramen ovale (PFO)
- Antiplatelet drugs
- Anticoagulation
- Carotid stenosis
- **Intracranial stenosis**

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ORIGINAL ARTICLE

Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

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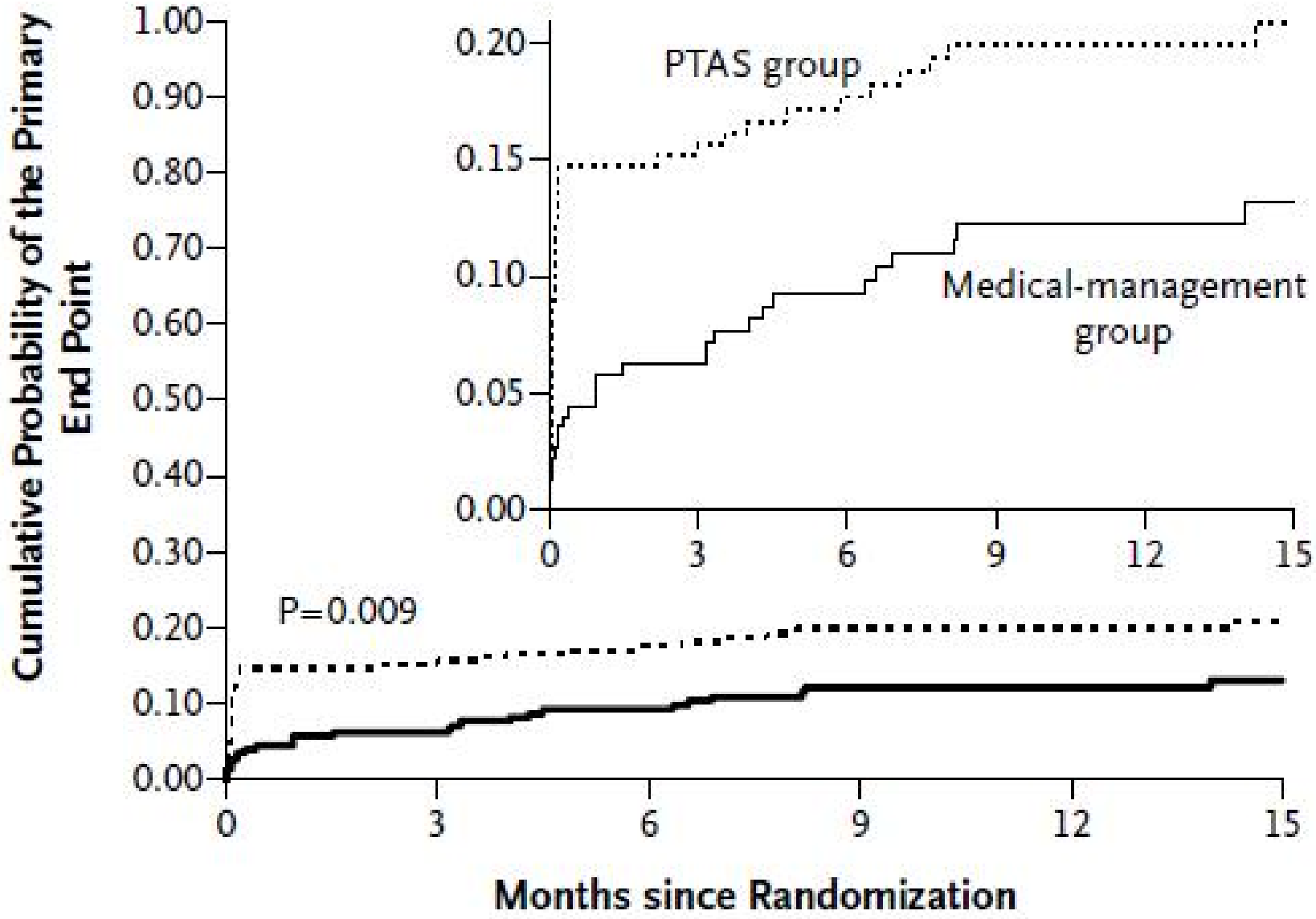

No. at Risk

Medical management group	227	196	164	132	115	92
PTAS group	224	182	153	125	98	83

Final Conclusions

- Combination antiplatelet therapy with aspirin plus clopidogrel in long term secondary stroke prevention is not superior to mono-therapy
- NOACs are superior to warfarin in patients with atrial fibrillation in terms of efficacy and safety
- PFO closure only in carefully selected patients
- Modest superiority of endarterectomy over stenting
- Intracranial stenosis should be treated with best medical therapy


Thank you for your attention