Transient Ischemic Attacks and Minor Strokes

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WMC Health Sciences Centre

Competing Interests Declaration

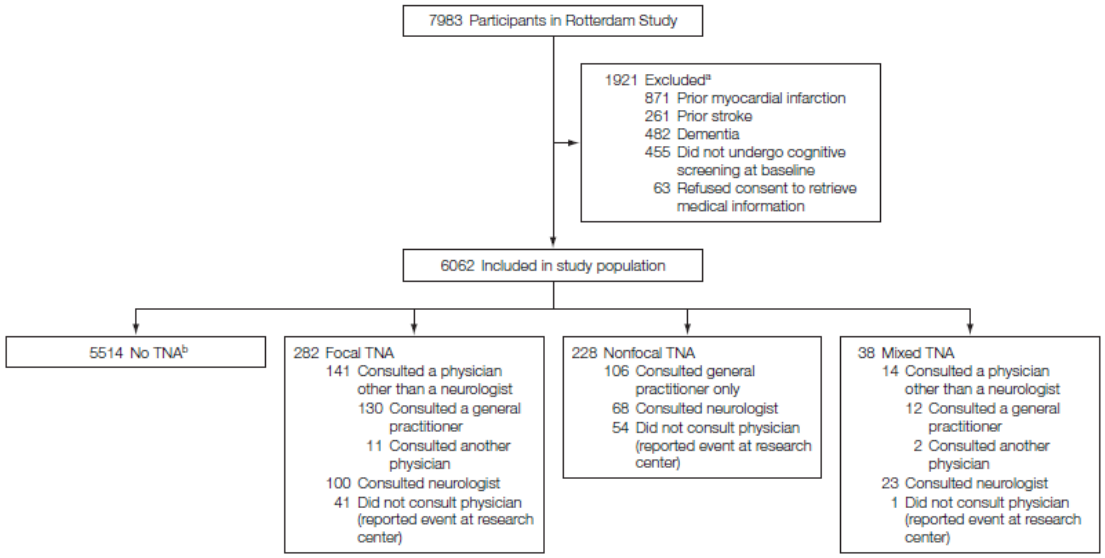
- Competing interests
  - chair the steering committee of the SENTIS trial and FastFlo Trial and was an advisor to CoAxia. I am also on the steering committee of the DIAS III & DIAS IV trials and Impact-24 trial.
- In the past 5 years, I have received speaker fees from:
    - Sanofi-Aventis/BMS, BI, Pfizer, Merck, Roche, Servier, AstraZeneca, Bayer
- In the past 5 years, I have served on advisory boards for:
    - AstraZeneca, BI, Bayer, Sanofi-Aventis/BMS, Roche, Pfizer

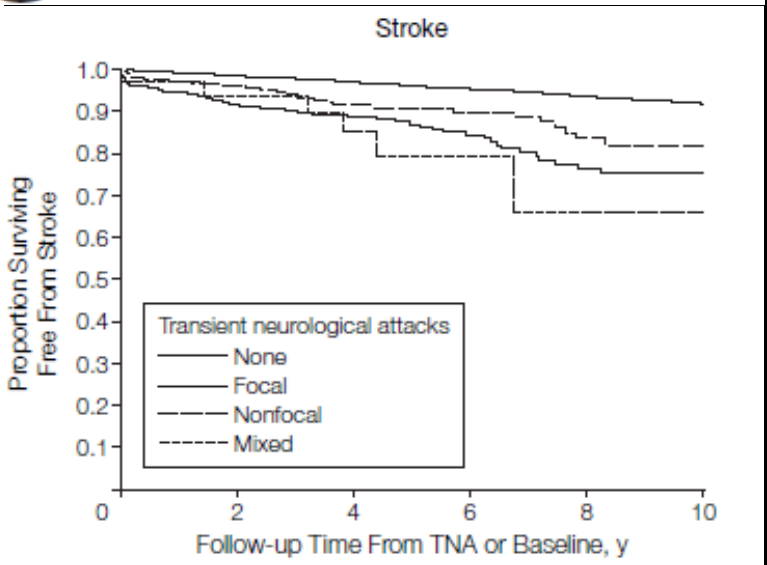
Outline/Objectives

1. The frequent “suspected TIAs” phone calls !!!!
2. The Acute Cerebrovascular Syndrome
3. Investigation Tempo
    1. CT or MRI
    2. Other investigations
4. Treatment to prevent recurrence

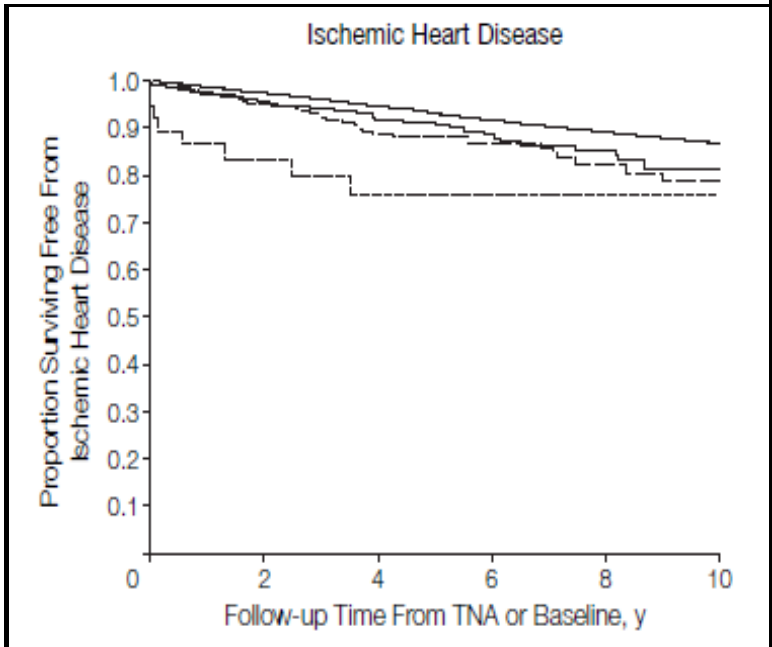
Incidence and Prognosis of Transient Neurological Attacks

JAMA. 2007;298(24):2877-2885





Results During 60 535 person-years, 548 participants developed TNA (282 focal, 228 nonfocal, and 38 mixed). The incidence rate per 1000 person-years was 4.7 (95% confidence interval [CI], 4.1-5.2) for focal TNA, 3.8 (95% CI, 3.3-4.3) for nonfocal TNA, and 0.6 (95% CI, 0.4-0.9) for mixed TNA. Participants with focal TNA were at higher risk of subsequent stroke than participants without TNA (n=46 vs 540; hazard ratio [HR], 2.14; 95% confidence interval [CI]; 1.57-2.91) but had an equal risk of ischemic heart disease and dementia. Nonfocal TNA patients were at higher risk of stroke (27 vs 540; HR, 1.56; 95% CI, 1.08-2.28) and dementia (30 vs 552; HR, 1.59; 95% CI, 1.11-2.26) than participants without TNA. Mixed TNA patients were at higher risk of stroke (6 vs 540; HR, 2.48; 95% CI, 1.11-5.56), ischemic heart disease (8 vs 779; HR, 2.26; 95% CI, 1.07-4.78), vascular death (8 vs 594; HR, 2.54; 95% CI, 1.31-4.91), and dementia (7 vs 552; HR, 3.46; 95% CI, 1.72-6.98) than participants without TNA.



Incidence and Prognosis of Transient Neurological Attacks

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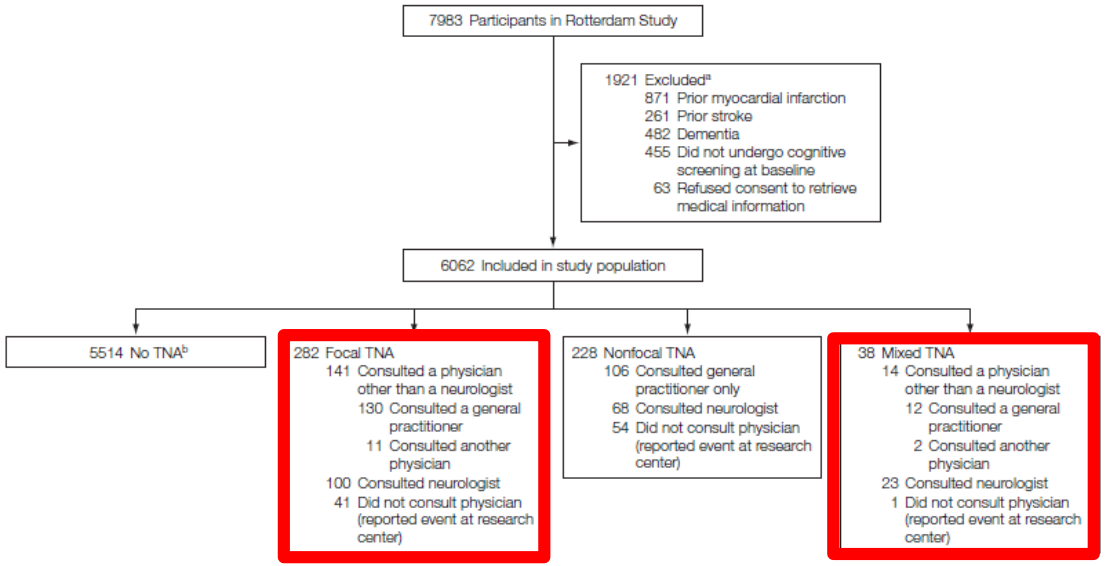

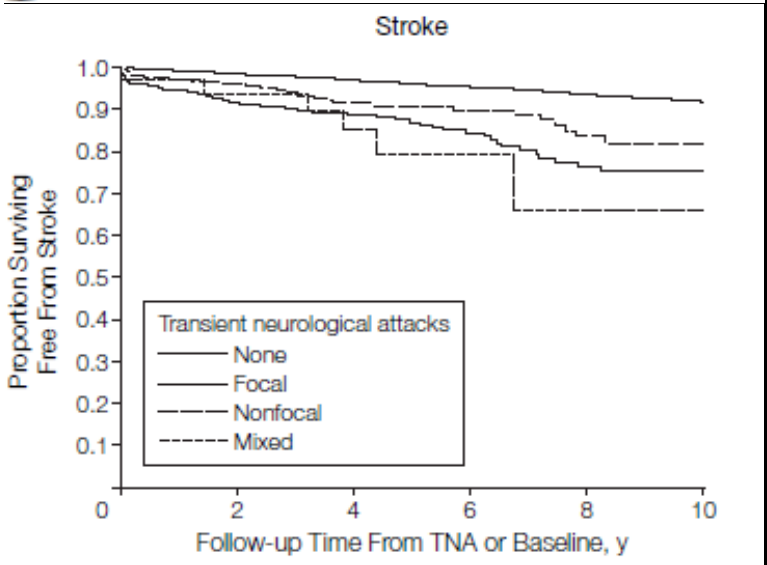

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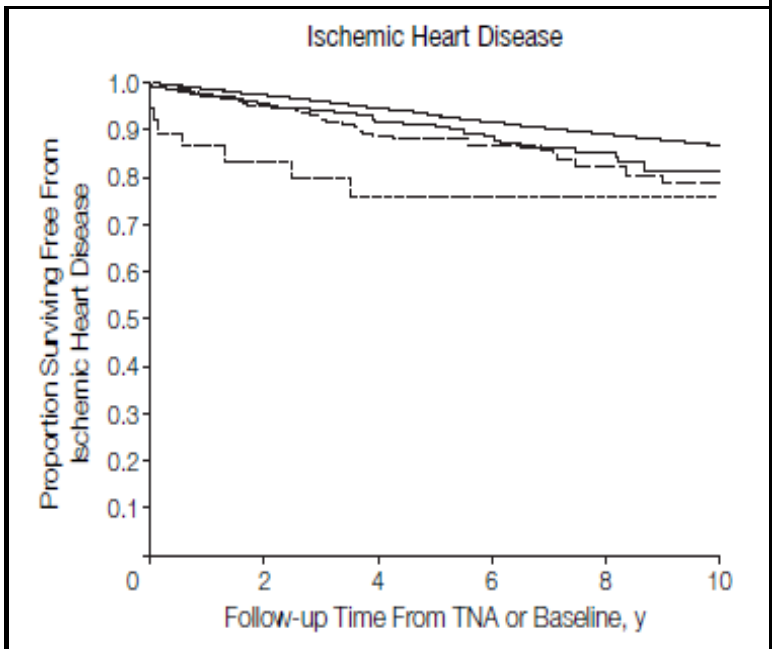
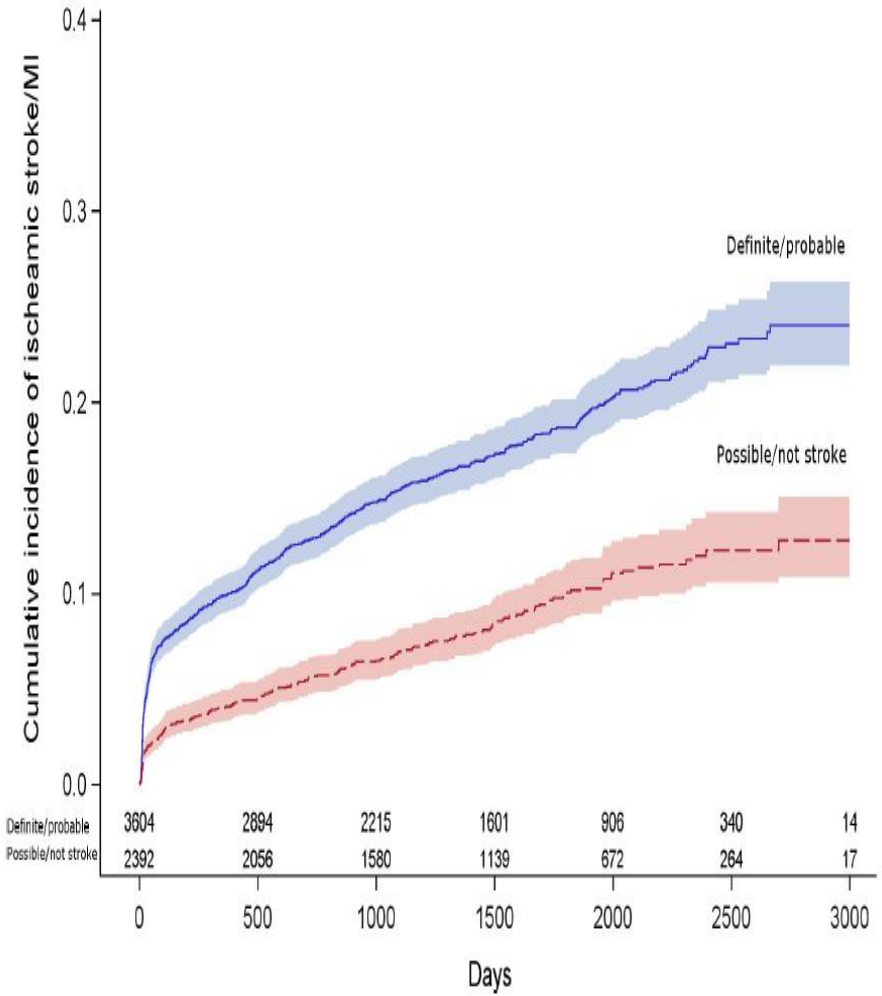


RESEARCH ARTICLE PLOS ONE | https://doi.org/10.1371/journal.pone.0210452 March 19, 2019

Clinical diagnosis of TIA or minor stroke and prognosis in patients with neurological symptoms: A rapid access clinic cohort



5,997 patients were seen from 2005–2013, who were diagnosed with TIA or minor stroke (n = 3604, 60%) or with other diagnoses (n = 2392, 40%). By 5 years the proportion of patients who had a subsequent ischaemic stroke or MI, in patients with a clinical diagnosis of minor stroke or TIA was 19% [95% confidence interval (CI): 17–20%], and in patients with other diagnoses was 10% (95%CI: 8–15%). Patients with clinical diagnosis of TIA or minor stroke had three times the hazard of stroke or MI compared to patients with other diagnoses [hazard ratio (HR)2.83 95%CI:2.13–3.76, adjusted age and sex] by 90 days post-event; however from 90 days to end of follow up, this difference was attenuated (HR 1.52, 95%CI:1.25–1.86). Older patients and those who had a history of vascular disease had a high risk of stroke or MI, whether or not they were diagnosed with minor stroke or TIA.

Conclusion

Although it is well known that patients with a diagnosis of TIA or minor stroke are at a high risk of recurrent stroke or MI, older patients, and patients with a history or vascular events who are not diagnosed with a TIA in rapid access TIA clinics also have a moderate to high risk of stroke in the long term. Careful attention to the control of vascular risk in these patients is justified.

Recognizing that it was a TIA?

Clinical diagnosis

“Tissue not duration of time”

“Brief episode (typically minutes - hrs)

“Highest risk very early following event”

Encourages immediate neurodiagnostic tests, facilitates rapid intervention, consistent with angina/MI distinctions

Albers GW et al. N EnglJ Med 2002;347:1713-1716).

Recognizing that it was a TIA?

Clinical diagnosis

“Tissue not duration of time”

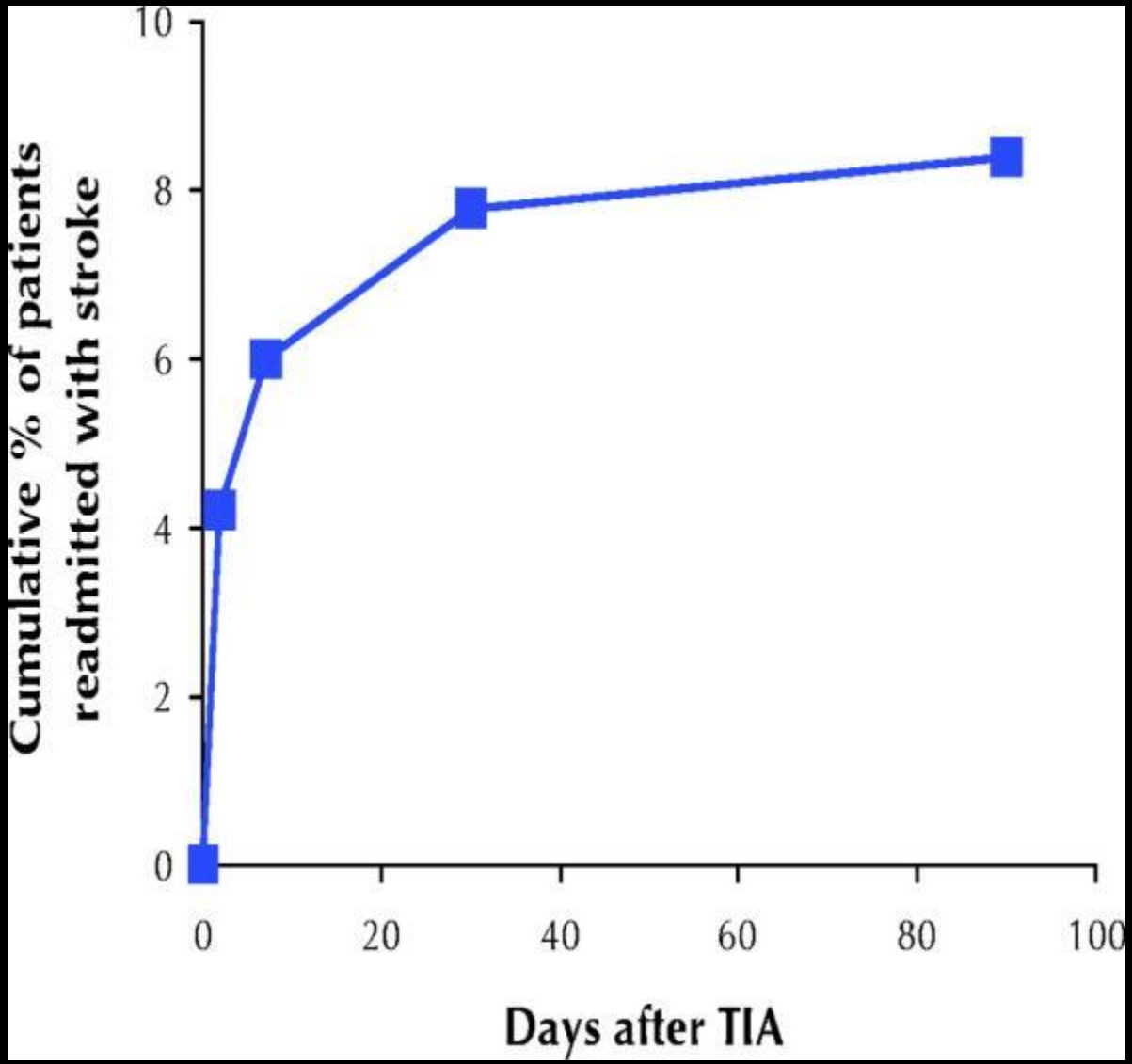
“Brief episode (typically <1h)

“Highest risk very early following event”

Encourages immediate neurodiagnostic tests, facilitates rapid intervention, consistent with angina/MI distinctions

Albers GW et al. N EnglJ Med 2002;347:1713-1716).

TIA Investigation Tempo: Emergent!



Gladstone, D. J. et al. CMAJ 2004;170:1099-1104

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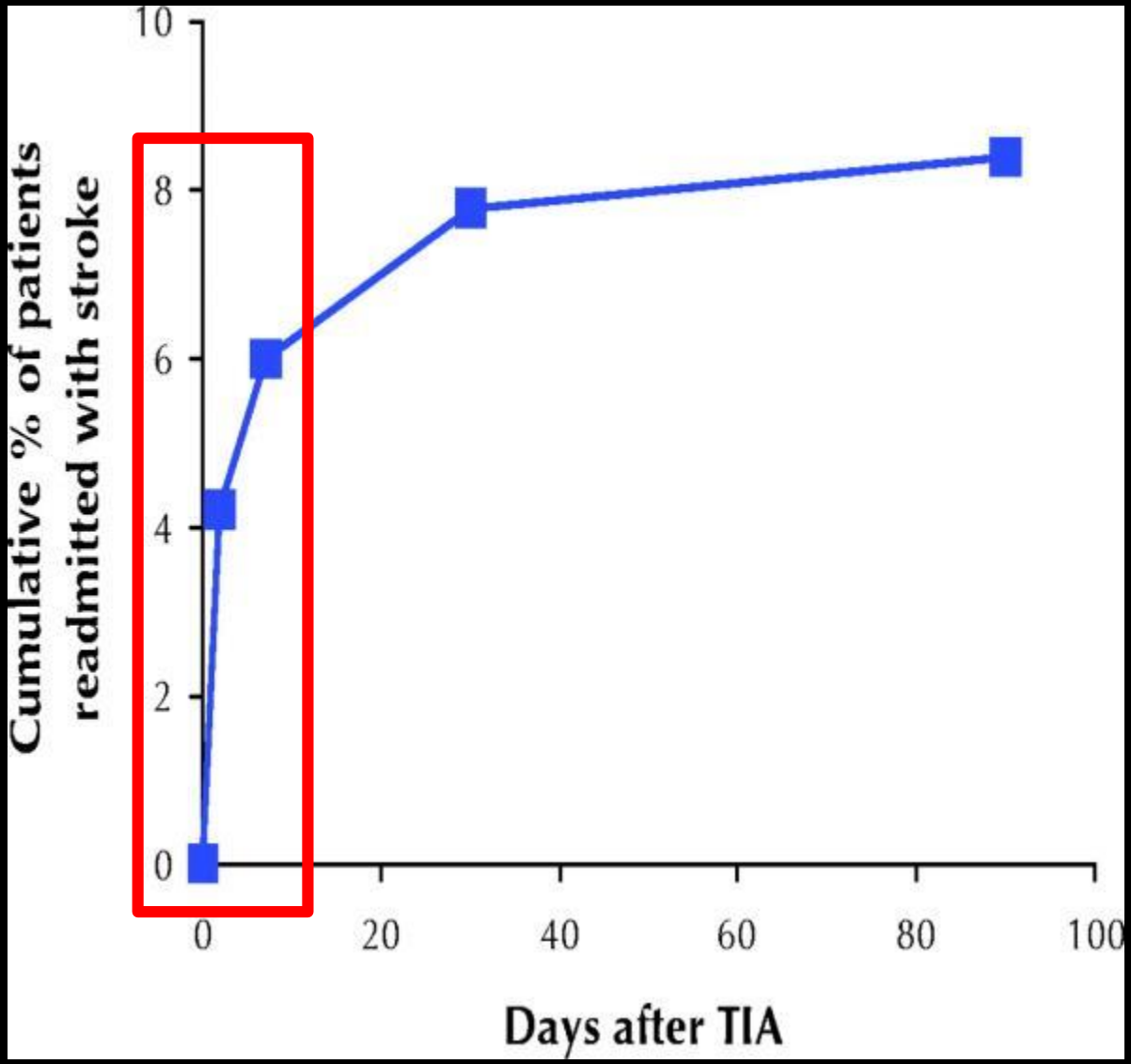


Gladstone, D. J. et al. CMAJ 2004;170:1099-1104

TIA Risk Stratification: $ABCD^2$ Score

A: age ≥ 60 years – 1 point

B: BP (systolic>140mmHg, diastolic>90 mmHg). Either 1 point. (max 1 point)

C: clinical – unilateral weakness =2, speech only = 1

D: Duration, ≥60 minutes =2, 10-59 =1, <10 =0

D2: Diabetes=1

Rothwell PM, Lancet 2005; 366:29-36, Johnston, SC, Lancet 2007;369:283-292.

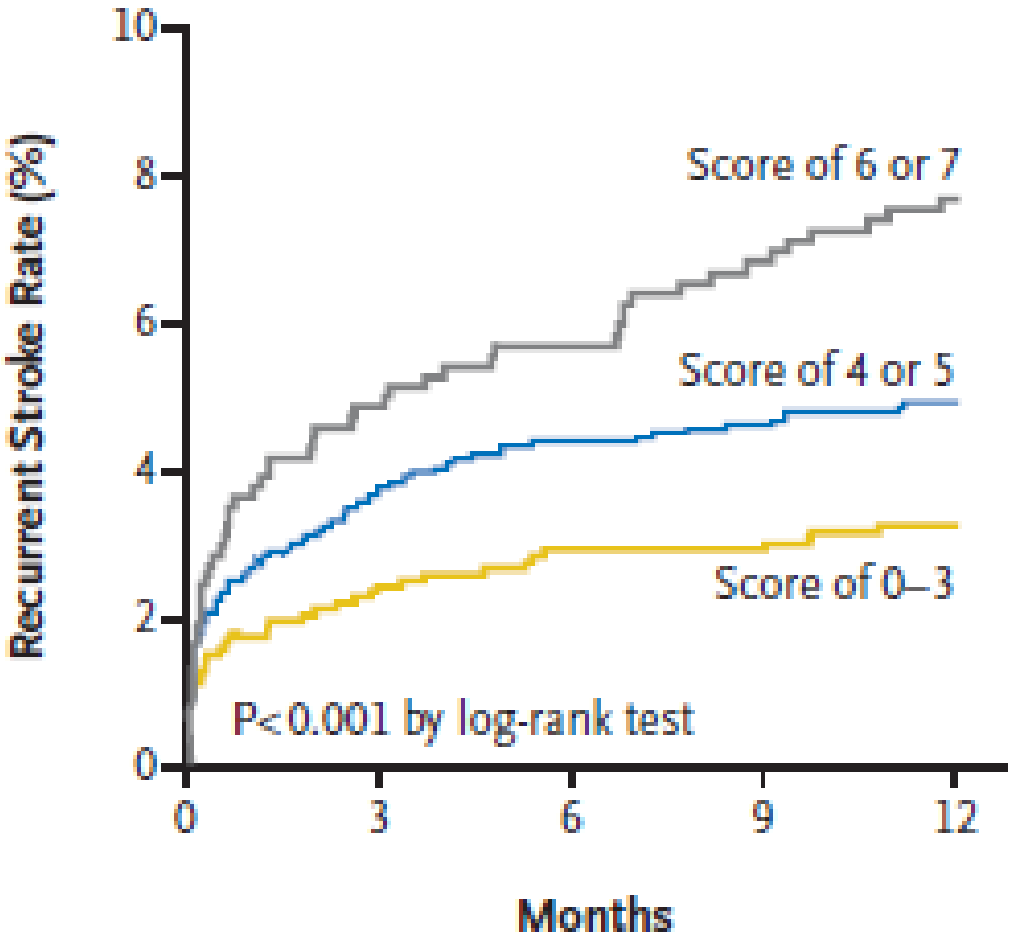
ORIGINAL ARTICLE

One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke

Pierre Amarenco, M.D., Philippa C. Lavallée, M.D., Julien Labreuche, B.S.T., Gregory W. Albers, M.D., Natan M. Bornstein, M.D., Patrícia Canhão, M.D., Louis R. Caplan, M.D., Geoffrey A. Donnan, M.D., José M. Ferro, M.D., Michael G. Hennerici, M.D., Carlos Molina, M.D., Peter M. Rothwell, M.D., Leila Sissani, B.S.T., David Školoudík, M.D., Ph.D., Philippe Gabriel Steg, M.D., Pierre-Jean Touboul, M.D., Shinichiro Uchiyama, M.D., Éric Vicaut, M.D., and Lawrence K.S. Wong, M.D., for the TIAregistry.org Investigators*

N Engl J Med 2016;374:1533-42.

B Rate of Recurrent Stroke According to ABCD² Stroke Risk Score



No. at Risk					
Score of 0–3	1294	1221	1175	1166	1063
Score of 4 or 5	1851	1701	1633	1625	1484
Score of 6 or 7	745	684	657	642	596

Stroke risk after transient ischemic attack in a Norwegian prospective cohort

BMC Neurology (2019) 19:2

Methods: From October, 2012, to July, 2014, we performed a prospective, multicenter study in Central Norway, enrolling patients with a TIA within the previous 2 weeks. Our aim was to assess stroke risk at 1 week, 3 months and 1 year after TIA, and to determine the predictive value of the dichotomized $ABCD^2$ score (0–3 vs 4–7) at each time point. We used data obtained by telephone follow-up and registry data from the Norwegian Stroke Register.

Results: Five hundred and seventy-seven patients with TIA were enrolled of which 85% were examined by a stroke specialist within 24 h after symptom onset. The cumulative incidence of stroke within 1 week, 3 months and 1 year of TIA was 0.9% (95% CI, 0.37–2.0), 3.3% (95% CI, 2.1–5.1) and 5.4% (95% CI, 3.9–7.6), respectively. The accuracy of the $ABCD^2$ score provided by *c*-statistics at 7 days, 3 months and 1 year was 0.62 (95% CI, 0.39–0.85), 0.62 (95% CI, 0.51–0.74) and 0.64 (95% CI, 0.54–0.75), respectively.

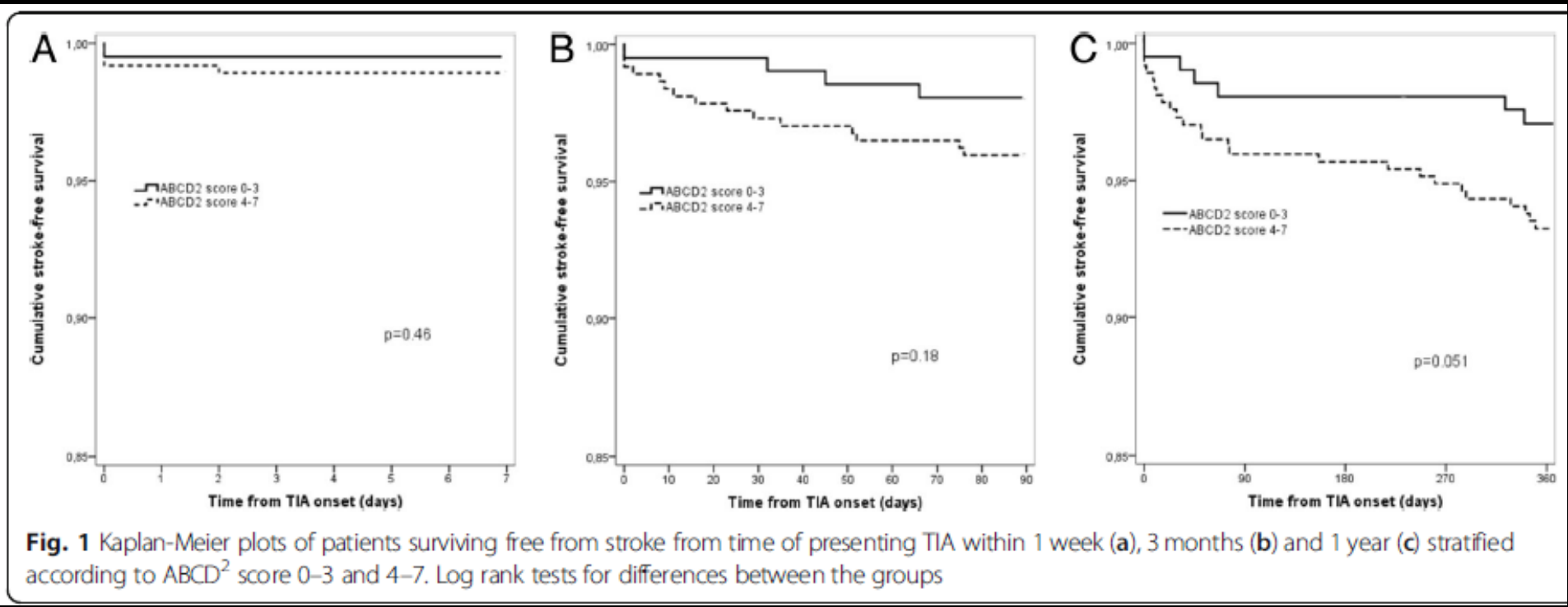
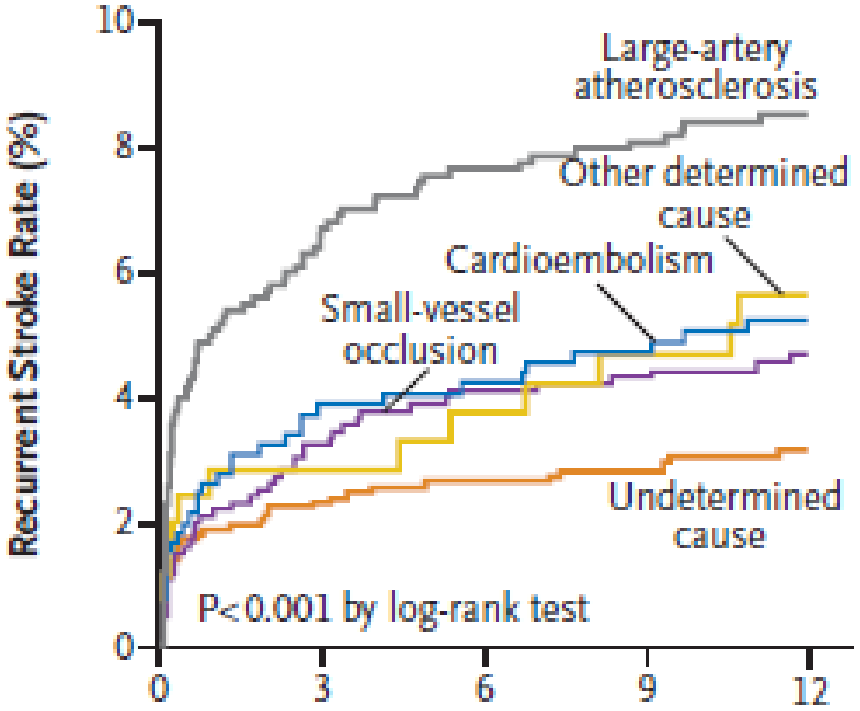


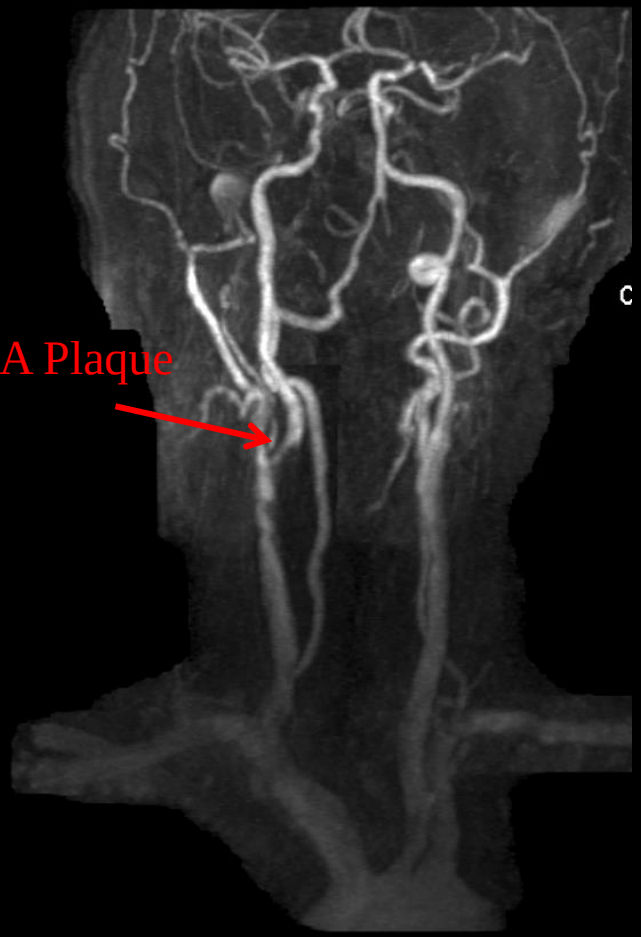
Fig. 1 Kaplan-Meier plots of patients surviving free from stroke from time of presenting TIA within 1 week (**a**), 3 months (**b**) and 1 year (**c**) stratified according to $ABCD^2$ score 0–3 and 4–7. Log rank tests for differences between the groups

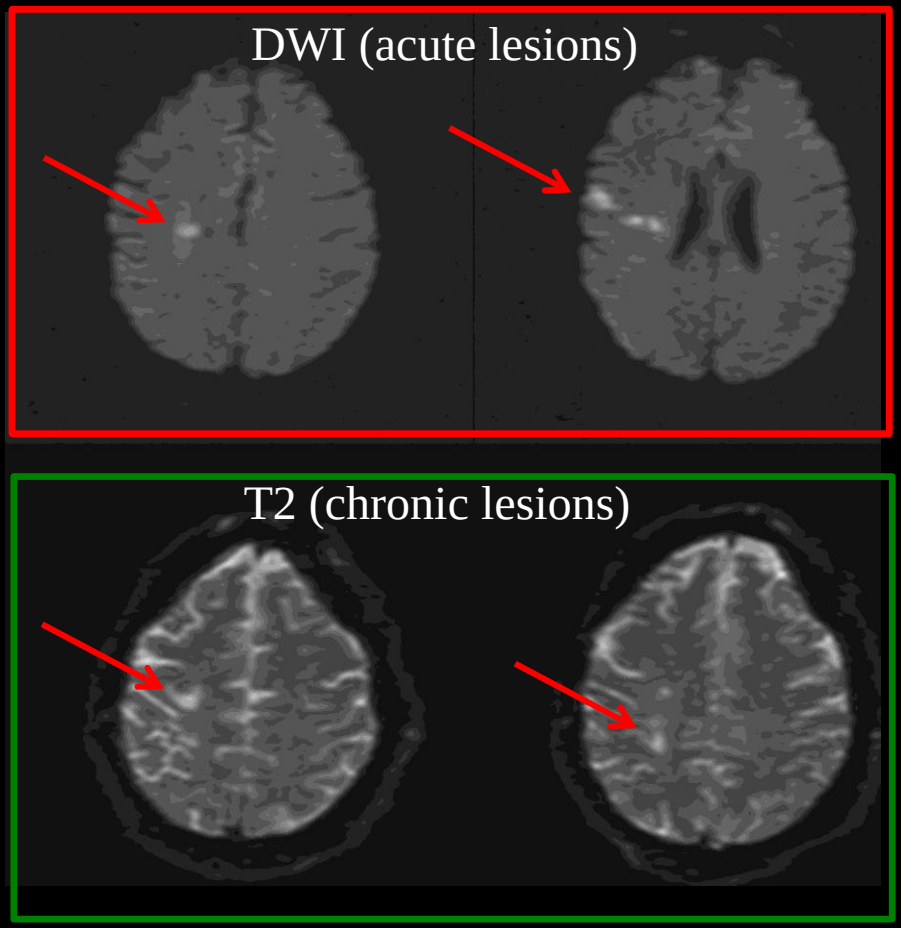
D Rate of Recurrent Stroke According to Cause of TIA or Minor Stroke (TOAST Classification)



No. at Risk					
Large-artery atherosclerosis	987	892	863	853	799
Small-vessel occlusion	983	905	862	857	790
Cardioembolism	641	584	570	561	494
Other determined cause	244	214	205	198	184
Undetermined cause	1354	1263	1206	1199	1085

MRI and MRA in ‘TIA’ diagnosis



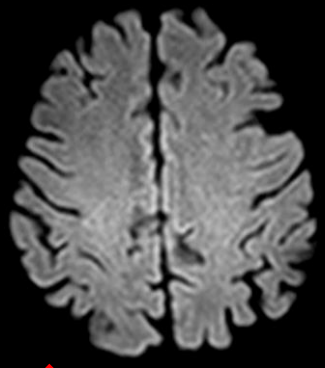


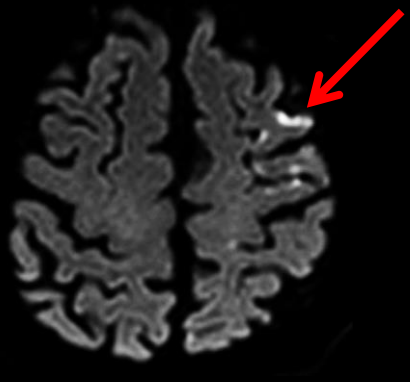
Unstable Plaque: Urgent CEA

Acute Cerebrovascular Syndrome

Infarction Absent

Infarction Present

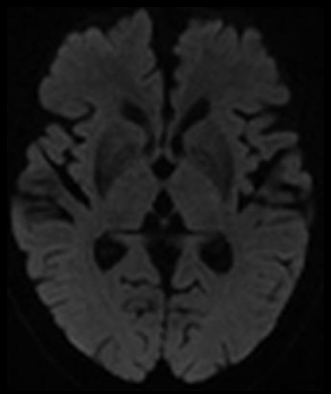




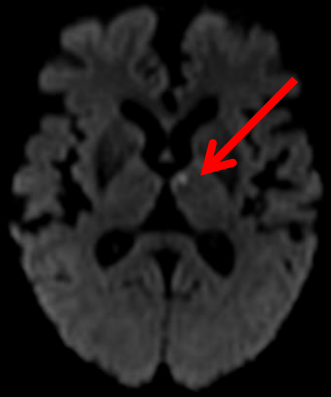
Mimics

TIA

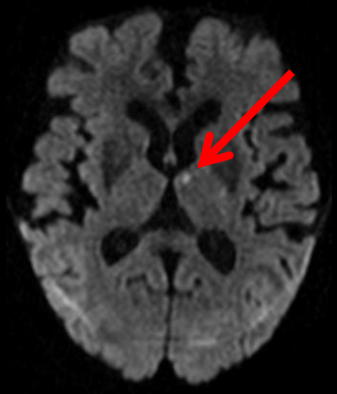
Infarct Below Resolution of DWI



DWI-Clinical



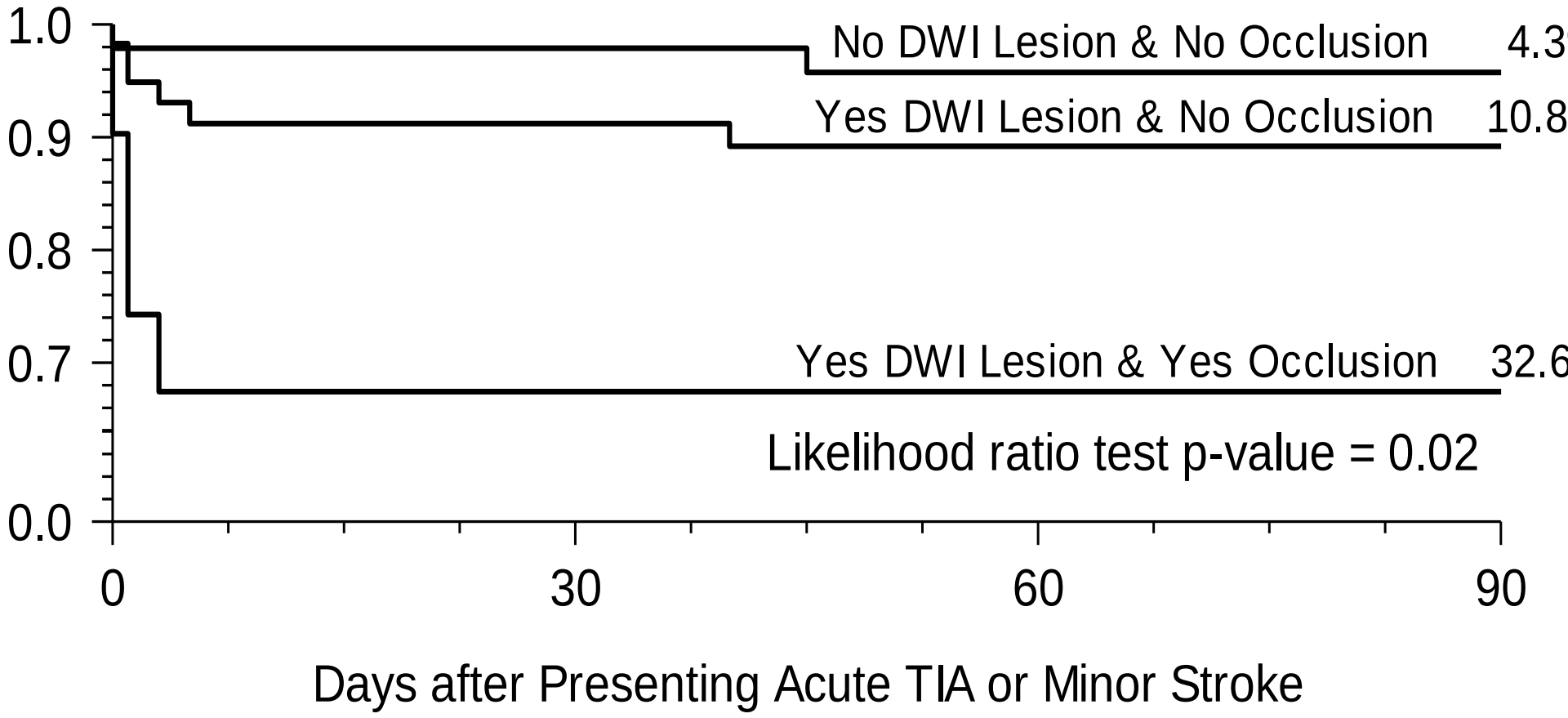
DTI



DWI-Isotropic Voxels

Event Free Survival Curve for New Stroke

Couttts SB et al. Annals of Neurology 2005;57:848-854

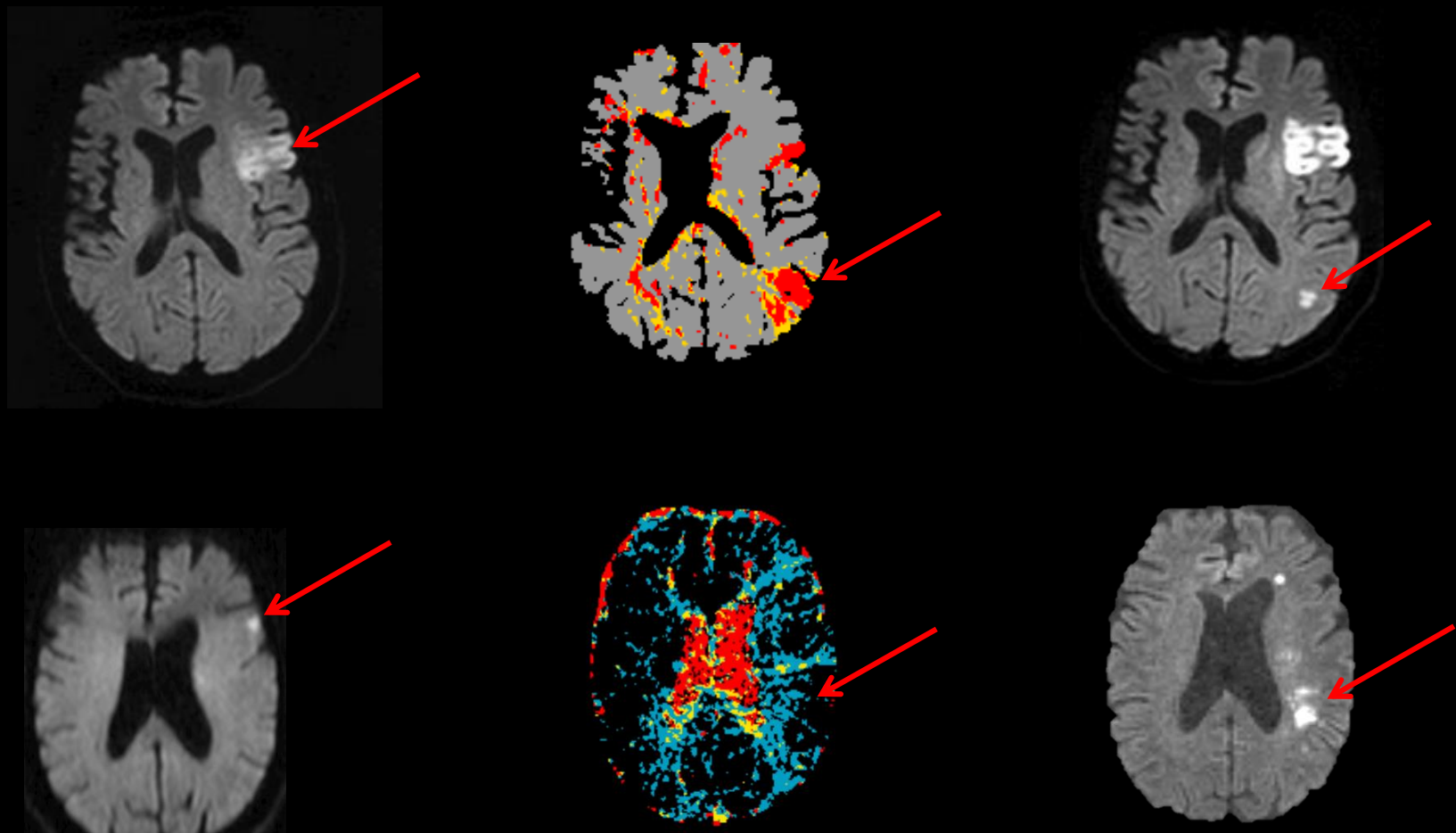


Perfusion Predicts Stroke Recurrence

Acute DWI

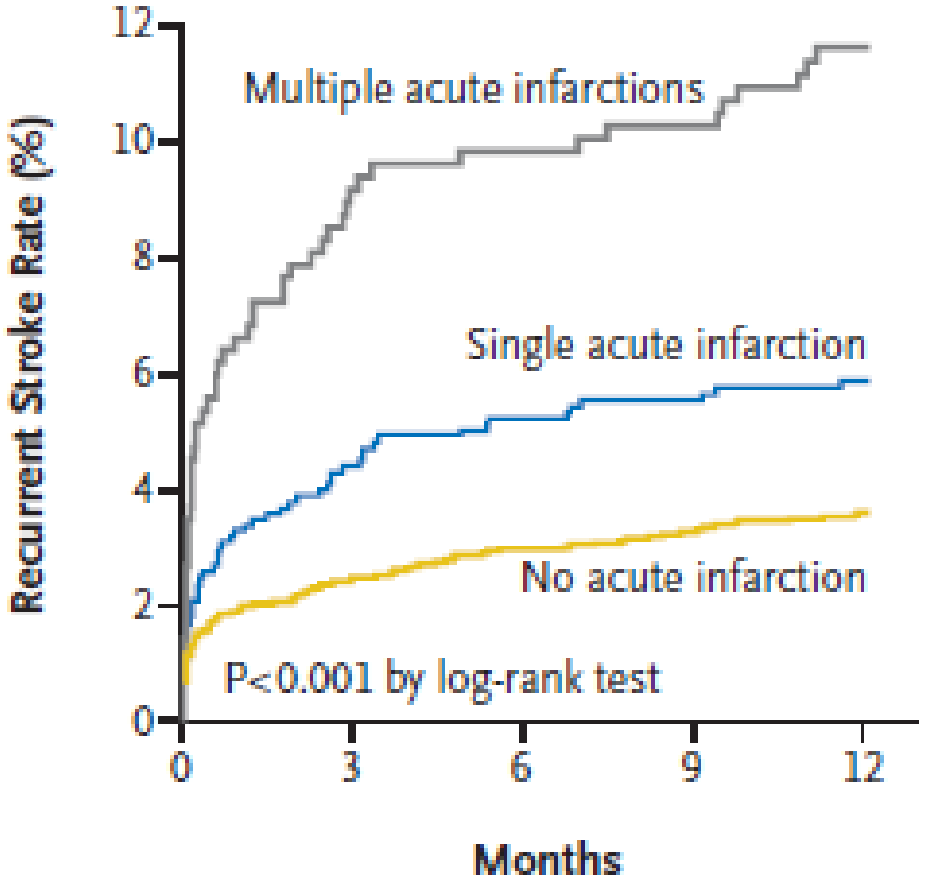
Acute PWI

Day 7 DWI



Asdaghi et al, Stroke, 2011

C Rate of Recurrent Stroke According to Finding on Brain Imaging



No. at Risk					
No acute infarction	2946	2699	2570	2542	2289
Single acute infarction	995	926	894	885	821
Multiple acute infarctions	481	414	397	394	357

Prognostic value of "tissue-based" definitions of TIA and minor stroke

Neurology® 2019;92:e2455-e2461.

Results

Among 1,033 patients (633 TIA; 400 minor stroke), 248 (24.0%) had acute lesions on DWI (13.9% of TIAs; 40.0% of minor strokes). A positive DWI was associated with an increased 10-year risk of recurrent ischemic stroke after an index TIA (hazard ratio [HR] 2.66, 95% confidence interval [CI] 1.28–5.54, $p = 0.009$) or a stroke with NIHSS 0–1 (3.03, 1.29–7.08, $p = 0.011$), but not after a stroke with NIHSS 2–3 (0.70, 0.24–2.10, $p = 0.53$). Ischemic stroke risk after DWI-positive TIA was at least equivalent to that after DWI-negative stroke (1.81, 0.82–4.00, $p = 0.14$). Among all patients, DWI positivity was most predictive of 10-year risk after cryptogenic events (4.68, 1.70–12.92, $p = 0.003$).

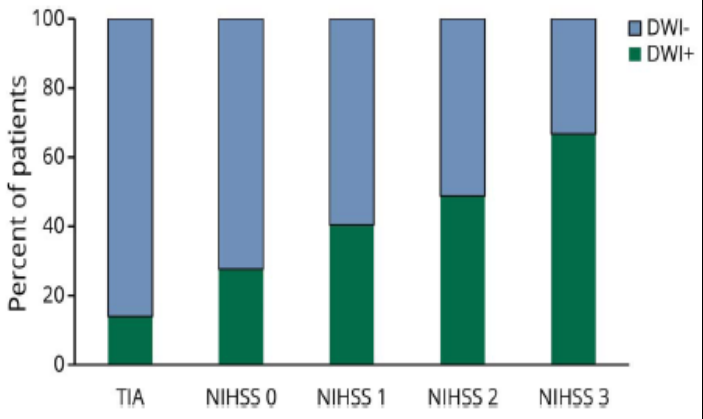
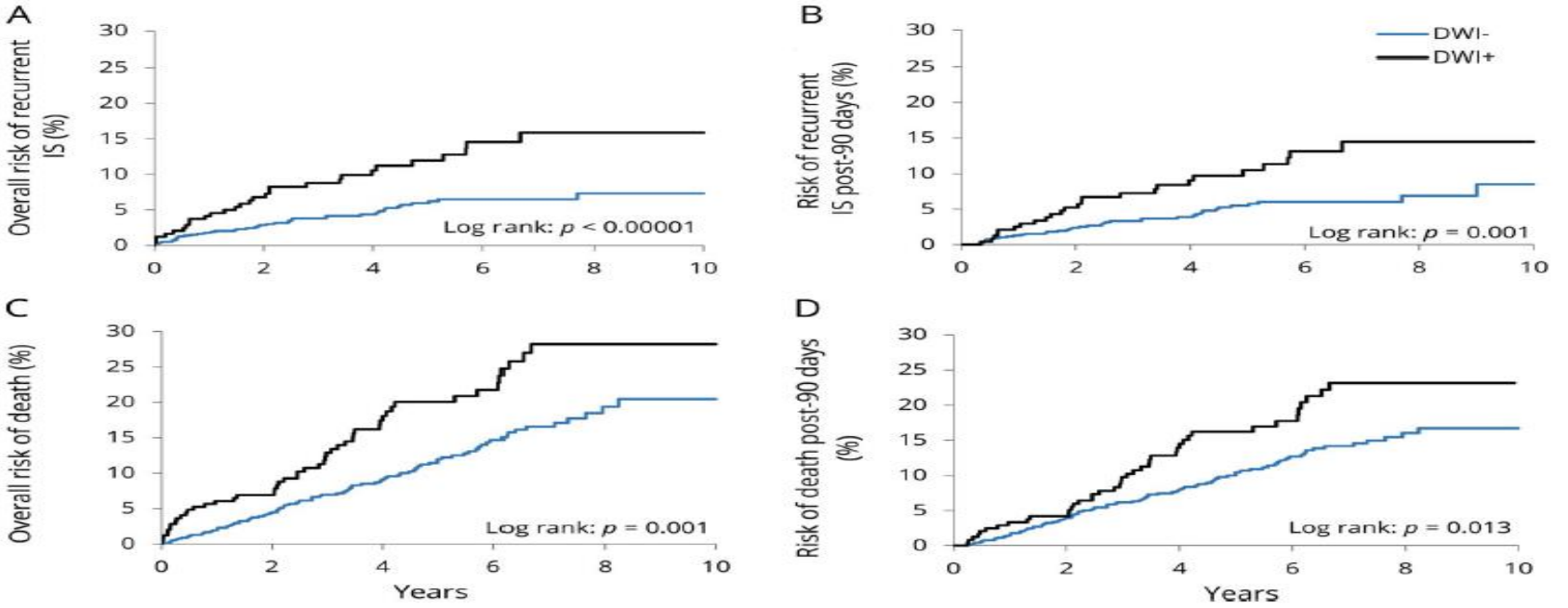


Figure 2 Kaplan-Meier survival graphs for 10-year risks of overall and post-90-day recurrent ischemic stroke (IS) and death



JAMA Neurology | Original Investigation

Rate and Prognosis of Brain Ischemia in Patients With Lower-Risk Transient or Persistent Minor Neurologic Events

Published Online: September 23, 2019.

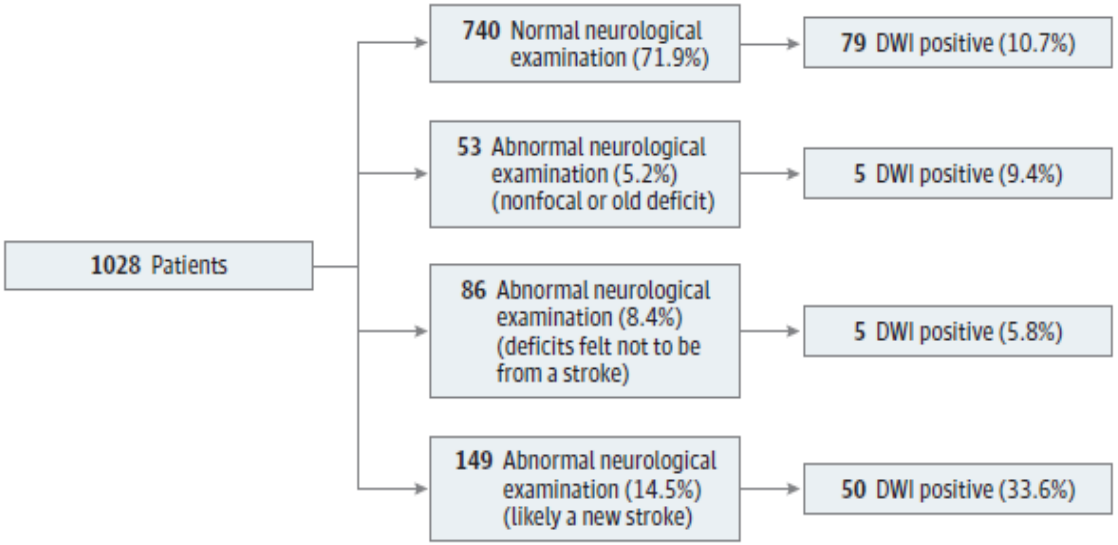


Table 3. Multivariable Analysis of Variables Associated With DWI-Positive Lesion Detected on MRI Scan[a]

Variable	OR (95% CI)
Age (per year)	1.02 (1.00-1.04)
Male sex	2.03 (1.39-2.96)
Any motor or speech symptoms	2.12 (1.37-3.29)
Ongoing symptoms	1.97 (1.29-3.02)
Abnormal results of initial neurologic examination	1.71 (1.11-2.65)
No prior identical symptomatic event	1.87 (1.12-3.11)

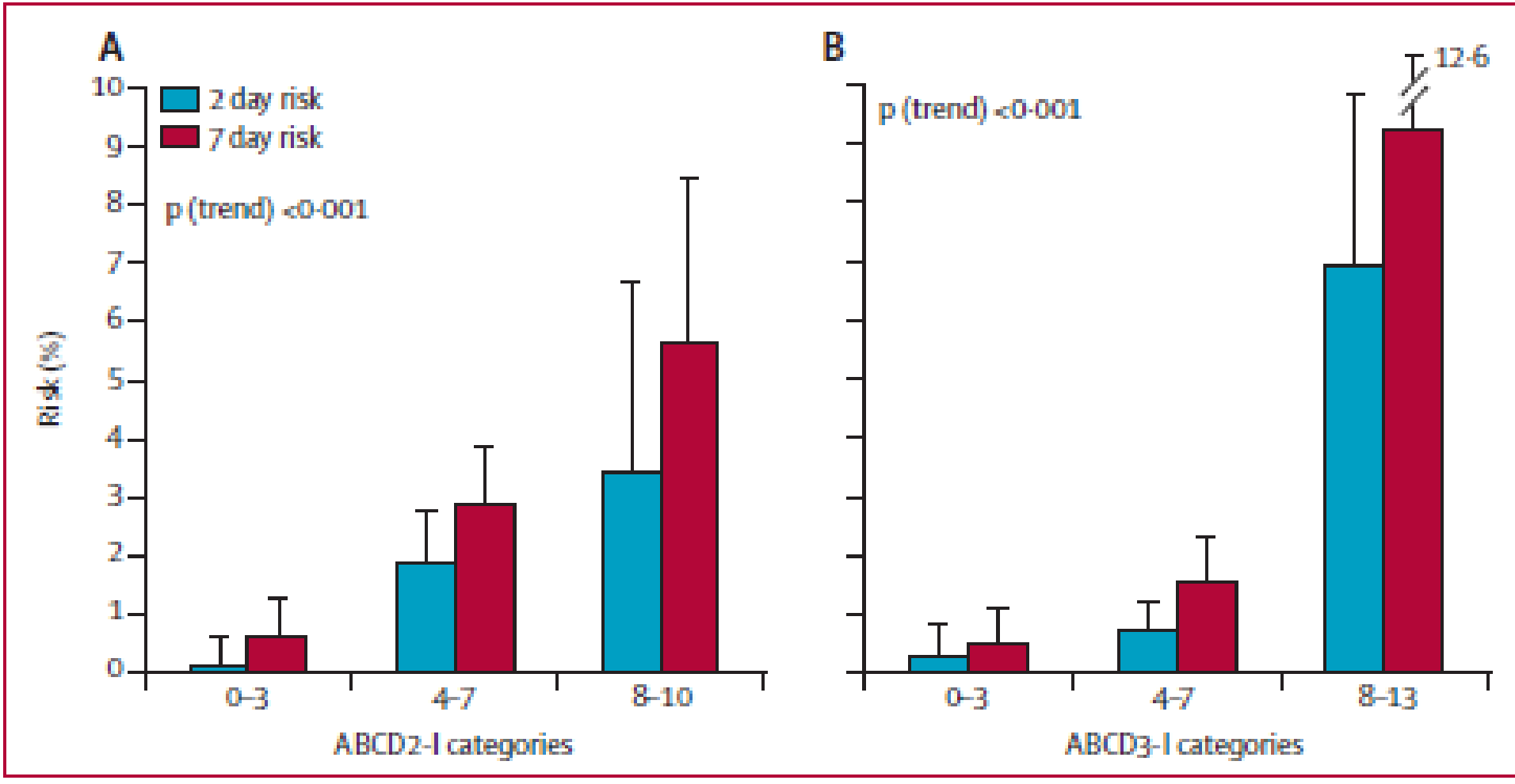
Table 4. Brain MRI and 1-Year Clinical Outcome Rates

Outcome	Patients, No. (%) (N = 1028)
Primary outcome	
Stroke on MRI results (DWI positive)	139 (13.5)
Secondary outcomes	
Recurrent ischemic stroke	7 (0.7)
Death	9 (0.9)
Myocardial infarction	4 (0.4)
Transient ischemic attack	9 (0.9)
Composite of ischemic stroke, MI, or death	20 (1.9)

Conclusions

We found that 13.5% of participants aged 40 years or older with transient or minor persistent nonmotor or speech neurologic symptoms or 5 minutes or less of motor or speech symptoms, who were referred to stroke neurologists with a possible diagnosis of TIA or minor stroke, had evidence of an acute stroke on neuroimaging. The final diagnosis was revised after brain MRI for 30.0% of patients. Because clinical features are not adequately discriminatory to obviate the need for MRI, a fast-head protocol MRI should be completed in similar patients within the first week after onset of symptoms.

ABCD 2 and ABCD3-I scores



TIA: Prognosis depends on symptoms and advanced imaging

	Low risk		High risk
Timing	weeks ago	days ago	hours ago
Duration	sec – few minutes		>10 minutes
Frequency	multiple		one to few
Sensory	yes with positive sx		no
Motor	no		yes
Speech	no		yes
Risk factors	no		Htn, DM,
Deficit dynamics	mild at onset		severe at onset
Imaging	negative		positive
	No rush to see/ discharge to clinic		See urgently/admit

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Outline/Objectives

1. The Acute Cerebrovascular Syndrome
2. Investigation Tempo
    1. CT or MRI (importance vs $$)
    2. Other investigations
3. Treatment to prevent recurrence

Mechanisms of Cerebral Ischemia

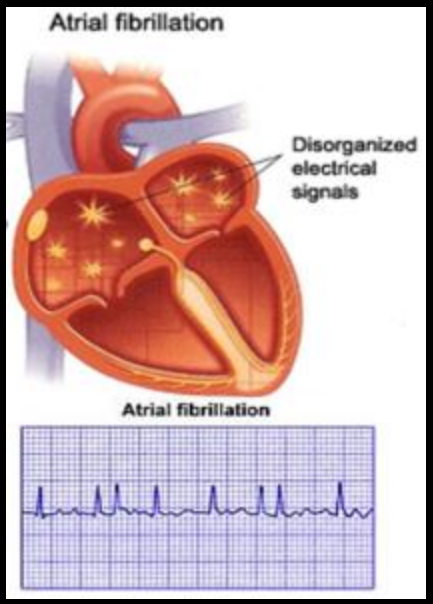
Lacunar Infarcts (LACI)

Cortical Infarcts (PACI)

Lipohyalinosis

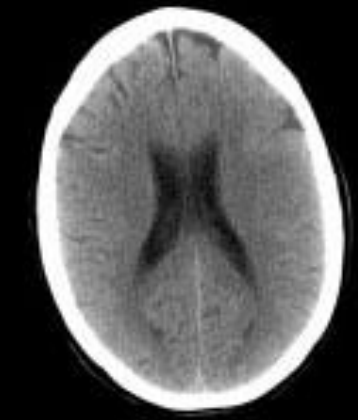
Artery-artery Embolism

Cardioembolism

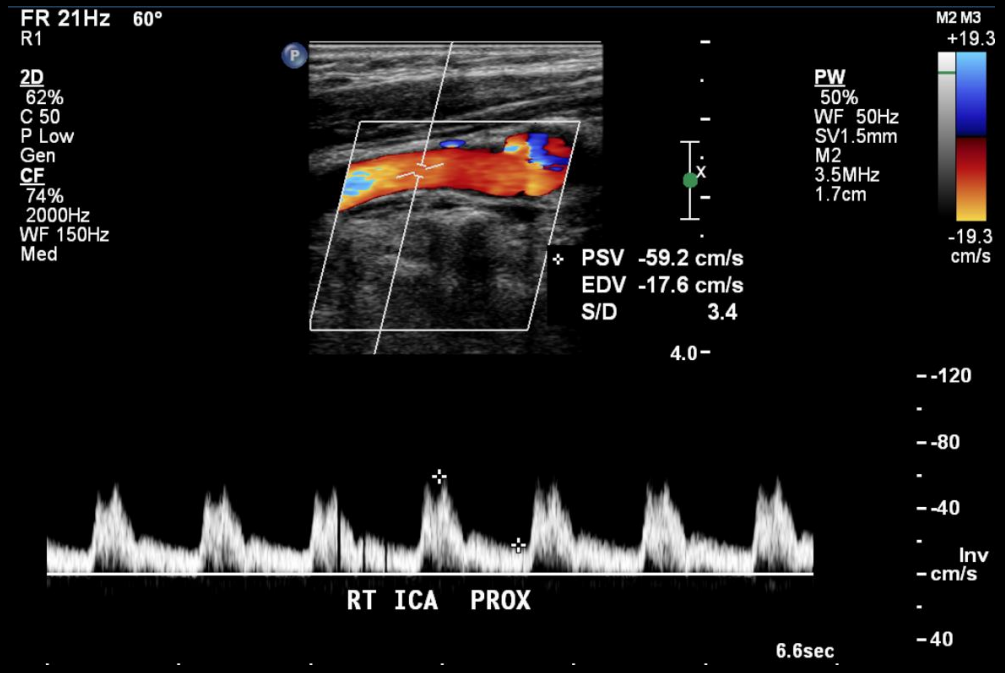


Investigating TIA and Stroke: Old School

CT Scan

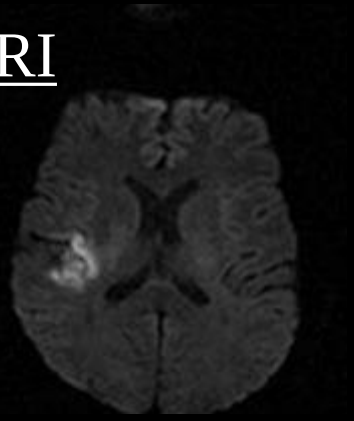


Doppler Ultrasound



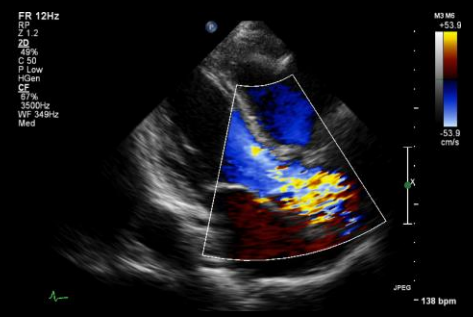
Urgent Investigations

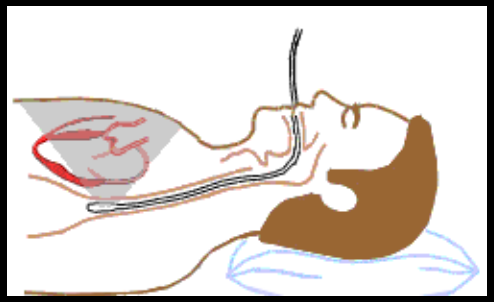
MRI



CTA

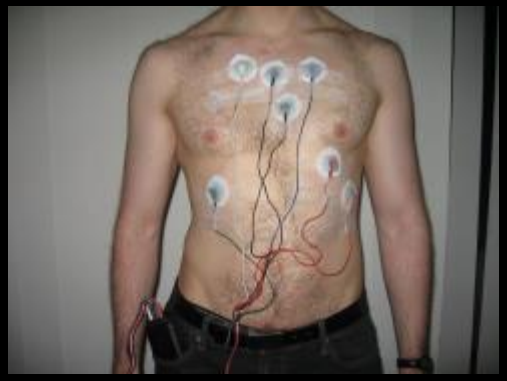
Echocardiogram





Holter Monitor

AF Detection Rate = 3%



External Loop Recorder

AF Detection Rate = 16%

Outline/Objectives

1. The Acute Cerebrovascular Syndrome
2. Investigation Tempo
    1. CT or MRI
    2. Other investigations
3. Treatment to prevent recurrence

Modifiable Risk Factors for Preventing the First Stroke

- Inactivity
- Obesity
- Dietary factors
- Diabetes
- Smoking
- Hyperlipidemia
- Hypertension

Not considering so-called "high-risk" prevention:
-atrial fibrillation/warfarin
-antiplatelet agents
-CE in asymptomatic pts

50% of total risk

Evidence for Preventing the First Stroke?

• Inactivity	Aerobic exercise
• Obesity	Weight loss
• Dietary factors	Better diet
• Diabetes	Glycemic control
• Smoking	Smoking cessation
• Hyperlipidemia	Statin therapy
• Hypertension	Treatment

(Straus, Majumdar, McAlister. JAMA. 2002)

Strategy # 1

- *To prevent the first stroke, treat hypertension aggressively*
  - *Target for most patients is still < 130 systolic and < 90 diastolic mmHg*
  - *Expect to use combination therapy in the majority of patients*

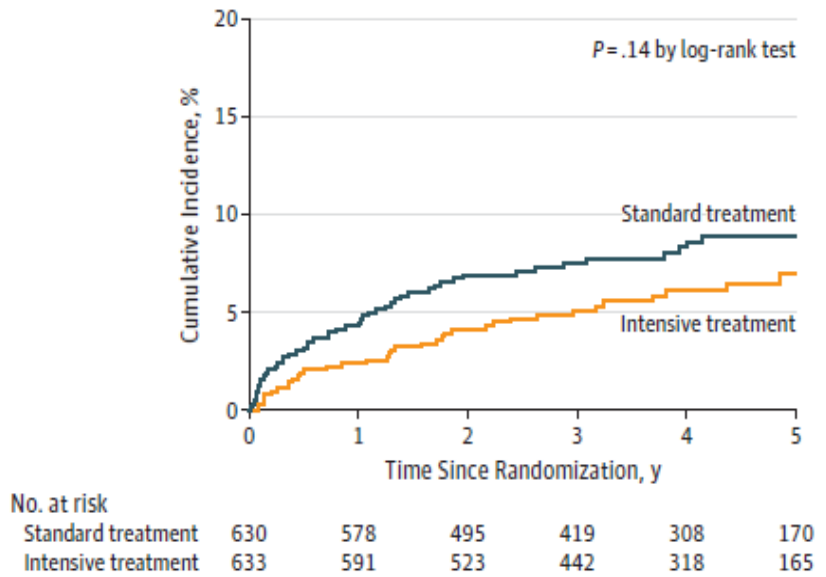
JAMA Neurology | Original Investigation

JAMA Neurol. 2019;76(11):1309-1318.

Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke

A Randomized Clinical Trial and Meta-analysis

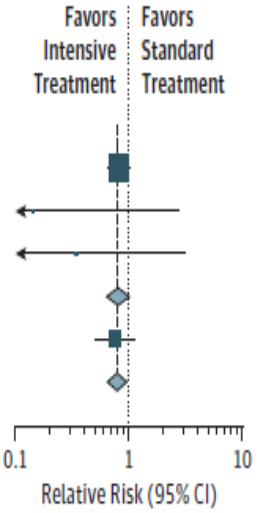
Figure 2. Cumulative Incidence of Stroke by Randomized Groups



No. at risk						
Standard treatment	630	578	495	419	308	170
Intensive treatment	633	591	523	442	318	165

Figure 3. Effects of Intensive Blood Pressure Lowering on Recurrent Stroke in a Meta-analysis of Randomized Clinical Trials

Source	No. of Events/No. of Patients: Intensive Treatment	No. of Events/No. of Patients: Standard Treatment	Relative Risk (95% CI)
Prior trials			
SPS3,[10] 2013	118/1501	147/1519	0.81 (0.64-1.02)
PAST-BP,[13] 2016	0/266	3/263	0.14 (0.01-2.72)
PODCAST,[14] 2017	1/41	3/42	0.34 (0.04-3.15)
Subtotal effect: I^2 = 0%, P = .05	119/1808	153/1824	0.80 (0.63-1.00)
RESPECT	39/633	52/630	0.75 (0.50-1.11)
Overall effect: I^2 = 0%, P = .02	158/2441	205/2454	0.78 (0.64-0.96)



CONCLUSIONS AND RELEVANCE Intensive BP lowering tended to reduce stroke recurrence. The updated meta-analysis supports a target BP less than 130/80 mm Hg in secondary stroke prevention.

Strategy # 2

- *To prevent ischemic stroke in high risk patients, use a statin to lower LDL cholesterol*
  - *LDL target for "high risk" is < 3.5 mmol/L*
  - *LDL target for "highest risk" < 1.7 mmol/L*

high risk = any 3 of LDL > 4.1, age >45M/55F, positive family history, smoking, hypertension, LVH;

highest risk = established atherosclerosis (including previous ischemic stroke) or diabetes

(Adapted from AHA Guidelines [2019] and Canadian Working Group [2017])

Other Strategies to Prevent First Stroke in High-Risk Patients?

1. Antiplatelet agents
2. Anticoagulation for atrial fibrillation
3. C/E for asymptomatic stenosis
4. Etc.

Anti-thrombotics and stroke prevention (1)

- ASA prevents the risk of recurrent stroke and other major vascular events by
- ~ 13-18%
- ASA “works” at doses as low as 0.5 mg/kg by irreversibly inactivating COX-1
- If a stroke has occurred on ASA – was it due to ASA failure?
- **THE EVIDENCE for switching from one agent to another after “failure” - none**

Anti-thrombotics and stroke prevention (2)

- Clopidogrel
- ASA-dipyridamole
- Warfarin
- DOACs
- Combination medications

Treatment Modification in Patient with Platelet Resistance/Failure

Aspirin Failure

- Evaluate disease mechanism
- Confirm compliance
- Exclude drug interactions – NSAIDS
- Increase dose ???
- Switch to clopidogrel, ticagrelor
- ASA/ERDP, or ? ASA + clopidogrel

Clopidogrel

- Evaluate disease mechanism
- Confirm compliance
- Exclude drug interactions
- Check PFA???
- Add aspirin - ? How long
- Switch to ASA/ERDP
- ? Triple therapy

OBM (opinion based medicine)

Anti-thrombotics and stroke prevention (3)

- ASA+Clopidogrel
  - CHANCE
  - POINT
- Ticagrelor
  - SOCRATES, THALES
- NOACs
  - NAVIGATE
  - RESPECT
  - COMPASS

The NEW ENGLAND JOURNAL of MEDICINE

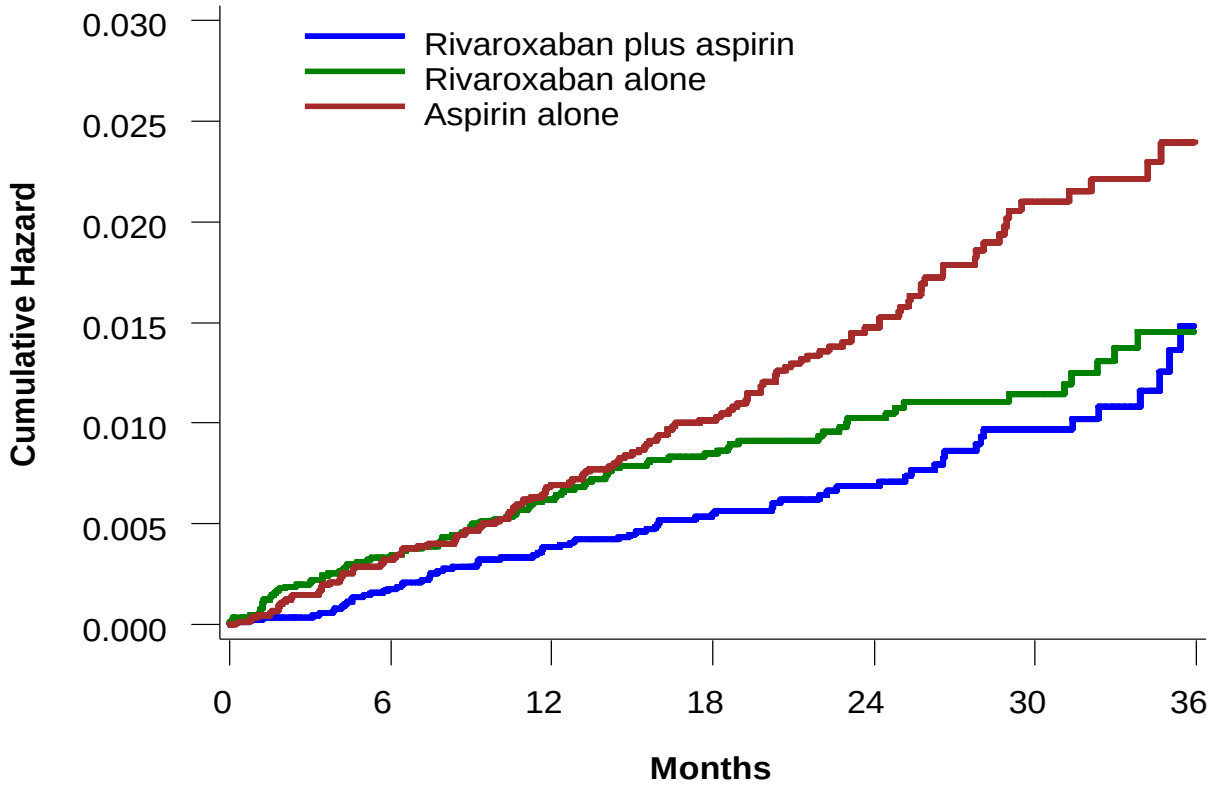
ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

Ischemic/Uncertain Stroke

A **Ischemic or Uncertain Stroke**

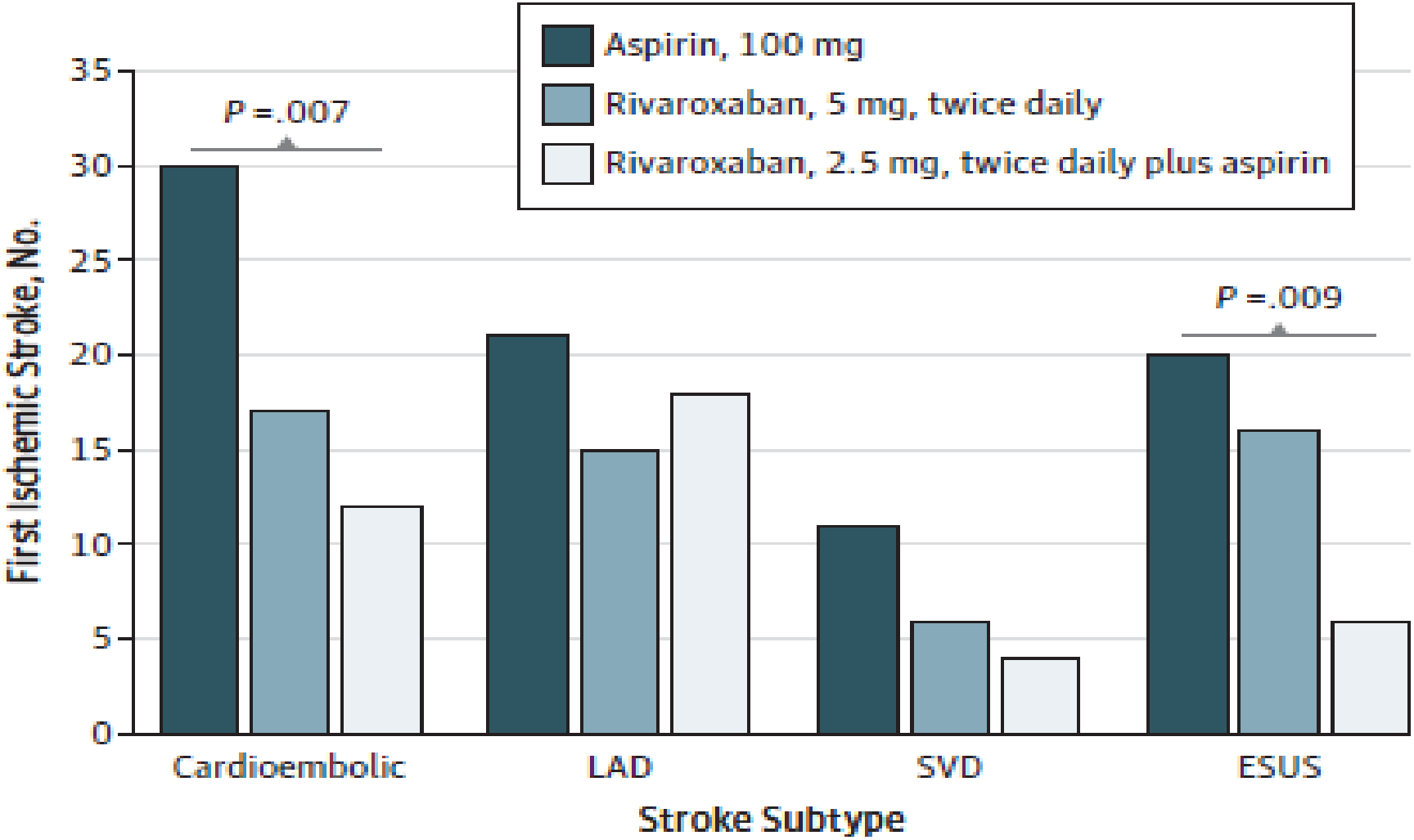


No. at Risk							
Rivaroxaban plus aspirin	9152	9069	7973	6374	3975	2259	673
Rivaroxaban alone	9117	9016	7898	6291	3943	2228	691
Aspirin alone	9126	9022	7874	6251	3951	2231	693

JAMA Neurology | Original Investigation

Association Between Low-Dose Rivaroxaban With or Without Aspirin and Ischemic Stroke Subtypes

A Secondary Analysis of the COMPASS Trial



Clinical Protocol CV010031

A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Response-Adaptive Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Revised Protocol 03

Incorporates Administrative Letter 01

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TIA/Minor stroke - Summary

1. Urgency in making diagnosis (TIA similar to ACS)
2. Vascular and cardiac imaging important
3. Promote vascular health
4. Treat hypertension aggressively
5. Treat dyslipidemia aggressively
6. Treat hypertension more aggressively
7. Anti-thrombotic options improving