AINAT SICILIA

Associazione Italiana Neurologi Ambulatoriali Territoriali

www.ainatsicilia.it

II CONGRESSO AINAT SICILIA

IRCCS CENTRO NEUROLESI MESSINA Bonino Pulejo

Luisa Vinciguerra

Ictus recidivanti

Recurrent Strokes

DEFINITION

Population-based studies exclude strokes:

- **within 28 or 21 days of the incident event**
- **events in the same vascular territory as the original event**

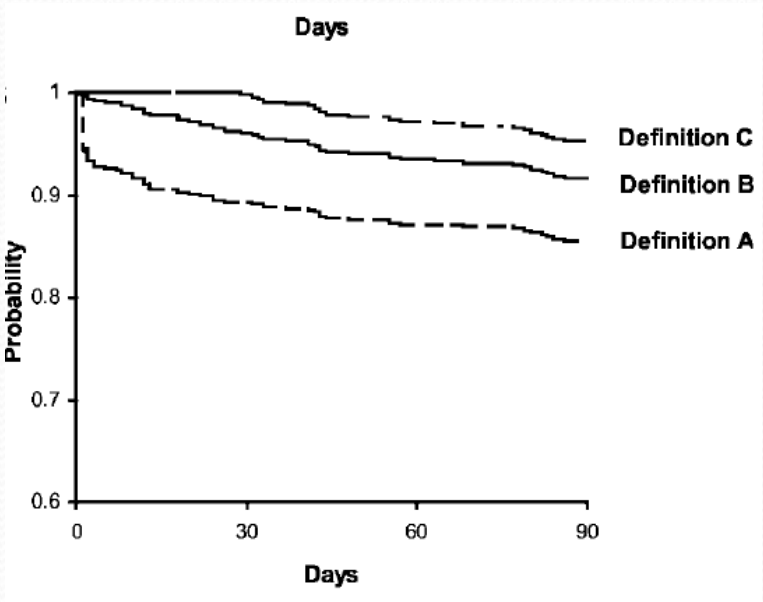
In contrast, other studies included:

- **events occurring 24 hours after the incident event**
- **a new focal neurological deficit "occurring at any time after the index stroke"**

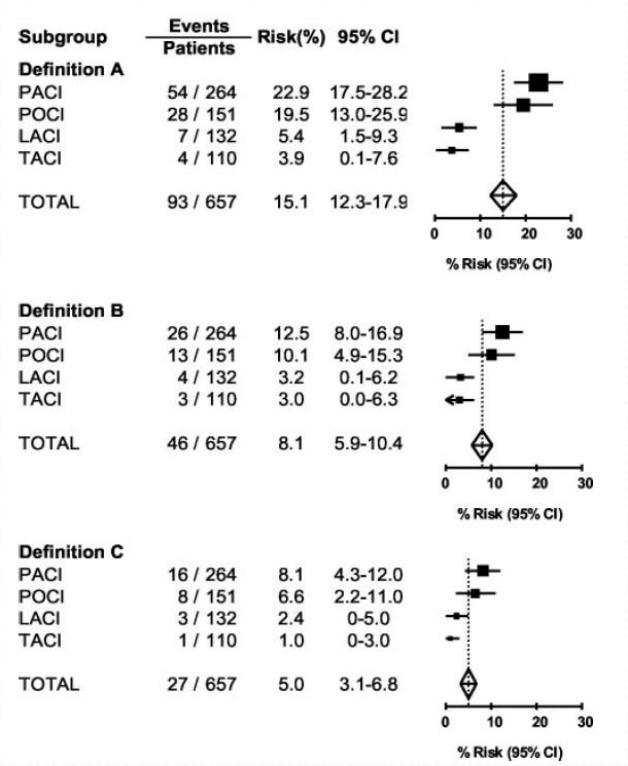
Sarti et al. Stroke. 2003;34:1833–1841. Coull et al. Stroke. 2004;35:1925-1929. Kolominsky-Rabas et al. Stroke. 1998;29:2501–2506. Lovett et al. Neurology. 2004;62:569–574.

Risk of Recurrent Stroke 3 Months After a First-Ever Ischemic Stroke According to the 3 Different Definitions in 2 Population-Based Studies (OXVASC and OCSP)

Definition	3-Month % Risk (95% CI)	
	OXVASC n=115	OCSP n=542
A Any recurrence >24 hours not attributable to edema brain shift or hemorrhagic infarction	18.3 (10.8 to 25.8)	14.5 (11.5 to 17.5)
B Any recurrence >21 days or if <21 days, new neurological deficit in different vascular territory	7.0 (1.6 to 12.4)	8.3 (5.9 to 10.8)
C Any recurrence >28 days	5.9 (1.0 to 10.9)	4.8 (2.8 to 6.7)



Kaplan–Meier curves for survival free of stroke after a first-ever ischemic stroke in the OXVASC and OCSP for each of the definitions of recurrence.



Coull et al. Stroke. 2004;35:1925-1929.

Recurrent Strokes

30% of strokes in population-based studies are recurrent events

Recurrent strokes are more likely to be disabling or fatal than first strokes

Coull et al. Stroke. 2004;35:1925-1929.

The equivalent risk after a first-ever ischemic stroke is usually reported as 2% to 6%

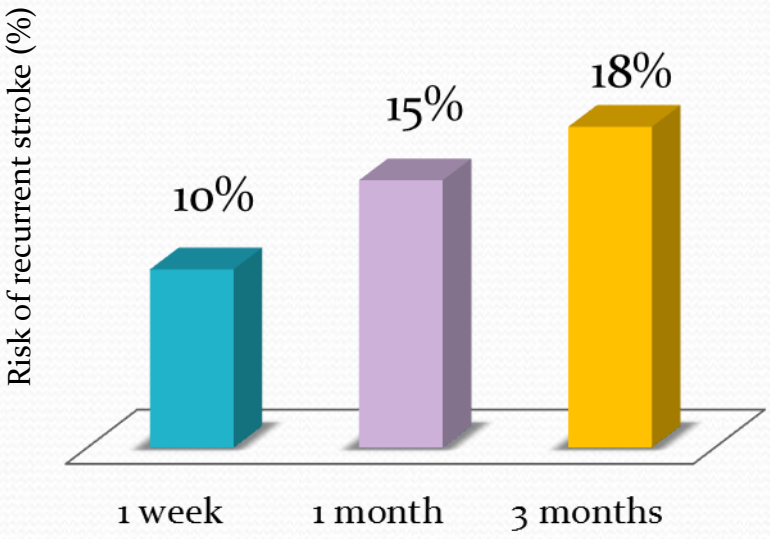
Approximately 2%–5% of recurrent stroke occurred early within 24–48 hours after the index event

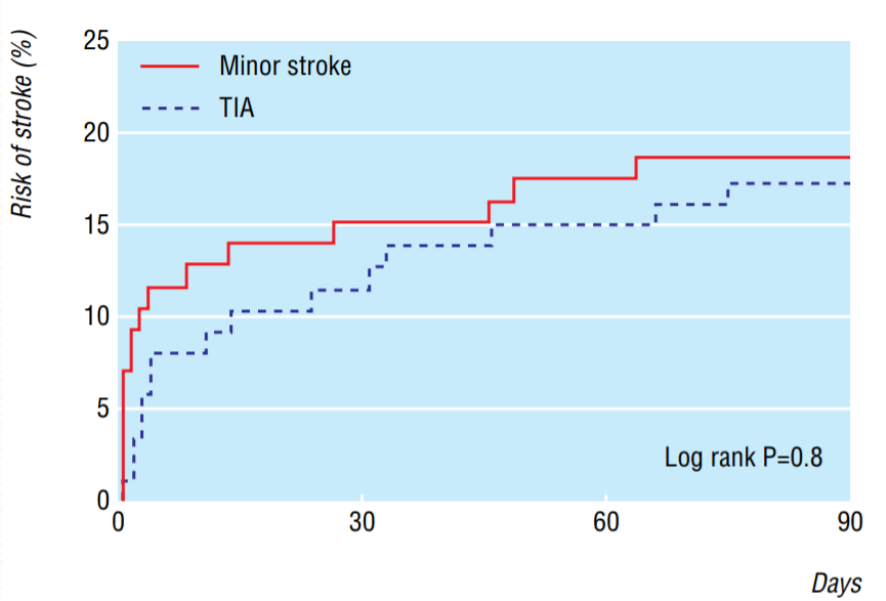
Wangqin R, et al. Stroke and Vascular Neurology 2017;0:e000088. Coull et al. Stroke. 2004;35:1925-1929. Lovett et al. Stroke. 2003;34:e138-e140. Sacco et al. Stroke, 1982:13;3.

After ischaemic stroke and TIA:

without treatment

The risk of stroke in the 3 months after a transient ischemic attack (TIA) is as much as 15% to 20% in population-based studies

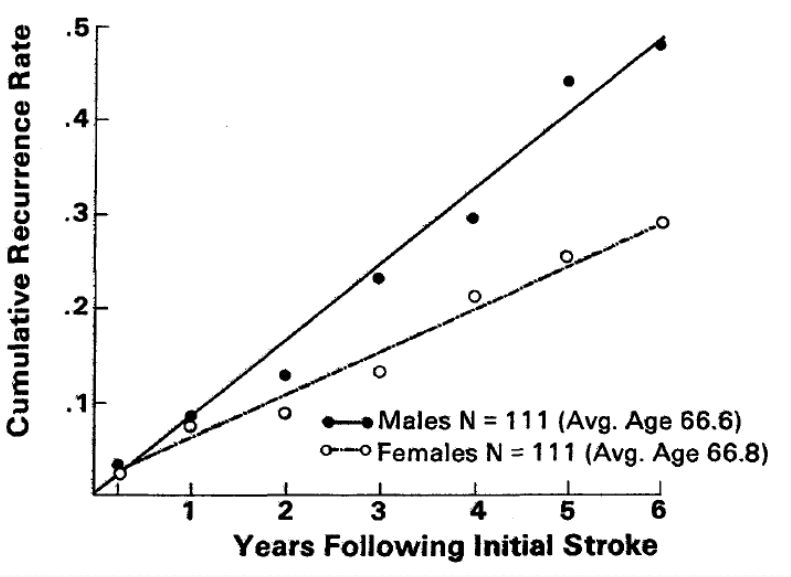


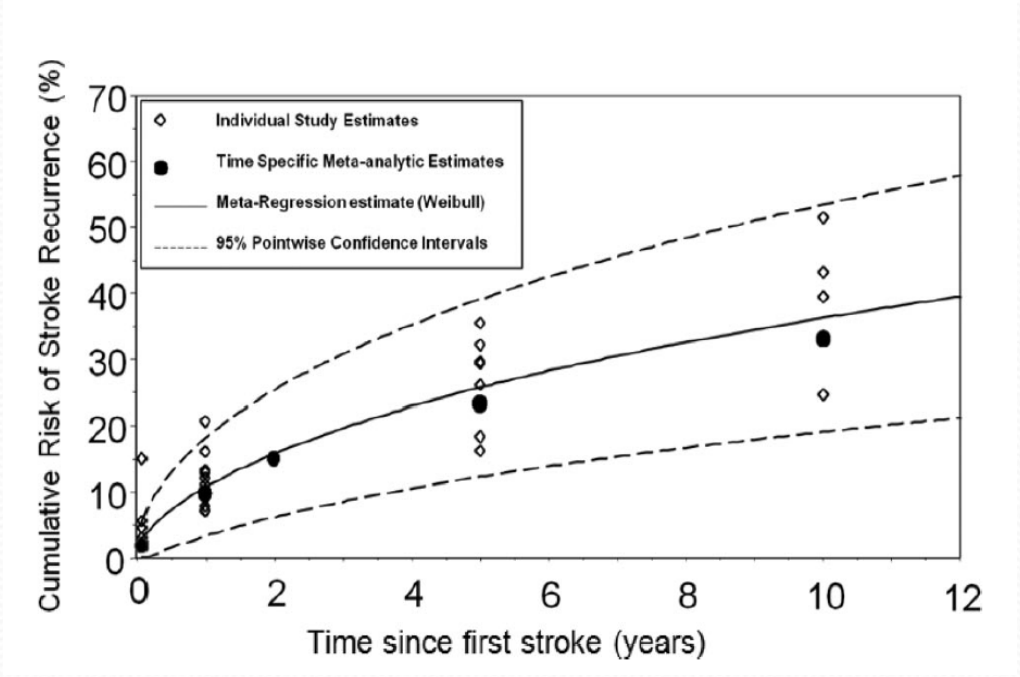


Cumulative risk of stroke after a transient ischaemic attack (TIA) or minor stroke

Coull et al. BMJ 2004; 328: 326. Hankey. Lancet. 2017;389:641-654.

The cumulative risk of stroke recurrence after first-ever stroke





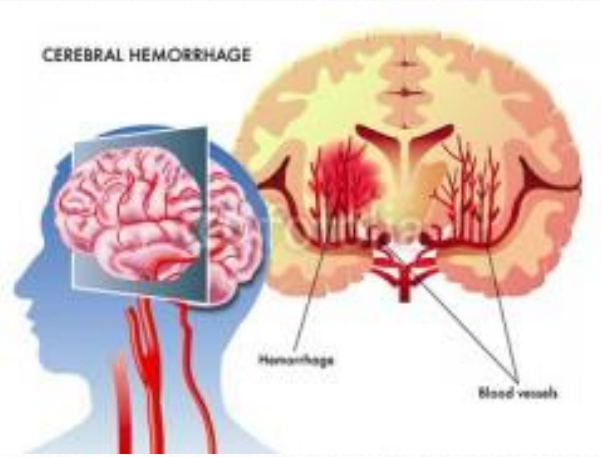
Mohan et al. Stroke 2011; 42: 1489–94. Coull et al. Stroke. 2004;35:1925-1929. Lovett et al. Stroke. 2003;34:e138-e140. Sacco et al. Stroke, 1982:13;3.

After haemorrhagic stroke:

The annual risks of recurrent intracerebral haemorrhage and ischaemic stroke are similar, from 1·3% to 7·4%

The risk of recurrent intracerebral haemorrhage is higher after

- **lobar intracerebral haemorrhage**
- **inadequate blood pressure control**



Poon et al. J Neurol Neurosurg Psychiatry 2014; 85: 660–67.
Biffi et al. JAMA 2015; 314: 904–12.

Scores to identify patients at early risk of recurrent stroke[32,33]

	Score for characteristic
ABCD³-I score[32]*	
Age ≥60 years	1
Blood pressure ≥140/90 mm Hg	1
Clinical features	
Speech impairment without weakness	1
Unilateral weakness	2
Duration	
10–59 min	1
≥60 min	2
Diabetes mellitus present	1
Dual TIA (index TIA plus ≥1 other TIA in preceding 7 days)	2
Imaging: ipsilateral ≥50% stenosis of internal carotid artery	2
Imaging: acute diffusion-weighted imaging hyperintensity	2

Recurrence risk estimator at 90 days[33] †‡	
Clinical	
History of TIA or stroke within the preceding month of index stroke	1
CCS aetiological stroke subtype	
Large artery atherosclerosis	1
Cardioaortic embolism	0
Small artery occlusion	0
Other causes	1
Undetermined causes	0
Brain MRI within first 72 h	
Multiple acute infarcts	1
Simultaneous infarcts in different circulations	1
Multiple infarcts of different ages	1
Isolated cortical infarcts	1

If the stated criteria are not met, a score of 0 is assigned. NA=not applicable. TIA=transient ischaemic attack. CCS=Causative Classification System for Ischemic Stroke. *Total range 0–13. †Total range 0–6. ‡Available at: http://www.nmr.mgh.harvard.edu/RRE-90.

Cumulative Risk of Recurrence Stratified According to the RRE Score

RRE Score	No. of Patients	No. of Patients With Recurrent Stroke	Cumulative Recurrence Rate, % (95% CI)
0	540	4	0.8 (0.0-1.6)
1	460	16	3.5 (1.7-5.3)
2	298	15	5.4 (2.7-8.1)
3	129	14	11.9 (6.0-17.8)
≥4	41	10	25.0 (11.7-38.3)

Abbreviation: RRE, Recurrence Risk Estimator.

Kiyohara et al. Stroke 2014; 45: 418–25. Arsava et al. JAMA Neurol 2016;73: 396–401. Hankey. Lancet. 2017;389:641-654.

The risk is higher with:

- Symptomatic atherosclerotic disease
- Vascular risk factors
- Active source of thrombosis
- Discontinued antiplatelet and antihypertensive therapy

For patients with atrial fibrillation the risk of stroke increases with:

- higher CHADS2
- CHA2DS2-VASc
- ABC (Age, Biomarkers [NT-proBNP and cTn-hs], and Clinical history [prior stroke or TIA]) stroke scores

Hijazi et al. Eur Heart J 2016;37: 1582–90.

CHADS2 and CHA2DS2-VASc

$CHADS_2$ score and stroke risk

Risk factor	Points
C - Congestive heart failure	1
H - Hypertension	1
A - Age >75 years	1
D - Diabetes	1
S - Prior Stroke or TIA	2

$CHADS_2$ score	Stroke rate per 100 patient-years
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

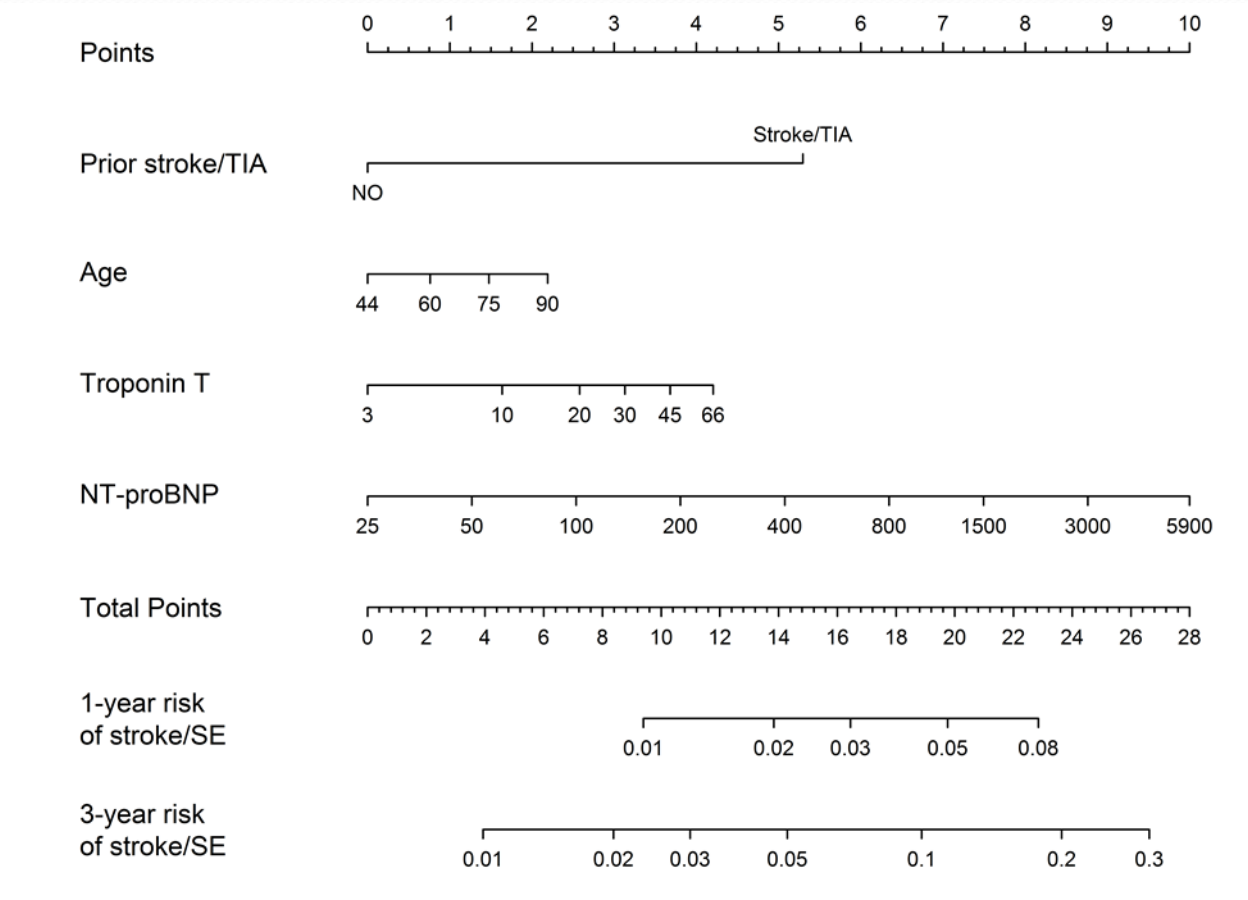
CHA_2DS_2-VASc score

Risk Factor	Score
C - Congestive heart failure	1
H - Hypertension	1
A - Age ≥ 75 yrs	2
D - Diabetes mellitus	1
S_2 - Prior stroke or TIA	2
V - Vascular disease	1
A - Age 65-74 years old	1
Sc - Sex category (female)	1

Gage et al. Circulation. 2004;110(16):2287-92. Gage et al. JAMA. 2001;285(22):2864-70. Lip et al. Am J Med 2010;123(6);484-488.

ABC-stroke risk score

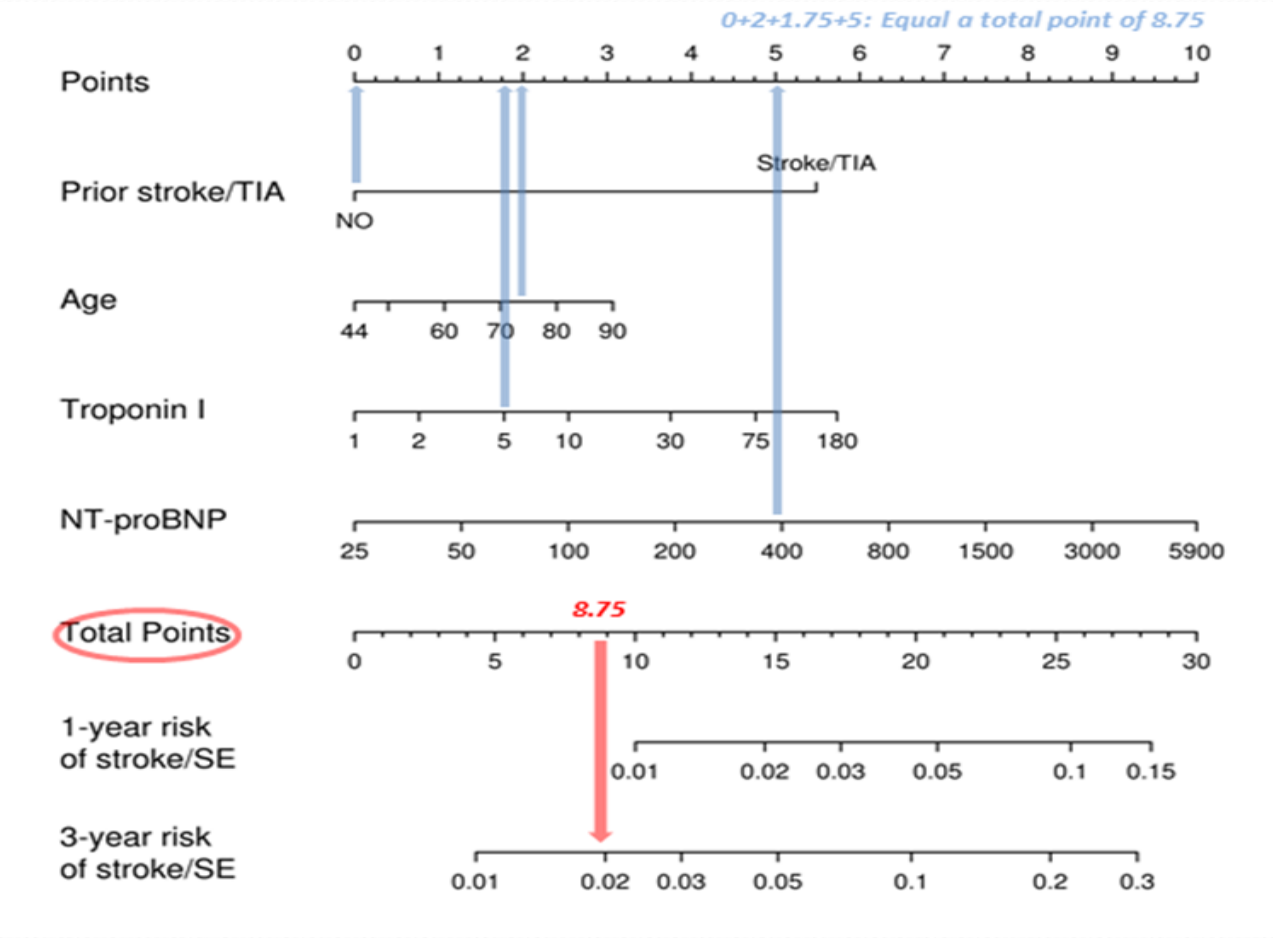
Nomogram for the new biomarker-based risk score: For each predictor, read the points assigned on the 0–10 scale at the top and then sum these points. Find the number on the 'Total Points' scale and then read the corresponding predictions of 1- and 3-year risk of stroke or systemic embolism below it. Continuous variables are represented from the 1st to the 99th percentiles. The prediction model is preferably used as a web-based calculator or app.



Hijazi et al. Eur Heart J 2016;37: 1582–90.

ABC-stroke risk score

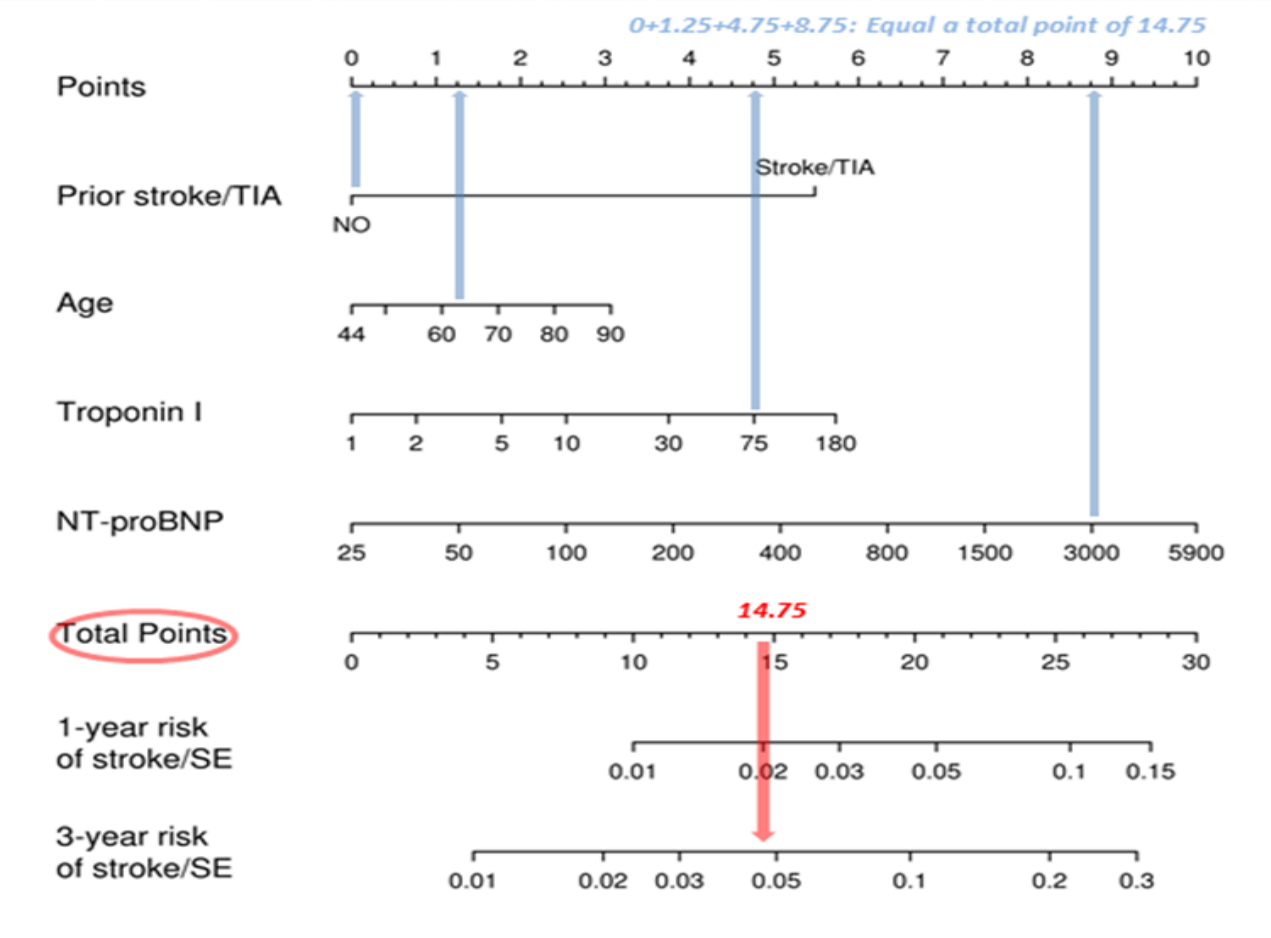
Example 1: A 75-year old woman with atrial fibrillation, hypertension, no prior stroke, troponin-I levels of 5 ng/L, and NT-proBNP levels of 400 ng/L. By using the ABC-stroke score nomogram receives 2p for age, 1.75p for troponin levels, and 5p for NT-proBNP levels. A total of 8.75 p would equal a predicted 1-year risk of stroke or systemic embolism below 1.0% and a 3-year risk of 2.0%.



Hijazi et al. Eur Heart J 2016;37: 1582–90.

ABC-stroke risk score

Example 2: A 64-year old man with atrial fibrillation, heart failure, troponin levels of 75 ng/L, and NT-proBNP levels of 3000 ng/L. By using the ABC-stroke score nomogram receives 1.25p for age, 4.75p for troponin, and 8.75p for NT-proBNP levels. A total of 14.75p would equal a predicted 1-year and 3-year risk of stroke or systemic embolism of 2.0% and 4.8%, respectively.



Hijazi et al. Eur Heart J 2016;37: 1582–90.

PREVENTING RECURRENT ISCHAEMIC STROKE OF ARTERIAL ORIGIN

Urgent initiation of effective secondary prevention after TIA and minor ischaemic stroke can reduce the risk of early recurrent stroke by 80%

Rothwell et al. Lancet 2007;370: 1432–42. Hankey. Lancet. 2017;389:641-654.

PREVENTING RECURRENT ISCHAEMIC STROKE OF ARTERIAL ORIGIN

	Proportion of patients with outcome		Risk ratio (95% CI)	Absolute risk reduction (%)
	Treatment group (%)	Control (%)		
Acute therapy in patients with TIA or ischaemic stroke				
Acute specialty unit (vs outpatient clinic)[35]				
Stroke at 90 days	2%	10%	0·20 (0·08–0·49)	12%
Aspirin (vs control)[43,81]				
Stroke at 6 weeks	1%	2%	0·45 (0·35–0·58)	1·3%
Stroke at 12 weeks	2%	4%	0·49 (0·40–0·60)*	1·8%
Disabling or fatal ischaemic stroke at 12 weeks	1%	2%	0·34 (0·25–0·46)*	1·4%
Ticagrelor (vs aspirin)[82]				
Stroke at 90 days	6%	7%	0·86 (0·75–0·99)*	0·9%
Dual antiplatelet therapy (vs single drug)[83]				
Stroke at about 90 days	6%	9%	0·69 (0·60–0·80)	2·8%
Carotid endarterectomy (vs medical therapy)[84]				
Any stroke or operative death at 5 years in patients with 70–99% carotid stenosis	15%	29%	0·53 (0·42–0·67)	13·9%
Any stroke or operative death at 5 years in patients with 50–69% carotid stenosis	17%	23%	0·77 (0·63–0·94)	5·6%
Ipsilateral ischaemic stroke and any operative stroke or death at 5 years in patients with 70–99% carotid stenosis	10%	24%	0·40 (0·30–0·54)	14·2%
Ipsilateral ischaemic stroke and any operative stroke or death at 5 years in patients with 50–69% carotid stenosis	12%	15%	0·82 (0·64–1·05)	NS; p=0·11
Carotid stent (vs carotid endarterectomy)[85–87]				
Any stroke or death[85]	25%	21%	1·41 (1·07–1·84)	4·3%
Any stroke at 5 years[86]	15%	9%	1·71 (1·28–2·30)*	5·8%
Fatal or disabling stroke at 5 years[86]	6%	6%	1·06 (0·72–1·57)*	NS; p=0·77
Ipsilateral carotid stroke at 5 years†[86]	5%	3%	1·29 (0·74–2·24)	NS; p=0·36

Rothwell et al. Lancet 2016; 388: 365–75. Sandercock et al. Cochrane Database Syst Rev 2014;,3: CD000029. Hankey. Lancet. 2017;389:641-654.

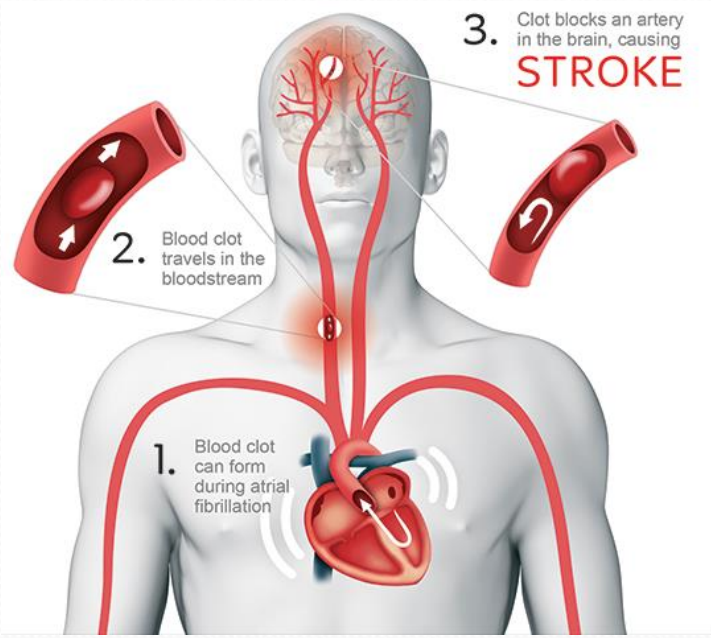
PREVENTING RECURRENT ISCHAEMIC STROKE OF ARTERIAL ORIGIN

Longer-term therapy in patients with TIA or ischaemic stroke				
Aspirin[88]				
Stroke per year	4%	5%	0·83 (0·72–0·96)	0·8%
Clopidogrel (*vs* aspirin)[89]				
Recurrent stroke at 2 years	11%	12%	0·90 (0·80–1·00)‡	1%
Aspirin plus ER dipyridamole (*vs* aspirin)[90]				
Recurrent stroke at 2·6 years	9%	11%	0·78 (0·68–0·90)*	2·3%
Aspirin plus ER dipyridamole (*vs* clopidogrel)[91]				
Recurrent stroke at 2·5 years	9%	9%	1·01 (0·92–1·11)*	NS; p=0·71
Cilostazol (*vs* aspirin)[92]				
Recurrent stroke at 3 years	5%	8%	0·67 (0·52–0·86)	2·7%
Blood pressure lowering by 5·1/2·5 mm Hg[93]				
Recurrent stroke at 3 years	9%	10%	0·78 (0·68–0·90) ‡	1·3%
LDL cholesterol lowering by 1 mmol/L[94]				
Recurrent stroke at 5 years	11%	12%	0·88 (0·78–0·99)	1·4%
Pioglitazone for insulin resistance[21]				
Stroke or myocardial infarction	9%	12%	0·76 (0·62–0·93)*	2·8%
Recurrent stroke at 4·8 years	7%	8%	0·82 (0·61–1·10)*	NS; p=0·19

Baigent et al. Lancet 2009;373: 1849–60. Liu et al. Hypertens Res 2009; 32: 1032–40. Amarenco et al. Lancet Neurol 2009; 8: 453–63. Hankey. Lancet. 2017;389:641-654.

PREVENTING RECURRENT ISCHAEMIC STROKE OF CARDIAC ORIGIN

Effect of secondary prevention strategies to prevent recurrent stroke				
Warfarin for atrial fibrillation (*vs* control)[95]				
Recurrent stroke at 2 years	9%	23%	0·36 (0·22–0·58)‡	14%
Direct oral anticoagulants (*vs* warfarin)[96]				
Stroke or systemic embolism at 2 years	5%	6%	0·86 (0·76–0·98)	0·8%
Left atrial appendage closure (*vs* warfarin)[97]				
Stroke or systemic embolism at 2·7 years	1·75% per year	1·87% per year	1·02 (0·62–1·7)*	NS; p=0·94
Patent foramen ovale closure (*vs* medical therapy)[98]				
Recurrent ischaemic stroke	0·7% per year	1·3% per year	0·58 (0·34–0·99)*	0·6%



Saxena et al. Cochrane Database Syst Rev 2004;2: CD000185. Ruff et al. Lancet 2014; 383: 955–62. Holmes et al. J Am Coll Cardiol 2015;65: 2614–23. Hankey. Lancet. 2017;389:641-654.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

In a multicenter, randomized, open-label trial, we assigned, in a 1:1:1 ratio, patients 16 to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, to transcatheter PFO closure plus long-term antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group) (randomization group 1). Patients with contraindications to

A total of 663 patients underwent randomization and were followed for a mean (±SD) of 5.3±2.0 years. In the analysis of randomization groups 1 and 2, no stroke occurred among the 238

CONCLUSIONS

Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT00562289.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

In this multinational trial involving patients with a PFO who had had a cryptogenic stroke, we randomly assigned patients, in a 2:1 ratio, to undergo PFO closure plus antiplatelet therapy (PFO closure group) or to receive antiplatelet therapy alone (antiplatelet-only group). Imaging of the brain was performed at the baseline screening and

We enrolled 664 patients (mean age, 45.2 years), of whom 81% had moderate or large interatrial shunts. During a median follow-up of 3.2 years, clinical ischemic stroke

CONCLUSIONS

Among patients with a PFO who had had a cryptogenic stroke, the risk of subsequent ischemic stroke was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone; however, PFO closure was associated with higher rates of device complications and atrial fibrillation. (Funded by W.L. Gore and Associates; Gore REDUCE ClinicalTrials.gov number, NCT00738894.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

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

In a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events, we randomly assigned patients 18 to 60 years of age who had a patent foramen ovale (PFO) and had had a cryptogenic ischemic stroke to undergo closure of the PFO (PFO closure group) or to receive medical therapy

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. Patients were followed for a median of 5.9 years. Treatment exposure in the two groups was unequal

CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

CONCLUSION

Despite these advances, the global burden of stroke remains substantial and is increasing as populations age

A standard definition of recurrent stroke is also required so that different studies can be compared or meta-analyzed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials

Further research therefore is needed to investigate the effect of acute stroke management and secondary prevention measures on the risk of stroke recurrence from the first weeks to beyond years after first stroke

Grazie

per

l'Attenzione