



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Features, frequency, short and long term outcome of recurrent TIA: a prospective observational study

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Introduction

- **TIA** is related to an increased risk of subsequent stroke (10% at 1-month)
→ **> 50%** of strokes occurring in the first 2 days after index TIA
- **20%** of all patients experiencing TIA symptoms have more than one episode within **hours** or **days** (**recurrent TIA**)



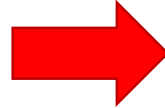
Definition and Evaluation of Transient Ischemic Attack

A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: *The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

J. Donald Easton, Jeffrey L. Saver, Gregory W. Albers, Mark J. Alberts, Seemant Chaturvedi, Edward Feldmann, Thomas S. Hatsukami, Randall T. Higashida, S. Claiborne Johnston, Chelsea S. Kidwell, Helmi L. Lutsep, Elaine Miller, and Ralph L. Sacco

Stroke

*Crescendo episodes of ischemia causing
stereotyped symptoms preceding the
development of early lacunar stroke (> 50%)*



The capsular warning syndrome: Pathogenesis and clinical features

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and P.F. Bladin, BSc, MD, FRACP

Introduction

- Data estimating **early** clinical outcome after recurrent TIA are inferable only from two large population-based prospective observational studies

Recurrent transient ischaemic attack and early risk of stroke: data from the PROMAPA study

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Population-based study of capsular warning syndrome and prognosis after early recurrent TIA

[Nicola L.M. Paul](#), MRCP, [Michela Simoni](#), MRCP, [Arvind Chandratheva](#), MRCP, PhD, and [Peter M. Rothwell](#), MD,



- ❖ *A clear relationship between specific etiologies and early stroke occurrence after recurrent TIA has not been established, with the sole exception of LAA*
- ❖ *Long and very long-term cerebrovascular outcome of patients with recurrent TIA remains largely uncharacterized as well as subsequent general cardiovascular risk*

Objectives

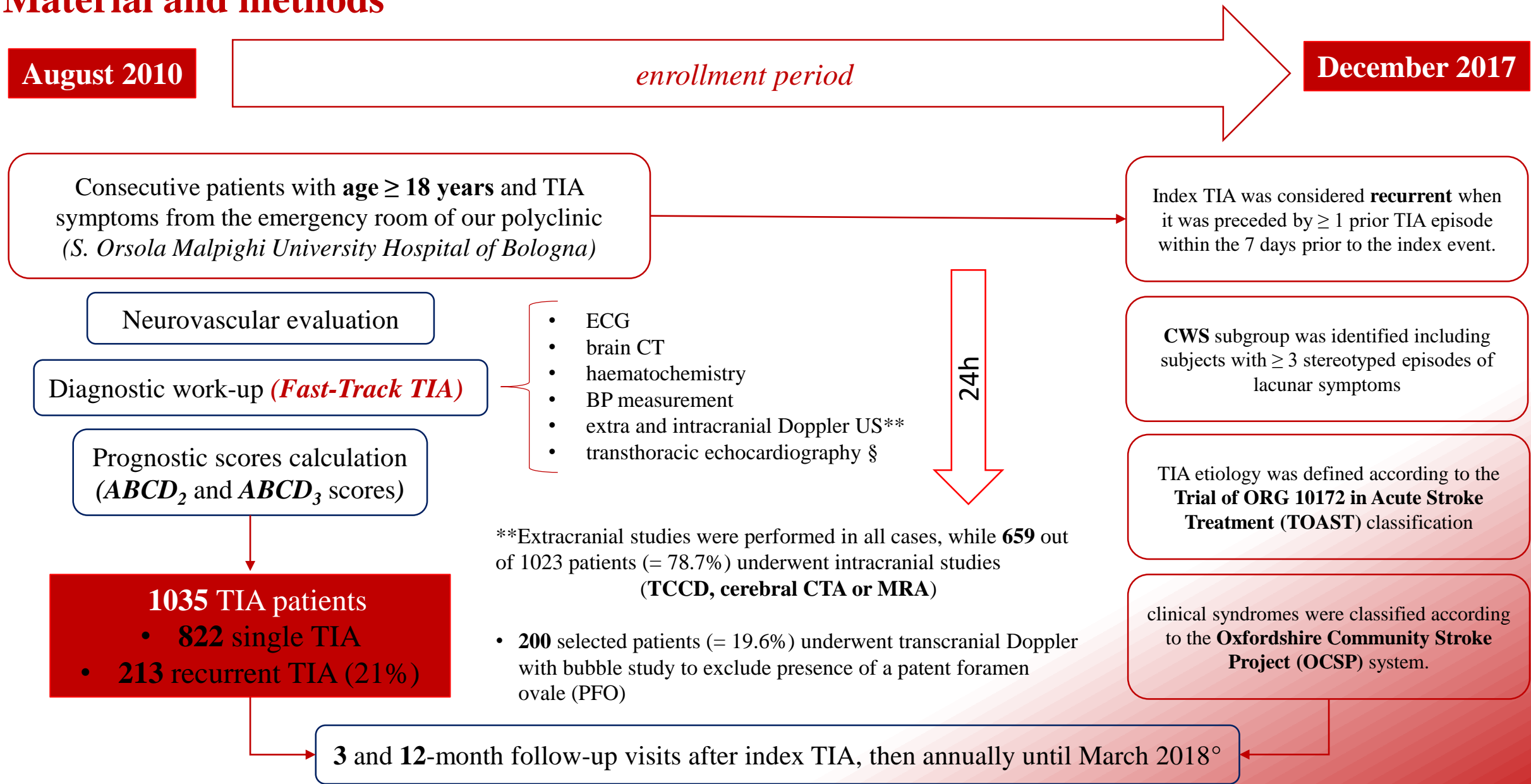
Primary

- to assess frequency, clinical, demographic and etiological features of recurrent TIA, among a prospective cohort of TIA patients
- to evaluate the occurrence of primary (stroke, acute coronary syndrome, vascular death) and secondary (TIA recurrence, cerebral hemorrhage, new onset atrial fibrillation, death due to any cause) outcomes at short (3-month), long (12-month) and very long (60-month) follow-up
- to identify short and long term independent predictors of stroke occurrence after recurrent TIA

- to evaluate concordance between index TIA and subsequent stroke etiologies
- to compare commonly used prognostic clinical score ($ABCD_2$, $ABCD_3$) in order to assess reliability in stroke risk prediction in our population

Secondary

Material and methods



Results

- The annual TIA frequency in our study resulted to be about **140 cases-year**. Considering that our hospital area covers about **250.000 users**, we estimated a global **TIA incidence** of about **56 cases per 100.000 person-year**
- in line with incidence reported by other Italian population studies (52-58 cases per 100-000 person-year) *Lauria et al. Acta Neurol Scand. 1996, Cancelli I et al. Stroke. 2011*
- As observed in OXVASC and PROMAPA studies recurrent TIA patients were more frequently **male** and **younger** than patients presenting with single TIA.

Demographical Characteristics	Single TIA (822)	Recurrent TIA (213)	p
Sex (male)	431 (52.4%)	130 (61.0%)	0.025
Age (years)	71.1 ± 14.8	69.0 ± 13.5	0.058



Results

- **prior history of coronary disease, cigarette smoking, dyslipidemia, AAP and ICA extracranial stenosis** were significantly related with the recurrent TIA phenotype

Clinical Characteristics	Single TIA (822)	Recurrent TIA (213)	p
<u>Anamnestic risk factors</u>			
Hypertension	559 (68.2%)	151 (70.9%)	0.457
Diabetes mellitus	127 (15.5%)	39 (18.3%)	0.346
Coronary disease	22 (2.7%)	14 (6.7%)	0.010
Atrial fibrillation	117 (14.3%)	20 (9.4%)	0.069
Cigarette smoking	95 (11.6%)	39 (18.3%)	0.012
Dyslipidemia	330 (40.2%)	106 (49.8%)	0.013
Aortic Arch pathology	8 (1.0%)	6 (2.8%)	0.049
Prior TIA/stroke	185 (22.5%)	52 (24.4%)	0.583
Extracranial ICA stenosis	119 (14.5%)	54 (25.4%)	<0.001
Peripheral artery disease	35 (4.3%)	12 (5.6%)	0.362
Acute/chronic heart failure	25 (3.0%)	6 (2.8%)	1.000
Alcohol consumption	24 (2.9%)	7 (3.3%)	0.821

Results

** according to TOAST classification

TIA etiology**	Single TIA (822)	Recurrent TIA (213)	p
LAA	143 (17.4%)	58 (24.4%)	0.002
Cardioembolic	193 (23.5%)	34 (16.0%)	0.020
Lacunar	161 (19.6%)	29 (13.6%)	0.029
Other determined etiology	20 (2.4%)	7 (3.3%)	0.472
Cryptogenic	302 (36.7%)	52 (24.4%)	0.001
CWS	0 (0.0%)	33 (15.5%)	<0.001



- Besides CWS, LAA was the most frequent etiology underlying recurrent TIAs, confirming results from the PROMAPA study

- CWS etiopathogenesis remains not well established → hemodynamic changes or stenosis involving branches of the middle cerebral artery (*Xu X et al. Magn Reson Imaging. 2016*)

<u>Cerebrovascular findings</u>			
Extracranial ICA stenosis	159 (20.2%)	63 (31.5%)	0.001
Intracranial stenosis	52/659* (7.9%)	12/156* (7.7%)	1.000
PFO	83/160* (51.9%)	27/40* (67.5%)	0.079



→ our data suggest that small vessel pathology plays a key rule in CWS

Results

- Independent predictors of stroke occurrence after recurrent TIA: the presence of an acute ischemic lesion (TIA with lesion), leukoaraiosis and a clinical presentation with dysarthria were the strongest independent predictors of 3 and 12-month stroke recurrence in patients with recurrent TIA.

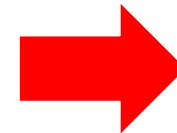
Cox regression analysis

3-month				
Variables	p	Hazard ratio	95% CI Lower	95% CI Upper
TIA with lesion	<0.001	14.856	5.693	38.768
Leukoaraiosis	0.038	2.706	0.898	5.921
Dysarthria	0.031	2.877	1.100	7.524
12-month				
Variables	p	Hazard ratio	95% CI Lower	95% CI Upper
TIA with lesion	<0.001	15.173	5.800	39.693
Leukoaraiosis	0.046	2.347	0.915	6.022
Dysarthria	0.030	2.902	1.110	7.584

Results

- **3-month** overall stroke risk = **2.3%** → in line with a recent systematic review analyzing studies in which the **Fast-Track** operative model had been applied (0.62 - 4.76%)
- Overall stroke occurrence at **12** and **60-month** follow-up resulted lower in comparison to data deriving from a European TIA registry (**2.8%** and **5.3%** vs 5.1% and 9.5% respectively) *Amarenco P et al. N Engl J Med. 2016, 2018*

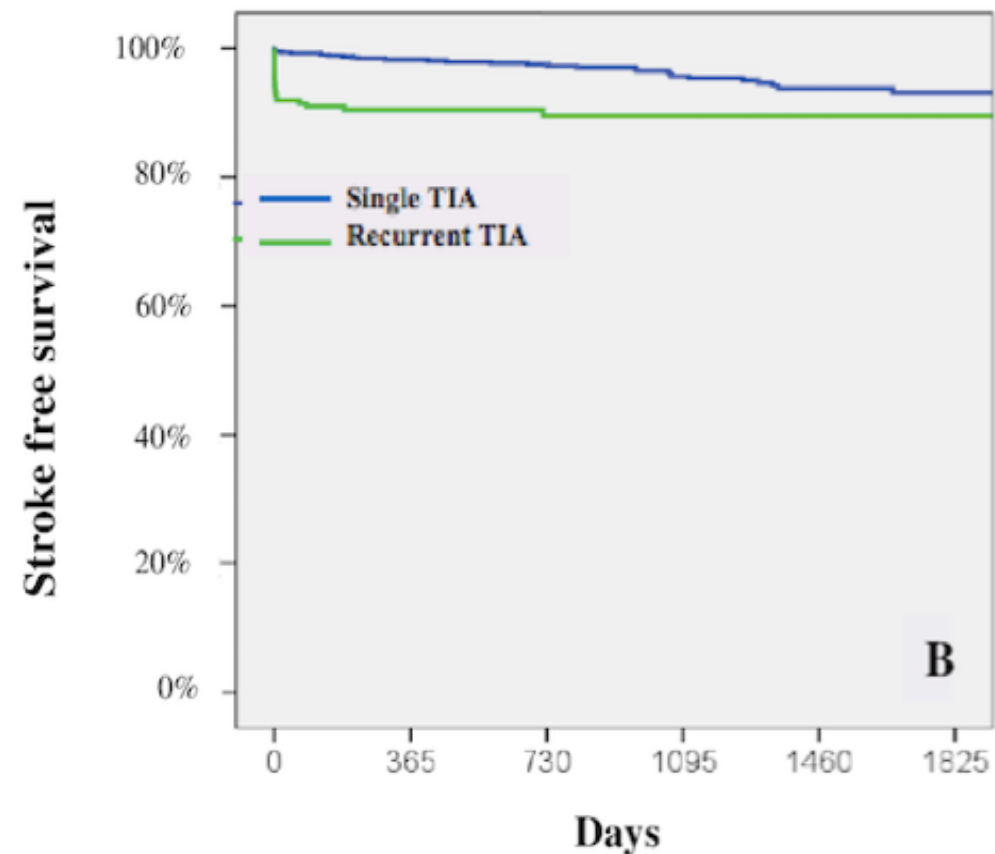
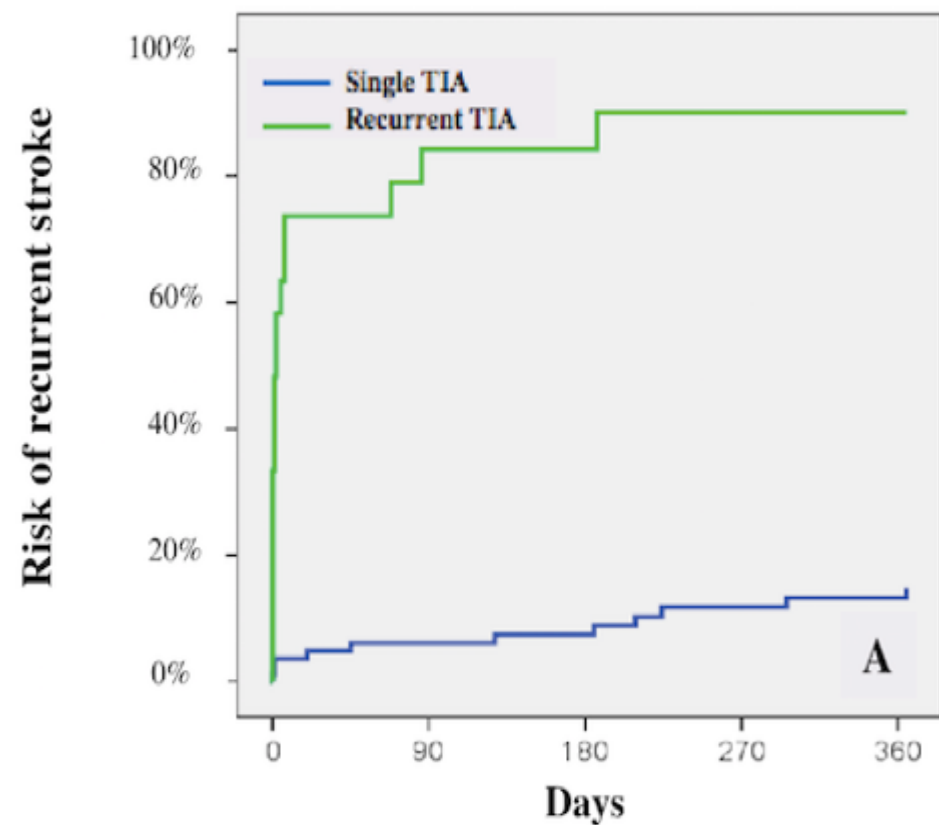
Primary outcome			
	Single TIA (822)	Recurrent TIA (213)	p
<u>Stroke</u>			
48-hour	3 (0.4%)	12 (5.7%)	<0.001
7-day	3 (0.4%)	15 (7.1%)	<0.001
3-month	6 (0.7%)	18 (8.5%)	<0.001
12-month	11 (1.3%)	18 (8.5%)	<0.001
24-month	18 (2.2%)	21 (10.0%)	<0.001
60-month	34 (4.1%)	21 (10.0%)	0.002



➤ **Stroke occurrence after recurrent TIA resulted significantly higher in comparison to single TIA patients at 3, 12 and 60-month follow-up.§**

§: confirmed by contingency analysis excluding CWS

Results

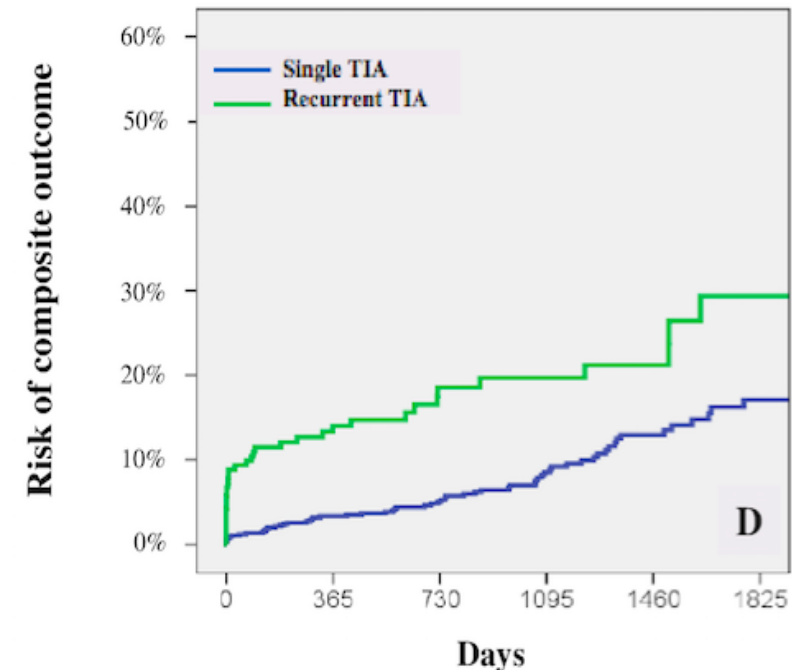
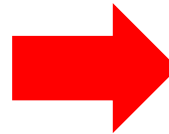


Results

- We observed that single TIA patients presented a 2-year risk of stroke occurrence of **2.2%** with a 5-year cumulative risk of **4.1%**
→ 50% of stroke episodes occurred within the first 2 years after index TIA
- Instead, recurrent TIA patients showed **equal 2-year risk and 5-year cumulative risk (10%)**
→ **risk factors prompt identification and correction is crucial in order to obtain a long-term risk reduction in recurrent TIA patients**
- Although our study failed to demonstrate statistically significant differences between recurrent and single TIA patients in terms of **other primary outcomes occurrence** (*acute coronary syndrome, vascular death*), a higher frequency was observed at each follow up in the recurrent TIA subgroup

Patients with recurrent TIAs showed a significantly higher incidence of **composite outcome**

→ **besides cerebrovascular involvement, multi-vessels alterations are frequent in recurrent TIA patients**



Results

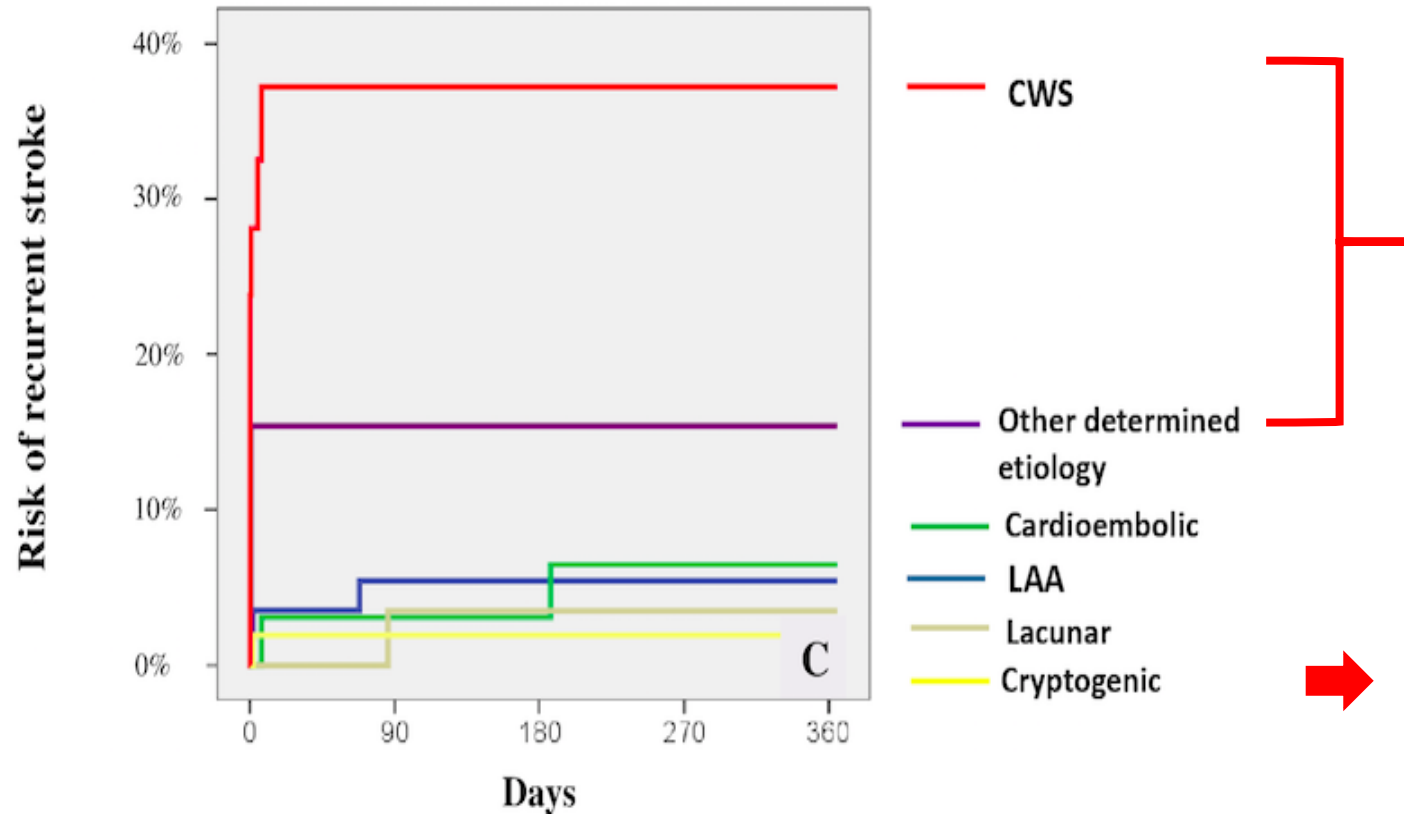
Single TIA

Recurrent TIA



Secondary outcomes			
<u>TIA recurrence</u>			
3-month	26 (3.2%)	9 (4.2%)	0.403
12-month	36 (4.4%)	12 (5.6%)	0.464
60-month	78 (9.5%)	17 (8.0%)	0.594
<u>Death by other causes</u>			
3-month	7 (0.9%)	2 (0.9%)	1.000
12-month	22 (2.7%)	9 (4.2%)	0.258
60-month	116 (14.1%)	29 (13.6%)	0.912
<u>Cerebral hemorrhage</u> (any follow-up)	6 (0.7%)	0 (0.0%)	0.356
<u>New onset atrial fibrillation</u> (any follow-up)	33 (4.0%)	2 (0.9%)	0.031

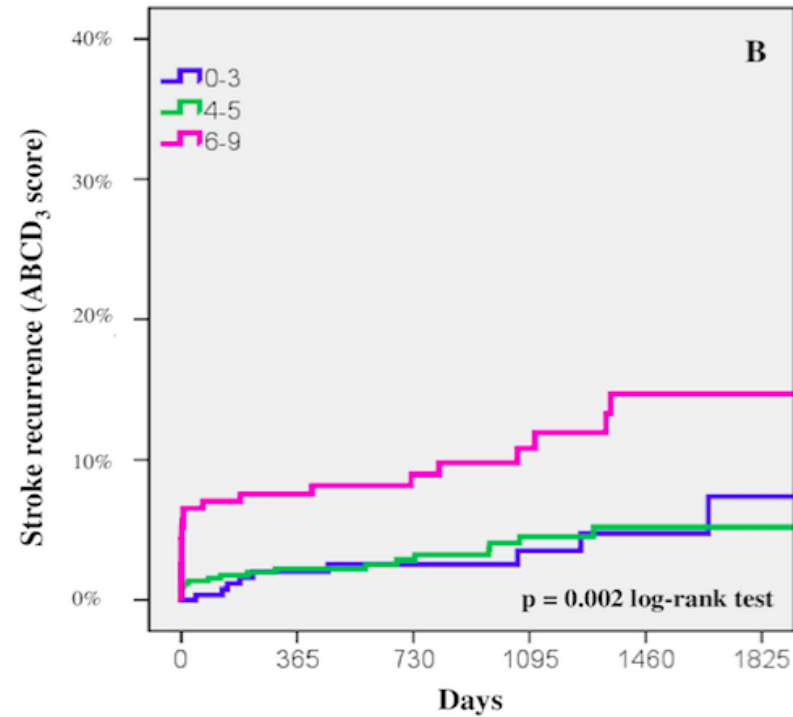
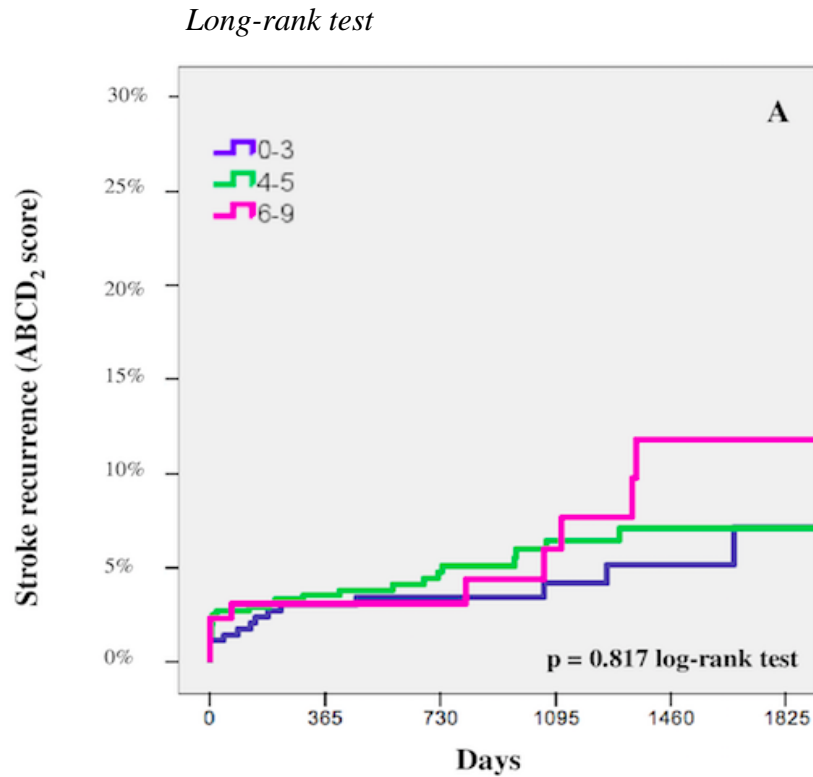
Results



CWS subgroup showed the greatest risk of stroke recurrence in the first 3 months after index TIA, followed by patients with **stroke of other determined etiology and LAA**

Conversely, the lowest risk was observed in **cryptogenic TIAs** both at 3 and 12 months.

Results



- Differently from ABCD₂ score, ABCD₃ score ranging from 6 to 9 was able to identify patients with higher risk of stroke occurrence
- This significant difference was observed during the entire follow-up → **strong impact of TIA recurrence in worsening prognosis**

Results

		STROKE					
		Large vessels	Cardio-embolic	Lacunar	Other causes	Cryptogenic	CWS
INDEX TIA	Large vessels	67.7%	0	33.3%	0	0	0
	Cardioembolic	0	100%	0	0	0	0
	Lacunar	100%	0	0	0	0	0
	Other causes	0	0	0	100%	0	0
	Cryptogenic	0	25%	0	0	75%	0
	CWS	0	0	0	0	0	100%

- index TIA and subsequent stroke etiology coincided when ischemic events were caused by **CWS, cardioembolism and other determined etiologies of stroke**
- We observed mixed concordance between TIA and strokes episodes caused by **large and small vessel disease** → sharing of common risk factors
- Most of cryptogenic TIAs were followed by cryptogenic strokes, as previously observed (*Li L et al. Lancet Neurol. 2015*)

Conclusions

- To our knowledge, our study was the first with focusing on long and very long-term outcome after recurrent TIA.
- Recurrent TIA is a frequent clinical entity accounting for >20% of all TIAs and it is associated either with a **high early and long term stroke risk** as well as to **specific risk and etiologic factors** (CWS, LAA)
- We found that the routinely use of clinical prognostic score considering **TIA recurrence** could better and promptly stratify even long term stroke risk
- We believe that our findings are reliable but our study does have some **limitations**:
 - ❖ the inability to perform in all cases brain MRI within 48 h from symptoms onset, therefore the proportion of patients with an acute ischemic lesion (TIA with lesion) could have been underestimated
 - ❖ For the same reason, we could not evaluate reliability of more sensitive prognostic scores (e.g. **ABCD₃-I**) requiring specific diagnostic investigation (*diffusion weighted MR imaging*)

Thanks for the attention!!!

