28.09.2023, Symposium Annuel du CCC
CHUV, Lausanne

Secondary stroke prevention:
Current status in Europe
Early anticoagulation after stroke in AF

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Disclosures

Stocks
None

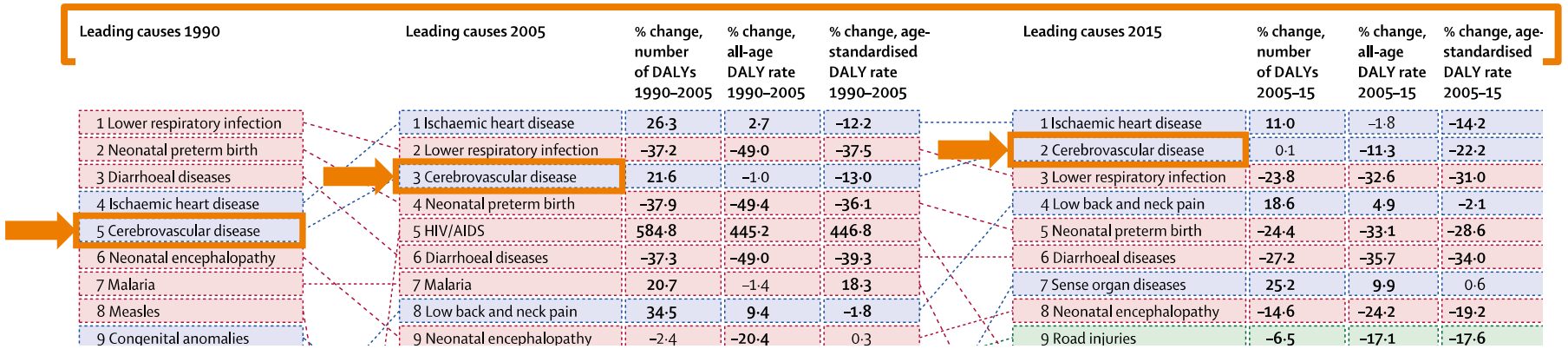
Drug trials (< 5 years)

- **PACIFIC STROKE**
- **OCEANIC STROKE**
- **OCEANIC AF**

Advisory boards & speaker fees (< 3 years)

- **Boeringher-Ingelheim**
- **Pfizer/BMS**
- **Bayer**
- **Daiichi Sankyo**
- **Ever-NeuroPharma**

Stroke is now the 2nd leading cause of disability globally



Leading causes 1990	Leading causes 2005	% change, number of DALYs 1990–2005	% change, all-age DALY rate 1990–2005	% change, age-standardised DALY rate 1990–2005	Leading causes 2015	% change, number of DALYs 2005–15	% change, all-age DALY rate 2005–15	% change, age-standardised DALY rate 2005–15
1 Lower respiratory infection	1 Ischaemic heart disease	26·3	2·7	−12·2	1 Ischaemic heart disease	11·0	−1·8	−14·2
2 Neonatal preterm birth	2 Lower respiratory infection	−37·2	−49·0	−37·5	2 Cerebrovascular disease	0·1	−11·3	−22·2
3 Diarrhoeal diseases	3 Cerebrovascular disease	21·6	−1·0	−13·0	3 Lower respiratory infection	−23·8	−32·6	−31·0
4 Ischaemic heart disease	4 Neonatal preterm birth	−37·9	−49·4	−36·1	4 Low back and neck pain	18·6	4·9	−2·1
5 Cerebrovascular disease	5 HIV/AIDS	584·8	445·2	446·8	5 Neonatal preterm birth	−24·4	−33·1	−28·6
6 Neonatal encephalopathy	6 Diarrhoeal diseases	−37·3	−49·0	−39·3	6 Diarrhoeal diseases	−27·2	−35·7	−34·0
7 Malaria	7 Malaria	20·7	−1·4	18·3	7 Sense organ diseases	25·2	9·9	0·6
8 Measles	8 Low back and neck pain	34·5	9·4	−1·8	8 Neonatal encephalopathy	−14·6	−24·2	−19·2
9 Congenital anomalies	9 Neonatal encephalopathy	−2·4	−20·4	0·3	9 Road injuries	−6·5	−17·1	−17·6

1990 2005 2015

What about different regions, and different age groups?

Disability burden of stroke in different age groups

	1	2	3	4	5	6	7	8	9	10
Early neonatal (0–6 days)	NN Preterm	NN Enceph	NN Sepsis	Congenital	Other NN	LRI	NN Haemol	STD	Diarrhoea	Meningitis
Late neonatal (7–27 days)	NN Sepsis	NN Preterm	NN Enceph	Congenital	LRI	Other NN	Diarrhoea	Meningitis	Malaria	NN Haemol
Post-neonatal (28–364 days)	LRI	Diarrhoea	Congenital	Malaria	PEM	Meningitis	HIV	Haemog	Iron	NN Preterm
1–4 years	Malaria	Diarrhoea	LRI	PEM	Iron	Congenital	Meningitis	Drowning	Skin	Haemog
5–9 years	Iron	Skin	LRI	Diarrhoea	Intest inf	Malaria	HIV	Asthma	Road injuries	Congenital
10–14 years	Iron	Skin	HIV	Conduct	Asthma	Road injuries	Anxiety	Intest inf	Migraine	Haemog
15–19 years	Road injuries	Skin	Depression	Iron	Back & neck	Self-harm	Migraine	Anxiety	Violence	HIV
20–24 years	Road injuries	Depression	Self-harm	Back & neck	Skin	Violence	HIV	Migraine	Iron	Other MSK
25–29 years	Road injuries	HIV	Back & neck	Depression	Self-harm	Migraine	Skin	Violence	TB	Drugs
30–34 years	HIV	Back & neck	Road injuries	Depression	Self-harm	Migraine	IHD	TB	Skin	Violence
35–39 years	HIV	Back & neck	Road injuries	Depression	IHD	Migraine	TB	Self-harm	Stroke	Other MSK
40–44 years	Back & neck	HIV	IHD	Road injuries	Depression	Stroke	Diabetes	Sense	TB	Migraine
45–49 years	IHD	Back & neck	Stroke	Diabetes	HIV	Depression	Road injuries	Sense	TB	Other MSK
50–54 years	IHD	Stroke	Back & neck	Diabetes	Sense	Depression	Lung C	COPD	Road injuries	TB
55–59 years	IHD	Stroke	Back & neck	Diabetes	Sense	COPD	Lung C	Depression	TB	CKD
60–64 years	IHD	Stroke	Diabetes	Back & neck	COPD	Sense	Lung C	CKD	LRI	Depression
65–69 years	IHD	Stroke	COPD	Diabetes	Sense	Back & neck	Lung C	CKD	LRI	Stomach C
70–74 years	IHD	Stroke	COPD	Sense	Diabetes	Back & neck	Lung C	LRI	Alzheimer's	CKD
75–79 years	IHD	Stroke	COPD	Sense	Diabetes	Alzheimer's	Back & neck	LRI	Lung C	CKD
≥80 years	IHD	Stroke	Alzheimer's	COPD	Sense	LRI	Diabetes	CKD	Back & neck	HTN HD

Rate of change 2005–15 (%)

−0·56 to −0·31 | −0·31 to −0·19 | −0·19 to −0·09 | −0·09 to −0·04 | −0·04 to 0·01
0·01 to 0·08 | 0·08 to 0·15 | 0·15 to 0·23 | 0·23 to 0·32 | 0·32 to 0·57

2015 years data

Disability burden of stroke in different age groups

	1	2	3	4	5	6	7	8	9	10
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≥80 years	IHD	Stroke	Alzheimer's	COPD	Sense	LRI	Diabetes	CKD	Back & neck	HTN HD

Rate of change 2005–15 (%)

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2015 years data

Stroke is a major cause of disability
In the working age groups

Guideline

EUROPEAN STROKE JOURNAL

Action Plan for Stroke in Europe 2018–2030

Bo Norrving[1], Jon Barrick[2], Antoni Davalos[3], Martin Dichgans[4], Charlotte Cordonnier[5], Alla Guekht[6], Kursad Kutluk[7], Robert Mikulik[8], Joanna Wardlaw[9], Edo Richard[10], Darius Nabavi[11], Carlos Molina[12], Philip M Bath[13], Katharina Stibrant Sunnerhagen[14], Anthony Rudd[15], Avril Drummond[16], Anna Planas[17] and Valeria Caso[18]; on behalf of the Action Plan for Stroke in Europe Working Group*

European Stroke Journal
2018, Vol. 3(4) 309–336

DOI: 10.1177/2396987318808719
journals.sagepub.com/home/eso

SAGE

Secondary prevention targets

- Including secondary prevention in **national stroke plans** with follow-up in primary/community care

- Ensuring that **90% of the stroke population should be seen by a stroke specialist** and have access to secondary prevention management (investigation and treatment)

- Ensure **access to key investigational modalities**: CT (or MR) scanning, carotid ultrasound, ECG, 24-hour ECG, echocardiography (transthoracic and transoesophageal), blood tests (lipids, glucose, HbA_{1c}, coagulation, erythrocyte sedimentation rate, C-reactive protein, autoantibodies)

- Ensuring **access to key preventative strategies**: lifestyle advice, antihypertensives, lipid lowering agents, antiplatelets, anticoagulants, oral hypoglycaemic agents and insulin, carotid endarterectomy, and PFO closure.

Original research article

EUROPEAN STROKE JOURNAL

Availability of secondary prevention services after stroke in Europe: An ESO/SAFE survey of national scientific societies and stroke experts

A Webb[1], MR Heldner[2], D Aguiar de Sousa[3], EC Sandset[4,5], G Randall[6], Y Bejot[7], B van der Worp[8], V Caso[9] and U Fischer[2]; On behalf of the ESO-SAFE Secondary Prevention Survey Steering Group

European Stroke Journal
2019, Vol. 4(2) 110–118

DOI: 10.1177/2396987318816136
journals.sagepub.com/home/eso

SAGE

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Availability of secondary prevention
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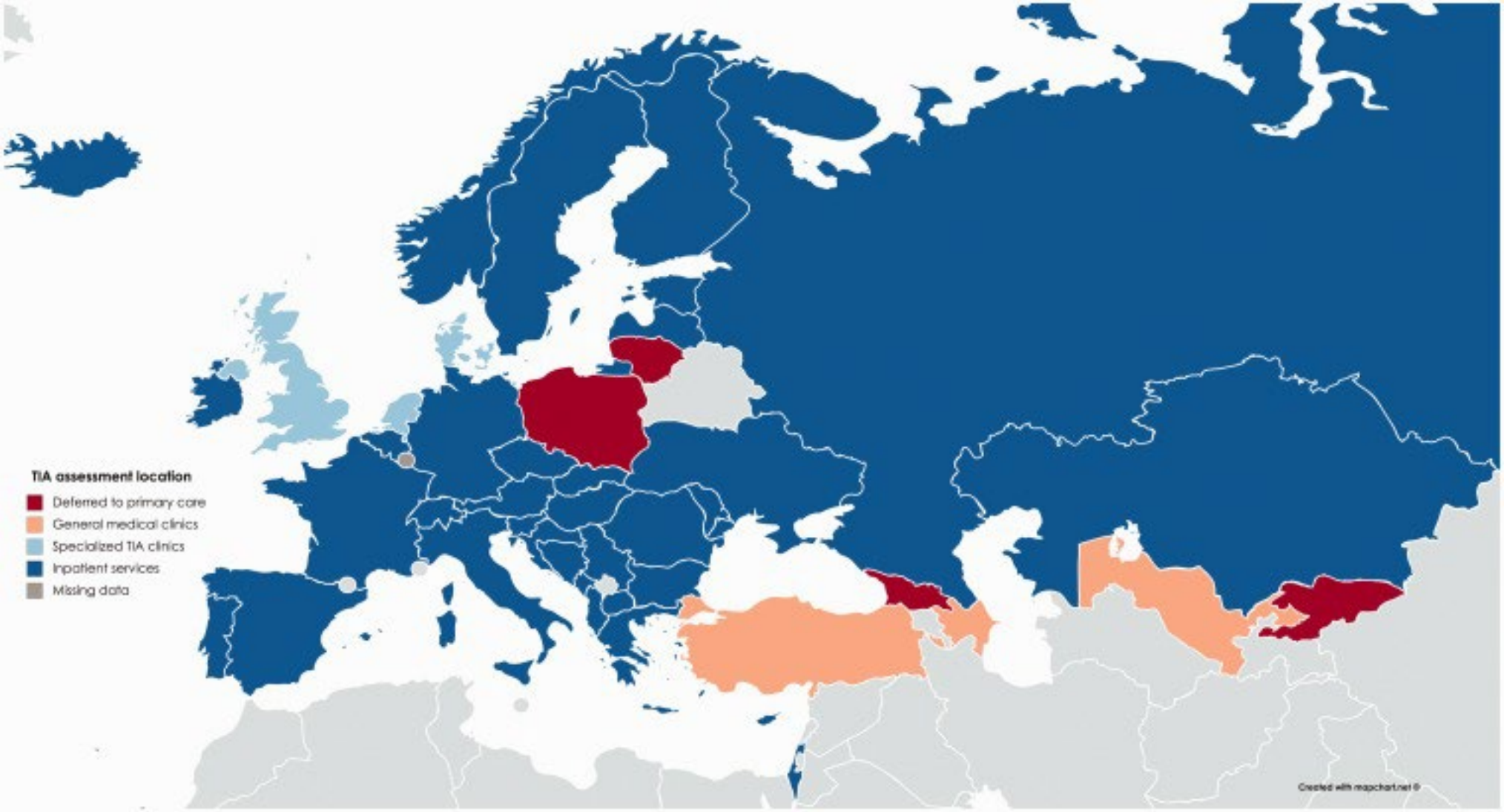
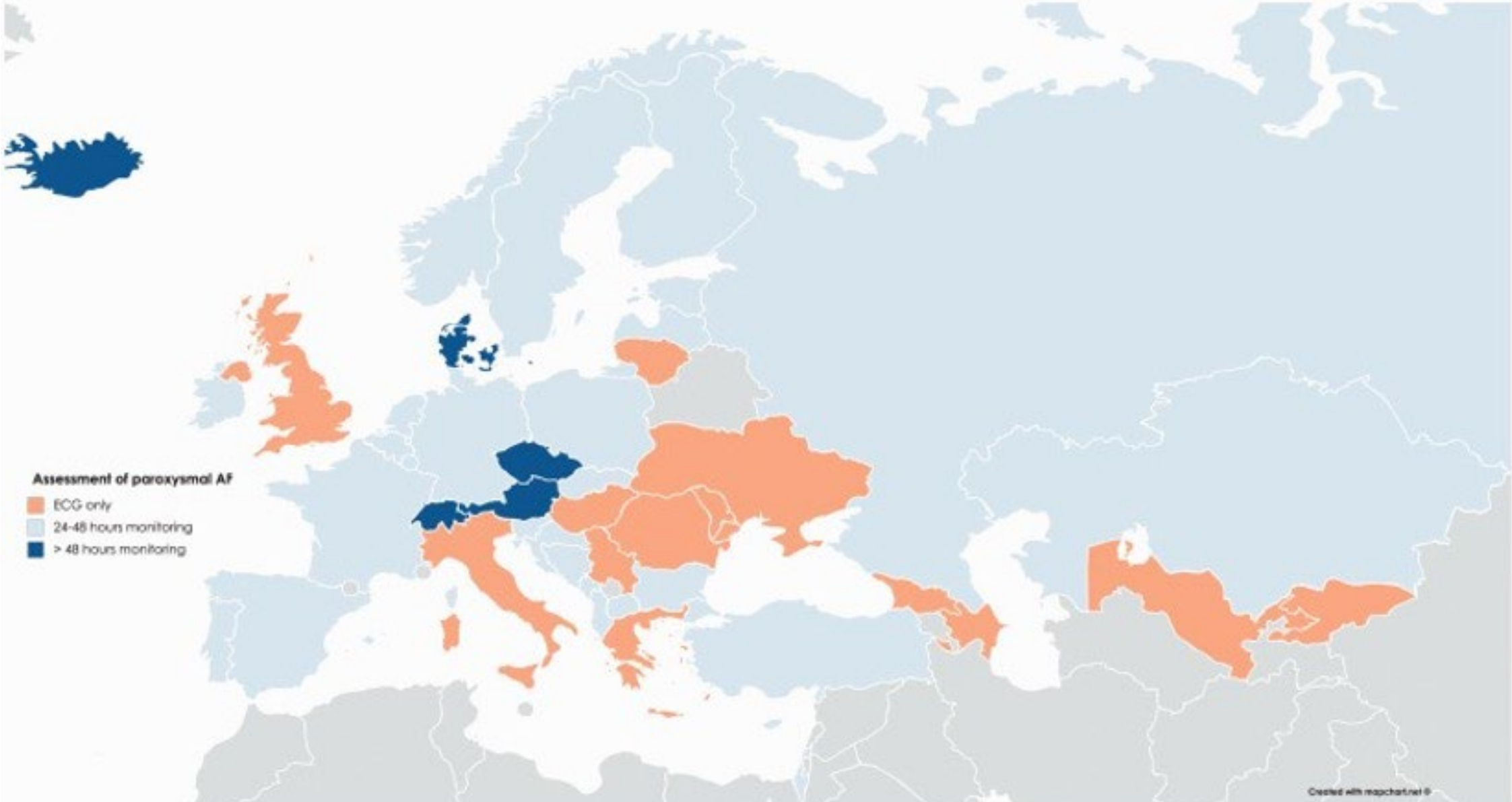


EUROPEAN STROKE JOURNAL

Original research article

European Stroke Journal
2019, Vol. 4(2) 110–118

Availability of secondary prevention



Check for updates

Original research article

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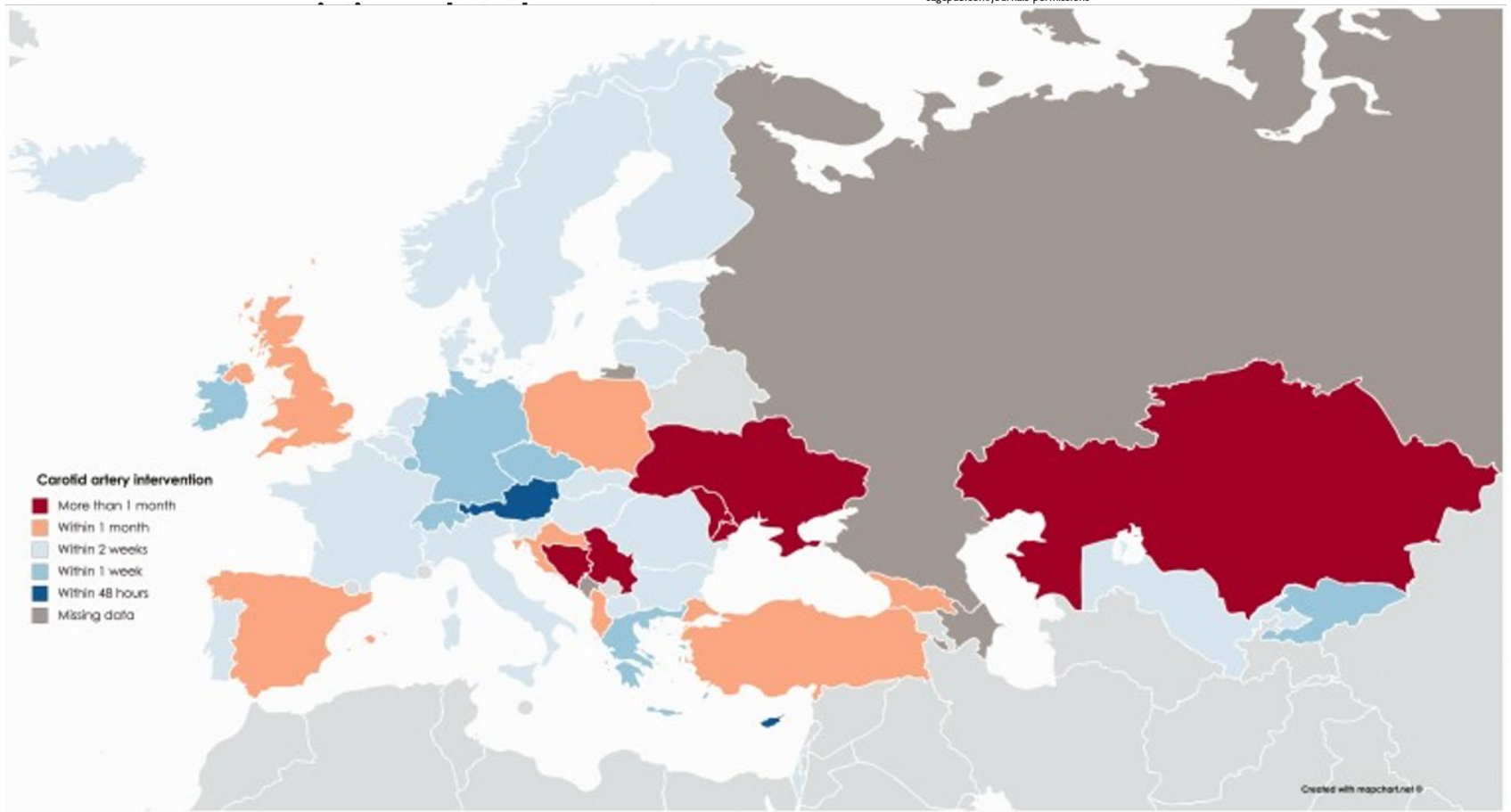
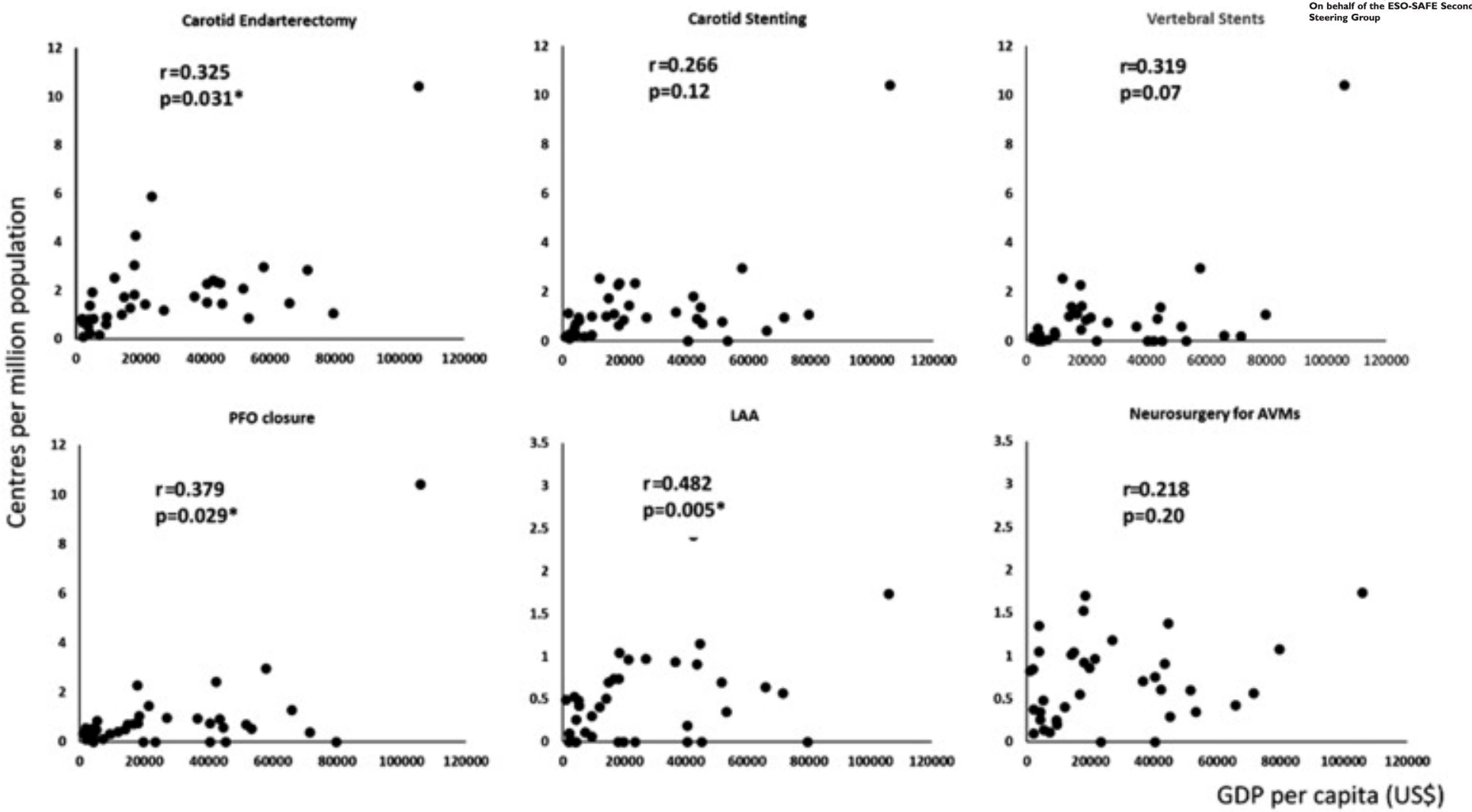


Interventions for 2° prevention



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Original research article

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DOI: 10.1177/2396987318816136
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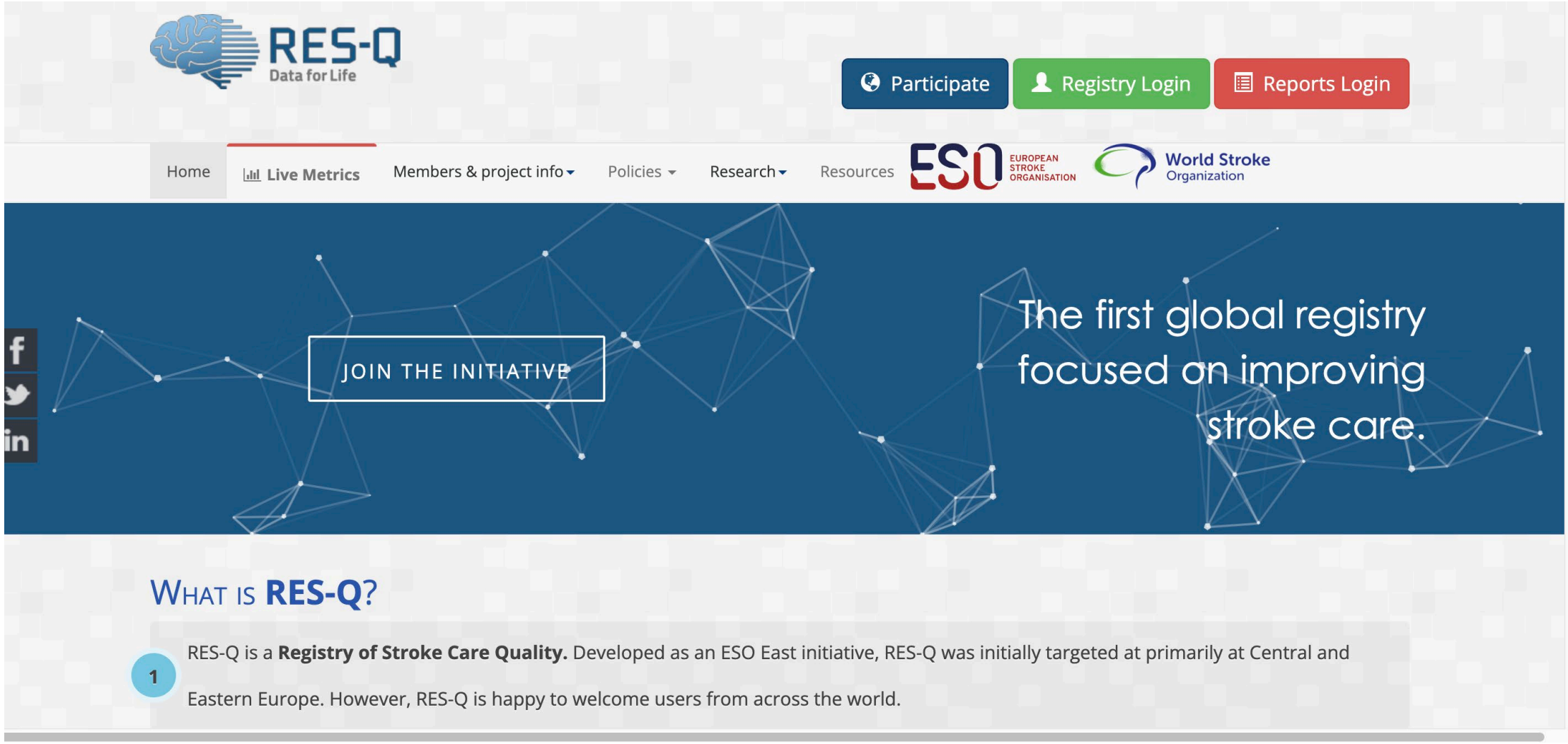
Evaluation of outcomes & quality improvement targets

Defining a **Common European Framework of Reference for Stroke Care Quality** that includes:
a) development or update of **European guidelines** for management of acute stroke care,
b) definition of a **common dataset** covering core measures of stroke care quality to enable accurate international comparisons of care both in hospital and in the community (including structure, process, outcome measures, and patient experience)

Assigning a named individual who is **responsible** for stroke quality improvement in each country or region

Establishing national and regional level systems for **assessing and accrediting stroke clinical services**, providing peer support for quality improvement, and making audit data routinely available to the general public

Collecting **patient-reported outcomes and longer-term outcomes** (e.g. 6 months and 1 year), covering both hospital and community care.


RES-Q
Data for Life
Participate
Registry Login
Reports Login
Home
Live Metrics
Members & project info
Policies
Research
Resources
ESO
EUROPEAN STROKE ORGANISATION
World Stroke Organization
JOIN THE INITIATIVE
The first global registry focused on improving stroke care.
WHAT IS RES-Q?
1
RES-Q is a Registry of Stroke Care Quality. Developed as an ESO East initiative, RES-Q was initially targeted at primarily at Central and Eastern Europe. However, RES-Q is happy to welcome users from across the world.

RES-Q in the world

2017

2300
total patients

200
total sites

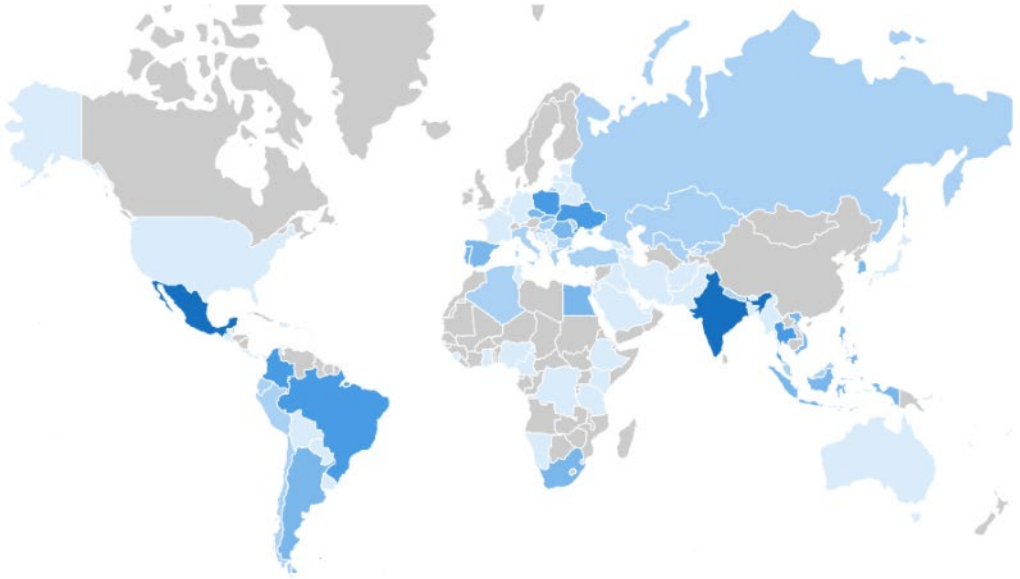
23
total countries

2023*

639 515
total patients

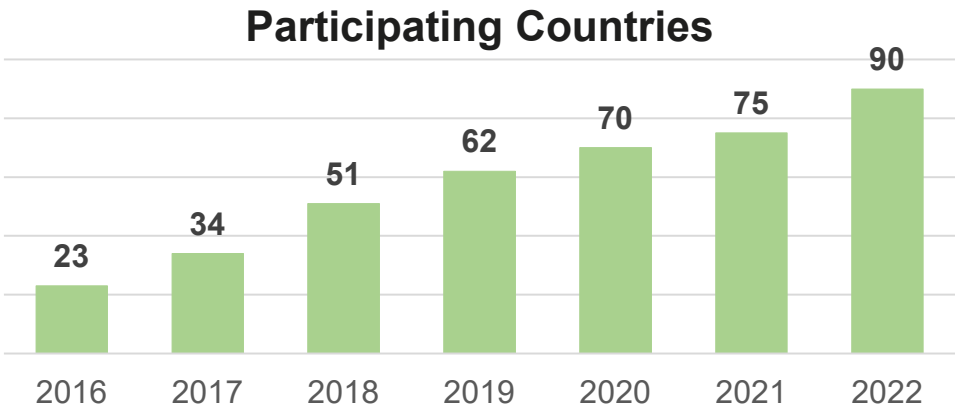
2 183
total sites

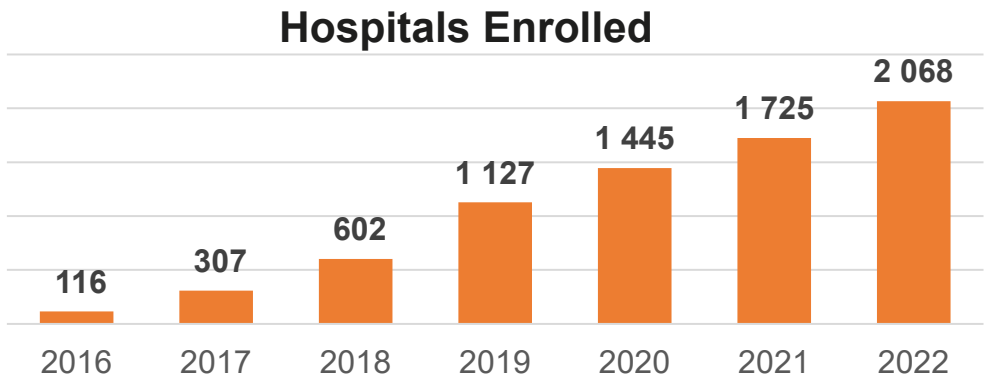
90
total countries

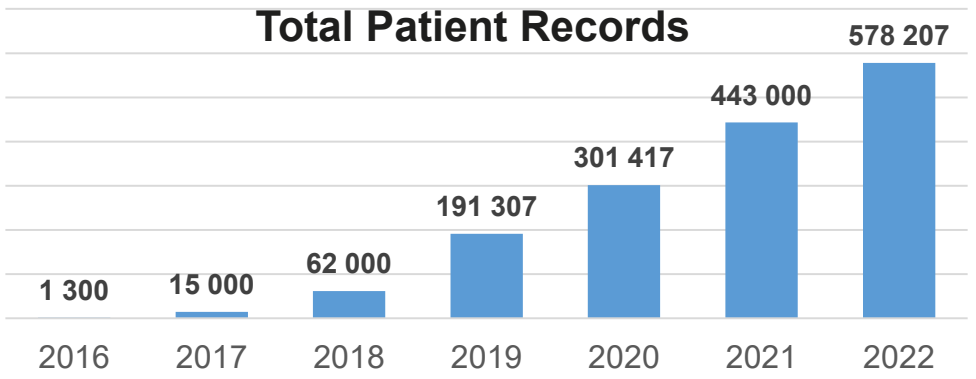


*RES-Q database as on 19th May 2023

RES-Q growth over the years



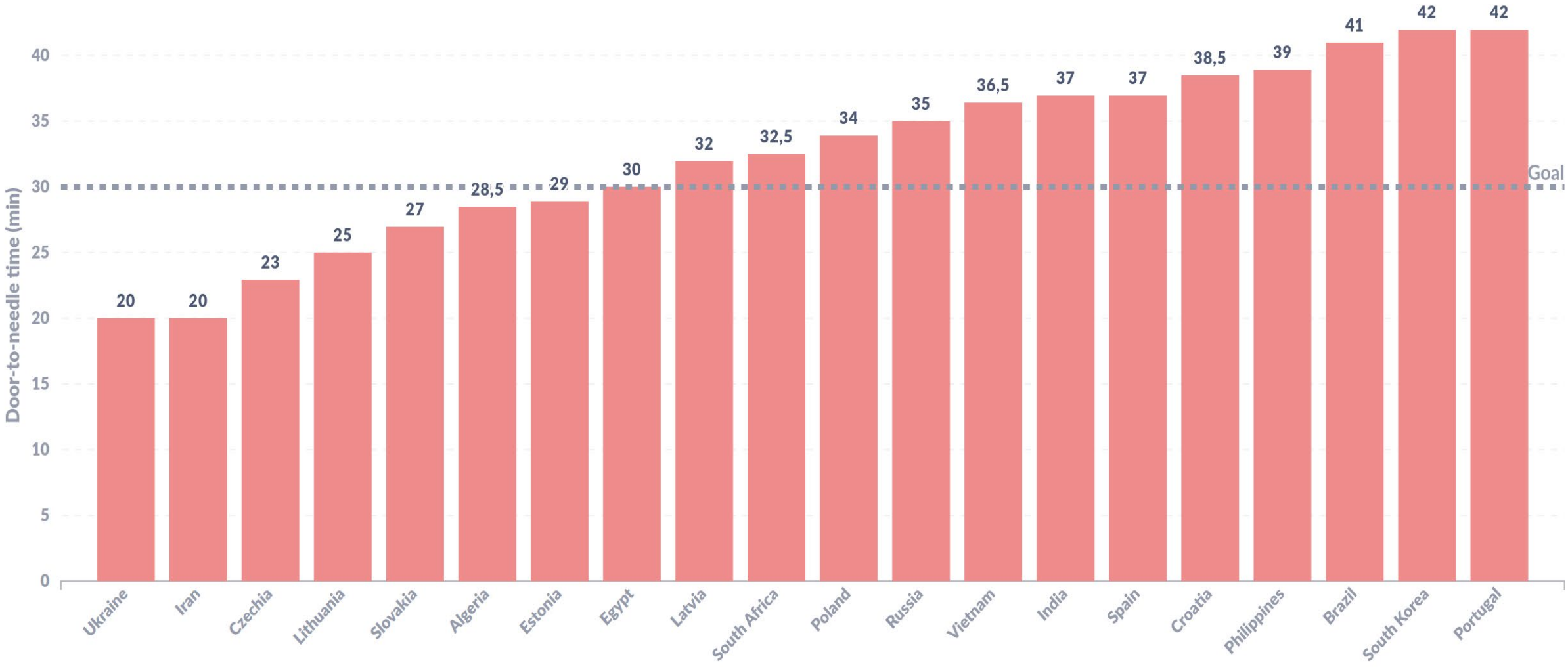




RES-Q Global results on key metrics - 2022

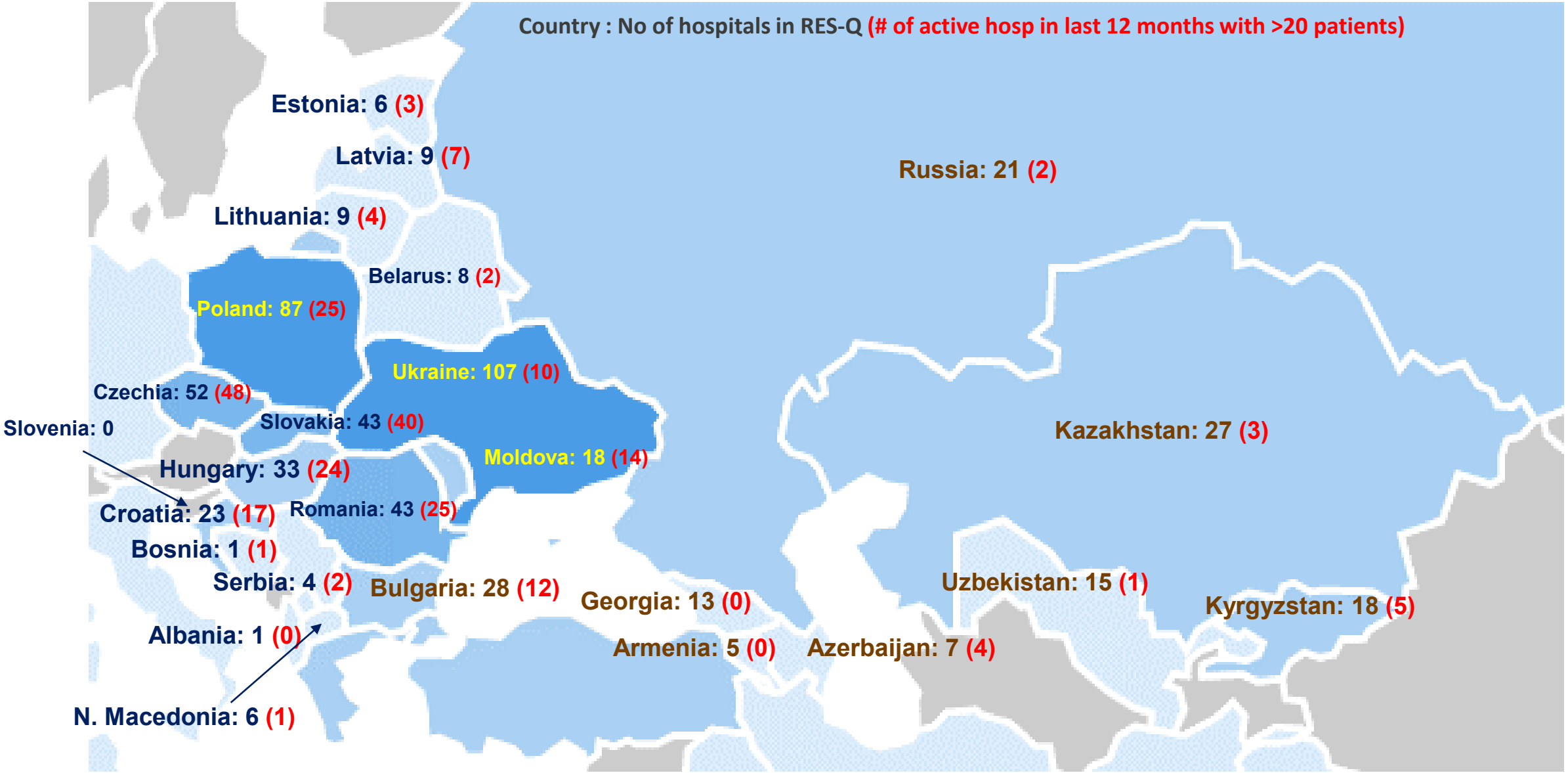
Door To Needle (DTN) from the hospitals capturing data in RES-Q

Median Global DTN is 36 mins



ESO-EAST registered hospitals in RES-Q

43% active hospitals who entered at least 20 patients in past 12 months.
No participation from any hospital from Albania, Armenia, Georgia



ESO-EAST key metrics performance 2021 & 2022

Metrics	2021 (50,409 pts)	2022 (46,512 pts)
Median age (years)	71	72
Median NIHSS at admission	7	6
ICU/stroke hospitalization (%)	74	73
Recanalization rate (IS strokes) (%)	33	37
Median Door-To-Needle time (min)	30	27
Median Door-To-Groin time (first hospital)(IS strokes) (min)	78	72
mTICI of value 2B, 2C, 3 rate (IS patients) (%)	83	82
Dysphagia screened (IS and ICH strokes) (%)	90	86
Discharged home on statins (IS strokes) (%)	83	80
Discharged home on antihypertensive (IS strokes) (%)	66	61
Anticoagulant prescribed (IS strokes with afib. flutter, discharged to home/social care) (%)	80	87
Antiplatelet prescribed (IS strokes without afib. flutter, discharged to home/social care) (%)	91	93
Median hospital stay (IS and ICH strokes)	8	7

Hospital overview

Date Range: January 1, 2023 - March 31, 2023 ×

Age interval | Sex | NIHSS interval | Stroke type | Thrombolysis done | Thrombectomy done

Demographics

Indicator	Hospital	Country
Number of stroke cases	87	1 215
Age [mean]	72	72
NIHSS performed [%]	82	94
NIHSS score [median]	11	6
BP systolic [mean]	154	157
BP diastolic [mean]	82	87
Glucose (mmol/L)[mean]	7,3	7,5
LDL cholesterol (mmol/L)[mean]	2,9	2,7
In hospital stroke [%]	1	3

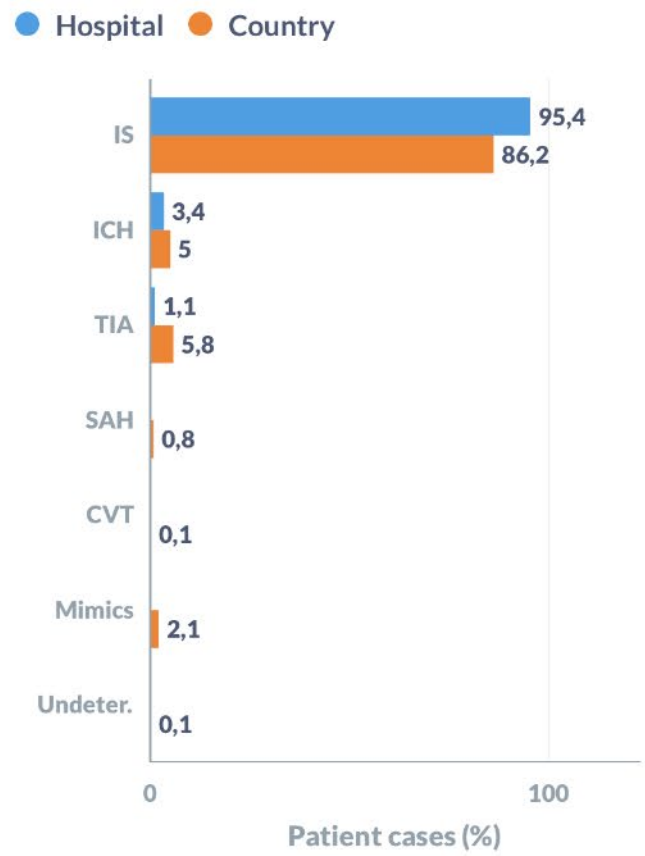
Rows 1-9 of 11

Risk factors/history

Indicator	Hospital	Countr
COVID positive [%]	13	
Hypertension [%]	68	7
Diabetes [%]	70	6
Hyperlipidemia [%]	34	3
Active smoker in last 10 years [%]	21	2
Previous ischemic stroke [%]	9	1
Previous hemorrhagic stroke [%]	2	
Atrial fibrilation or flutter [%]	20	1
Cor. artery disease/previous MI [%]	21	1

Rows 1-9 of 11

Stroke type distribution



Post-acute Care

Discharge

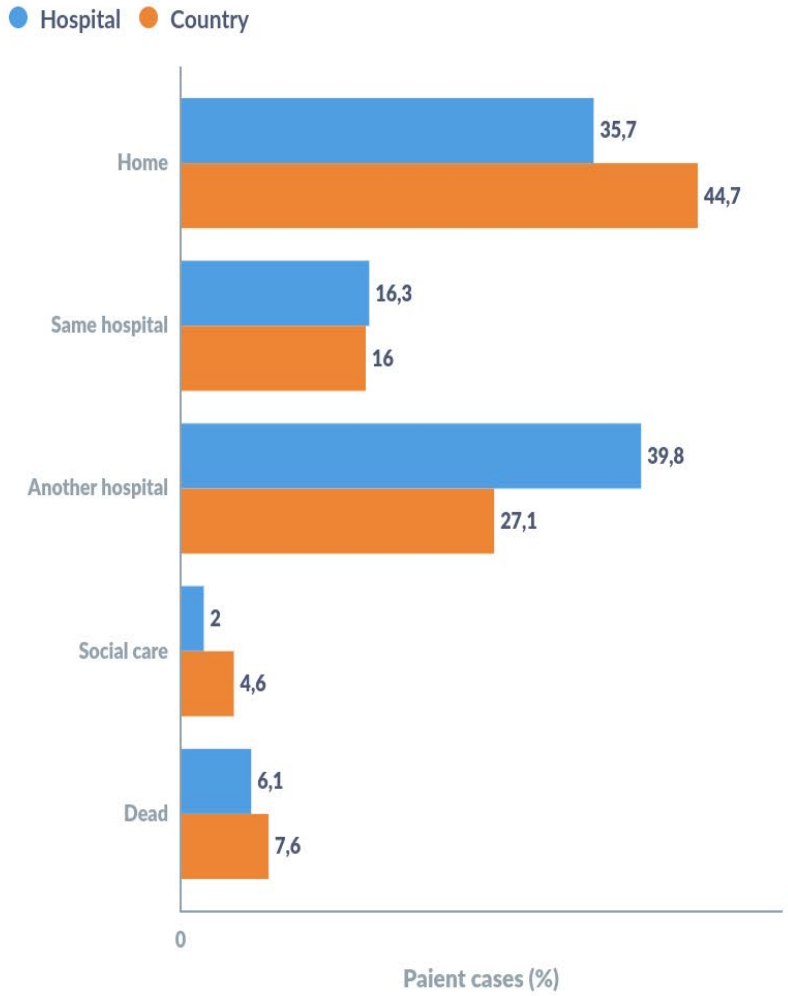
Treatment at discharge home/social care (1)

Indicator	Hospital	Country
Antidiabetic at discharge [%]	24	23
Antihypertensive at discharge [%]	68	76
Antiplatelets at discharge [%]	73	70
Aspirin (ASA) at discharge [%]	65	58
Cilostazol at discharge [%]	0	0
Clopidrogel at discharge [%]	46	36
Ticagrelor at discharge [%]	0	0
Ticlopidine at discharge [%]	0	0
Prasugrel at discharge [%]	0	0
Dipyridamol, slow release at discharge [%]	0	0
Other antiplatelet at discharge [%]	0	0

Treatment at discharge home/social care (2)

Indicator	Hospital	Country
Anticoagulants at discharge for AFIB+ [%]	71	84
Anticoagulants at discharge planned for AFIB+ [%]	0	5
Warfarin at discharge for AFIB+ [%]	14	3
Heparin at discharge for AFIB+ [%]	0	10
Dabigatran at discharge for AFIB+ [%]	29	31
Rivaroxaban at discharge for AFIB+ [%]	0	5
Apixaban at discharge for AFIB+ [%]	29	36
Edoxaban at discharge for AFIB+ [%]	0	0
Other anticoagulant at discharge for AFIB+ [%]	0	0
Statin at discharge [%]	73	82

Discharge destination



Clinical Trial > Stroke. 2023 May;54(5):1172-1181. doi: 10.1161/STROKEAHA.122.041660.
Epub 2023 Mar 23.

Divergence Between Clinical Trial Evidence and Actual Practice in Use of Dual Antiplatelet Therapy After Transient Ischemic Attack and Minor Stroke

Eleonora De Matteis [1], Federico De Santis [1], Raffaele Ornello [1], Bruno Censori [2], Valentina Puglisi [2], Luisa Vinciguerra [2], Alessia Giossi [2], Pietro Di Viesti [3], Vincenzo Inchingolo [3], Giovanni Matteo Fratta [3], Marina Diomedi [4], Maria Rosaria Bagnato [4], Silvia Cenciarelli [5], Chiara Bedetti [2 5], Chiara Padiglioni [5], Tiziana Tassinari [6], Valentina Saia [6], Alessandro Russo [6], Marco Petruzzellis [7], Domenico Maria Mezzapesa [7], Martina Caccamo [7], Giuseppe Rinaldi [8], Alessandra Bavaro [8], Maurizio Paciaroni [9], Maria Giulia Mosconi [9], Matteo Foschi [1 10], Pietro Querzani [10], Francesco Muscia [11], Serena Gallo Cassarino [11], Paolo Candelaresi [12], Antonio De Mase [12], Maria Guarino [13], Letizia Maria Cupini [14], Enzo Sanzaro [15], Andrea Zini [16], Salvatore La Spada [17], Carmela Palmieri [18], Federica Nicoletta Sepe [19], Simone Beretta [20], Cristina Paci [21], Emanuele Alessandro Caggia [22], Maria Vittoria De Angelis [23], Laura Bonanni [24], Gino Volpi [25], Rossana Tassi [26], Francesca Pistoia [1], Umberto Scoditti [27], Agnese Tonon [28], Giovanna Viticchi [29], Giampietro Ruzza [30], Patrizia Nencini [31], Anna Cavallini [32], Danilo Toni [33], Stefano Ricci [5], Simona Sacco [1]; READAPT Study Group

Collaborators, Affiliations + expand

PMID: 36951052 DOI: 10.1161/STROKEAHA.122.041660

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The real-world use of DAPT is broader than RCTs. Most patients did not meet the RCT criteria because of the severity of ischemic stroke, lower risk of TIA, late DAPT start, or lack of antiplatelet loading dose.

PMID: 36951052 DOI: 10.1161/STROKEAHA.122.041660

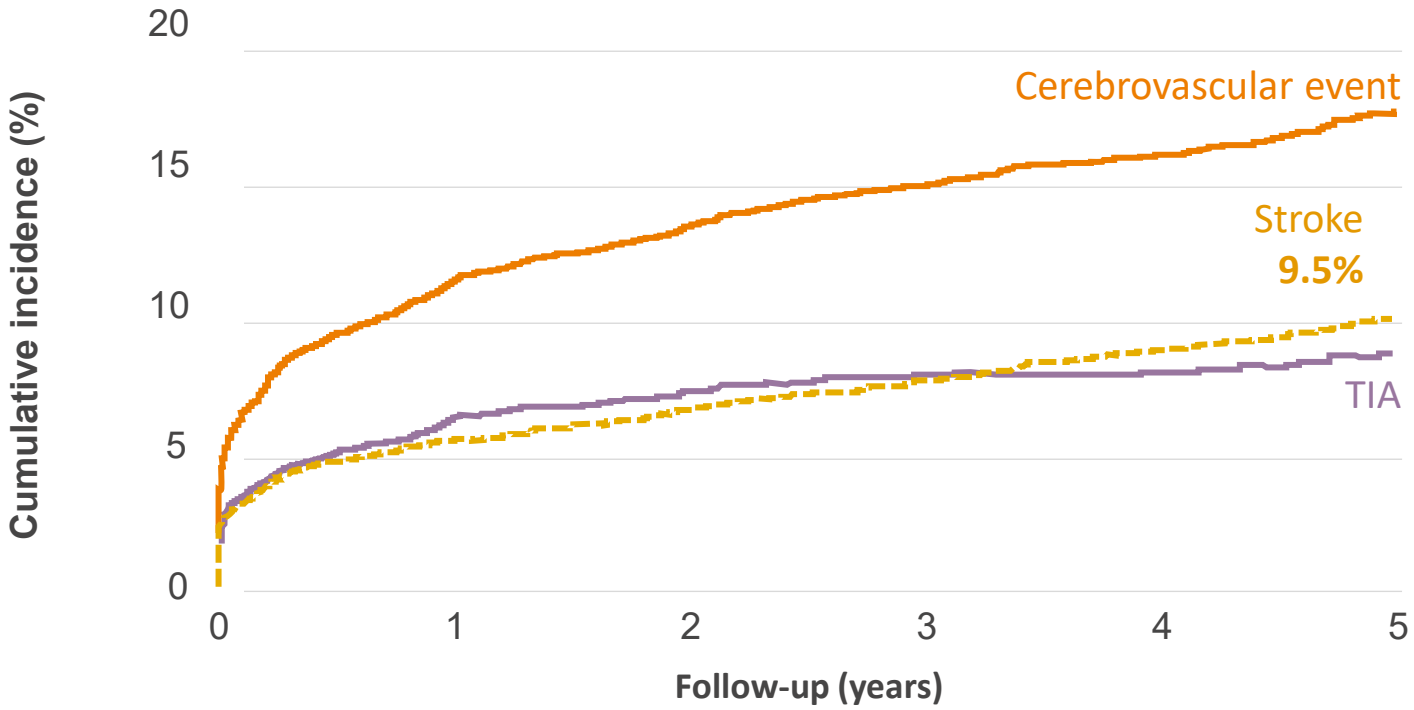
There is a Medical Need for Alternative Treatment Options After an Acute Ischemic Stroke or High-Risk TIA

The **long-term residual risk of recurrent stroke remains high** for patients with prior ischemic stroke or TIA treated with SAPT[1]

Antithrombotic strategies aim to provide a **reduction in the risk of ischemic events without an increased risk of bleeding**[2]

Long term **DAPT does not reduce the risk of recurrent stroke** in patients with **lacunar ischemic stroke, and increases the risk of major bleeding** versus ASA alone*,[3]

Cumulative event rate# at 5 years in patients with TIA and minor stroke ≤7 days (N=3847)[4]



*As shown in a double-blind trial of 3020 patients assigned to receive clopidogrel or placebo on a background of ASA. The primary outcome was any recurrent stroke. #The primary outcome was the composite of non-fatal ischemic or hemorrhagic stroke or non-fatal ACS or cardiovascular death. Secondary outcomes included the cumulative incidence of any cerebrovascular event, any stroke, and TIA , recurrent TIA, all-cause death, any bleeding and modified Rankin score at last follow-up.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.

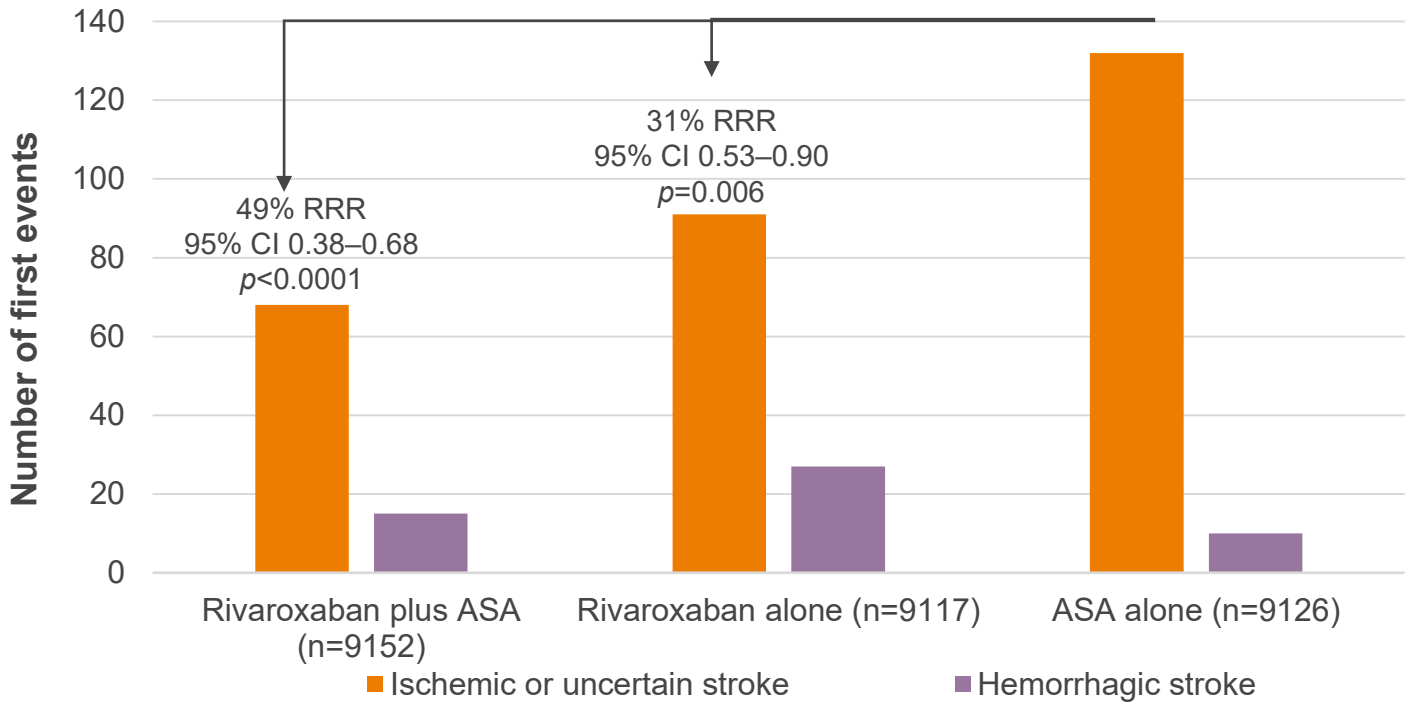
1. Diener H-C *et al. Lancet* 2004;364:331–337. 2. Del Brutto VJ *et al. J Am Coll Cardiol* 2019;74:786–803. 3. SPS3 Investigators. *N Engl J Med* 2012;367:817–825. 4. Amarenco P *et al. N Engl J Med* 2018;378:2182–2190.

The COMPASS Trial Supports the Utility of Dual Pathway Inhibition for Secondary Stroke Prevention[1,2]

FXa inhibition plus antiplatelet therapy

The randomized, double-blind, double-dummy, Phase III COMPASS study demonstrated a reduction in the risk of ischemic or uncertain stroke with rivaroxaban and ASA compared with ASA alone in patients with chronic CAD or PAD at high risk of ischemic events[1,2]

Incidence of stroke according to stroke type in the COMPASS study*[1]

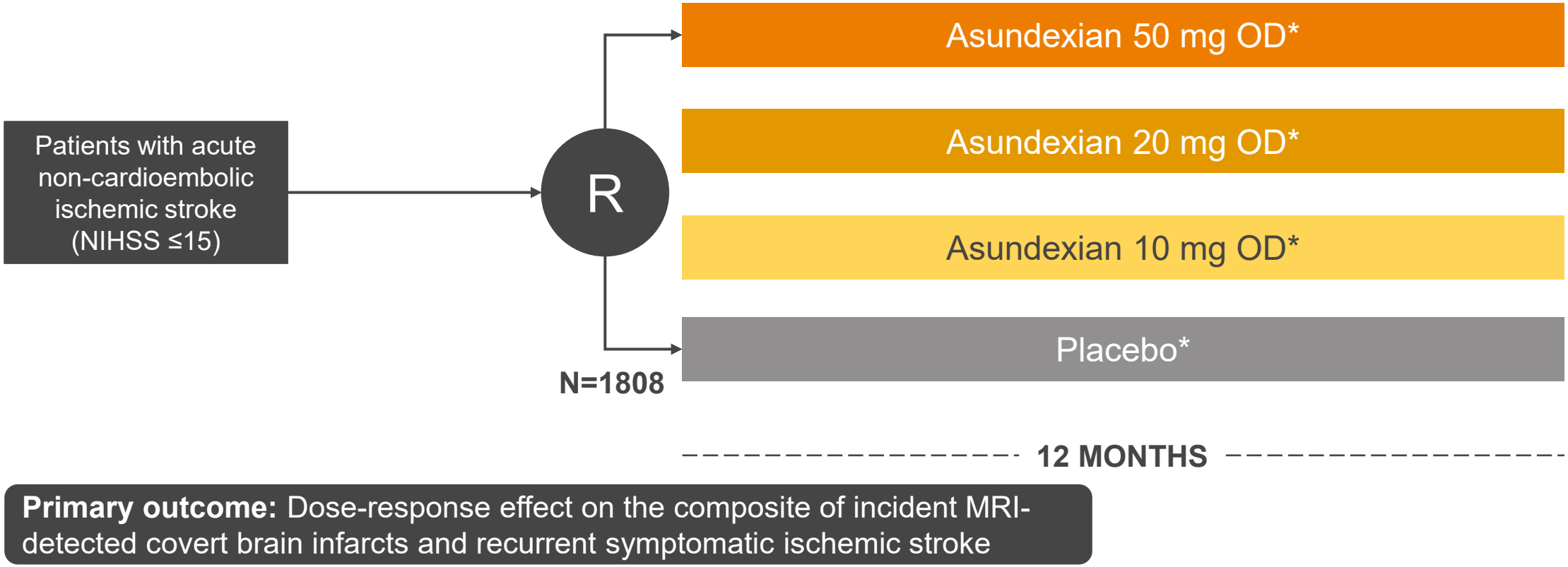


*Primary efficacy outcome: Composite of cardiovascular death, myocardial infarction and stroke.[1,2]
ASA, acetylsalicylic acid; CAD, coronary artery disease; CI, confidence interval; FXa, activated Factor X; PAD, peripheral artery disease; RRR, relative risk reduction.

1. Sharma M *et al. Circulation* 2019,139:1134–1145. 2. Eikelboom JW *et al. N Engl J Med* 2017;377:1319–1330.

Phase II PACIFIC-STROKE Study Design

Multicenter, randomized, placebo-controlled, double-blind, dose-finding, Phase II study of the oral FXIa inhibitor asundexian in patients following an acute non-cardioembolic ischemic stroke



Primary outcome: Dose-response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischemic stroke

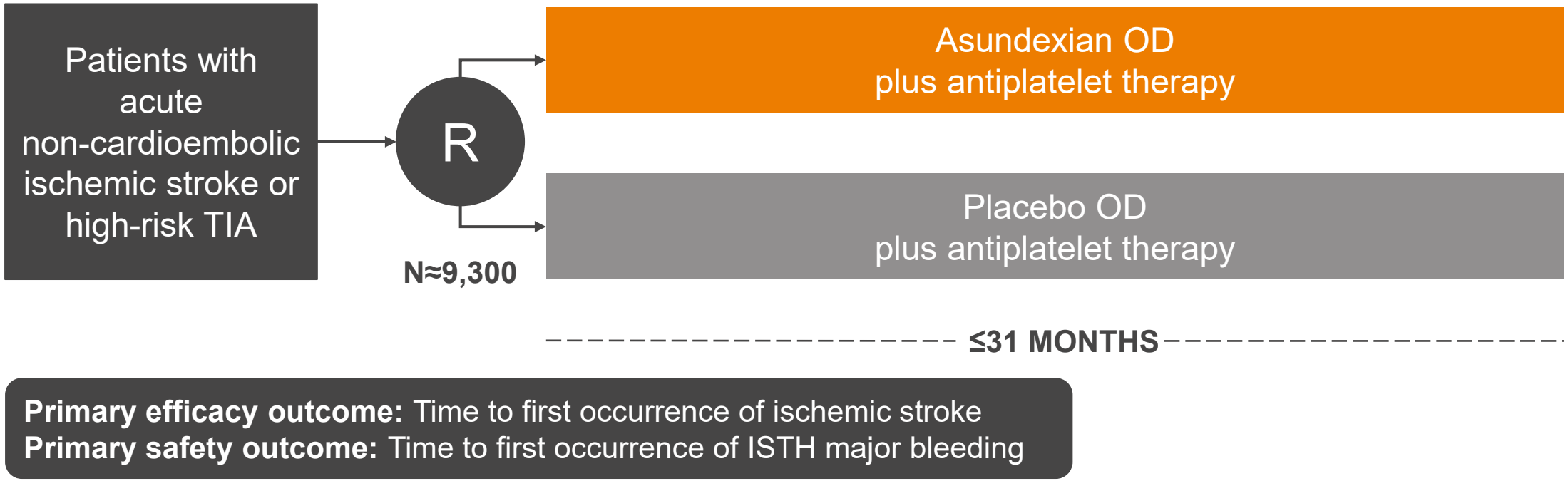
*Plus antiplatelet background therapy according to standard of care.

FXIa, activated Factor XI; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; OD, once daily; R, randomization.

Shoamanesh A *et al. Lancet* 2022;400:997–1007.

Phase III OCEANIC-STROKE Study Design[1,2]

Multicenter, international, randomized, placebo-controlled, double-blind, parallel-group, event-driven, Phase III study of the oral FXIa inhibitor asundexian for the prevention of ischemic stroke (active, recruiting)



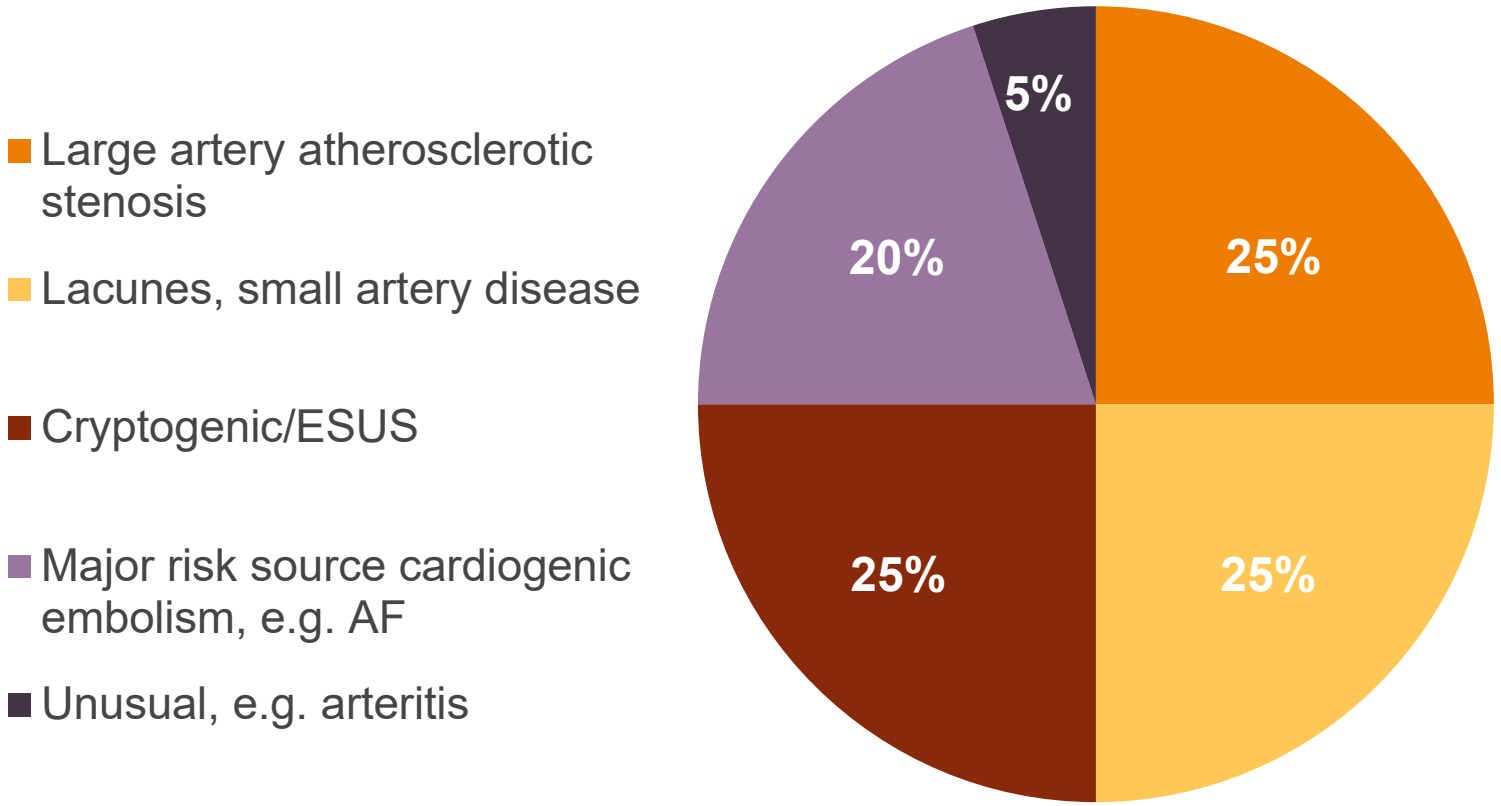
.

FXIa, activated Factor XI; ISTH, International Society on Thrombosis and Haemostasis; OD, once daily; R, randomization; TIA, transient ischemic attack.

1. Bayer. 2023. https://clinicaltrials.gov/ct2/show/NCT05686070. 2. Bayer AG. https://www.bayer.com/media/en-us/bayer-initiates-landmark-phase-iii-study-program-to-investigate-oral-fxia-inhibitor-asundexian/ [accessed August2023].

87% of Strokes are Classified as Ischemic[1]

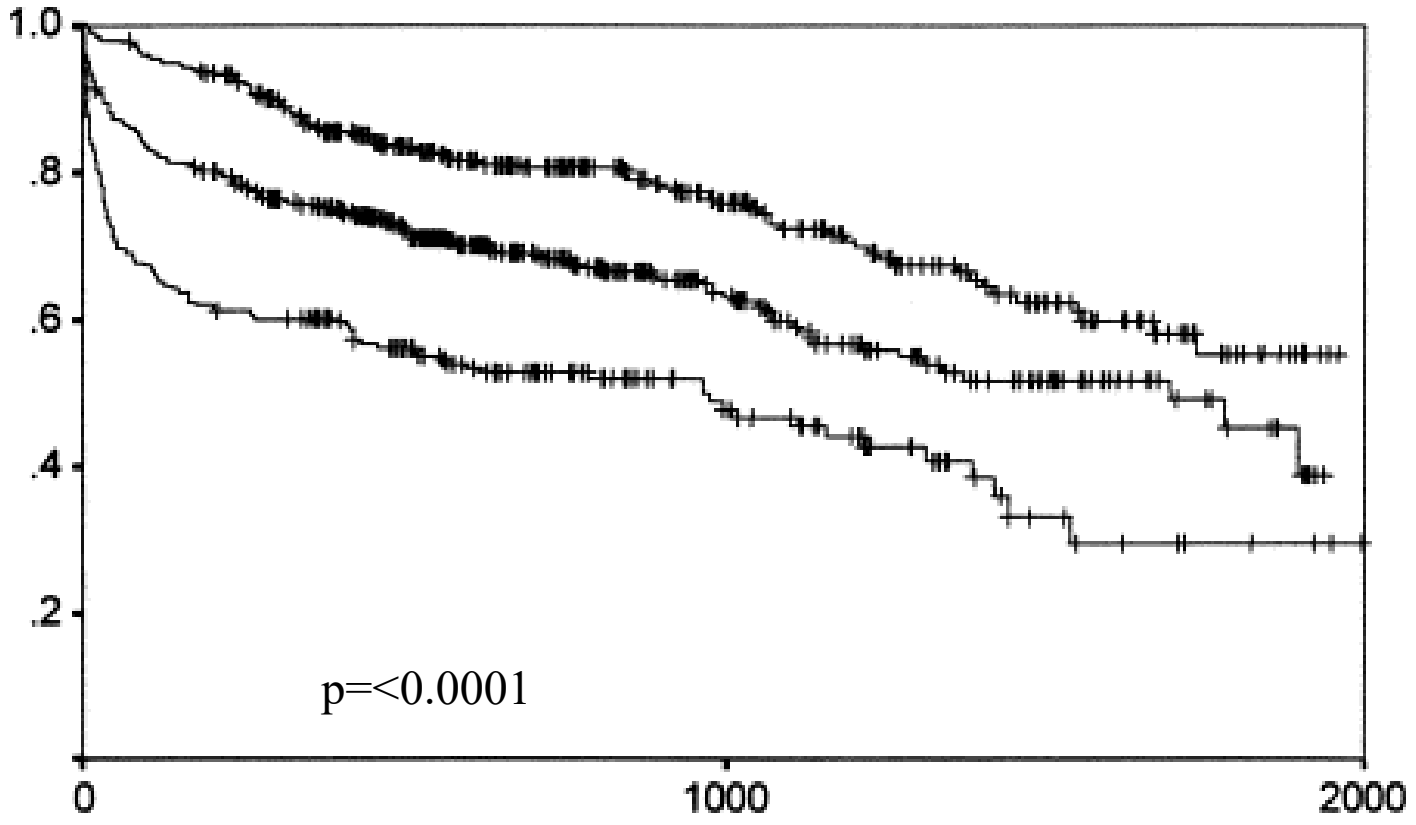
Distribution of ischemic stroke subtypes across North American and European studies[2]



*The remaining 25% consist of 20% major-risk source cardiogenic emboli and 5% unusual (e.g. dissections, arteritis).
AF, atrial fibrillation; ESUS, embolic stroke of undetermined source.

1. Kleindorfer DO *et al. Stroke* 2021;52:e364–e467. 2. Hart RG *et al. Lancet Neurol* 2014;13:429–438.

Survivors after a first-ever stroke by etiology



Lac=339

Athero=435

Cardiac=224

De Jong et al J Clin Epidemiol 2003

Why is cardioembolic stroke associated with more severe prognosis?

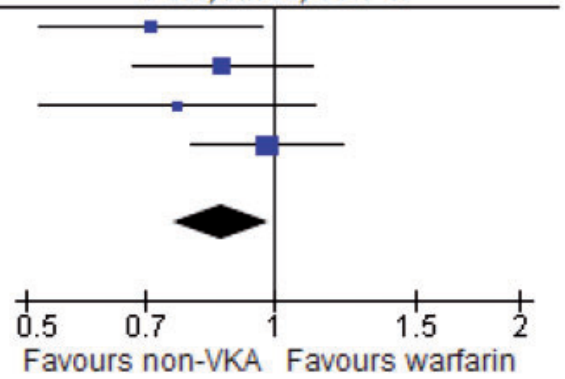
- More severe stroke at onset
- Absence of collaterals
- High risk of early recurrence
- High risk of early hemorrhagic transformation
- High risk of long-term recurrence

NOACs in secondary stroke prevention

Any stroke

Study or Subgroup	non-VKA Events	non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	67	1694	96	1742	18.9%	0.71 [0.52, 0.97]
ENGAGE AF-TIMI 48 (60mg)	118	1976	136	1991	28.9%	0.87 [0.67, 1.12]
RELY (150mg)	47	1233	59	1195	12.3%	0.76 [0.52, 1.13]
ROCKET-AF	171	3754	172	3714	39.8%	0.98 [0.79, 1.22]
Total (95% CI)		**8657**		**8642**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	403		463			

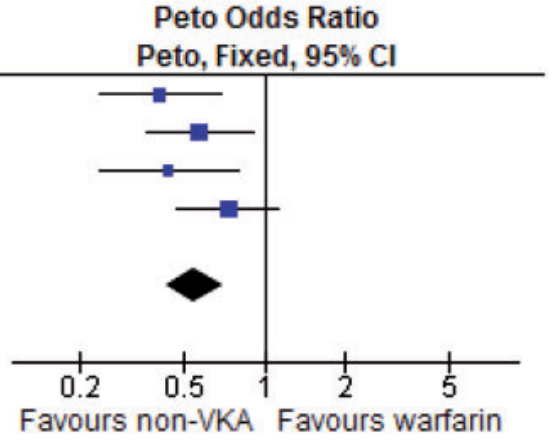
Heterogeneity: Chi² = 3.27, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 2.10 (P = 0.04)



Intracranial bleeding

Study or Subgroup	non-VKA Events	non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	15	1694	41	1742	22.0%	0.40 [0.24, 0.68]
ENGAGE AF-TIMI 48 (60mg)	27	1976	48	1991	29.4%	0.57 [0.36, 0.90]
RELY (150mg)	13	1233	30	1195	16.9%	0.43 [0.24, 0.79]
ROCKET-AF	34	3754	46	3714	31.6%	0.73 [0.47, 1.13]
Total (95% CI)		**8657**		**8642**	**100.0%**	**0.54 [0.42, 0.70]**
Total events	89		165			

Heterogeneity: Chi² = 3.60, df = 3 (P = 0.31); I² = 17%
Test for overall effect: Z = 4.81 (P < 0.00001)



Ntaios et al, International Journal of Stroke 2017

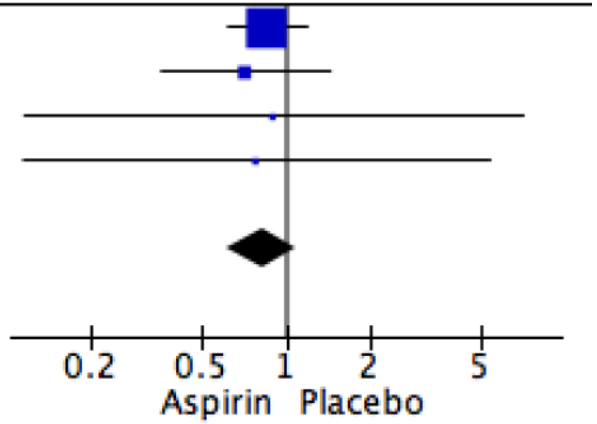
Effect of aspirin versus placebo on stroke or thromboembolism in patients with previous ischemic stroke or TIA and atrial fibrillation

Aspirin

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Anonymous 1993 (1)	94	404	99	378	78.6%	0.85 [0.62, 1.18]
Diener 1996 (2)	17	104	23	107	17.2%	0.71 [0.36, 1.43]
Farrell 1991 (3)	3	13	2	8	2.0%	0.90 [0.12, 7.03]
Farrell 1991 (4)	5	21	2	7	2.2%	0.78 [0.11, 5.34]
Total (95% CI)		**542**		**500**	**100.0%**	**0.83 [0.62, 1.10]**
Total events	119		126			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.22$, df = 3 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 1.29 (P = 0.20)



(1) Aspirin 300 mg; (2) Aspirin 25 mg twice daily; (3) Aspirin 1200 mg; (4) Aspirin 300 mg

Klijn, Paciaroni et al; Eur Stroke J 2019

Clinical trials on NOACs and timing to start anticoagulation

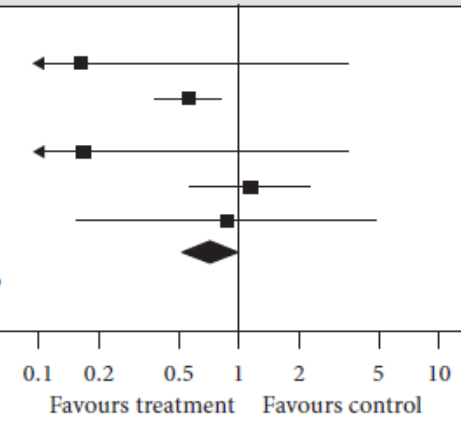
- ARISTOTLE: Patients with a previous intracranial haemorrhage (ICH) or any stroke within 7 days before random assignment were excluded.
- RE-LY: excluded patients with a stroke within 14 days or severe stroke within 6 months before screening
- ROCKET AF: excluded patients with a severe, disabling stroke within 3 months or any stroke within 14 days before randomization
- ENGAGE AF-TIMI 48: excluded patients with stroke within the previous 30 days

Easton JD et al. Lancet Neurol. 2012

Anticoagulants started within 48 h

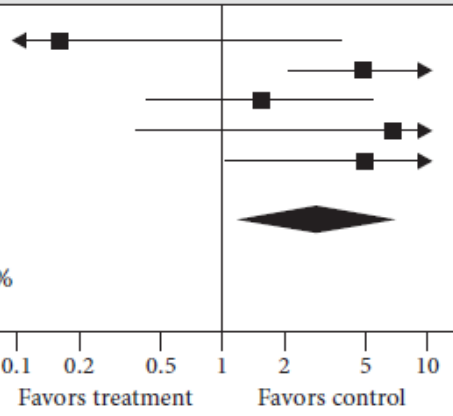
a Outcome: recurrent stroke (anticoagulants vs. aspirin or placebo)

Study or subcategory	Anticoagulants n/N	Aspirin or placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
CESG [17]	0/24	2/21		1.99	0.16 (0.01–3.51)
IST heparin any dose [16]	44/1,557	79/1,612		59.81	0.56 (0.39–0.82)
TOAST [21]	0/143	2/123		2.05	0.17 (0.01–3.56)
HAEST [20]	19/224	17/225		29.92	1.13 (0.57–2.24)
TAIST [28]	4/256	2/112		6.23	0.87 (0.16–4.84)
Total (95% CI)	2,204	2,093		100.00	0.68 (0.44–1.06)
Total events: 67 (anticoagulants), 102 (aspirin or placebo)					
Test for heterogeneity: $\chi^2 = 4.77$, d.f. = 4 ($p = 0.31$), $I^2 = 16.1\%$					
Test for overall effect: $Z = 1.72$ ($p = 0.09$)					



a Outcome: hemorrhagic stroke (anticoagulants vs. aspirin or placebo)

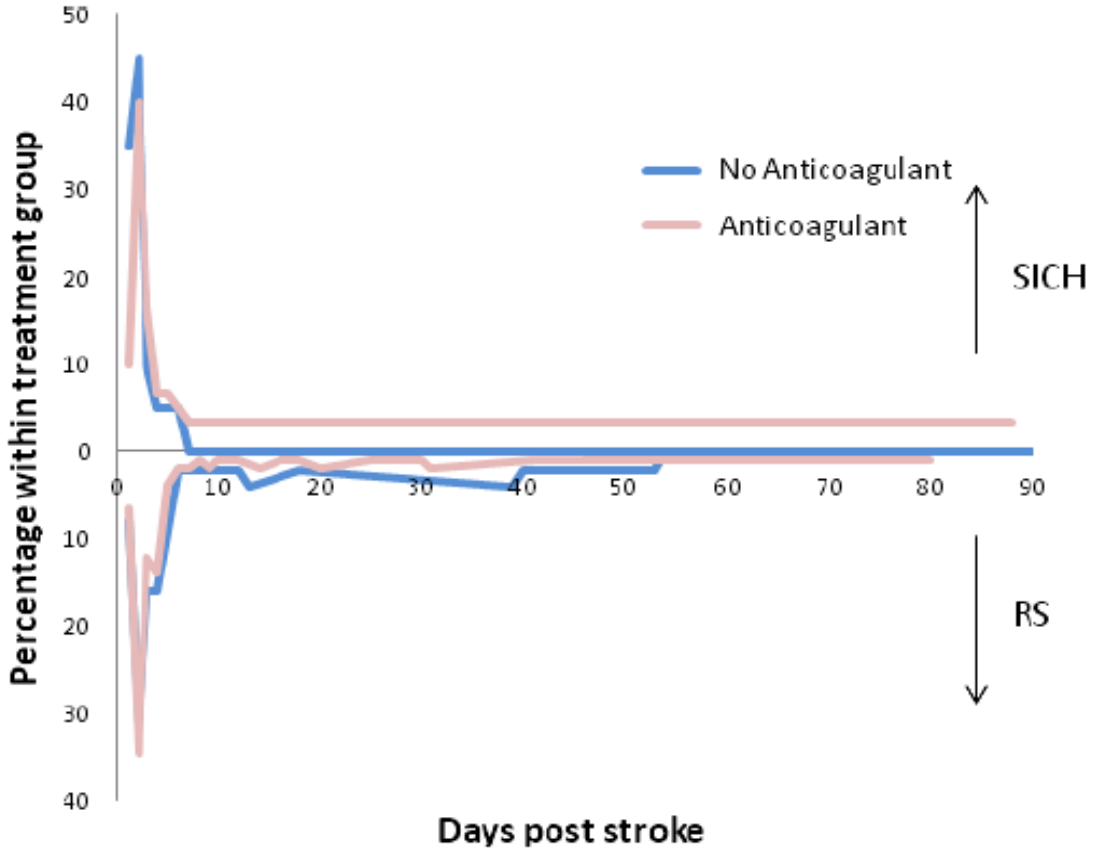
Study or subcategory	Anticoagulants n/N	Aspirin or placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
CESG [17]	0/24	2/21		7.17	0.16 (0.01–3.51)
IST heparin any dose [16]	32/1,557	7/1,612		37.99	4.81 (2.12–10.93)
HAEST [20]	6/224	4/225		25.94	1.52 (0.42–5.46)
TAIST [18]	7/256	0/112		8.16	6.76 (0.38–119.45)
Camerlingo et al. [23]	10/94	2/85		20.74	4.94 (1.05–23.23)
Total (95% CI)	2,155	2,055		100.00	2.89 (1.19–7.01)
Total events: 55 (anticoagulants), 15 (aspirin or placebo)					
Test for heterogeneity: $\chi^2 = 6.41$, d.f. = 4 ($p = 0.17$), $I^2 = 37.6\%$					
Test for overall effect: $Z = 2.34$ ($p = 0.02$)					



Paciaroni et al, Stroke 2007

Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA

A. H. Abdul-Rahim[a], R. L. Fulton[a], B. Frank[b], T. Tatlisumak[c], M. Paciaroni[d], V. Caso[d], H.-C. Diener[b], K. R. Lees[a] and for the VISTA collaborators*



80% of patients with recurrent stroke had the event within 2-3 days

European Journal of Neurology 2014, **0**: 1–8

Stroke
Journal of the American Heart Association

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study

Maurizio Paciaroni, Giancarlo Agnelli, Nicola Falocci, Valeria Caso, Cecilia Becattini, Simona Marcheselli, Christina Rueckert, Alessandro Pezzini, Loris Poli, Alessandro Padovani, Laszló Csiba, Lilla Szabó, Sung-Il Sohn, Tiziana Tassinari, Azmil H. Abdul-Rahim, Patrik Michel, Maria Cordier, Peter Vanacker, Suzette Remillard, Andrea Alberti, Michele Venti, Umberto Scoditti, Licia Denti, Giovanni Orlandi, Alberto Chiti, Gino Gialdini, Paolo Bovi, Monica Carletti, Alberto Rigatelli, Jukka Putaala, Turgut Tatlisumak, Luca Masotti, Gianni Lorenzini, Rossana Tassi, Francesca Guideri, Giuseppe Martini, Georgios Tsivgoulis, Kostantinos Vadikolias, Chrissoula Liantinioti, Francesco Corea, Massimo Del Sette, Walter Ageno, Maria Luisa De Lodovici, Giorgio Bono, Antonio Baldi, Sebastiano D'Anna, Simona Sacco, Antonio Carolei, Cindy Tiseo, Monica Acciarresi, Cataldo D'Amore, Davide Imberti, Dorjan Zabzuni, Boris Doronin, Vera Volodina, Domenico Consoli, Franco Galati, Alessio Pieroni, Danilo Toni, Serena Monaco, Mario Maimone Baronello, Kristian Barlinn, Lars-Peder Pallesen, Jessica Kepplinger, Ulf Bodechtel, Johannes Gerber, Dirk Deleu, Gayane Melikyan, Faisal Ibrahim, Naveed Akhtar, Maria Giulia Mosconi, Valentina Bubba, Ilenia Silvestri and Kennedy R. Lees

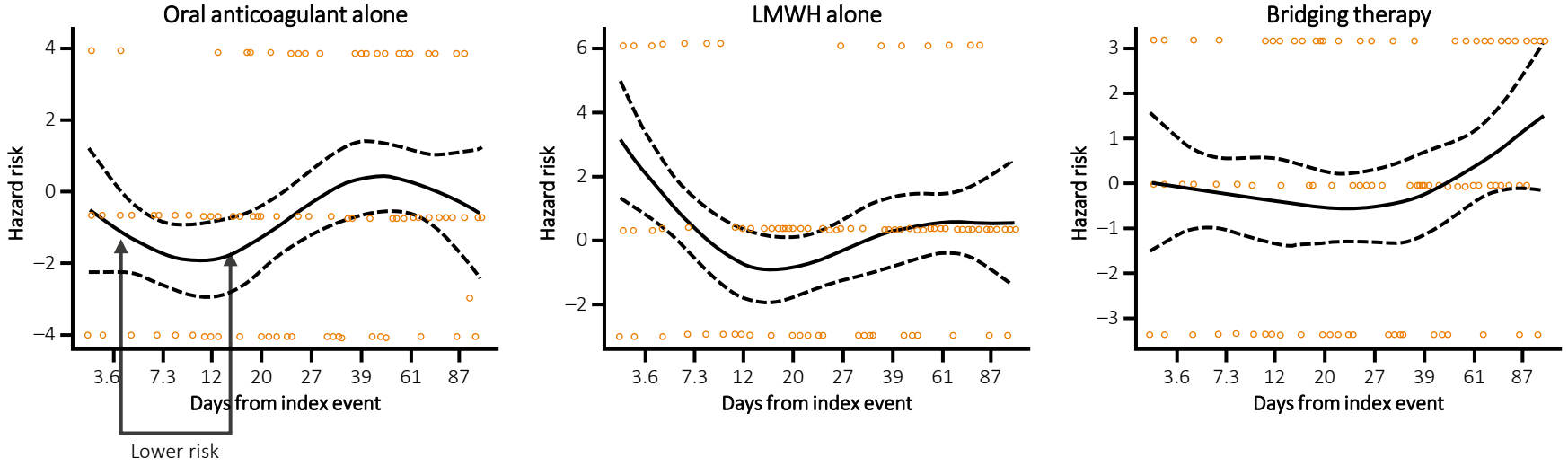
Stroke. 2015;46:2175-2182; originally published online June 30, 2015;
doi: 10.1161/STROKEAHA.115.008891
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation

Effect of anticoagulation and its timing: The RAF study

The different risks of the combined outcome events associated with the day of initiating anticoagulant treatment in patients treated with different types of anticoagulant therapy (A, oral anticoagulant alone; B, low molecular weight heparin alone; C, bridging therapy, low molecular weight heparin followed by oral anticoagulants) in a Cox proportional hazard model in which anticoagulant therapy was treated as a time-varying covariate.



	Coef	exp (coef)	Se (coef)	z	Pr (>|z|)
Bridging therapy	0.3214	1.3791	0.2577	1.247	0.2122
LMWH	0.3986	1.4897	0.2898	1.375	0.1691
ORAL alone	–0.4749	0.6220	0.2750	–1.727	0.0842

LMWH, low molecular weight heparin

Paciaroni et al. Stroke. 2015;46:2175–82

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) Study

Maurizio Paciaroni, MD; Giancarlo Agnelli, MD; Nicola Falocci, PhD; Georgios Tsivgoulis, MD; Kostantinos Vadikolias, MD; Chrysoula Liantinioti, MD; Maria Chondrogianni, MD; Paolo Bovi, MD; Monica Carletti, MD; Manuel Cappellari, MD; Marialuisa Zedde, MD; George Ntaios, MD; Efstathia Karagkiozi, MD; George Athanasakis, MD; Kostantinos Makaritsis, MD; Giorgio Silvestrelli, MD, PhD; Alessia Lanari, MD, PhD; Alfonso Ciccone, MD; Jukka Putaala, MD; Liisa Tomppo, MD; Turgut Tatlisumak, MD; Azmil H. Abdul-Rahim, MD; Kennedy R. Lees, MD; Andrea Alberti, MD; Michele Venti, MD, PhD; Monica Acciarresi, MD; Cataldo D'Amore, MD; Cecilia Becattini, MD; Maria Giulia Mosconi, MD; Ludovica Anna Cimini, MD; Rossana Soloperto, MD; Luca Masotti, MD; Vieri Vannucchi, MD; Gianni Lorenzini, MD; Rossana Tassi, MD; Francesca Guideri, MD; Maurizio Acampa, MD; Giuseppe Martini, MD; Sung-Il Sohn, MD, PhD; Simona Marcheselli, MD; Nicola Mumoli, MD; Maria Luisa De Lodovici, MD; Giorgio Bono, MD; Karen L. Furie, MD; Prasanna Tadi, MD; Shadi Yaghi, MD; Danilo Toni, MD, PhD; Federica Letteri, MD; Tiziana Tassinari, MD; Odysseas Kargiotis, MD; Enrico Maria Lotti, MD; Yuriy Flomin, MD; Michelangelo Mancuso, MD; Miriam Maccarrone, MD; Nicola Giannini, MD; Fabio Bandini, MD; Alessandro Pezzini, MD; Loris Poli, MD; Alessandro Padovani, MD, PhD; Umberto Scoditti, MD; Licia Denti, MD; Domenico Consoli, MD; Franco Galati, MD; Simona Sacco, MD; Antonio Carolei, MD; Cindy Tiseo, MD; Vanessa Gourbali, MD; Giovanni Orlandi, MD; Martina Giuntini, MD; Alberto Chiti, MD; Elisa Giorli, MD; Gino Gialdini, MD; Francesco Corea, MD, PhD; Walter Ageno, MD; Marta Bellesini, MD; Giovanna Colombo, MD; Serena Monaco, MD; Mario Maimone Baronello, MD; Theodore Karapanayiotides, MD, PhD; Valeria Caso, MD, PhD

J Am Heart Assoc. 2017;6:e007034. DOI: 10. 1 161/JAHA.117.007034

RAF-NOAC : when to start NOAC after stroke ?

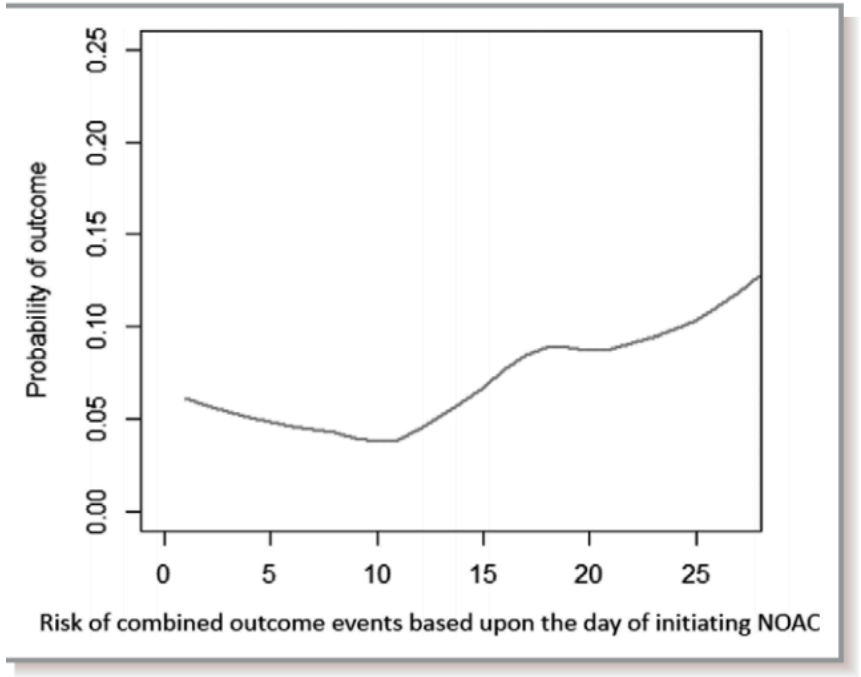


Figure 2. Combined risks of outcome events (ischemic and hemorrhagic) depending on the time between onset and initiation of therapy with non–vitamin K oral anticoagulants (NOACs). The lower risk of the combined outcome event was within 14 days.

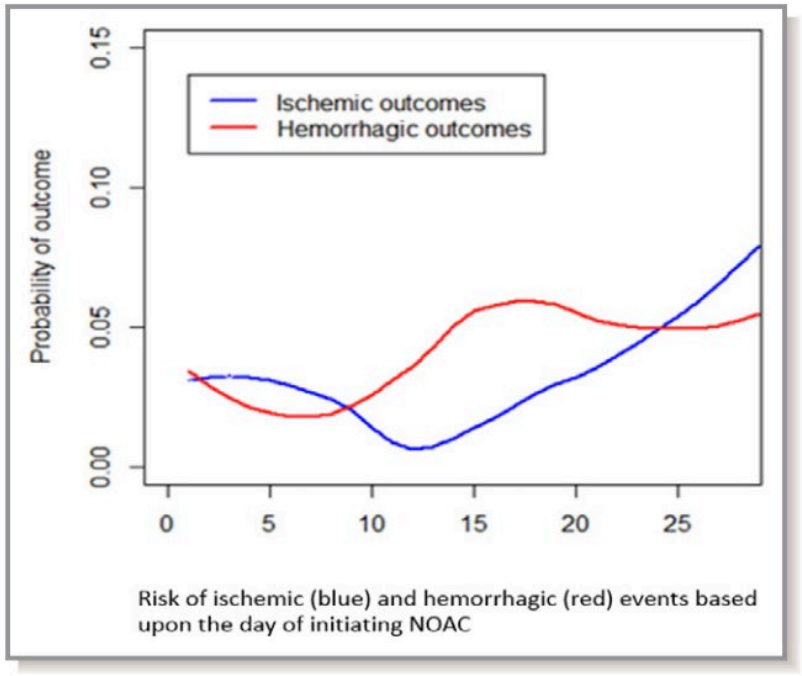


Figure 3. Risks of outcome events depending on the time between onset and initiation of therapy with non–vitamin K oral anticoagulants (NOACs).

RAF-NOAC : when to start NOAC after stroke ?

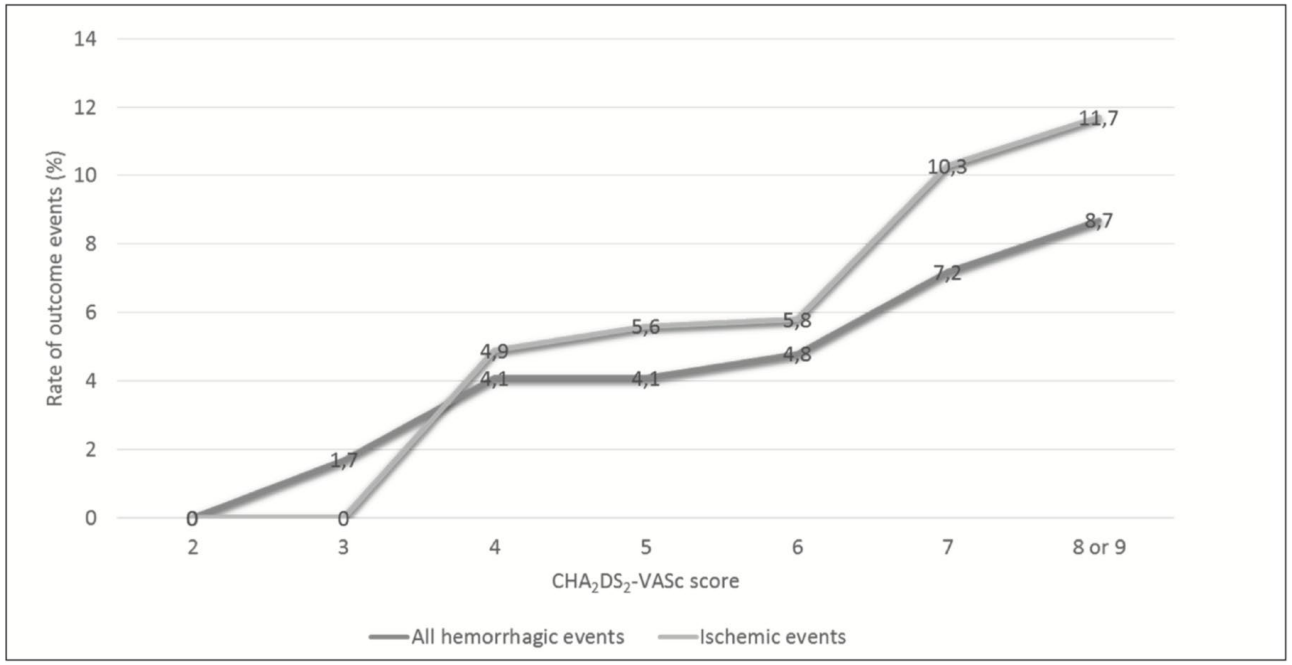
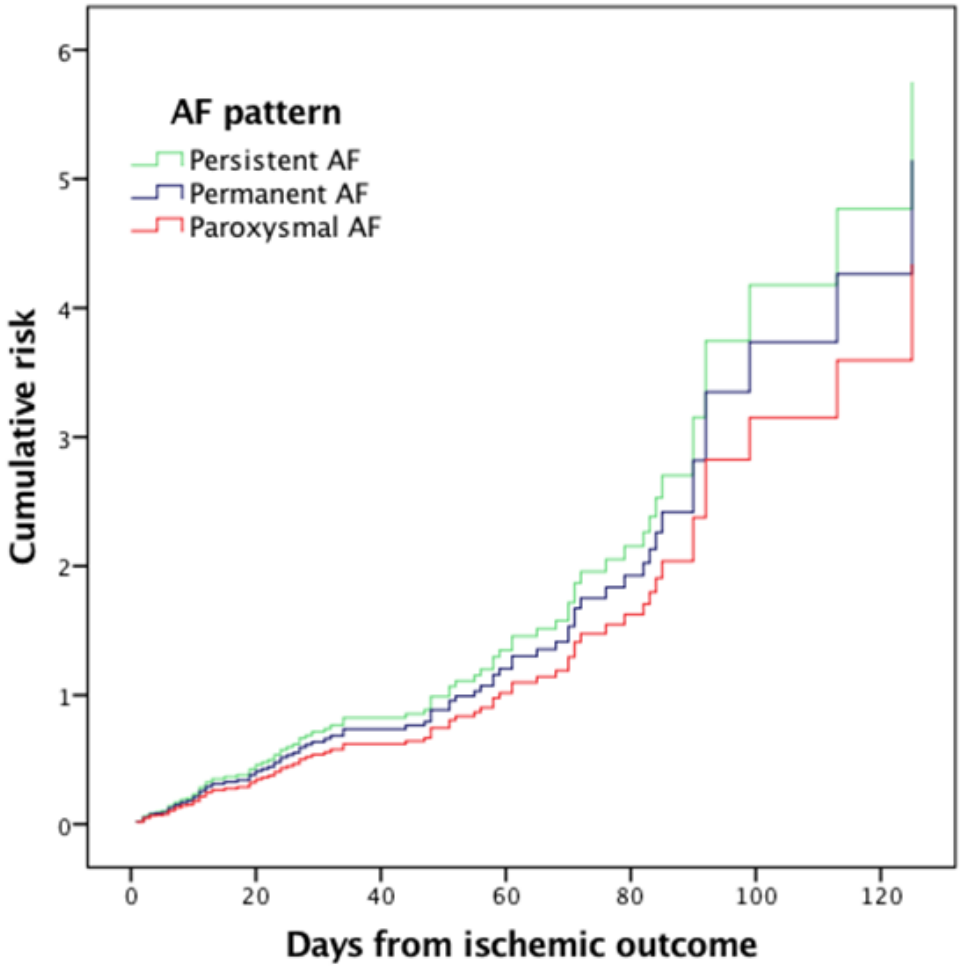


Figure 1: Risk of an ischaemic recurrence or haemorrhagic event within 90 days according to CHA_2DS_2-VASc score in patients with acute stroke and AF.

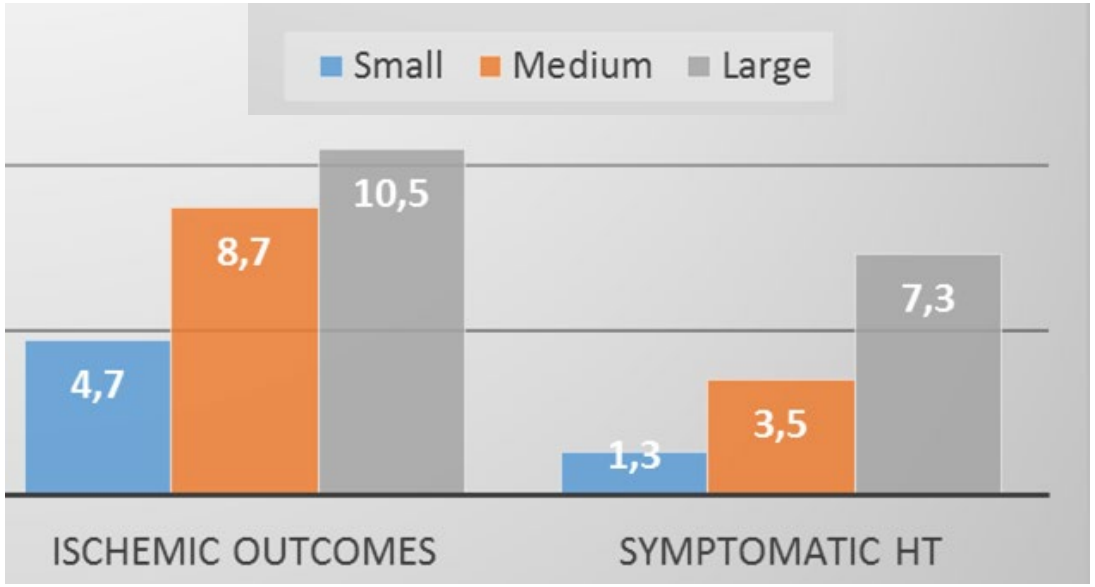
Paciaroni et al, Thromb Hemost 2016

RAF-NOAC : AF-pattern and recurrence risk



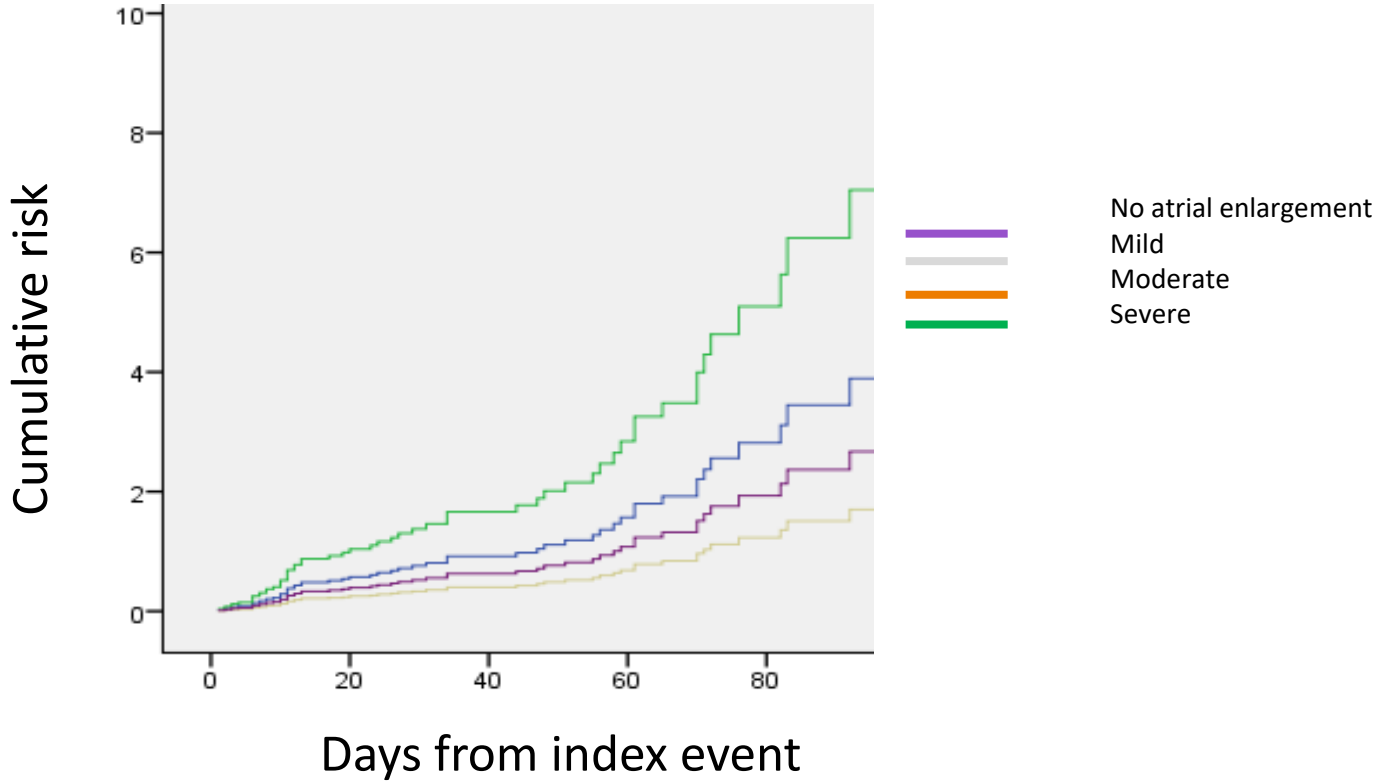
Paciaroni et al, ESJ 2018

RAF-NOAC : ischemic and haemorhagic events depend on stroke lesion seize



Paciaroni et al, Thromb Hemost 2016

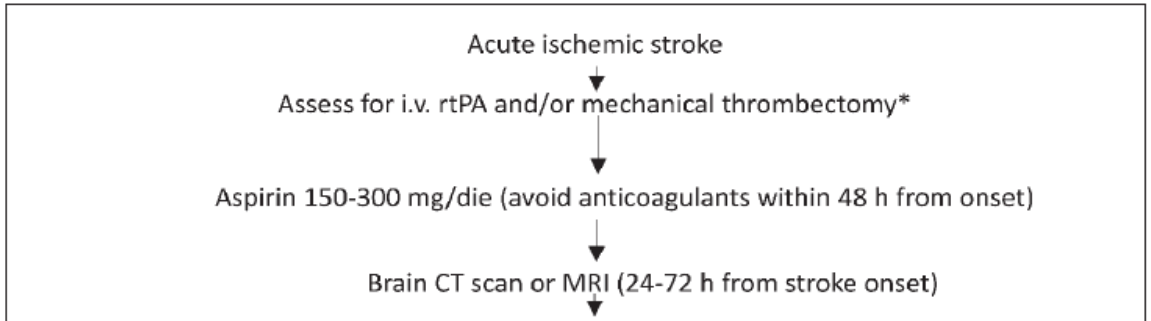
RAF-NOAC: isk of recurrent stroke depends on atrial enlargement



Reference: no atrial enlargement
Mild atrial enlargement: HR 0.64 (95% CI 0.28-1.40), p=0.3
Moderate atrial enlargement: HR 1.47 (95% CI 0.54-4.00), p=0.4
Severe atrial enlargment: HR 2.64 (95% CI 1.00-6.97), p=0.049

Paciaroni et al, J Neurol 2015

ESO recommendation: Lesion size-based timing of NOAC initiation in acute stroke with AF



Expert opinion (Delphi vote: 6/7 agree, 1/7 disagree).

We suggest antiplatelet therapy in the first 48 h after ischemic stroke associated with AF.

We consider it reasonable to start anticoagulant therapy at day 3 or 4 from the index stroke in patients with mild stroke and small infarcts (<1.5 cm) and at day 7 for moderate infarcts.

For large infarcts, anticoagulation treatment might be best delayed for 14 days after the index stroke.

ESO now uses lesion size as an important criterion for anticoagulant timing

Klijn CJM, et al. Eur Stroke J 2019
Paciaroni M, et al. Thromb Haemost 2016;116:410–16

Early recurrent thromboembolic events and major bleeding after stroke with AF

The ALESSA risk stratification schema

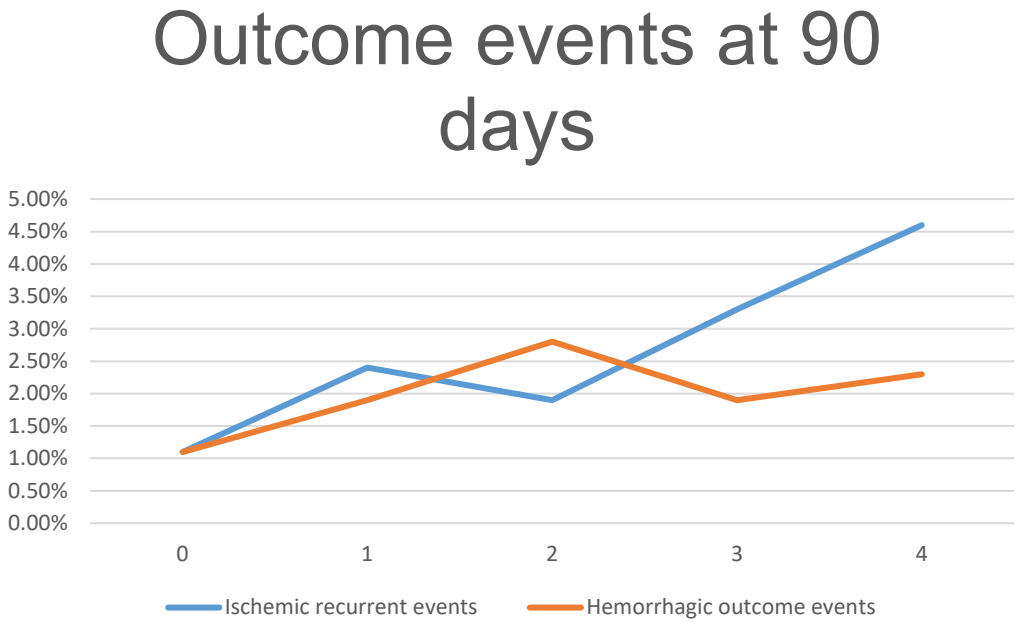
ALESSA score

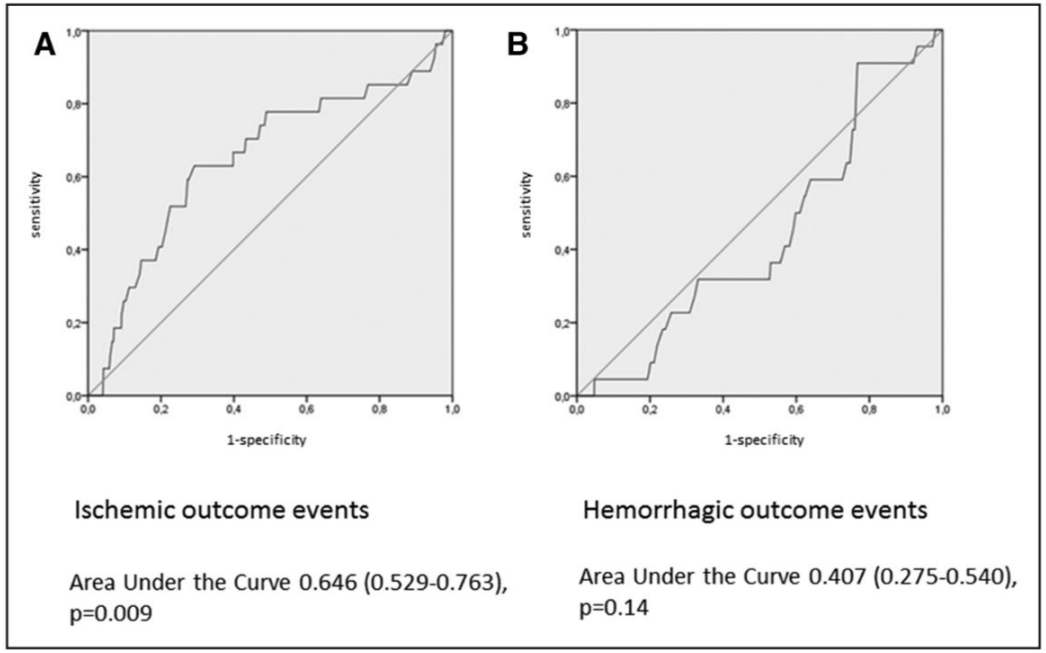
- **A**ge ≥80 years	2 points
- Age 70-79 years	1 point
- **LES**ion greater than 1.5 cm	1 point
- **S**evere **a**trial enlargement	1 point

Paciaroni et al, Stroke 2017

Early recurrent thromboembolic events and major bleeding after stroke with AF

The ALESSA risk stratification schema





Paciaroni et al, Stroke 2017

Trials assessing the use of early or delayed anticoagulation with NOACs in patients with previous ischaemic stroke and AF

	ELAN[1]	OPTIMAS[2]	TIMING[3]	START[4]
Drug	Rivaroxaban, dabigatran, apixaban or edoxaban <48 hours after symptom onset or at day 6+1 day after major ischaemic stroke	Apixaban, Dabigatran, Edoxaban or Rivaroxaban at standard doses (dose reduction based on clinical criteria)	Choice of NOAC (apixaban, dabigatran, edoxaban or rivaroxaban) <4 days after stroke	Randomized time to delay of anticoagulation: 60 hours, 132 hours, 228 hours or 324 hours
Comparator	Any NOAC after day 3+1 day (minor ischaemic stroke) or day 6+1 day (moderate ischaemic stroke) or day 12+2 day (major ischaemic stroke)	NOAC >7–<14 days after stroke onset	Choice of NOAC (apixaban, dabigatran, edoxaban or rivaroxaban) 5–10 days after stroke onset	Comparing four treatment arms to each other
Estimated enrolment, N	2000	3478	3000	1000
Follow up: primary outcome	30±3 days after randomisation	90 days	90 days	30 days
Design	An international, multicentre, randomised-controlled, two-arm, assessor-blinded study	A randomized, open-label, phase II open platform study	A multicenter registry-based non-inferiority, randomized controlled clinical trial	Prospective, adaptive, randomized, single blind, controlled "dose-exploration" trial
Primary outcome	Composite of major bleeding, recurrent ischaemic stroke, systemic embolism and/or vascular death at 30±3 days after randomisation	Composite outcome: recurrent symptomatic ischaemic stroke, symptomatic ICH and systemic embolism	Composite outcome of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality	Recurrent ischemic event: any symptomatic ischemic stroke or systemic embolism*; Haemorrhagic Event: any symptomatic haemorrhagic transformation, other symptomatic ICH, or major extracranial haemorrhage*

*Evidenced by CT or MRI

AF, Atrial fibrillation; CT, Computed tomography; MRI, Magnetic resonance imaging; NOAC, Non-vitamin K antagonist oral anticoagulant; OD, once daily

[1]ClinicalTrials.gov Identifier: NCT03148457
[2]EudraCT, 2018-003859-38; ISRCTN17896007
[3]ClinicalTrials.gov Identifier: NCT02961348
[4]ClinicalTrials.gov Identifier: NCT03021928

Circulation

ORIGINAL RESEARCH ARTICLE

Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study

Jonas Oldgren, MD, PhD*; Signild Åsberg, MD, PhD*; Ziad Hijazi, MD, PhD; Per Wester, MD, PhD; Maria Bertilsson, MSc; Bo Norrving, MD, PhD; for the National TIMING Collaborators

TIMING results

Early	0-4 days	450 patients
Delayed	5-10 days	438 patients

Sample size: 3000 patients

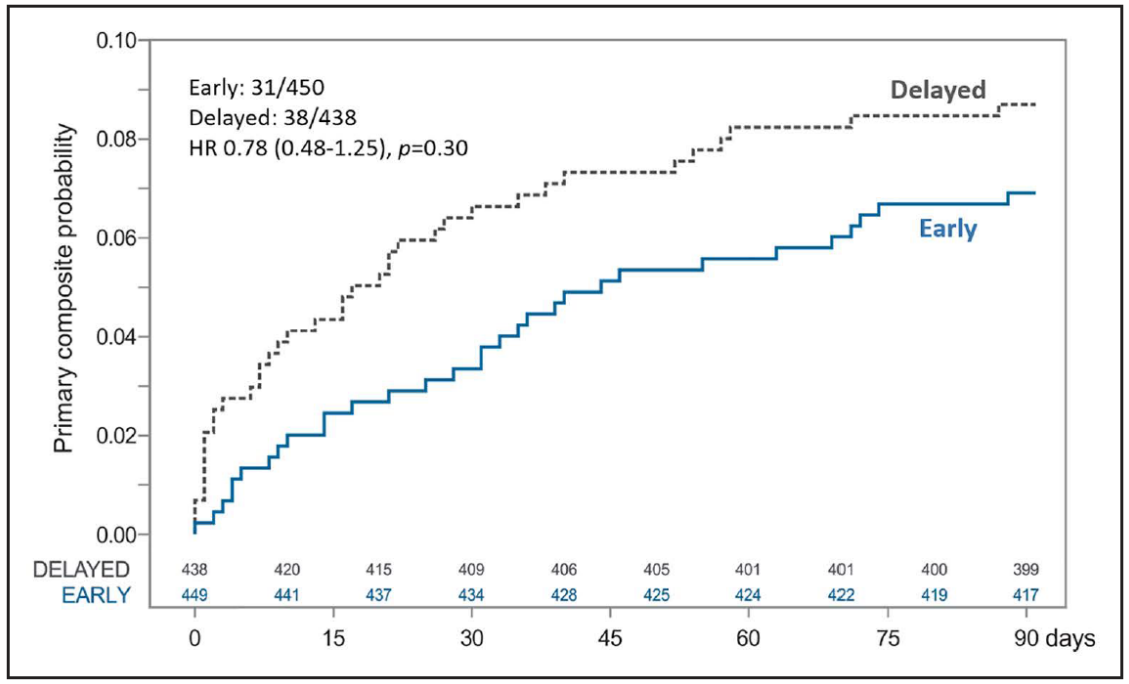


Figure 3. Time to the primary composite outcome and Cox proportional hazards analysis for early vs delayed initiation of NOAC until 90 days.

Primary outcome was a composite of ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality. HR indicates hazard ratio; and NOAC, non–vitamin K antagonist oral anticoagulant.

Oldegren et al; Circulation 2022

TIMING results

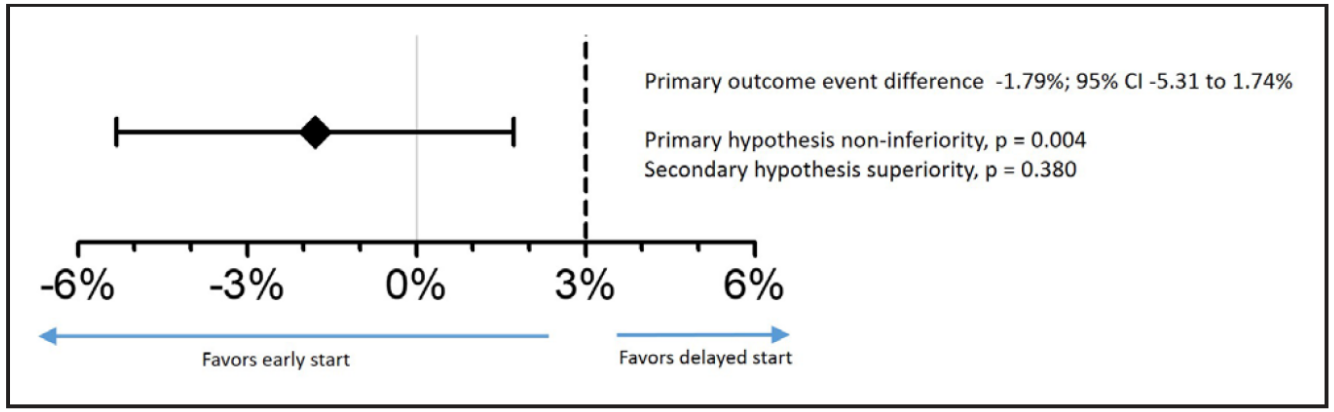


Figure 2. Risk difference in the primary composite outcome for early vs delayed initiation of NOAC at 90 days.
Primary outcome was a composite of ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality. Primary hypothesis testing for noninferiority at an absolute 3% margin, and secondary hypothesis testing for superiority. NOAC indicates non–vitamin K antagonist oral anticoagulant.

Oldegren et al; Circulation 2022

TIMING results

- No patients experienced a sICH

At 28 days
- 10 major bleedings
  - 7 in the early group (1.6%)
  - 3 in the delayed group (0.7%)

Oldegren et al; Circulation 2022

ELAN protocol

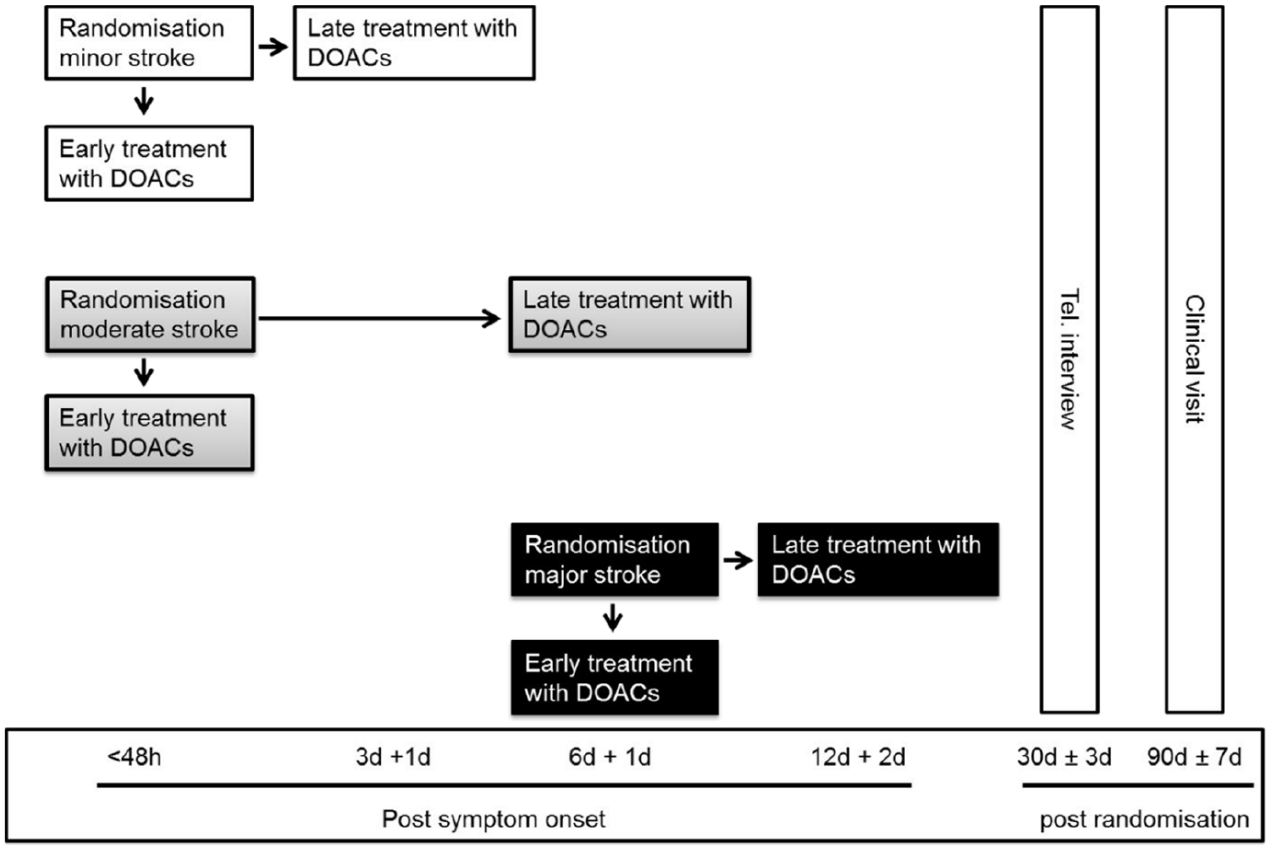
Study Protocol

EUROPEAN STROKE JOURNAL

European Stroke Journal
1–9

DOI: 10.1177/23969873221106043
journals.sagepub.com/home/eso
SAGE

Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN (ELAN): Protocol for an international, multicentre, randomised-controlled, two-arm, open, assessor-blinded trial



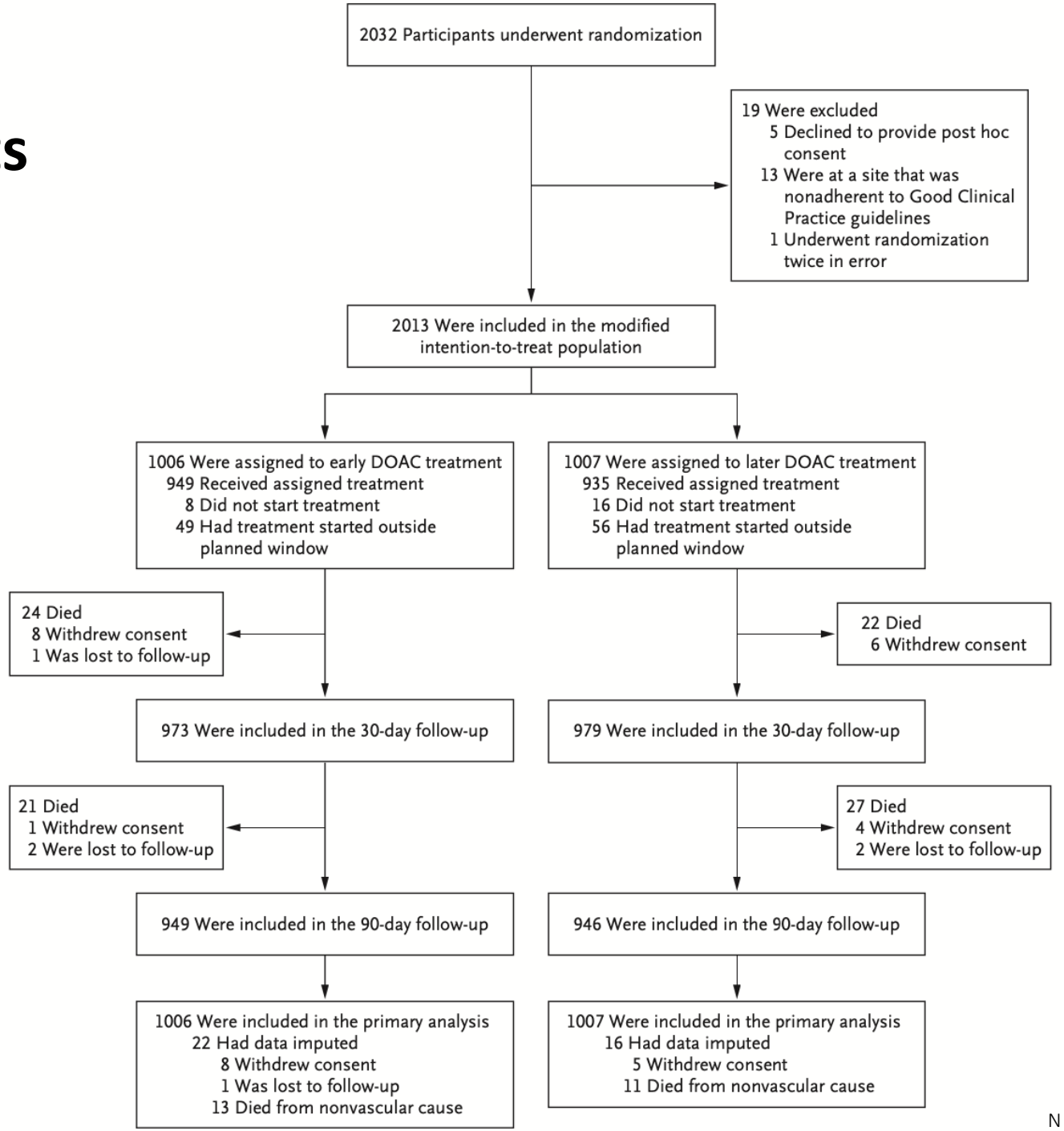
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

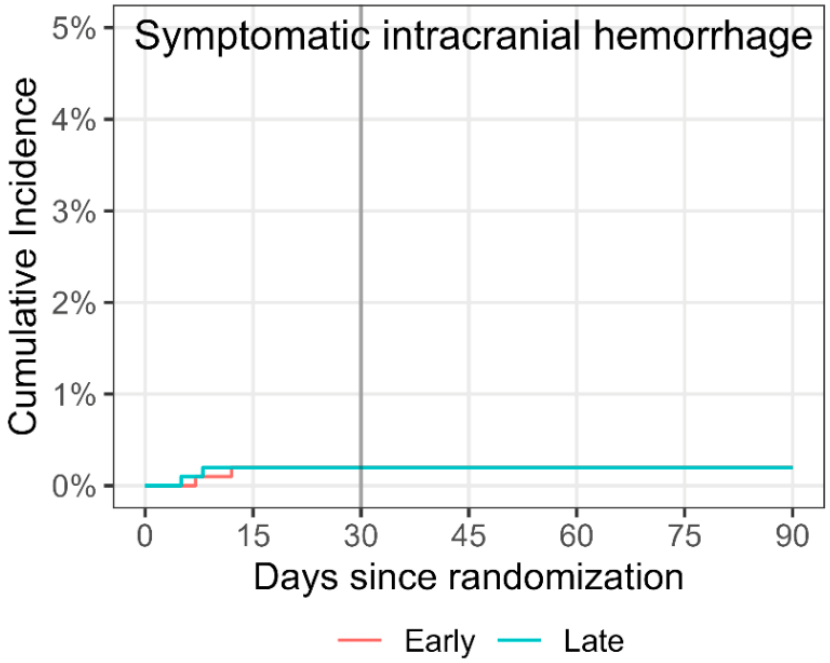
U. Fischer, M. Koga, D. Strbian, M. Branca, S. Abend, S. Trelle, M. Paciaroni, G. Thomalla, P. Michel, K. Nedeltchev, L.H. Bonati, G. Ntaios, T. Gattringer, E.-C. Sandset, P. Kelly, R. Lemmens, P.N. Sylaja, D. Aguiar de Sousa, N.M. Bornstein, Z. Gdovinova, T. Yoshimoto, M. Tiainen, H. Thomas, M. Krishnan, G.C. Shim, C. Gumbinger, J. Vehoff, L. Zhang, K. Matsuzono, E. Kristoffersen, P. Desfontaines, P. Vanacker, A. Alonso, Y. Yakushiji, C. Kulyk, D. Hemelsoet, S. Poli, A. Paiva Nunes, N. Caracciolo, P. Slade, J. Demeestere, A. Salerno, M. Kneihsl, T. Kahles, D. Giudici, K. Tanaka, S. Räty, R. Hidalgo, D.J. Werring, M. Göldlin, M. Arnold, C. Ferrari, S. Beyeler, C. Fung, B.J. Weder, T. Tatlisumak, S. Fenzl, B. Rezny-Kasprzak, A. Hakim, G. Salanti, C. Bassetti, J. Gralla, D.J. Seiffge, T. Horvath, and J. Dawson, for the ELAN Investigators*

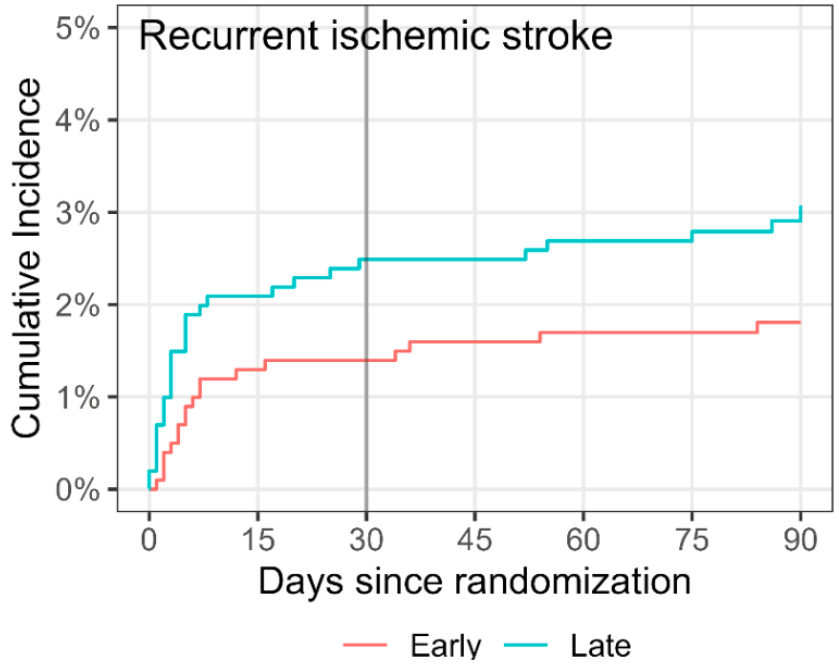
ELAN results

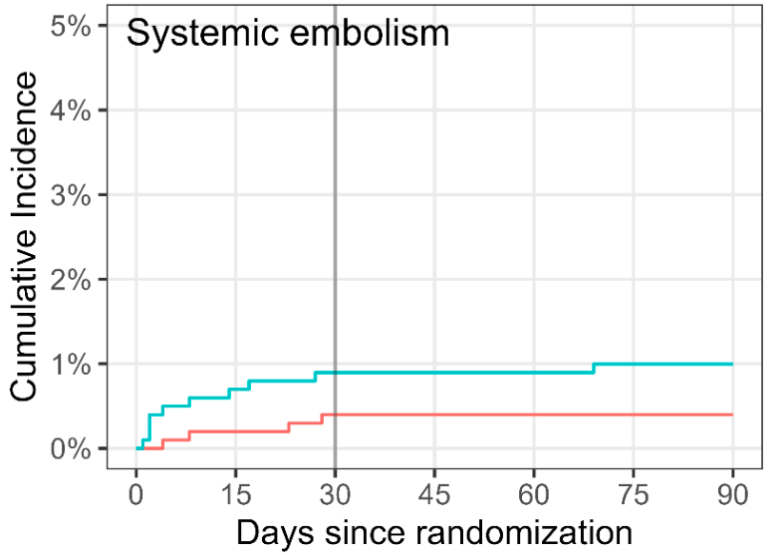


N Engl J Med 23 May, 2023

ELAN results







N Engl J Med 23 May, 2023

How to start anticoagulation

after ischemic stroke

- **When** to start DOAC :

➢ TIA	Start day 0
➢ Minor/moderate stroke	Start day 0-2
➢ Major stroke	Start day 7

Thank you very much for your attention!