Quando iniziare la terapia anticoagulante nella fase acuta dell'ictus ischemico cardioembolico associato a fibrillazione atriale

Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation

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Lancet Neurol 2018

Background

- About 13–26% of all acute ischemic strokes are related to non-valvular atrial fibrillation (AF), the most common cardiac arrhythmia globally.

- Deciding when to initiate oral anticoagulation in patients with non-valvular AF is a longstanding, common, and unresolved clinical challenge.

- Although the risk of early recurrent ischemic stroke is high in this population, early oral anticoagulation is suspected to increase the risk of potentially harmful intracranial hemorrhage, including hemorrhagic transformation of the infarct.

- This assumption, and current treatment guidelines, are based on historical, mostly observational data from patients with ischemic stroke and AF treated with heparins, heparinoids, or vitamin K antagonists (VKAs) to prevent recurrent ischemic stroke.

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Background

- Randomised controlled trials have subsequently shown that direct oral anticoagulants (DOACs) are at least as effective as VKAs in primary and secondary prevention of atrial fibrillation-related ischemic stroke, with around half the risk of intracranial hemorrhage.

- However, none of these DOAC trials included patients who had experienced ischemic stroke recently (within the first few weeks).

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International Journal of Stroke WSO

Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

George Ntaios[1], Vasileios Papavasileiou[2], Hans-Chris Diener[3], Konstantinos Makaritsis[1] and Patrik Michel[4]

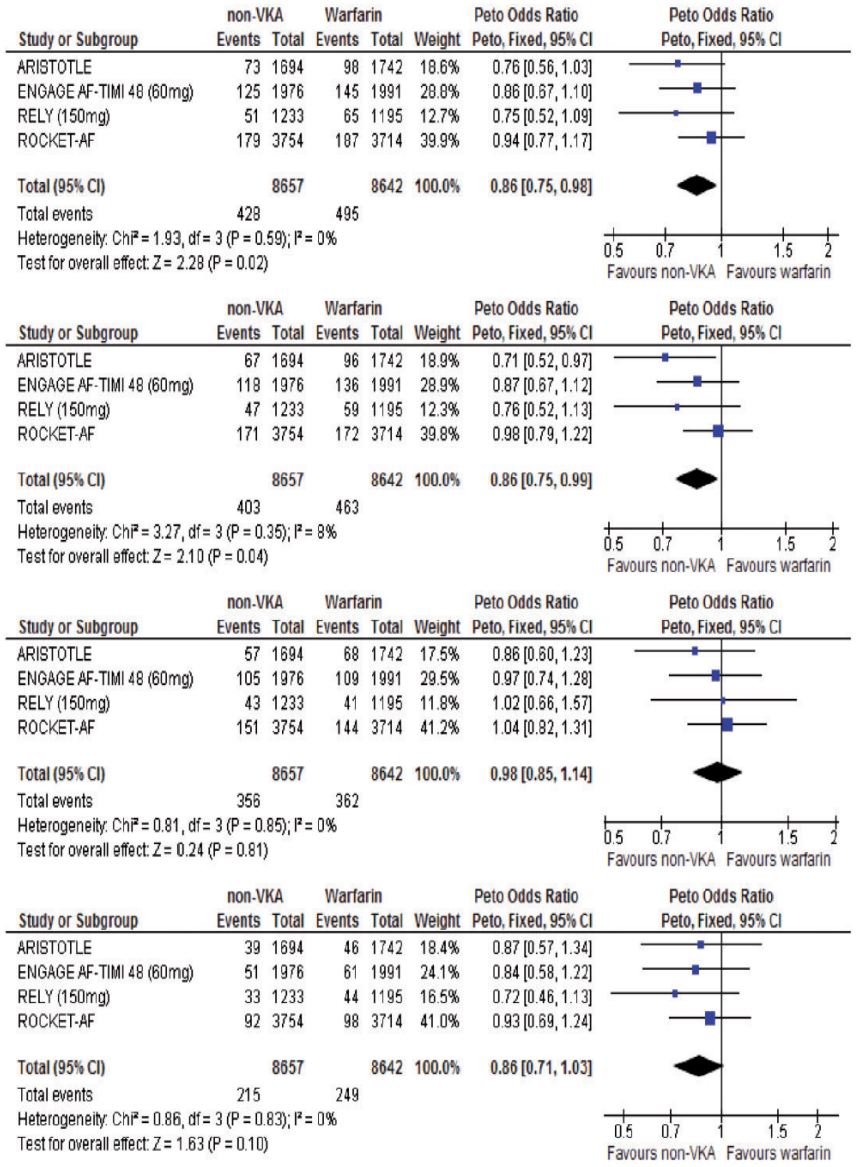
Stroke and/or Systemic embolism

RRR 13.7%

RRA 0.78%

NNT 127

Figure 2. Forest plot of the effects of non-VKAs versus warfarin on efficacy outcomes (panel A: stroke or systemic embolism/pane B: stroke/panel C: ischemic or unknown stroke/panel D: disabling or fatal stroke) in patients with atrial fibrillation and previous stroke or transient ischemic attack. VKA: Vitamin K antagonist.



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Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

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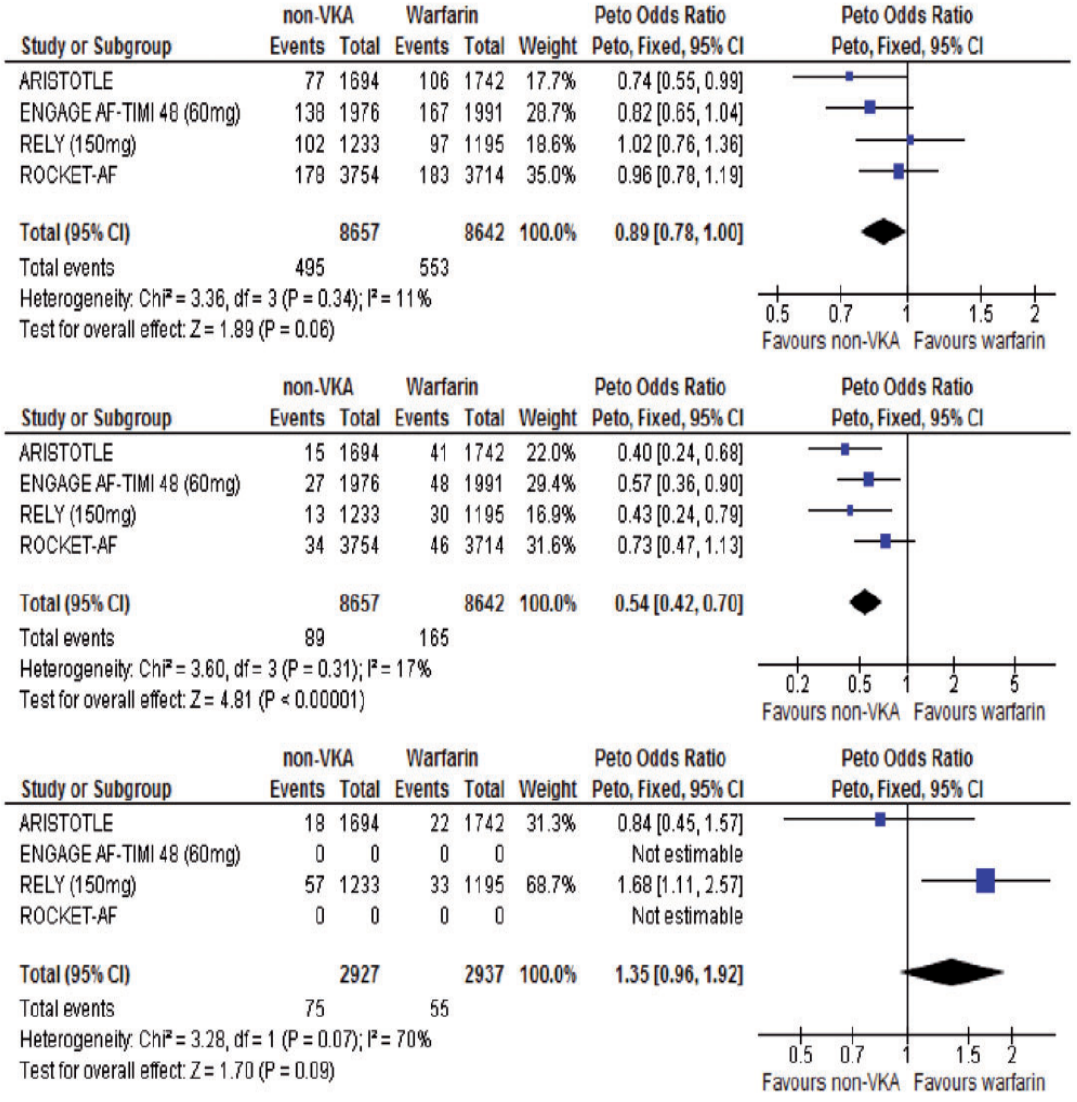
Intracranial bleeding
RRR 46%
RRA 0.88%
NNT 113

Figure 4. Forest plot of the effects of non-VKAs versus warfarin on safety outcomes (upper panel: major bleeding/middle panel: intracranial bleeding/lower panel: major gastrointestinal bleeding) in patients with atrial fibrillation and previous stroke or transient ischemic attack. VKA: Vitamin K antagonist.



RCT	Exclusion criteria
RE-LY	-Stroke with severe disability (mRS 4-5) in the previous 6 months -Stroke in the previous 2 weeks
ROCKET-AF	-Stroke with severe disability (mRS 4-5) in the previous 3 months -Stroke in the previous 2 weeks -TIA in the previous 3 days
ARISTOTLE	-Stroke in the previous week
ENGAGE-AF	-Stroke in the previous 30 days

Search strategy and selection criteria

We identified references for this Rapid Review by searches of PubMed between Jan 1, 2016, and July 20, 2018, using the search terms "ischaemic stroke" OR "ischemic stroke" AND "atrial fibrillation" OR "non-valvular atrial fibrillation" OR "AF" AND "oral anticoagulation" OR "direct oral anticoagulants" OR "new oral anticoagulants" OR "novel oral anticoagulants" OR "DOAC" OR "NOAC" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban". Only papers published in English were considered. Additionally, we searched our personal records and abstracts from international conferences in the past five years (2013—18; eg, the European Stroke Organisation Conference 2018 and others) for relevant publications or data. For the section on early anticoagulation, we selected publications presenting original data and published in English. In addition, we searched PubMed, personal records, and an internet search engine (ie, Google) using the search terms "guidelines", "secondary prevention", "stroke", "atrial fibrillation", and "oral anticoagulation" OR "DOAC" OR "direct oral anticoagulants" to identify guidelines from relevant organisations (national or international expert committees).

Recent developments

- Prospective observational studies and two small randomised trials have investigated the risks and benefits of early DOAC administration initiation (most with a median delay of 3–5 days) in mild-to-moderate AF-associated ischemic stroke.

- These studies reported that early DOAC treatment was associated with a low frequency of clinically symptomatic intracranial hemorrhage or surrogate hemorrhagic lesions on MRI scans, whereas later DOAC-administration initiation (i.e., >7 days or >14 days after index stroke) was associated with an increased frequency of recurrent ischemic stroke.

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Summary of studies on early initiation of anticoagulant treatment in patients with recent AF-related ischemic stroke

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	Study population	Patients' median age, median stroke severity, and infarct size*	Median timing of anticoagulation administration initiation	Follow-up period	Recurrent ischaemic stroke†	Intracranial haemorrhage†
Observational studies with clinical follow-up of ≥3 months						
Seiffge et al[44] (NOACISP)	204 (155 DOAC treated)	79 years; NIHSS score 4; no information on infarct size	5 days (≤7 days for 65% [n=100] of DOAC-treated patients)	At least 3 months	7·7% per year (5·1% per year for DOAC administration ≤7 days vs 9·3% per year for DOAC administration >7 days, p=0·53)	1·3% per year
Arihiro et al[45] (SAMURAI-NVAF)	1192 (466 DOAC treated)	78 years; NIHSS score 3; 24% small, 48% medium, and 28% large infarcts	5 days for DOAC	3 months	8·5% per year (VKA) and 10·1% per year (DOAC, p>0·05)	1·2% per year (VKA) vs 0·8% per year (DOAC)
Paciaroni et al[46] (RAF-NOAC)	1127 (all DOAC treated)	76 years; NIHSS score 8; 41% small, 33% medium, and 22% large infarcts	No overall median reported (8 days for dabigatran and rivaroxaban, 7 days for apixaban)	3 months	7·8% per year	6·4% per year
Wilson et al[51]	1355 (475 DOAC)	76 years; NIHSS score 4; 18% large infarcts	11 days (≤4 days for 26% [n=358] of patients)	90 days	5·7% per year (combined DOAC and VKA)	0·6% per year (combined DOAC and VKA)
Observational studies with clinical follow-up within 3 months or with surrogate outcome imaging markers						
Macha et al[47]	243 (all DOAC treated)	78 years; NIHSS score 5; 17% small infarct or TIA, 70% medium, and 13% large infarcts	From 1·7 days for small infarct or TIA to 6·7 days for large infarcts (≤7 days for 89·7% [n=218] of DOAC-treated patients)	In hospital	Not reported	1 case of symptomatic and 2 cases of asymptomatic intracranial haemorrhage
Cappellari et al[48]	147 (all DOAC treated)	79 years; NIHSS score 8; 54% small, 22% medium, and 24% large infarcts	3·3 days (≤3 days for 66% [n=97] of patients; ≤7 days for all patients)	CT scan at 7 days	No case observed	8 cases of asymptomatic intracranial haemorrhage (7 new, 1 before DOAC treatment)
Gioia et al[49]	60 (all rivaroxaban treated)	74 years; NIHSS score 2; median DWI lesion volume 7·9 mL	3 days	MRI scan at 7 days	1 case	No cases of symptomatic intracranial haemorrhage, 8 cases of asymptomatic petechial haemorrhage
Deguchi et al[50]	300 (186 DOAC treated)	77 years; NIHSS score 7; no information on infarct size	3 days for DOAC, 7 days for VKA	In hospital	No case observed	2 cases of intracranial haemorrhage, 1 case of extracranial haemorrhage
Observational studies with a majority of patients receiving VKAs or heparins						
Abdul-Rahim et al[40]	1300 (no DOAC-treated patients)	73 years; NIHSS score 14; no information on infarct size	2 days	90 days	8·2% of patients (107 events in 1300 patients)	2·3% of patients had symptomatic intracranial haemorrhage (30 events in 1300 patients)
Paciaroni et al[75]	1029 (93 DOAC treated)	77 years; NIHSS score 9; 37% small, 36% medium, and 27% large infarct	8·5 days for DOAC, 12·1 days for VKA	3 months	77 events (including TIA and systemic embolism)	37 events (including major extracranial haemorrhages)
Randomised controlled trials with patients receiving DOACs						
Hong et al[41]	195 (95 rivaroxaban treated)	70 years; NIHSS score 2; median DWI lesion volume 2·6 mL	2 days	MRI scan at 4 weeks	1 case	30 new haemorrhagic lesions (all asymptomatic)

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

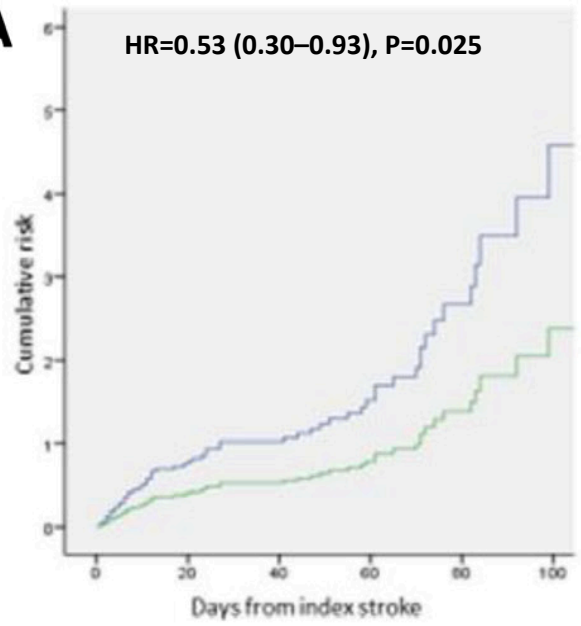
Stroke
Journal of the American Heart Association
American Heart Association | American Stroke Association

International multicenter prospective observational study on **1029** patients with acute ischemic stroke and AF

Paciaroni et al., Stroke 2015

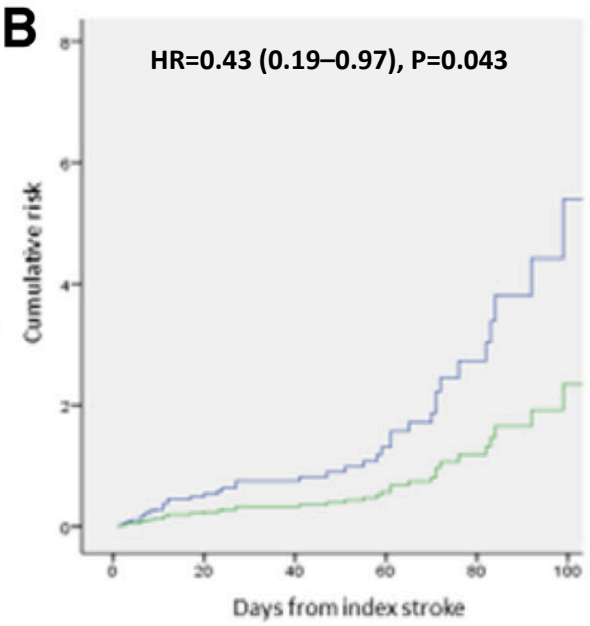
All outcome events

A



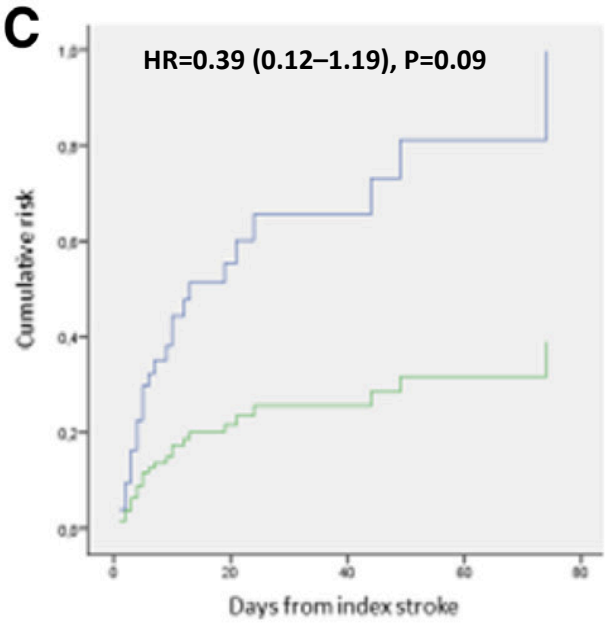
Ischemic outcome events (stroke, TIA, systemic embolism)

B



Symptomatic cerebral bleedings

C



Green, anticoagulation between 4 and 14 days from stroke onset
Blue, other treated patients (treatment before 4 or after 14 days)

Starting anticoagulation for secondary ***between 4 and 14 days*** from stroke onset seems to be associated with the best efficacy/safety profile.

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

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Paciaroni et al., Stroke 2015

At multivariate analysis:

- **High CHA_2DS_2-VASc score**
- **High NIHSS**
- **Large ischemic lesions**
- **Type of anticoagulant administered** (**LMWH** vs oral anticoagulants alone)

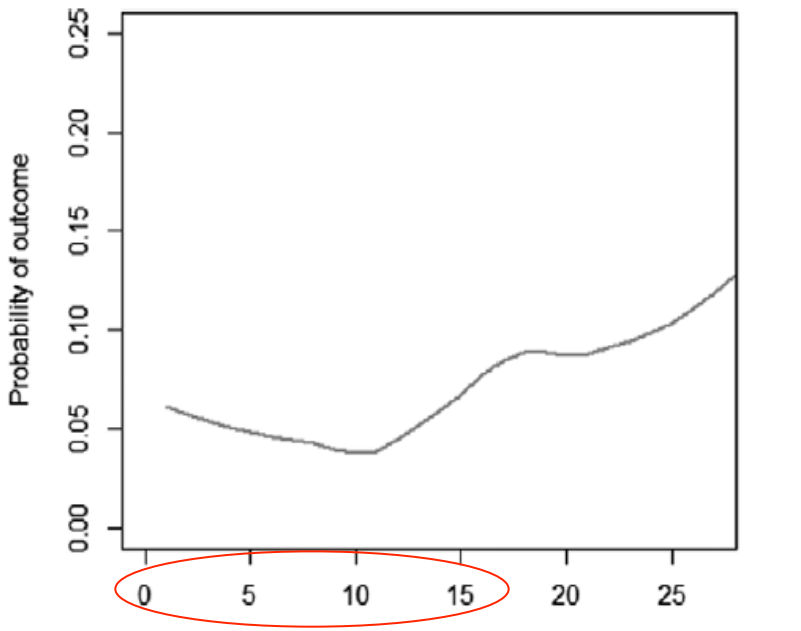
each independently led to a greater risk of recurrence and bleedings.

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

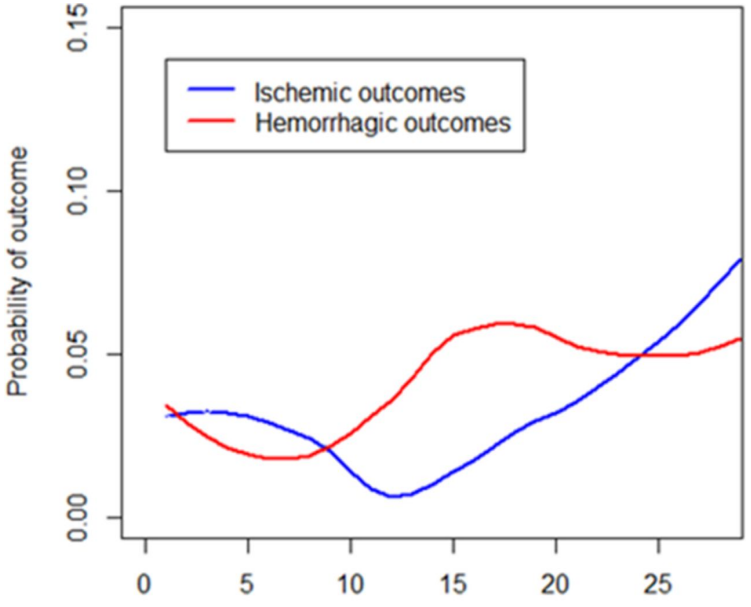
Paciaroni et al., J Am Heart Assoc 2017

International multicenter prospective observational study on **1127** patients with acute ischemic stroke and AF treated with NOACs

- *Treatment with NOACs was associated with a* ***combined 5.2% rate of ischemic embolic recurrence (2.8%) and severe bleeding (2.4%) within 90 days****.*
- ***80% of the patients received NOACs within 15 days of the index stroke****.*

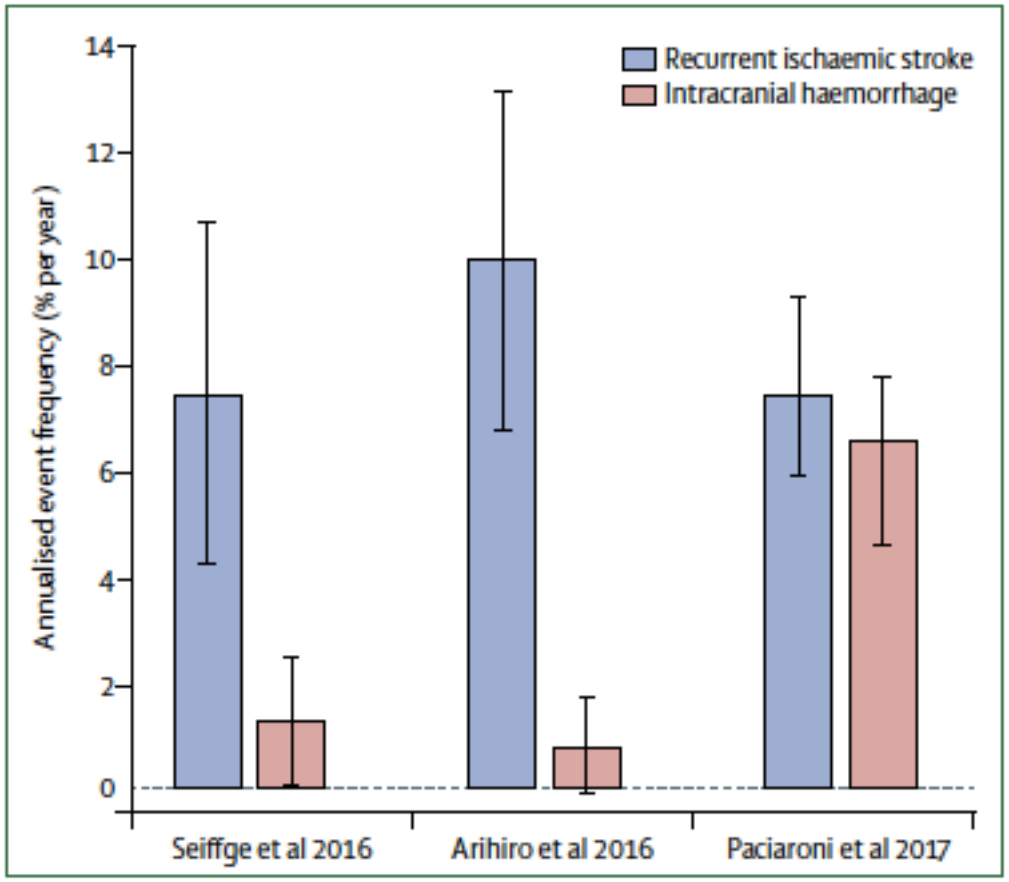


Risk of combined outcome events based upon the day of initiating NOAC



Risk of ischemic (blue) and hemorrhagic (red) events based upon the day of initiating NOAC

Risk of recurrent ischemic stroke and intracranial hemorrhage in patients with AF and a recent ischemic stroke



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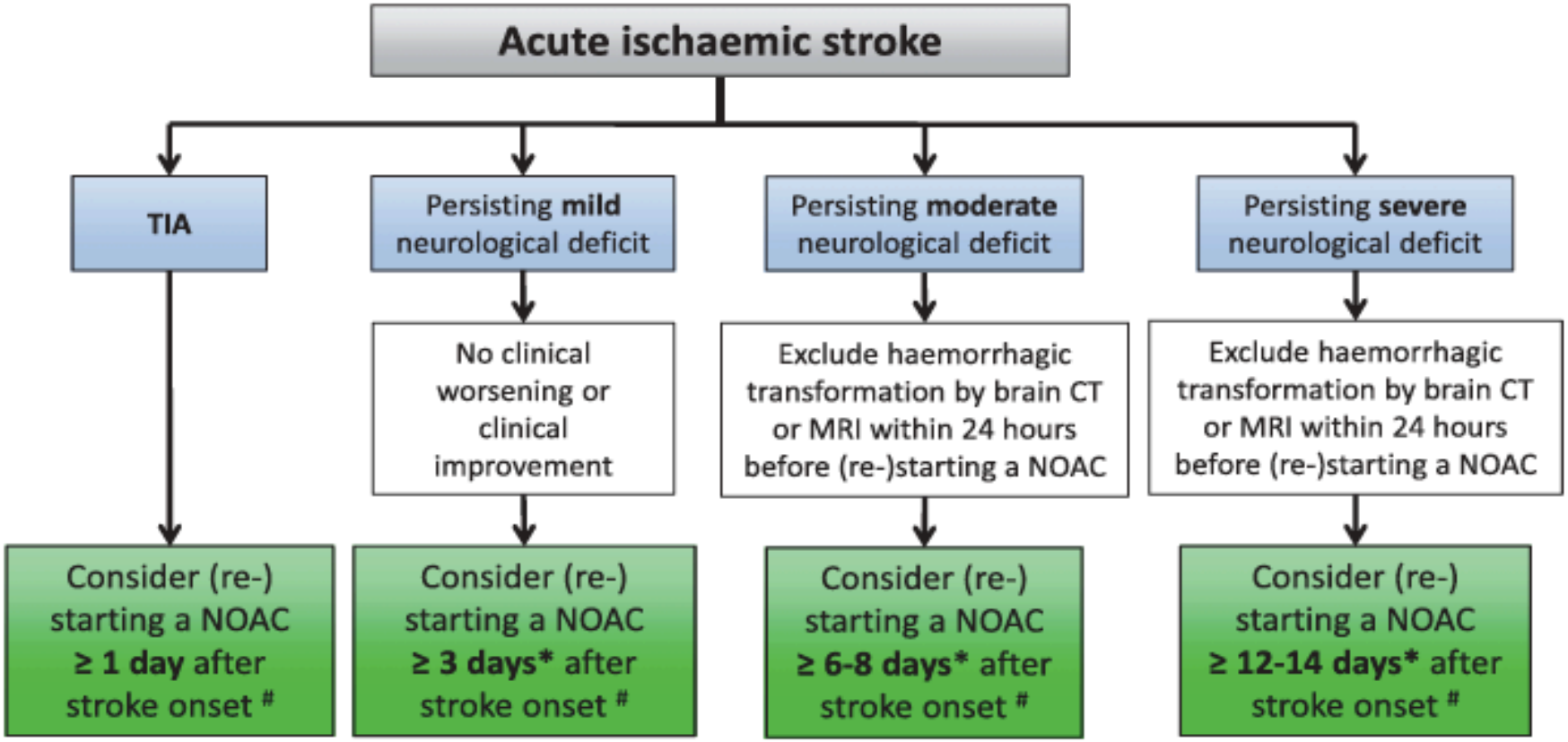
ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–64
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Steffel et al., Eur Heart J 2018

(Re-) initiation of anticoagulation after TIA/stroke



Where next?

- Adequately powered randomised controlled trials comparing early to later oral anticoagulation with DOACs in ischemic stroke associated with AF are justified to confirm the acceptable safety and efficacy of this strategy.
- Four such randomised controlled trials (collectively planned to include around 9000 participants) are underway, either using single cutoff timepoints for early versus late DOAC-administration initiation, or selecting DOAC-administration timing according to the severity and imaging features of the ischemic stroke.
- The results of these trials should help to establish the optimal timing to initiate DOAC administration after recent ischemic stroke and whether the timing should differ according to stroke severity. Results of these trials are expected from 2021.

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Summary of ongoing randomised controlled trials investigating early versus late initiation of direct oral anticoagulant treatment in patients with recent AF-related ischemic stroke

	Planned sample size	Intervention (early initiation of anticoagulant treatment)	Control (late initiation of anticoagulant treatment)	Follow-up period	Primary outcome	Patients with haemorrhagic transformation included	NIHSS exclusion criteria	Estimated end of study
ELAN (NCT03148457)	2000	<48 h after symptom onset (minor and moderate stroke) or at day 6 (±1 day) after symptom onset (major stroke)*	Current recommendations (ie, minor stroke after day 3 [±1 day], moderate stroke after day 6 [±1 day] and major stroke after day 12 [±2 days])*	30 days (secondary outcomes after 90 days)	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death, or a combination of these outcomes)	Yes	No exclusion criteria	October 2021
OPTIMAS (EudraCT, 2018-003859-38)	3474	≤4 days after acute ischaemic stroke	7–14 days after acute ischaemic stroke	90 days	Composite outcome at 90 days (combined incidence of recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage [including extradural, subdural, subarachnoid and intracerebral haemorrhage, and haemorrhagic transformation of the qualifying infarct], and systemic embolism)	Yes	No exclusion criteria	2021–22
TIMING (NCT02961348)	3000	≤4 days after acute ischaemic stroke	5–10 days after acute ischaemic stroke	90 days	Composite outcome (recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality, or a combination of these outcomes)	Yes	No exclusion criteria	December 2020
START (NCT03021928)	1500 (1000 patients with mild or moderate stroke, 500 with severe stroke)†	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke†	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10 ,14, or 21 days for severe stroke†	30 days (secondary outcomes after 90 days)	Composite of any CNS haemorrhagic or other major haemorrhagic events and the ischaemic events of stroke or systemic embolism within 30 days of the index stroke	Yes	Score >3 and score <23	August 2021

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Current suggested strategy

- Enrolment of eligible patients with ischemic stroke and AF in ongoing randomised controlled trials is suggested on the basis of current guidelines and evidence from observational studies and clinical trials.

- If enrolment in a trial is not possible, clinicians will need to use the data to weigh potential risks and benefits of early DOAC administration although evidence is currently scarce to make strong recommendations.

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Timing for initiation of direct oral anticoagulant administration