Anticoagulation in the early phase of non-valvular atrial fibrillation-related acute ischemic stroke: where do we stand?

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ABSTRACT

The balance between the risk of early stroke recurrence and hemorrhagic transformation represents the cornerstone of practical management of non-valvular atrial fibrillation (NVAF)-related acute ischemic stroke (AIS). Patients who receive antithrombotic therapy as secondary prevention in the early phase of NVAF-related AIS have a better prognosis compared with patients who do not receive antithrombotic treatment. Recently, the RAF study showed that the best efficacy/safety profile was associated with anticoagulation started between 4 and 14 days from stroke onset. Based on the RAF study, the 2018 American Heart Association/American Stroke Association (AHA/ASA) guidelines suggest starting anticoagulants between 4 and 14 days from stroke onset with a class of recommendation IIa. Strong evidence for the use of direct oral anticoagulants (DOACs) in the early phase of NVAF-related AIS is lacking, because this kind of patients were excluded from phase III randomized clinical trials (RCT) and *ad hoc* RCTs are ongoing. However, the real life evidence suggests that early starting time of DOACs in patients with NVAF-related AIS is safe and associated with low recurrence risk and all-cause mortality. In the present review the Authors provide an update on anticoagulation in the early phase of NVAF-related AIS with focus on DOACs.

Introduction

Non-valvular atrial fibrillation (NVAF)-related acute ischemic strokes (AIS) represent about one fourth of overall strokes and the most feared stroke subtype due to higher mortality and morbidity risk and more severe functional sequelae compared to other subtypes.[1]

Preventing stroke recurrences avoiding hemorrhagic transformation (HT) represents the cornerstone of secondary prevention in NVAF-related AIS. In the absence of secondary pharmacological prevention, the risk of early embolic stroke recurrence is about 1% per day in the first two weeks.[2] HT represents the most feared complication in patients with AIS. Cardioembolic stroke represents one of the main risk factors for HT together with systemic thrombolysis, large vessel stroke etiology, large size infarcts and diabetes.[3] The risk of HT in patients with cardioembolic stroke is three-five folds increased.[3] The incidence of HT in patients with cardioembolic stroke is about 7-10% in the first two weeks from stroke onset. In the VISTA registry 80% of stroke recurrence and HT occurred within day 2 after stroke events.[4] Both stroke recurrence and symptomatic HT are associated with poor prognosis in terms of morbidity, mortality, increased length of hospital stay (LOS) and neurological sequelae.[2,3,5,6] Of note, the occurrence of HT is associated with delay of starting anticoagulation after stroke onset.[6] Table 1 summarizes the classification of HT.

Oral anticoagulants represent the first therapeutic choice for secondary stroke prevention in atrial fibrillation (SPAF).[7] A meta-analysis showed that, in patients with history of stroke, the number needed to treat (NNT) for preventing one stroke by using warfarin was 14 *versus* placebo and 24 *versus* antiplatelets.[8] Patients who receive antithrombotic therapy as secondary prevention in the early phase of NVAF-related AIS have a better prognosis compared with

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patients who do not receive antithrombotic treatment.[4] In the VISTA registry the incidence of stroke recurrence, symptomatic intracranial bleeding, all-cause mortality and 90-day modified Rankin scale (mRS) ≥4 in patients with NVAF-related AIS not receiving antithrombotic treatment was 19.8%, 9.3%, 40.7% and 65.3%, respectively compared with patients receiving vitamin K antagonists (VKAs) (10.6%, 2.9%, 25.5% and 46.6%, respectively) or VKAs plus antiplatelets (6.7%, 1.9%, 17.8% and 54.5%, respectively).[4] Baseline median National Institute of Health Stroke scale (NIHSS) score ranged from 16 in patients not receiving antithrombotics to 14 in patients receiving anticoagulants plus antiplatelets.[4] The median starting time of anticoagulants in the VISTA registry was 2 days (interquartile range, 1-4).[4]

Despite the prognostic advantages, the optimal timing for starting anticoagulants in the acute phase of NVAF-related AIS remains a clinical dilemma. In patients receiving systemic thrombolysis none additional antithrombotic therapy is indicated in the first 24 h.[7] Aspirin started after 24 h in patients receiving systemic thrombolysis or as soon as possible in patients not receiving systemic thrombolysis is the most appropriate secondary prevention in the first 48 h from stroke onset, whereas anticoagulation in this temporal window is unfavorable for the highest risk of HT.[7,9] Recently, the RAF study showed that starting anticoagulation with VKAs [*i.e.* reaching international normalized ratio (INR) ≥2.0] in AIS was associated with a 90-days incidence of transient ischemic attack (TIA)/stroke recurrence or systemic embolism of 6.4% (10.6% in patients non receiving antithrombotic therapy, P=0.023) and hemorrhagic events of 5.4% (3.8% in patients non receiving antithrombotic therapy, P=0.31) and the best efficacy/safety profile was with a start time between 4 and 14 days. The mean time for reaching INR ≥2 was 12.1±15.8 days.[2] In the RAF study the mean baseline NIHSS score was 9.2±7.3. About one fourth (27.1%) of patients had large infarct size.[10] Definition of infarct size in the RAF study is summarized in Table 2 and examples of infarct size in Figure 1. Based on the RAF study, the latest (2018) American Heart Association/American Stroke Association (AHA/ASA) guidelines suggest to start anticoagulants between 4 and 14 days from stroke onset with a class of recommendation IIa.[7] This temporal window seems wide in the clinical context, and in the single patient the decision on when anticoagulants should be started, if closer to the fourth or fourteenth day, is difficult and at the same time fundamental. The analysis of subgroups of the RAF study showed that CHA_2DS_2-VASC score, NIHSS score, size of brain ischemic lesions and left atrial size each independently, could help in the appropriate timing for starting VKAs.[10,11]

Direct oral anticoagulants in the secondary prevention of stroke

Evidence for the use of direct oral anticoagulants (DOACs) in the acute phase of NVAF-related AIS is lacking, because this kind of patients were excluded from the phase III randomized clinical trials (RCTs) on DOACs in SPAF.[12,13] Exclusion criteria related to AIS in phase III RCTs are summarized in Table 3. However about 14,000 patients enrolled in phase III RCTs on DOACs in SPAF had suffered from a previous TIA/stroke (Table 4). A *post-hoc* analysis of phase III RCTs comparing DOACs *versus* warfarin in SPAF showed a good efficacy/safety profile of DOACs in patients with history of previous TIA/stroke. Compared to warfarin, absolute risk reduction (ARR), relative risk

Table 1. Classification of hemorrhagic transformation in acute ischemic stroke.

Hemorrhage infarction type1 (HI1)	Small isolated hyperdense petechiae
Hemorrhage infarction type2 (HI2)	More confluent hyperdense petechiae throughout the infarct zone; without mass effect
Parenchymal hematoma type1 (PH1)	Homogeneous hyperdensity occupying <30% of the infarct zone without mass effect
Parenchymal hematoma type2 (PH2)	Homogeneous hyperdensity occupying >30% of the infarct zone with mass effect

Table 2. Definition of infarct size in RAF and RAF-NOACs studies.

Small infarct size	Less than 1.5 cm in the anterior or posterior circulation
Medium infarct size	Lesion in a cortical superficial branch of MCA, in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of PCA, or in a cortical superficial branch of ACA
Large infarct size	Anterior lesions involved the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery or were in 2 cortical superficial branches of the MCA, in a cortical superficial branch of MCA associated with the MCA deep branch, or in >1 artery territory (*e.g.*, MCA associated with anterior cerebral artery territory); lesions ≥1.5 cm in the brain stem or cerebellum

MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery.

reduction (RRR) and NNT were 0.78%, 13.7% and 127, respectively, for preventing stroke or systemic embolism, while ARR, RRR and NNT were 0.88%, 46% and 113, respectively, for preventing intracranial bleeding.[14]

Despite the absence of strong literature evidence, DOACs seem to represent a great opportunity in patients with NVAF-related AIS, due to their favorable pharmacological and safety profiles. Based on Expert opinion, guidelines suggest starting DOACs immediately in patients with NVAF-related TIA, after ≥3, 6-8 and 12-14 days in mild (NIHSS score <8), moderate (NIHSS 8-16) or severe (NIHSS score >16 stroke).[15]

Direct oral anticoagulants in the early phase of non-valvular atrial fibrillation-related acute ischemic stroke: update on available evidence

Phase II clinical trials

The TRIPLE-Axel was a phase II RCT comparing low dose rivaroxaban (10 mg) for five days followed by full dose (20 mg, or 15 mg in patients with creatinine clearance 30-49 mL/min) *versus* warfarin with a target INR of 2.0-3.0 for four weeks in 183 patients with mild (NIHSS ≤4) NVAF-related AIS. This trial showed no difference between the two arms

Table 3. Exclusion criteria in phase III randomized clinical trials on direct oral anticoagulants in stroke prevention in atrial fibrillation.

RCT	Exclusion criteria
RE-LY	Stroke with severe functional sequelae (modified Rankin scale) in the previous 6 months Acute stroke in the previous two weeks
ROCKET-AF	Stroke with severe functional sequelae (modified Rankin scale) in the previous 3 months Acute stroke in the previous two weeks TIA in the previous 3 days
ARISTOTLE	Stroke in the previous week (44 patients suffering from TIA or stroke in the previous 7-14 days and 187 suffering from TIA or stroke in the previous 14-30 days were enrolled in the study)
ENGAGE-AF	Stroke in the previous 30 days

RCT, randomized controlled trials; TIA, transient ischemic attack.

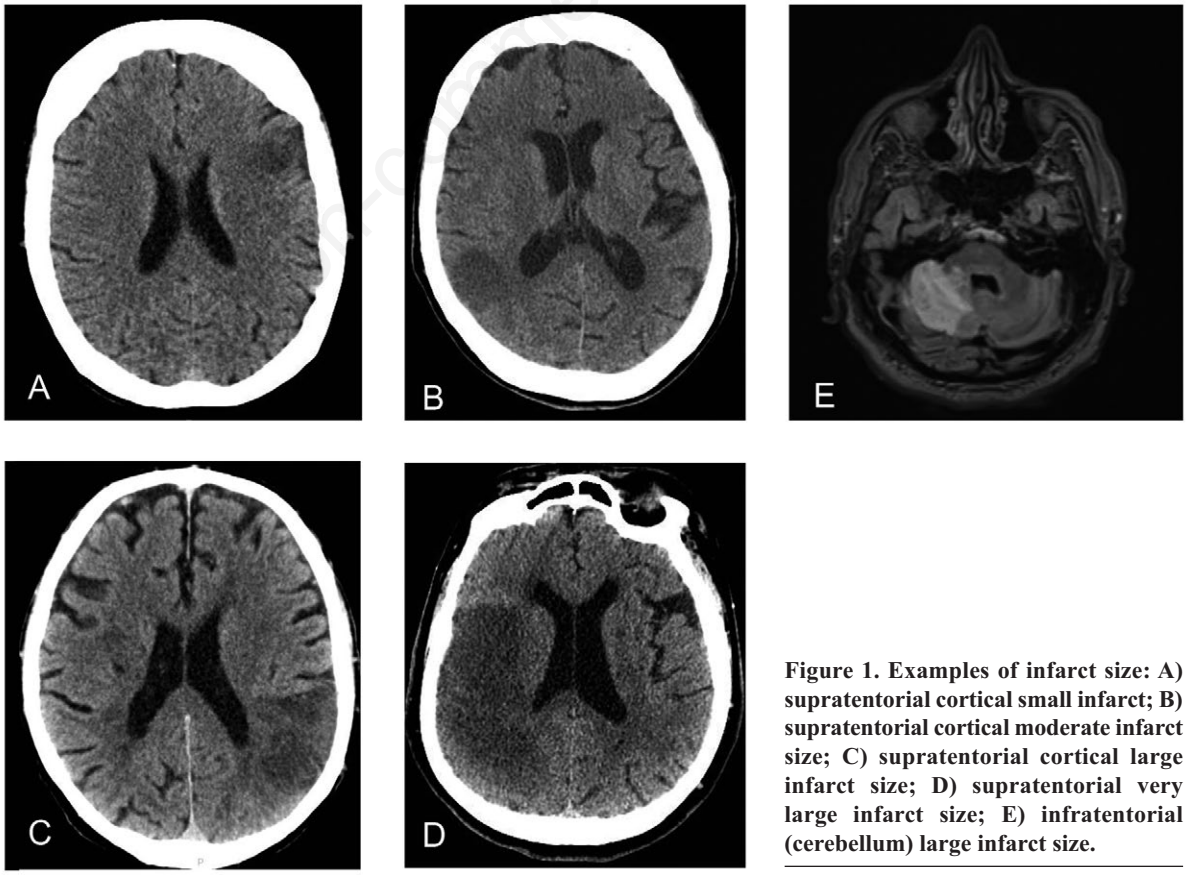

Figure 1. Examples of infarct size: A) supratentorial cortical small infarct; B) supratentorial cortical moderate infarct size; C) supratentorial cortical large infarct size; D) supratentorial very large infarct size; E) infratentorial (cerebellum) large infarct size.

in the primary composite endpoint of stroke recurrence and/or new intracranial bleeding.[16] Patients receiving rivaroxaban showed a significant shorter LOS (4.0 *vs* 6.0 days, P<0.001).[16]

Phase III and phase IV clinical trials

Until now, phase III and phase IV clinical trials aimed to analyze efficacy and safety of DOACs in the early phase of NVAF-related AIS are ongoing and results have not been published yet. Table 5 summarizes the design of planned clinical trials in this context.

Real life evidence

In the last years a lot of literature evidence about the introduction of DOACs in the early phase of NVAF-related AIS was available. More recently, Masotti *et al*. provided a summary of this literature evidence.[17] The Authors analyzed Pubmed database searching for published articles until June 2018 reporting data on 90-day prognosis of patients receiving DOACs in the first two weeks after NVAF-related AIS. They built their search by combining the terms *oral anticoagulants, stroke, acute, early* by using the Boolean operators *AND/OR*. The search was restricted to English language articles, adults (≥18 years), words in title/abstract. Finally, the search strategy was refined by reviewing the bibliography of retrieved articles. Only studies including DOACs and reporting endpoints, such as 90-day TIA/stroke recurrence, HT or intracranial bleeding and all-cause mortality were considered for the analysis. The Authors identified eight studies[18-25] satisfying the criteria of their search, with different methodology (five prospective observational, two retrospective and one prospective, open label, single arm design). Overall, the eight studies included 2187 patients (49.3% females) of whom 830 were treated with rivaroxaban, 729 with dabigatran, 475 with apixaban and 6 with edoxaban. For 147 data on the type of DOAC used were not available. In all the studies mean or median age of patients was over 70 years. About one third of patients were treated with urgent reperfusion therapy, and about one fifth of patients had large infarct size. Median or mean NIHSS ranged from 2 to 8 points. Median time of starting DOACs ranged from 2 to 8 days, and in seven out of eight selected studies, median or mean starting time was ≤5 days. About 42% of patients received low dose of DOACs. Ninety-day TIA/stroke recurrence, HT/intracranial bleeding and all-cause mortality occurred in 2.3%, 0.93% and 1.5% of patients, respectively. The Authors concluded that, awaiting results of phase III RCTs, the findings of their overview could open a new scenario, supporting the use of DOACs as the possible treatment of choice in the early phase of NVAF-related AIS, and highlighting that 90-day prognostic outcomes were lower than those reported in the previous studies (Table 6).[4,17] However, the Authors, recognized that their review had limitations. In fact, the interpretation of their results should take into account that the selected studies had different designs, none of them had a comparison group, the average stroke severity was mild (median or mean NIHSS at hospital admission is ≤8), about 40% of patients were treated with low doses of DOACs, even if the reason of dose reduction was almost never reported and finally, the follow-up was limited to 90 days.

Recently, data on the 2-year follow-up of the SAMURAI-NVAF registry, examining the long-term risk-benefit profile among patients receiving warfarin

Table 4. General characteristics of patients with history of previous transient ischemic attack/stroke enrolled in phase III randomized clinical trials.

	RE-LY dabigatran 110 mg	RE-LY dabigatran 150 mg	ROCKET-AF rivaroxaban	ARISTOTLE apixaban	ENGAGE-AF edoxaban
Number	1195	1233	3754	1694	5973
Mean age (years)	70.7±9.4	70.8±10.1	71 (64-76) Median (IQR)	70.1±9.5	70.4±9.2
Females	35.9%	37.8%	39%	37%	38.2%
$CHADS_2$ score ≥3	90%	90.2%	nr*	92%	nr**
Aspirin at moment of enrollment	39.9%	39.7%	38%	31%	28.2%
Previous AMI	nr	nr	14%	17%	nr
Systemic blood hypertension	77%	77.3%	85%	83%	86.2%
Diabetes	22.4%	23.7%	25%	26%	26.6%
Heart failure	nr	nr	51%	27%	42.4%
Paroxysmal AF	nr	nr	19%	nr	26.1%
Persistent or permanent AF	nr	nr	81%	nr	73.9%

nr, not reported; AF, atrial fibrillation; AMI, acute myocardial infarction; IQR, interquartile range. *Median $CHADS_2$ score 4 (3-5); **$CHADS_2$ score ≥4 (67%).

Table 5. Study design of ongoing phase III and phase IV clinical trials on direct oral anticoagulants in the early phase of non-valvular atrial fibrillation related acute ischemic stroke (source clinicaltrials.gov 2018, October 31).

Study	Design	Inclusion criteria	DOAC	Dose	Comparators	DOAC starting time	Expected number	Primary endpoints
RELAXED	Multicenter observational non-interventional single arm	TIA or AIS in the middle cerebral artery territory	Rivaroxaban	ClCr >50 mL/min 15 mg; ClCr 15-49 mL/min 10 mg	None	Within 30 days	2000 pts	3-months stroke recurrence 3-months major bleeding
TIMING	Multicenter, open-label, RCT	AIS within 72 h from onset	All DOACs	According to habitual clinical practice	Early start (≤4 days) *versus* delayed (5-10 days) start of DOAC therapy	≤4 days or 5-10 days	3000 pts	3-months composite stroke recurrence, intracranial bleeding and all-cause mortality
RASS	Observational single arm	Acute minor stroke (NIHSS score <8) within 24-h from onset or TIA	Rivaroxaban	NR	None	NR	100 pts	Symptomatic HT
SEDMAN	Prospective multicenter case-control investigator-initiated study	AIS or TIA in the last 14-days	Dabigatran	According to habitual clinical practice	Acenocumarol	<14 days	500 pts	1-year TIA/stroke or systemic embolism 1-year CRNM and major bleeding
START	Multicenter interventional parallel-assignment outcomes-assessor RCT	AIS (infarct size >1.5 cm or NIHSS score >4)	All DOACs	According to habitual clinical practice	Early start *versus* delayed start of DOAC therapy	3 days *vs* 6 days *vs* 10 days *vs* 14 days	1000 pts	30-day stroke recurrence 30-day any symptomatic HT, other intracranial bleeding or major *extracranial bleeding*
AOD	Prospective observational	AIS	All DOACs	According to habitual clinical practice	None	NR	420 pts	12-month stroke recurrence
ATIS-NVAF	Multicenter open-label RCT	TIA or AIS in the last 8 days and NVAF and past history of atherothrombotic diseases	All DOACs or warfarin plus dual or mono antiplatelet drug	According to habitual clinical practice (warfarin INR 2.0-3.0)	DOAC or warfarin plus DAPT *vs* DOAC or warfarin plus MAPT	NR	400	Composite cardiovascular events and major bleeding
ELAN	Multicenter interventional assessor-blinded RCT	AIS	All DOACs	According to habitual clinical practice	Early *versus* late treatment by DOACs	*Early*: 48 h in small and moderate infarct size; 6+1 day in large infarct size *Late*: 3+1 day small infarct size; 6+1 day moderate infarct size; 12+2 large infarct size	2000	30-day composite stroke recurrence, systemic embolism, major bleeding, cardiovascular death

DOAC, direct oral anticoagulant; TIA, transient ischemic attack; AIS, acute ischemic stroke; CrCl, creatinine clearance; RCT, randomized clinical trial; NIHSS, National Institute of Heath Stroke scale; NR, not reported; HT, hemorrhagic transformation; CRNM, clinically relevant non major bleeding; NVAF, non-valvular atrial fibrillation; DAPT, dual antiplatelet therapy; MAPT, mono antiplatelet therapy; INR, international normalized ratio.

or DOACs, were published: estimated cumulative incidences of stroke and systemic embolism within 2 years were similar between warfarin and DOACs users, but deaths and intracranial hemorrhages were significantly lower among the latter.[26]

Implications for clinical practice

The decision on the optimal time for starting anticoagulants in the acute phase of NVAF-related AIS remains a challenge. Before DOACs era the introduction of anticoagulation in the early phase of NVAF-related AIS was strongly underused. In a previous multicenter study performed in Tuscany at the beginning of this decade (2011), only about one fourth of patients with NVAF-related AIS received VKAs before hospital discharge. More than one half of patients were discharged on antiplatelet therapy.[5]

Defining the risk of stroke recurrence and HT is of fundamental importance for anticoagulation starting time. Combining patients of RAF and RAF-NOACs studies, Paciaroni *et al*. found that older age, infarct size ≥1.5 cm and severe left atrial enlargement are significantly associated with long-term prognosis in patients suffering from NVAF-related AIS. Therefore, the Authors derived and validated the ALESSA score (Table 7), which has a good predictive power in predicting stroke recurrence (area under the receiving operating characteristic curve 0.646 [95% confidence interval (CI): 0.529-0.763], while the power to predict hemorrhagic events is low (AUC 0.407, 95% CI: 0.275-0.540).[27]

After DOACs marketing, the confidence in their use in patients with NVAF and venous thromboembolism together with their favorable pharmacological profile (rapid onset of action and lower risk of intracranial bleeding compared with VKAs) has led physicians to consider the use of DOACs in the early phase of NVAF-related AIS despite the absence of data in phase III RCTs. In a previous study performed in the Internal Medicine Ward of Santa Maria Nuova Hospital, Florence, Italy, Moroni *et al.* demonstrated that in the era of DOACs the percentage of patients with NVAF-related AIS who underwent anticoagulation before hospital discharge was 69.5% and this percentage increased from 62.5% in 2014 to 88% in 2016.[18] In this study, enclosed with the review by Masotti *et al.*, 90-day stroke recurrence, intracranial bleeding and all-cause mortality were 1%, 0% and 3% respectively. In the study by Moroni *et al*. median mRS at hospital discharge and after 90-day in patients receiving DOACs was 3 (1-4) and 2 (1-3), respectively. In patients not receiving DOACs mRS at hospital discharge and after 90-day was 5 (4-5) and 5 (4-6), respectively. 90-day all-cause mortality in patients not receiving DOACs was 57.1%. Age, severe neurological sequelae and renal impairment were associated with failure to prescribe DOACs.[18] Similar results were found by Deguchi *et al*. who found that warfarin use at admission, higher mRS score and renal impairment were associated with failure to prescribe DOACs.[28] In the study by Moroni *et al*. it was observed that the delay in DOACs introduction was associated with infarct size. In fact, patients with small stroke received DOACs with a delay of 3.2±2.2 days, those with a medium stroke received DOACs after 5.2±3.3 days, and those with a large stroke received DOACs after 6.4±2.9 days. Moreover, the delay of DOACs starting was associated with NIHSS score. Patients with NIHSS scores <8 received DOACs with a delay of 4.1±3.1 days, those with NIHSS scores in the range 8-16 with a delay of 6.7±3.7 days, and the delay for patients with NIHSS scores >16 was 6.5±3.8 days[18]). Similar results were found by Deguchi *et al*.[29] in the SAMURAI Study in which the delay of DOACs introduction was associated with severity of stroke and by Macha *et al*. who found that the delay in DOACs starting time was associated with infarct size and localization.[30] Of note

Table 6. 90-day prognosis in patients with non-valvular atrial fibrillation related acute ischemic stroke according to different antithrombotic treatment.

	Number	Age (years)	Median NIHSS score Median (IQR)	90-day stroke recurrence	90-day intracranial bleeding	90-day all-cause mortality
VISTA Registry (no antithrombotics)	182	77.1±9.0	16 (11-21)	19.8%	9.3%	40.7%
VISTA Registry (antiplatelets)	162	75.8±10.0	15 (11-19)	8.6%	1.9%	27.8%
VISTA Registry (anticoagulants)	518	73.4±10.1	14 (10-18)	10.6%	2.9%	25.5%
RAF study (anticoagulants)	766	77.2±9.5	6 (3-12.5)	6.4%	5.4%	NR
Real life studies with DOACs pooled	2187	73.5±13-82.1±8 (range)	2-8 (range)	2.3%	0.9%	1.5%

NIHSS, National Institute of Heath Stroke scale; IQR, interquartile range; NR, not reported.

Macha *et al*. found that the delay of DOACs starting time progressively increased whether patients had TIA, non-extensive supratentorial infarct, infratentorial infarct or extensive supratentorial infarct, respectively.[30] More interestingly, in the RAF-NOACs study Paciaroni *et al*. found a 5.2% 90-day incidence of the composite endpoint TIA/stroke recurrence, systemic embolism and major intracranial and extracranial bleeding compared to 12.6% in the RAF study. The best temporal window associated with lower risk of the composite endpoint was between 3 and 14 days from stroke onset, while starting DOACs within 48 h or after 14 days was associated with a 12.4 and 9.1% 90-day incidence of the composite endpoint, respectively.[10,19]

Consequently, based on available literature evidence and recommendations, it could be speculated about the fact that patients with small supratentorial infarct size, mild stroke severity (NIHSS score <8) and low HT risk could start anticoagulation close to third-fourth day, while patients with large supratentorial infarct size or infratentorial infarct, serious stroke severity (NIHSS score >16) and high HT risk could start anticoagulation close to fourteenth day. Patients with medium infarct size, mild stroke severity (NIHSS 8-16) and low HT risk could start anticoagulation between 6 and 10 days from stroke onset. It should be remarked that in the RAF study, patients with high CHA_2DS_2-VASC score and moderate-severe left atrial enlargement were at higher risk of composite endpoint TIA/stroke recurrence and HT, whereas patients receiving bridging therapy with low molecular weight heparins were at higher risk of HT. Therefore, additional factors other than infarct size and NIHSS score should be taken into account when deciding about DOACs starting time. Table 8 summarizes variables favoring the choice to early starting (within one week) of DOACs in NVAF-related AIS.

Table 7. The ALESSA score.

Variable	Score
Age ≥80 years	2
Age 70-79 years	1
Infarct size >1.5 cm	1
Severe left atrial enlargement	1

Conclusions

Anticoagulation represents the best choice for secondary prevention in patients suffering from NVAF-related AIS. The optimal timing for starting anticoagulation in this context remains unclear despite the RAF study showed that starting anticoagulation within the 4 to 14 days temporal window from stroke onset is associated with lower risk of stroke recurrence and/or HT.[10] Awaiting findings from ongoing prospective RCTs on DOACs introduced in the early phase of NVAF-related AIS, the real life evidence suggests that starting DOACs in this context seems safer and associated with lower stroke recurrence and all-cause mortality risk compared to traditional treatment.

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Table 8. Pros and cons for early (within 7 days) introduction of direct oral anticoagulant.

Pros	Cons
TIA	Moderate-large infarct size
Small infarct size	NIHSS score ≥8
NIHSS score <8	mRS ≥4
mRS score ≤3	PH1 HT
Any HT absent	PH2 HT
CHA_2DS_2-VASC ≥4	CHA_2DS_2-VASC <4
Moderate-severe left atrial enlargement	Left atrial enlargement absent

To be considered as adjunctive factors to delay DOACs starting time:
- Neurological instability
- Need for gastrostomy or other surgical procedures
- Need for carotid surgery
- Uncontrolled blood hypertension
- Infratentorial localization
- Age ≥85 years

TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke scale; mRS, modified Rankin scale; PH, parenchymal hematoma; HT, hemorrhagic transformation; DOACs, direct oral anticoagulants.

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