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Review Article

Acute Ischemic Stroke Due to Anticoagulation Failure: New Challenging Issues in the DOACs Era

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ABSTRACT

Primary and secondary prevention of cardio embolic stroke is a key issue in Neurological and Cardiological clinical practice. Anticoagulation proved to be clearly effective, both with Vitamin K Anticoagulants and in the last years with Direct Oral Anticoagulants, in preventing acute ischemic stroke. The proportion of patients prescribed with these drugs is constantly rising in the last decades. However, the occurrence of an anticoagulation failure is responsible for a relevant and increasing proportion of ischemic strokes. In fact, those patients have a different and peculiar risk factors profile, require a more extensive diagnostic work-up to clarify stroke etiopathogenesis and need physicians to pay more attention to drug-to-drug and food-to-drug interactions. Moreover, reperfusion therapies are allowed only under specific conditions. The aim of this paper is to review the available evidence around acute ischemic strokes due to anticoagulation failure and to discuss their main clinical management issues. We draw attention on the need for a more widespread anticoagulation monitoring also with DOACs and to the growing evidence of their drug and food interactions. Data showed herein mean to be a useful and easy clinical guide in this subset of acute ischemic strokes.

Keywords: Anticoagulation failure; DOACs; VKAs; Acute ischemic stroke; Stroke etiopathogenesis

INTRODUCTION

Prevention of cardio embolic ischemic stroke is a key issue in the field of vascular diseases. Both Cardiologists, in the setting of a "cerebrovascular primary prevention" of Atrial Fibrillation (AF) patients, and Neurologists establishing "secondary stroke prevention" are involved.

Recent improvements in diagnostic protocols and in Acute Ischemic Stroke (AIS) management have been raising the proportion of patients with a recognized cardio embolic mechanism [1]. Surveys of stroke patients' treatment regimens demonstrate that anticoagulant therapy prescription has been increasing across time in the last decades [2,3]. Consequently, although the occurrence of an ischemic stroke in patients under anticoagulant therapy considering altogether both First Ever Ischemic Stroke (FEIS) and Recurrent Ischemic Stroke (RIS) accounted for a minor proportion (2.5 to 10% of all AIS) [4,5], this proportion is expected to be higher nowadays and to raise even more in the upcoming years.

Multiple and heterogenous factors have been considered to explain an anticoagulation failure, often making difficult to distinguish between an apparent and a true one: patients' adequate compliance, other drugs interference, multiple coexisting stroke mechanisms and risk factors, powerful incidental stroke triggers [6,7], etc. After a long-lasting experience with Vitamin K Anticoagulants (VKAs) in cardio embolic stroke, the Direct Oral Anticoagulants (DOACs) era was welcomed with the hope of a safer and more effective prevention treatment, which furthermore will have substantially pushed away the need of clinical and laboratory monitoring. However, ischemic strokes under DOACs still occur and reasons for anticoagulation failure are not yet completely understood. The COVID-19 pandemic is shedding new lights on the additional role of acute inflammatory triggers of vascular damage and on mechanisms of acquired transient coagulopathy, possibly independent of anticoagulation or overstepping its efficacy.

The aim of this review is to synthetize and discusses the reasons of anticoagulation failure in ischemic stroke, the new issues emerging around anticoagulation failure after DOACs approval. The boundaries of the same concept of "anticoagulation failure" are discussed as well as the increasing demand for laboratory monitoring of DOACs.

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METHODS

Two reviewers (FJ and FK) independently searched for articles in several electronic resources: CINAHL Complete, EBM. ACP Journal club, EBM. Cochrane central register of controlled trials, EBM. Cochrane clinical answers, EBM. Cochrane database of systematic reviews, EBM. Cochrane methodology register, EBM. Database of abstracts of reviews of effects: DARE, EBM. Health technology assessment, EBM. NHS economic evaluation database, Ebook collection EBSCOhost, Elsevier ScienceDirect, Journal Citation Reports, JSTOR: Journal Storage Project, Nursing Reference Center Plus, Ovid Clinical Edge, ProQuest Ebook Central, PubMed/MEDLINE, Scopus, Social Science Research Network (SSRN), Springer Standard Collection (SpringerLink), Web of Science, Wiley Online Library, Zenodo. Search entry terms were: "anticoagulation failure"; "stroke and anticoagulation"; "stroke despite anticoagulation"; "first-ever ischemic stroke and anticoagulation"; "primary stroke prevention in atrial fibrillation"; "secondary stroke prevention in atrial fibrillation". The abstracts of the articles have been screened and then selected according to the following inclusion criteria: i. RCT and case series; ii. Papers in English only; iii. articles dealing with ischemic stroke occurring in anticoagulated patients, regardless of the primary aim of the study if the presented data were significantly related to anticoagulation failure; iv. Articles published in peer-reviewed journal only. At the same time the following exclusion criteria were applied: i. papers without complete data; ii. Papers discussing hemorrhagic anticoagulation adverse events only; iii. Case reports, unless of peculiar interest for the topic. The final selected papers with a disagreement between the two reviewers have been discussed together with the other Authors.

Anticoagulation failure in the DOACs era

The following paragraphs cover the so far available evidence on the main raising issues in anticoagulation failure after the DOACs massive inflow into clinical practice. We will not deal with comorbidities that prolong DOACs half-life and consequently increase bleeding risk, such as renal and liver failure. Similarly, we will not go into details of more infrequent stroke etiologies such as anti-phospholipid syndrome, cancer related stroke and latent inherited mutations causing thrombophilia [8-10].

Clinical features of FEIS in anti-coagulated patients

Few data are available on FEIS in Non-Valvular Atrial Fibrillation (NVAF) anti-coagulated patients. A large retrospective clinical study based on data from the China National Stroke Registry published in 2014 assessed that pre-stroke warfarin therapy is associated with a significant reduction of initial stroke severity: major stroke risk was reduced by 32% [11]. Interestingly, also patients with subtherapeutic INR had less severe FEIS. Other interesting clinical features were highlighted by this study: pre-stroke antihypertensive treatment, hyperlipidemia? And good education was correlated with less severe strokes. Speaking of DOACs in the subset of stroke primary prevention in AF patients the American College of Cardiology Foundation recently claimed that oral anticoagulation reduces the risk of stroke by 60% to 80% compared with no anticoagulation, and more specifically that DOACs significantly reduce the risk of stroke by 19% compared with warfarin and reduce hemorrhagic stroke by 50% [12].

Mazurek et al reported in a large cohort of AF patients in primary prevention (44.5% treated with anticoagulation) a stroke rate at 1 year of 0.8% in guideline-adherent and 3.1% in undertreated subjects, compared to a stroke rate in a secondary prevention group of 5.4% and 9.4% respectively. Authors do not provide any clinical feature of their FEIS [13]. Purrucker et al. analyzed in detail the etiologies underling AIS occurring in consecutive stroke patients with known AF and on oral anticoagulation: approximately 2/3 of the 341 patients included in the final analysis were FEIS, the others being RIS; 63% of the whole cohort was taking DOACs. In summary, they found other potential or uncertain stroke etiologies in 70.8% of patients treated with DOACs and in 46.1% of patients treated with VKAs. Unfortunately, no data is available on FEIS only, as well as no clinical comparison was done with AIS not on anticoagulation [2]. Meinel et al. examined the Swiss Stroke registry and found that, compared to AIS in AF patients not taking anticoagulants, AIS in AF anticoagulated patients (78% FEIS; near 52.4% patients treated with DOACs) had higher proportion of hypertension, diabetes, and dyslipidemia, had less severe stroke at onset and a slightly better 3 months functional outcome (despite low rate of reperfusion treatment) [3].

Clinical features of RIS in anti-coagulated patients

According to a recent study, the risk of a subsequent RIS might be higher in NVAF associated stroke patients with prior anticoagulation than in those without prior anticoagulation. In detail, developing AIS under anticoagulation may be itself a risk factor for RIS, with a cumulative incidence of 5.3% for RIS with prior anticoagulation versus 2.9% for RIS without prior anticoagulation [6]. Many underlying mechanisms could explain this relationship: (1) suboptimal drug adherence, which seems to be the main one, above all in VKAs patients [13-15]; (2) other drug management pitfalls, like inappropriate cessation and inappropriate dosing [7,14]; (3) patients with NVAF and severe atrial fibrosis, at higher vascular risk [16]; (4) underlying competing stroke risk factors and stroke etiologies besides AF, like large artery atherosclerosis and small vessel disease [15], in which hypertension, hypercholesterolemia, diabetes, kidney failure, etc. seem to be more frequent and to promote prothrombotic state; (5) subjective variability of anticoagulants' activity, such as CYP2C9 and VKORC1 gene mutations playing a role in patient response to VKAs or peculiar DOACs pharmacokinetics [15].

In the study conducted by Rizos et al. on AIS and Transient Ischemic Attack (TIA), 8.7% of patients admitted along a 2-year period were found to be on VKAs. Only about one third of patients were confirmed to be RIS and their proportion was significantly higher in anti-coagulated stroke (36.5% vs. 23.0%). Cardiovascular risk factors – congestive heart failure, arterial hypertension, and diabetes – were more prevalent in the anti-coagulated group. Although Authors did not provide distinct data between FEIS and RIS, prior stroke proved an independent predictor of bad outcome at 3 months [4]. In a more recent study, exploring the effect of prior anticoagulation, both with DOACs and VKAs, on the clinical outcome of AISs or TIAs in NVAF [17], the proportion of RIS was even higher among the anticoagulated patients (50% in the DOACs group, 43% in the AVKs group and 18% in the control one). Differently from the study by Rizos, prior warfarin treatment was associated with a lower risk of death or disability at 3 months, but not after 2 years follow-up: prior OAC treatment was

associated with a higher risk of RIS at 2 years even after adjusting for CHA2DS2-VASc score, leading to the assumption that anti-coagulated patients might have other risk factors for ischemic events, not adequately treated with anticoagulation.

VKAs and DOACs in the neurological setting: Effectiveness and cost-effectiveness ratio

The DOACs approval in the last years represented an alternative to VKAs in stroke primary and secondary prevention. As a new option, the advantages of DOACs are a similar or better effectiveness, more stable kinetics, they are less burdened with hemorrhagic side effects, they seem to have fewer drugs or dietary interactions; moreover, their rates of persistence and patients' compliance are higher than with VKA, mainly due to the unneeded regular coagulation monitoring [18]. Some uncertainties about the cost-effectiveness comparison between the two classes of drugs might raise considering partial information, such as drug cost itself or the positive relationship between good vascular outcome and VKAs patients with high Time in Therapeutic Range (TTR). However, considering altogether direct and indirect costs (drug itself, drug management, coagulation monitoring, hospitalization and care costs resulting from both bleeding and thromboembolic events) DOACs proved overall less expensive than VKAs [19].

VKAs and DOACs in the neurological setting: Drugs and dietary interferences

Drugs, herbal medicines, and food interactions affecting warfarin and acenocumarol are several and well known, due to inhibition of the expression and/or activity of CYP450 enzymes, which is involved in their metabolism, or to drugs' modifications within the gastrointestinal environment, or to direct vitamin K dietary intake. Dabigatran, instead, is not metabolized by CYP450 and factor Xa inhibitors are sensitive to strong CYP3A4 inhibitors only. This is the main reason why DOACs display less common and clinically relevant drug-drug interactions. However, they are substrate for P-glycoprotein 1 (P-gp); thus, several antibiotics and some other medications significantly modify their plasmatic concentrations. Some of those drugs are commonly used in cardio and cerebrovascular settings or in neurological patients. Verapamil, Amiodarone and Digoxin are strong P-gp inhibitors, which could increase DOACs plasmatic levels and consequently patient's hemorrhagic risk, while Carbamazepine, Fenobarbital and Phenytoin are P-gp and CYP3A4 inducers, which decrease DOACs plasmatic levels and could lead on the contrary to a higher thromboembolic risk. Oxcarbazepine, Topiramate and Valproic Acid are weaker P-gp inducers [20,21], likely with little interferences with DOACs plasmatic levels. New antiepileptic drugs such as Perampanel, Brivaracetam and Lacosamide seem to show no relevant CYP3A4 and/or P-gp interactions [21,22]. Proton Pump Inhibitors, another class of medications very frequently used in the neurological setting, reduce the absorption of Dabigatran up to 30%, although with unclear clinical relevance [23]. There is no evidence for other pharmacokinetic effect of PPI and other DOACs coadministration. In addition, clinical data suggest that PPIs significantly reduce gastrointestinal bleeding in DOACs patients' follow-up [24]. The use of prednisone, another CYP3A4 inducer, could decrease DOACs levels, and a recent survey found that it is non-infrequently used in AF patients [25].

The list of foods and herbal medicines that interfere with DOACs plasmatic levels is growing. Some of them are P-gp activity inhibitors, including Gingko Biloba, Curcumin, Green tea, Capsaicin, Black pepper; on the contrary, Genipin, Quercetin and molecules in Mango and Soy milk are P-gp inducers [23]. Although the clinical relevance of these interactions is still debated, it is important to take into consideration the nutraceutical intake and dietary habits in patient's medical history of VKAs patients, as well as of DOACs ones.

VKAs monitoring and DOACs plasmatic levels

Traditionally, coagulation monitoring with VKAs is well documented and does not represent a novelty or a debated issue in stroke unit management. Both bleeding and thromboembolic risk clearly depend on the International Normalized Ratio (INR) being within a target range [10]. The rate of ischemic stroke in patients with INR<2.0 rapidly increase from 2% to 8% per patient-year while approaching to INR 1.0. A minority – although relevant – proportion of patients experience ischemic stroke despite INR>3.0 [18], mainly due to other concurrent vascular risk and trigger factors.

The emerging parallel scenario in DOACs treated patients is nowadays less clear. Three main reasons of uncertainty are: 1. The inaccurate assessment of their anticoagulation effect with the routine coagulation assays (PT, aPTT), 2. The lack of routine recommendations for coagulation monitoring in those patients, and 3. Clear evidence-based therapeutic ranges for DOACs are still lacking.

Acute thromboembolic events are included in specific emergent indications in which DOACs activity measurement is desirable (such as acute bleeding and before surgical procedures) [26,27]. However, despite the growing proportion of patients treated with DOACs, still nowadays laboratory measurements are not widespread in acute stroke management, often perceived of interest only to include/exclude patients from reperfusion therapies [27]. In this specific emergent circumstance (as detailed further in this paper), a hemostatic safety threshold of $\leq$ 30 ng/ml has been proposed to safely administer fibrinolytic drugs [26], which raises up to 50 ng/ml in other case series and becomes even as higher as 100 ng/ml in selected patients [28-30]. These discrepancies reveal the need of establishing evidence-based standard references in the AIS setting. Low plasma through levels of DOACs proved to predict a higher risk of early RIS in a cohort of 397 patients. Plasma trough levels in some patients with early RIS were as high as 100 ng/ml [31]. In a retrospective analysis of 292 heterogeneous patients treated with DOACs, approximately 28% of them showed plasma levels out of range [32]. Interestingly, the proportion of patients below the expected levels rose from 1.7% in bleeding subset to 11.8% in routine monitoring outpatients, to increase up to 13.5% in breakthrough thrombosis patients. In a case-control study of DOACs treated patients, Nosal et al. recently showed that the 43 FEIS they enrolled had significantly lower levels compared to controls [33]. Noteworthy is that, in both studies, AIS was associated with higher plasma trough levels in patients treated with Apixaban (mean around 70 ng/ml) than with other DOACs (mean around 40 ng/ml) [31,33]. In 177 AIS with plasma levels of DOACS available, Macha et al. (2019) demonstrated that admission NIHSS was inversely correlated with plasma levels

themselves [29]. In summary, there is mounting evidence that several patients treated with DOACs have low plasma levels and that they are at higher risk of AIS, both in primary and secondary stroke prevention. Consequently, the extension of DOACs monitoring to cerebrovascular prevention strategies, beyond the emergent decision on reperfusion therapy, seems to be indicated in a significant proportion of patients.

Reperfusion therapies in anti-coagulated patients

As stated in 2019's update of American Guidelines (AHA/ASA) for the early management of patients with AIS, patients on VKA are eligible for Intra Venous Thrombolysis (IVT) if they present within the 4.5 hours' time window and their INR is $\leq$ 1.70 [34]. Case series suggest that Prothrombin Complex Concentrates (PCC) could be used to reverse the effect of VKAs in patients who are eligible for IVT and have INR>1.7, but the PCC can lead to a worsening of patients' neurological deficits as it might enhance coagulation. For this reason, the European Stroke Organization (ESO) 2020's guidelines do not recommend this practice. On the contrary, oral anticoagulation was not a contraindication to Mechanical Thrombectomy (MT) in randomized controlled trials, regardless the range of anticoagulation. ESO 2020's guidelines claims that MT appears to be safe in patients with AIS who have been pre-treated with VKA and with INR >1.7 [35].

Although data from randomized clinical trials are lacking, there is an increasing attention on reperfusion therapy in patients on DOACs treatment. We know that current major stroke guidelines recommend against routine IVT within 48 hours of a DOAC intake, unless specific DOAC coagulation assays are performed [28]. Meinel et al. analyzed several aspects of prior anticoagulation in patients with AIS and AF and illustrate the reasons leading to withhold IVT in DOACs patients: the most frequent reason was a high DOACs plasma level, followed by stroke-related reasons with unclear risk-benefit and the unavailability of DOAC measurement [3]. Evidence from case series suggests that plasma DOAC levels of 20-50 ng/mL was shown to be safe for IVT therapy, while IVT with DOAC levels of 50-100 ng/mL should be taken into consideration only after careful risk/benefit assessment; it should be instead withheld in patients with levels >100 ng/mL [28]. Moreover, a systematic meta-analysis of available reports revealed that 366 DOACs patients have been treated with IVT within 48 hours from the last drug dose (53% below 24 hours), without previous reversal agents, without plasmatic specific dosages and without an increased rate of sICH [36]. So far, further studies are desirable to determine IVT feasibility early after DOACs last dose, but early treatment seams safe at least in selected patients and a Japanese consensus guide states that IVT is allowed if the time span from the last dose of DOACs exceeds 4 hours [37]. Few data are available about IVT preceded by pretreatment with DOACs reversal agents: an increased risk of sICH transformation and early mortality with Idaracizumab (approved by FDA and EMA for Dabigatran) was observed [36]. Evidence for andexanet alpha (approved for rivaroxaban or apixaban) is even more limited and unconclusive. AHA/ASA guidelines do not currently recommend administration of reversal agents to perform IVT in patients with ischemic stroke on DOACs [34]. Some observational cohort studies provide evidence that MT in DOACs patients with LVO has the same rates and safety outcomes compared to patients on VKAs and with no anticoagulation therapy [28]. A meta-analysis of data from 4 RCT suggests similar safety and outcomes between patients treated with or without IVT prior to EVT, supporting the concept of bypassing IVT when MT can be started immediately [38].

DOACs switch when anticoagulant failure

There is no clear evidence in Literature of the benefit – in terms of RIS prevention – of switching anticoagulation drug [28]. In the IAC study, switching anticoagulant class in AIS patients with NVAF was not associated with a reduced risk of recurrent events [14]. The same was observed as well by Seiffge et al. These authors suggest that this issue might deserve further prospective investigation in larger study populations [15]. A recent survey among US neurologists, most of them also trained in vascular diseases, revealed a very heterogenous behavior, while dealing with AIS occurring during anticoagulation: 38% of them routinely switched between agents, 42% did not and 20% added an antiplatelet agent [39]. However, in the absence of evidence-based guidelines, the current practical approach is limited: 1. to adjust the DOAC dose in case of failure if this was inappropriately low, or 2. to change to a different DOAC, if failure occurred in appropriately dosed DOAC but with low plasmatic levels [27]. However, other suggestions, like to check for other stroke mechanisms and triggers, to improve the management of risk factors, to consider drugs and herbal medicine pharmacokinetic interactions, and finally to monitor DOACs levels in patients at risk for AIS (both in primary and secondary prevention setting) seem to have at least the same relevance.

Reasons for anticoagulation failure

The most common reason for anticoagulation failure seems to be the occurrence of treatment management errors. Wong et al. reported that anticoagulation errors of prescription or compliance are as high as 41% in a cohort of AIS and NVAF patients. These issues were almost equally frequent with VKAs and DOACs in their study [7]. Purrucker et al. also found a high proportion of prescription errors, but this was higher in VKAs (63.8%) than in DOACs group (49.8%) [2]. This data, however, highlight the importance of distinguishing between an "apparent anticoagulation failure" (i.e., scarce patient's compliance, drug interruption for surgery or invasive procedures and subtherapeutic dose prescription) and a "true anticoagulation failure" (i.e., other competing stroke mechanisms, drug-drug interactions, and incidental metabolic interferences). The boundary between the two seems much more indefinite among DOACs patients than among VKAs ones, due to the low level of diffusion of laboratory monitoring. The 95% of Purrucker's patients undergoing AIS despite "effective" anticoagulation had at least one additional (though only potential or uncertain) cause of AIS, suggesting the need for a more accurate diagnostic work-up to adequate/individualize medical prevention treatment [2]. Table 1 summarizes the possible mechanisms of anticoagulation failure and outlines the optional additional examinations required to demonstrate and treat them.

Table 1: Reasons for VKAs and DOACs failure in acute stroke patients.

		Possible mechanism	Options in the work-up strategy
Apparent Failure	Patient's scarce compliance		Detailed medical history Coagulation monitoring
	Anticoagulant suspension for surgical/invasive procedures		
	Subtherapeutic dose		
True Failure	Concurrent interfering drugs/herbal medicines/foods	P-gp inducers CYP3A4 inducers	
	Other competing stroke mechanism	Aortic arch atheroma and large artery disease Small vessel disease Paradoxical embolism (PFO) Procoagulant state overcoming coagulation effect/independent from coagulation cascade mechanism Thrombophilia (defect of protein C, S, ATIII, Leiden, MTHFR) Antiphospholipid syndrome Vasculitis	Focus medical history on stroke triggers (infections, known/occult cancer) Vascular imaging (including lower limbs) Brain MRI TT and TE echocardiography TCD Coagulation and immunological testing
	Incidental transient comorbidities	Renal failure Liver failure	Laboratory testing

Lessons from COVID-19

The COVID-19 ongoing pandemic is revealing as a new challenging clinical scenario in the stroke field. The infection proved to be both a cause of AIS, in those cases that developed a clear pro coagulant state, and a trigger factor, in those patients with several vascular risk factors already present. COVID-19 infection has also become one of the most studied diseases in the modern medicine and specific mechanisms of pro coagulant, inflammatory and endothelial damage have been progressively elucidated [40,41]. The consequences of COVID-19 infection on anti-coagulated patients have been the focus of few studies. In an uncontrolled observational series of 107 COVID-19 patients (about 2/3 mild out-patients and 1/3 moderate to severe) and previously anti-coagulated for AF or prior venous thromboembolism, Lachant and colleagues found no thrombotic complications and very low rate of hemorrhagic events [42]. They suggest that therapeutic anticoagulation might protect from COVID-19 related coagulopathy. Other Authors reported similar evidence, a low rate of thrombotic events or a better clinical outcome in COVID-19 anti-coagulated patients, thought always in small clinical series [43-45]. On the contrary, our group reported a series of AIS cases in mild to severe COVID-19 patients occurring despite therapeutic anticoagulation [46]. These data are observational in nature and come from different care settings, however, taken as a whole, might suggest that the relationship between COVID-19 and AIS is complex, with some patients taking advantage of oral anticoagulation and some other patients in which it is insufficient to protect them from stroke risk.

DOACs plasmatic levels have been also studied in COVID-19 patients exclusively regarding the possible drug-to-drug interactions. Among 33 patients, Potere et al. indicate that dexamethasone (CYP3A4 and P-gp inducer) treatment did not significantly affect DOACs levels [47]. Interestingly, Authors report that among the 33% of patients with peak DOACs levels below the expected reference range, 2/3 of them had low levels even off-dexamethasone. Other Authors reported that co-treatment with antiviral drugs (lopinavir, ritonavir or darunavir) in COVID-19 patients increased c-trough levels of DOACs up to 6 times and they make them at higher bleeding risk [48]. Apart from pharmacokinetic interferences with specific treatment used in COVID-19, these data suggest that a substantial proportion of patients with DOACs might be unprotected despite adequate dosage, lending additional complexity to the relationship between COVID-19 and AIS.

DISCUSSION

We have herein discussed the main issues while dealing with AIS despite anticoagulation. The same "anticoagulation failure" definition seems the first and starting issue, disclosing some uncertainties across Literature, which is even more complicated since almost all the available studies, mixed VKAs and DOACs patients. In our opinion, a distinction between an "apparent" and a "true failure" might be relevant, as summarized in Table 1. All these patients need an additional effort to unveil the etiopathogenetic factors of their AIS, but this might be more relevant in "true failure" ones. Moreover, the role of concurrent, transient stroke triggers or risk factors is also an unsolved issue. In this perspective, the lessons of the increasing Literature on AIS and COVID-19 infection, is likely to prompt new studies on the role of acute infections. To our knowledge, there is no clear epidemiological data establishing the occurrence of stroke triggers in acute stroke setting and we do not still know how unusual or frequent they might be.

The second relevant issue is the low availability of DOACs plasmatic levels, and the lack of references values tailored on AIS prevention. The need for them is increasing not only in the hyper acute setting – i.e., for including/excluding patients in/from reperfusion treatments – but also in monitoring at least some chronic cerebrovascular patients. The prevalence of drug-to-drug and food-to-drug interactions might be in fact higher than previously thought even in DOACs patients. The occurrence

of other stroke risk factors is also to be considered, above all in those patients with DOACs therapy with plasma trough and peak levels within therapeutic range: some of their risk factors could be potentially better treated with anti-platelets drugs.

Thus, from the neurovascular perspective, future research should focus on efficacy reference values for DOACs with the dual aim of 1. Including some DOACs failure in intravenous thrombolytic ischemic stroke treatment 2. Establishing reference values for ischemic stroke prevention. Studies aiming at establishing the efficacy of switching between different anticoagulants and characterizing patients with a favorable risk/benefit for dual anticoagulant and antiplatelet therapy are desirable as well.

Finally, the suggestions herein reported should be considered with caution according to the low level of evidence of most of the studies available on this topic.

CONCLUSION

Anticoagulation failure is a peculiar subset of acute ischemic stroke, which need additional work-up and clinical attention. The introduction of DOACs in vascular prevention regimens brought unquestionable improvements in patient's management and safety and this is practically demonstrated by the constantly rising proportion of patients treated with those drugs. However, among other uncertainties, plasmatic dosages of DOACs should become accessible routinely, both in acute setting and in patients' follow-up, not only to allow/exclude patients from reperfusion therapies, but also to unveil undertreated or resistant patients in which stroke might be related to other mechanisms or emerging drug-to-drug and food-to-drug interactions could occur.

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