

## Challenges of antithrombotic treatment after embolic stroke - case presentation

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### ABSTRACT

Atrial fibrillation (AF) represents one of the most common preventable causes of stroke, conferring a fivefold increased risk of stroke. The risk of stroke caused by AF is underestimated, many AF episodes being asymptomatic. Embolic strokes caused by AF can be prevented using anticoagulant therapy. The ESC (European Society of Cardiology) guidelines for patients with AF recommend anticoagulant therapy if the risk for embolic stroke / systemic embolism, evaluated with the CHA2DS2-VASc score, is high. Bleeding is the major complication of anticoagulant therapy. For every patient taking anticoagulant medication, HAS-BLED score assessing the risk of bleeding needs to be performed. The priorities in treating patients with atrial fibrillation are protection against embolic events and minimal risk of hemorrhagic events. Vitamin K antagonists, despite their accessibility and long term use, have important limitations. New/direct oral anticoagulants are better options, with at least identical efficacy and higher safety profile. In real life, the choice of the appropriate anticoagulant agent could be challenging.

**KEY WORDS:** atrial fibrillation, embolic stroke, anticoagulant treatment

**Introduction.** Ischemic strokes represents 80-90% of all strokes, and have a tendency to increase their incidence in our country. Among ischemic strokes subtypes, 20% are embolic, being caused mainly by cardiac sources of embolism - mostly by atrial fibrillation. In 25% of ischemic strokes, despite extensive investigation, the etiology remains unknown – this group is called “cryptogenic stroke”. In the last years, there is persuasive evidence that the majority of cryptogenic strokes are thromboembolic [1].

Atrial fibrillation (AF) represents one of the most common preventable causes of stroke, conferring a fivefold increased risk of stroke, meaning a 4,5% annual risk for stroke [2]. Prevalence of AF is increasing, due to ageing of population. In ATRIA study, prevalence of AF was 0,1% in persons under 55 years of age, but 9% in persons aged over 80 years [3]. In a separate registry for embolic strokes of undetermined source (called ESUS), 30% of all ischemic strokes were attributable to AF [4]. The risk of

stroke caused by AF is underestimated, many AF episodes being asymptomatic.

AF-related ischaemic strokes also tend to be more severe than atherothrombotic strokes [5] with 2 fold increase in mortality rates [6] and greater disability (more severe motor deficit or aphasia) [7],[8].

Embolic strokes caused by AF can be prevented using anticoagulant therapy. Use of vitamin K antagonists (VKA) such as warfarin or acenocumarol, decrease with 70% the incidence of embolic strokes and with 25% the death rate in this group of patients [9]. Irrespective of which drugs are used, the overall impact of anticoagulation on AF-related ischaemic events at the population level has probably been small due to widespread under-treatment, particularly in the elderly [2].

The ESC (European Society of Cardiology) guidelines for patients with AF recommend anticoagulant therapy if the risk for embolic stroke and systemic embolism is high. This risk is evaluated using a standardized score – the CHA2DS2-VASc

score [10], [11]. For patients with 1 pt score, anticoagulation may be considered, but for AF patients with score  $\geq 2$ , anticoagulation is mandatory.

Treatment with anticoagulants reduces significantly the risk of ischemic stroke, but also increases the risk for bleeding. Bleeding is the major complication of anticoagulant therapy. The major determinants of vitamin K antagonist-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy [12].

The criteria for defining the severity of bleeding varies considerably between studies. Bleeding complications are categorized as minor or major depending on their severity. According to ISTH (International Society on Thrombosis and Hemostasis) criteria for major bleeding in non-surgical patients are: criteria for major bleeding in non-surgical patients are: (a) fatal bleeding, and/or (b) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or (c) bleeding causing a fall in hemoglobin level of 2 mg/dl or more, or leading to transfusion of two or more units of whole blood or red cells [13]. Minor bleedings, such as skin bruises or nosebleeds, occur annually in 6–10% of patients on VKAs and major bleedings, including (fatal) intra-organ bleeds, occur in 1–3% of VKA treated patients per year [14].

For every patient taking anticoagulant medication, another score, assessing the risk of bleeding has to be performed: the HAS-BLED score [15].

Vitamin K antagonists, despite their accessibility and long term use, have maintained some important limitations: unpredictable response at the same dose, narrow therapeutic window (INR between 2 and 3), frequent dose adjustments required, routine INR monitoring, food and drug interactions, slow onset of effect and long

persistence of effect after treatment interruption.

The priorities in treating patients with atrial fibrillation are protection against embolic events – like ischemic stroke and decreasing the risk of hemorrhagic events due to treatment. At this point, patient's and doctor's priorities could be different. The doctors fear mostly of the bleeding complications, but the patients fear mostly post-stroke disabilities, which are perceived as being worse than death.

This bleeding risk associated with anticoagulant therapy is, probably, the most important factor for under-treatment of the patients with atrial fibrillation. Most ischemic strokes occur in patients which are not receiving correct or therapeutical anticoagulation. In a very recent observational study including 94.474 patients with acute ischemic stroke and known history of AF, 8.8% were receiving non-vitamin K antagonist oral anticoagulants (NOACs) and only 7.6% were receiving therapeutic warfarin (INR  $\geq 2$ ) preceding the stroke. Surprisingly, 83.6% of patients were not receiving therapeutic anticoagulation: 13.5% had subtherapeutic warfarin anticoagulation (INR  $< 2$ ) at the time of stroke, 39.9% were receiving antiplatelet therapy only, and 30.3% were not receiving any antithrombotic treatment. Therapeutic anticoagulation was associated with lower odds of moderate or severe stroke and lower odds of in-hospital mortality [16].

The choice of an anticoagulant agent represents a challenge in some situations. Data from the literature and the 2016 ESC guidelines recommend the use of a new/direct oral anticoagulant instead the use of vitamin K antagonists. New oral anticoagulants, or direct oral anticoagulants are better options than VKAs, having at least a non-inferior therapeutic effect comparative to warfarin, and a clear safety profile, especially by decreasing the incidence of intracranial bleeds. NOACs have a rapid onset of action and a reduced half-life, have a predictable and constant therapeutic effect,

have no food and lesser drug interactions. There is no need for routine INR monitoring.

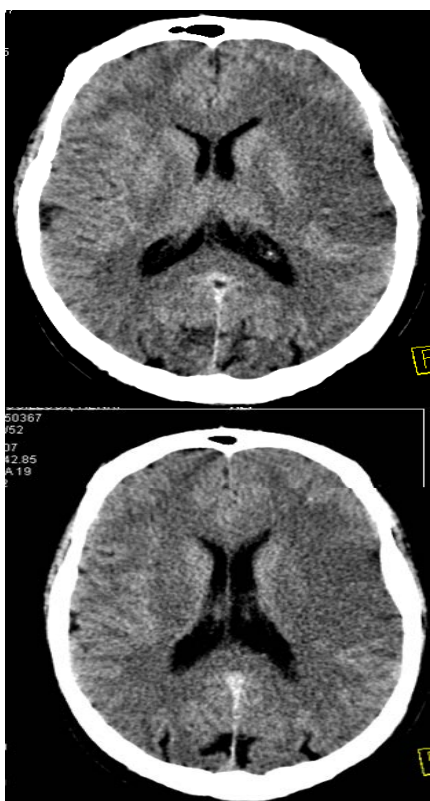
In many situations, the choice of an anticoagulant agent is individualized, depending on patient and drug characteristics, and, in our country, on patient economical status. Choosing optimal anticoagulant treatment could be challenging even in simple clinical situations.

**Case presentation.** We present the case of a 69-year old male, retired farmer, which complains suddenly at awakening in the morning, of right side weakness and language troubles. The patient is right-handed, and his medical history include treated arterial hypertension. His previous medication is perindopril, 5 mg qid. Arriving in the Emergency department his blood pressure is 180/90 mmHg, his heart rate was arrhythmic; neurological examination founds right hemiparesis of moderate intensity and mild Broca aphasia. His NIHSS score is 10 points. An emergency CT scan reveals an ischemic lesion in the superficial territory of the left middle cerebral artery (MCA).

No thrombolysis was performed. His ECG in ED shows atrial fibrillation. The symptoms were attributed to an embolic stroke in the left MCA territory, and the patient was hospitalized in the Neurology department. Biochemical tests show BUN values of 42 mg/dl, creatinine values of 1,25 mg/dl – meaning a glomerular filtration rate (GFR) of 61 mL/min/1.73 m<sup>2</sup> indicating KDOQI stage 2 of chronic kidney disease. Also, total cholesterol level was 220 mg/dl, with LDL-cholesterol of 125 mg/dl. The other biological parameters were in normal ranges.

CHA2DS2-VASc score was 4 pts (1 pt for hypertension, 2 pts for stroke and 1 pt for age between 65 and 74 years). HAS-BLED score was 3 points (1 pt for abnormal kidney function, 1 pt for stroke and 1 pt for age >65 years). According to 2016 ESC guidelines [11], the patient has a clear indication for anticoagulant treatment.

Patient was initially treated with low dose LMWH (nadroparine), and after 7 days anticoagulant treatment was initiated with acenocumarol at 2 mg/day. INR values are shown in table 1.



INR day 1	INR day 3	INR day 5	INR day 8
1,17	2,41	3,20	6,00

The patient shows labile INR values, and his HAS-BLED score increases at 4 points. Dose of acenocumarol was reduced at 1 mg/day, and the INR values are shown in table 2.

INR day 10	INR day 12	INR day 14
2,33	1,85	1,89

Patient was discharged on day 14, with treatment recommendations of: acenocumarol 1mg/day, perindopril 5 mg/day, atorvastatin 20 mg/day. Neurologic status at discharge was recovering, with a 3/5 BMRC right hemiparesis and a mild Broca aphasia.

Three months later, patient was admitted again to the Emergency Department for a severe language trouble, persisting for 24 hours. An emergency CT scan shows increasing of the previous ischemic area in the left MCA territory, corresponding to a new ischemic lesion. Patient's ECG conforms the AF, and INR values were 1,52, below the therapeutic range. The patient was admitted again to the Neurology department, with a diagnosis of repetitive ischemic stroke with embolic mechanism in the left MCA territory, with right spastic hemiparesis (3/5 BMRC grade) and complete Broca aphasia. A Duplex sonography shows an atherosclerotic plaque on the posterior wall of his left internal carotid artery (ICA), with thrombotic risk, causing a 50% stenosis.

The therapeutic options for this case are: (1) increasing the dose of acenocumarol – with the risk of overdosing, (2) maintaining the same dose of acenocumarol and adding aspirin for atherothrombosis prevention, (3) replacing VKA with a new oral anticoagulant (NOAC) or combining NOAC with aspirin.

The 2016 ESC guidelines state that “AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR (Time in Therapeutic Range) is not well controlled despite good adherence....”[11].

Our choice and patient's choice was to switch to a NOAC. The patient has no indication for the lower dose of NOAC, so the high dose was chosen. Higher doses of NOAC have superior efficacy to warfarin in reducing embolic events, with a better safety profile in reducing bleeding events.

The 2016 ESC guidelines [11] did not recommend combinations of anticoagulants and platelet inhibitors. This combination provides little benefit in decreasing either AF-related stroke or cardiovascular events, but carries an important risk of major hemorrhage compared with either treatment alone [17].

The patient was discharged after 10 days, with anticoagulant treatment with a

NOAC at high dose, atorvastatin 40 mg/day, perindopril 5 mg/day, metoprolol 50 mg/day.

The patient and his family give their consent for publishing this clinical data.

**Conclusions.**In this particular case, the suboptimal anticoagulant treatment caused the repetition of the stroke, which carries an exacerbation of the disability level of the patient. The choice of a NOAC seems to be a better solution for this patient, but it also carries the risk of impersistence on the same agent, or the risk of lowering the dose for economic reasons of the patient. These situations could be avoided by improving communication with the patient; the patient should be aware of the embolic risk carried by atrial fibrillation and of the importance of maintaining the recommended dose. Patient should be informed of the benefices and risks of anticoagulant treatment, and should be the most reliable partner in monitoring long term anticoagulant therapy.

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