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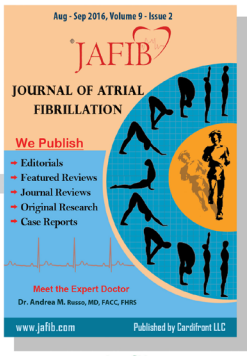

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Search For The Ideal Antithrombotic Drug: Utopian Task Likely Is Implemented Already

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Abstract

Atrial fibrillation is the most prevalent cardiac arrhythmia with a high risk of ischemic stroke. Thromboprophylaxis plays a key role in prevention of cardioembolic and non-cardioembolic events. Oral antithrombotic drugs are most often used to reduce hypercoagulable state. Patients may suffer from both under- and overtreatment compromising the outcomes. Medication peculiarities at large are well-known and widely debated. Non-adherence to antithrombotic drug regimen poses a significant risk of stroke. There is a pressing need for more detailed delineation of risk factors, namely by incorporation of the letter "N" (meaning "Non-adherence to drug therapy") into the well-known risk score alphanumeric display: CHA2DS2N-VASc. Better delineation of risk factors related to antithrombotic treatment as well as those related to treatment for congestive heart failure, hypertension, diabetes are desirable. Similarly, the bleeding risk score formula HAS-BLED might be improved by an additional risk factor, marked as the symbol "E", meaning "Excessive antithrombotic dosing" i.e. HAS-BLEDE. Improved formulas would help raise the predictive scores value and awareness for clinicians facing the problem of non-adherence to treatment regimen. If patients properly followed the prescribed drug therapy regimen it would potentially reveal that we already have ideal or near ideal antithrombotic drug(s). These drugs, herein non-specified, are widely used, but due to non-adherence they are not categorized as the best ones. That is why considerable efforts are focused on continued research and new developments.

Introduction

Atrial fibrillation (AF) affects millions of people worldwide and is one of the most common causes of stroke.[1,2] Up to 15-30% of ischemic strokes are caused by cardiac sources of emboli being associated with poor prognosis.[3] Non-paroxysmal AF is associated with a highly significant increase in thromboembolism and death.[4,5] Ischemic stroke is a heterogeneous entity with diverse causes, including lacunar infarction, cerebrovascular stenosis, and emboli of sundry types, including fat, air, atheromata, septic vegetations, and calcific debris from left-sided heart valves in addition to thromboemboli originating from variety of sources.[6,7]

Thromboprophylaxis with oral anticoagulants is the mainstay for stroke prevention, reducing the annual incidence of stroke in AF patients by more than 60%.[8] Some studies have shown that for people with AF and previous transient ischemic attack, anticoagulant use can reduce recurrent stroke by two-thirds, and all vascular events can be reduced by one-half.[9] Long-term ischemic stroke risk however, coexists in this group of patients. Thromboembolic complications are not fully preventable even by careful protection of double, triple or multiple drug therapy.[10] Any intense antithrombotic therapy, however, generates bleeding complications. Nevertheless, favorable, acceptable and even excellent clinical results might be achieved by old/conventional or novel drug therapy. In this regard collaboration and discipline from patients is much needed. We have noticed that irregular intake of antithrombotic drugs is often accompanied by the impairment of clinical outcomes in patients with AF or with other risks of ischemic events. Many patients are prone to empirical approach and to their own motivation on dosage. In general, adherence to long-term therapies in any chronic disease is poor.[11] That is why we focus on a newly emerged clinical problem medication non-adherence being associated with undue risk of clinical or subclinical ischemic events and/or hemorrhage. It deserves attention, starting by its proper identification, or in the words of Bosworth and colleagues[12] – a call for action!

Key Words:
Atrial Fibrillation, Antithrombotic Therapy, Stroke, Bleeding Complications, Risk Score Acronym, Adherence, Non-Adherence.

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None.

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Requirements for Antithrombotic Medication

The ideal antithrombotic drug should inhibit thrombosis without affecting hemostasis.[13] In terms of practical drug development for an ideal anticoagulant Kunitada and colleagues[14] pointed out three minimum requirements – oral availability, minimum bleeding propensity, and a mechanism based on direct inhibition of an activated coagulation factor. There are a number of other requirements: drugs should possess a long half life, absorbed after oral administration, provide wide therapeutic range, high degree of safety and efficacy

profile, high tolerability, predictable antithrombotic effect, devoid of side effects or regular laboratory control, fixed regular dosage, low rate of bleeding complications, little or no interaction with plasma proteins, food and other drugs, prompt partial or complete reversibility as needed during and post interventional procedure and last but not the least comprise low cost.[4,13,15] Oral anticoagulants should prevent ischemic stroke in AF, especially among patients at moderate to high risk of thromboembolic events.[10,16,17] This goal might be achieved if drugs were used regularly as prescribed.

There are controversies associated with clinical use of various drugs – antithrombotics, antiplatelet agents and/or novel oral anticoagulants.[18-21] In this analysis we will not tackle the issue of establishing ratings of specific drug(s) or identifying ideal ones. It is very likely that we already have very effective antithrombotic(s). However, a large proportion of ischemic patients are still managed in a chaotic manner by their own "strategies". It hampers accurate determination of drug capabilities and the clinical efficacy of antithrombotic drugs. Further patient education might help discourage deviation from prescribed dosage of antithrombotics.

Quality of Treatment: Problems Related to Medication Non-Adherence

In order to establish an adequate preventive strategy it is crucial to identify the cause of the embolism.[3] After a complete diagnostic workup up to 30% of strokes remain with undetermined cause, and most of them are attributed to an embolic mechanism suggesting a cardiac origin.[22]

According to Cate and other clinicians[23,24] non-adherence to medication is a potential threat to the safe use of oral anticoagulants. Consensus is that with cardiovascular medication for chronic use the non-adherence rate adds up to 50%, translating to about 125,000 deaths in the USA annually.[12,25] There are reports which postulate that as many as 40% of patients still do not adhere to their treatment regimens.[26,27] Almost 50% of chronically ill patients do not take their medication as regularly as prescribed even though it is obligatory for a successful medication therapy.[25,28] This makes non-adherence to medications one of the largest and most expensive disease categories.[29] Recently Kim and colleagues[30] have stated that a substantial proportion of patients with AF are not treated optimally including inappropriateness of antithrombotic use, especially before stroke.

Stroke patients are potentially at high risk for medication non-persistence because they require long-term therapy, are more likely to have cognitive or physical impairments, and are often depressed.[31] Obviously, we face age-related behavioral peculiarities – forgetfulness, ignorance, indifference, empirical/intuitive self-dose readjustment etc. In the absence of certain symptoms and of reason for patients' motivation, adherence drops and this may occur with novel oral anticoagulant therapy, where symptoms are absent, most apparently in AF patients.[23] It can be expected that in the management of novel anticoagulants non-adherence may reach comparable figures (± 50%) if no measures to boost adherence are being taken.[23] Our unpublished data show that this phenomenon merits further investigation.

Adherence (compliance) is the degree to which a patient follows a treatment regimen;[32] adherence requires that the prescription is obtained promptly and the drug is taken as prescribed in terms of dose, dosing interval and duration of treatment. However, only about half the people who leave a doctor's office with a prescription take the drug as directed.[32] Factors for non-adherence can be categorized into 3 major groups: socioeconomic, communication-related, and motivational.[33] Bosworth et al.[12] have indicated that multifactorial basis for non-adherence calls for multifaceted solution.

The problem of poor patient adherence has been extensively researched, but the rates of non-adherences have not changed much in the past 3 decades.[29] The AF Investigators found that, despite appropriately prescribed, and one in the three was not taking any anticoagulants at all at the time of their stroke.[34] AF patients deliberately, carelessly or occasionally fail to protect themselves from serious complications. The propensity to ignore doctor's instructions leads to the impairment of quality of treatment.

Recently Ullman[24] has stressed that adherence in AF falls into two categories. The first is physician adherence to published guidelines while the other one is the rigor with which patients follow their prescribed treatment. A noteworthy fact is that healthcare providers play a unique and important role in assisting patients' healthy behavior changes.[29] As with physician non-adherence to guidelines, patient non-adherence to treatment increases morbidity, mortality and health care costs.[34] Obviously the physicians and pharmacists deal with uncertainty from this point of view. That is why serious antithrombotic therapy strategies are compromised. Although the strategies to enhance patient adherence exist in the literature, they are often too complex and not practicable for busy practicing physicians.[29]

Uncertainty remains over optimal antithrombotic treatment of patients with AF.[35] There are two major hurdles to achieve absolute clinical efficacy: thrombosis/thrombembolism, and hemorrhage. In rare cases it can also be drug intolerability. Real practice however differs from clinical trials and from anticoagulation clinics also from the safety point of view;[18] discrepancies in clinical outcomes are elucidated with investigations of antithrombotic efficacy under strict medical control. The rate of major bleeding, for example, in real life was more than double than that reported in anticoagulation clinics.[19,20] Such outcomes are attributed to iatrogenic and patient-dependent reasons.

More recent studies have shown, that appropriate anticoagulation rates of high risk patients as high as 80% are attainable.[36] Hypothetically clinicians already do have optimal (if not ideal) antithrombotic drug(s) likely enabling full control of the clinical entity. Difficulty in estimation of drug efficacy incorporates the uncertainty of whether the ischemic complication occurs due to under-treatment or due to an atherothrombotic event. Secondly and most importantly, both ischemic and bleeding complications may take place due to under-treatment and over-treatment: it depends largely on patients' behavioral peculiarities. "Medicine won't work if you don't take them" – a statement of the World Health Organization (WHO, 2003) related to the medication adherence.[37] That is why patients do not achieve maximum clinical benefit.[25] Such cases underscore the benefit of antithrombotic drugs while at the same time question their efficacy.

When choosing the appropriate therapeutic approach, it is relevant to balance the degree of ischemic protection provided by antithrombotic therapy with the "iatrogenic" bleeding risk.[38] The use of warfarin, antiplatelets, novel anticoagulants, double and triple therapy (dual antiplatelet plus anticoagulant) are widely discussed.[10,18,38] Nevertheless, the abovementioned risks persist. Cate in 2013[23] has stressed that adherence should become a major topic

of discussion; policy makers, consumers, physicians and insurers should take their responsibility and start discussing the options for maximizing adherence, preferably in a patient centered manner.

Considerations According to Supplementation of Risk Factors in Acronymic Scheme CHA_2DS_2-VASc

AF confers an excess risk of stroke, but this risk is not homogeneous, and depends on the presence or absence of various risk factors.[39] Some of these factors were properly selected, compacted and declared in 2001.[38,40] The CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke/transient ischemic attack/thromboembolism [Doubled], Vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], Age 65-75 years, sex category [female]) is used clinically for stroke risk stratification in AF.[41]

Since 2001 an initial risk scoring system $CHADS_2$[39] underwent evolution. Currently adopted risk score formula CHA_2DS_2-VASc might be supplemented by an indication of non-adherence to antithrombotic drug regimen as follows: CHA_2DS_2N-VASc, where "N" means "Non-adherence" risk factor. Better delineation of risk factors related to antithrombotic treatment as well as those related to treatment for congestive heart failure, hypertension, diabetes are desirable. The symbol "N" actually reflects both physician (care provider) and patient adherence to given guidelines. Thus, both parties share the responsibility of lege artis therapy.

The additional risk factor incorporated into the formula potentially contributes to more accurate stroke risk stratification and more effective stroke prevention. "N" risk factor emerges when drug treatment is initiated and established. Last but not least, this new ingredient will likely allow to better identify risk criteria (low/moderate/high) in AF patients. Finally, the eligibility of "N" risk factor in the risk score stratification scheme is open for discussion.

Overanticoagulation-Related Risk

Many risk factors for stroke are also risk factors for bleeding on oral anticoagulation.[42] Currently, clinical scores for bleeding risk estimation are much less well validated than stroke risk scales.[43] Singer et al.[44] have provided quantitative assessments of the net clinical benefit of warfarin anticoagulation among patients with AF; by comparison of outcomes of intracranial hemorrhage and AF-related ischemic stroke they weighted intracaranial hemorrhage being 50% worse than ischemic stroke. In general, overanticoagulation is considered to be an alarming clinical problem.

Importantly, risk factors for bleeding include patient-related and treatment-related factors.[45] Patient-related factors include age, previous episodes of bleeding, anemia (hematocrit less than 30%), hypertension, heart disease, cerebrovascular disease, history of gastrointestinal hemorrhage, active peptic ulcer or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant anti-inflammatory (NSAIDs), and use of other medication or natural remedies.[16,45] Hylek and colleagues[46] have declared that 26% of patients stopped warfarin within the first year, mostly due to perceived safety issues. Reportedly, treatment related factors are as follows: duration, intensity and variability of warfarin treatment, concomitant use of aspirin, and support patients received from their providers and home environments.[10,19,45]

On the basis of a nationwide cohort study Lamberts and co-authors[35] have declared their main finding – an immediate high risk of bleeding with recommended triple therapy; the risk was continually elevated in comparison with less intense antithrombotic regimens. They also added that triple therapy has no safe therapeutic window. Hemorrhagic risk however should not prevent antithrombotic drug prescription but should focus medical attention on the patient.[18]

Some selective and most important risk factors were incorporated into the bleeding risk stratification acronym HAS-BLED.[42] HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) bleeding risk schema has been proposed as a simple, easy calculation to assess bleeding risk in AF patients, whereby some caution and regular review of the patient is needed, following the initiation of antithrombotic therapy, whether with oral anticoagulation or antiplatelet therapy.[47] Wan and colleagues[48] have emphasized that bleeding risk is multifactorial and also intimately related to quality of anticoagulation control.

Enhancement of the HAS-BLED scheme by the involvement of supplementary bleeding risk factor is highly desirable. The definition "excessive antithrombotic dosing", marked by symbol "E" potentially might represent this relevant clinical problem. Thus, the modified acronym reflecting unduly designed and/or implemented therapy might be delineated as follows: HAS-BLEDE with an assumed one additional risk score. It could indicate an enhanced vigilance to ill-performed antithrombotic therapy and clinical threats. Again, both parties, i.e. the physician (health professional) and the patient take on the responsibility of lege artis therapy. Eventually, consensus on a proposal could be attained and validated.

If the patients were precisely following the prescribed well-designed therapy regimen it would perhaps reveal that we already have ideal or near ideal antithrombotic drug or drugs. These drugs likely are widely used, but due to non-adherence/non-compliance they are not categorized as the best ones. That is why the research and new developments continue.

Conclusions

Antithrombotic therapy in AF patients in respect to stroke prevention is considered to be an important strategic approach. Some inadequacies and poor compliance to medication or medical instructions are trailed; this conceals the real antithrombotic efficacy and clinical outcomes of patients, suffering from atrial fibrillation and ischemic stroke threats. More effective prevention of ischemic events may be reached by the careful use of antithrombotic drugs currently available. An overall estimation of their efficacy is limited and hampered by non-adherence to medication. This suggests the need for the incorporation of an additional risk factor "N" (meaning "Non-adherence to medication") into the alphanumeric risk score system, i.e. CHA_2DS_2N-VASc. This will increase the visibility of existing risk factor and allow to achieve better clinical results. Similarly, bleeding risk score formula might be enriched by the symbol "E" (meaning "Excessive antithrombotic dosing"), i.e. HAS-BLEDE. Improved formulas should raise the predictive scores value and awareness for clinicians facing the problem of non-adherence to treatment regimen. The value and clinical applicability of new alphanumeric developments are to be debated. Further efforts are required to minimize the risks of AF treatment preferably by more accurate adherence to medication.

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