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Risk assessment in contemporary outpatients with non-valvular atrial fibrillation recently on vitamin K antagonists

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

Presentada por:

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Bajo la dirección de:

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El profesor Dr. José Ramón González Juanatey, Catedrático del Departamento de Medicina de la Universidad de Santiago de Compostela y Jefe de Servicio de Cardiología y Unidad Coronaria del Complejo Hospitalario Universitario de Santiago de Compostela,

CERTIFICA QUE:

La presente memoria, titulada "Risk assessment in contemporary outpatients with non-valvular atrial fibrillation recently on vitamin K antagonists", que presenta D. Rami Riziq Yousef Abumuaileq para optar el grado de Doctor por la Universidad de Santiago de Compostela, ha sido realizada bajo su dirección en el servicio de Cardiología y Unidad Coronaria del Complejo Hospitalario Universitario de Santiago de Compostela, y autorizan su presentación a fin de que pueda ser juzgada por el tribunal correspondiente.

Y para que así conste, y a los efectos oportunos, firman la presente en Santiago de Compostela, a 18 de febrero de 2016.

Fdo.: Dr. **José Ramón González Juanatey**

To my family

Abbreviations:

A.D. Anno Domini (Latin, in the year of our lourd).

AF. Atrial fibrillation.

ATRIA. Anticoagulation and Risk Factors in Atrial Fibrillation.

B.C. Before Christ.

CKD. Chronic kidney disease.

CKD-EPI. The Chronic Kidney Disease Epidemiology Collaboration.

ECG. Electrocardiogram.

eGFR. Estimated glomerular filtration rate.

GFR. Glomerular filtration rate

ICH. Intracranial hemorrhage.

INR. International normalized ratio.

MDRD-4. The 4-variable Modification of Diet in Renal Disease.

NOACs. New oral anticoagulants.

NVAF. Non-valvular atrial fibrillation.

PINRR. Proportion of international normalized ratios in range.

RR. Relative risk.

TE. Thromboembolic.

TIA. Transient ischemic attack.

TTR. Time within therapeutic range.

VKAs. Vitamin K antagonists.

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Justifications and objectives

Atrial Fibrillation (AF) is known to be the most commonly sustained cardiac rhythm disorder, and is considered a major cause of health care expenditure. Despite that AF is usually not a life-threatening arrhythmia, it affects the quality of life significantly mainly as a result of its anatomic, hemodynamic, and thromboembolic (TE) consequences. This means that AF is associated with very important socioeconomic problems, such as permanent disability, cognitive disturbance, hospitalization, and absence from work.

Assessing the risk of poor anticoagulation control in patients with non-valvular atrial fibrillation recently on vitamin K antagonists*:*

Among the negative effects and consequences of AF, it is known that AF increases the risk of embolic stroke by five fold. Furthermore, stroke in AF is associated with greater mortality and morbidity, with more disability and longer hospital stays compared to stroke event in patient without AF. Vitamin K antagonists (VKAs) are still the most used oral anticoagulants in patients with non-valvular atrial fibrillation (NVAF) and are highly effective for the prevention of TE complications in these patients. However, achieving the best benefit and safety from VKAs in the clinical practice remains a major challenge mainly because of their unpredictable anticoagulant response. Several reports indicate a strong relation between poor quality of international normalized ratio (INR) control and the increased rates of both stroke and major hemorrhage in patients on VKAs. Various large cohort studies demonstrate that the level of the quality of INR control in real life practice is still below the optimal level of time within therapeutic range (TTR) or the proportion of international normalized ratios in range (PINRR) of 70%.

It is well known that previous long term records of INR values are the best estimate of anticoagulation control in patients who are on VKAs for a long time. However, for VKAs naïve patients or patients who are recently on VKAs, there is substantial interest to find a tool that can predict how they will do with VKAs at intermediate and long term in real life practice. Moreover, with the availability of new oral anticoagulants (NOACs), the landscape of anticoagulation management in NVAF has been revolutionized as these new drugs are considered safer than VKAs. It is now clear that there is a strong need to characterize VKAs naïve AF patients who are at risk of having poor INR control as these patients would need more follow-up visits or they will be suitable candidates for NOACs in order to avoid poor INR control-related complications such as thromboembolism and major bleeding. Fortunately, a quantitative clinical score (i.e. SAMe-TT_2R_2) was recently conceived to help clinicians in identifying patients who can do well on VKAs. However, the derivation and the internal validation cohorts of the SAMe-TT_2R_2 score were derived from a clinical trial which was not designed to assess the quality control of anticoagulation and as the SAMe-TT_2R_2 takes into account the race of patients as an important factor to predict the quality of INR control. These facts increase the need to test the SAMe-TT_2R_2 predictability in real life Galician patients with NVAF recently (i.e. for a better assessment of the SAMe-TT_2R_2 score) on VKAs. Moreover, there are strong arguments to investigate the effects of other comorbidities like cardiovascular diseases and renal dysfunction which usually accompany AF and there is still assumption about their negative effects over the quality of INR control.

***A continuous need to evaluate current thromboembolic and bleeding risk scores and to define new risk factors in real life patients with non-valvular atrial fibrillation**:*

Really, there has always been a strong motivation to improve the decision making process and the management plan in patients with NVAF, so there is a continuous need to evaluate current TE and bleeding risk scores and to define new risk factors.

Clinicians increasingly appreciate that TE risk in AF patients is not homogeneous and is altered by the presence of certain risk factors. For instance, AF may coexist with systemic hypertension, heart failure and/or coronary artery disease which may influence both the approach to management and the treatment options, since the presence of these risk factors adds to AF-related TE complications, so the coexistence of the prior risk factors is an indication for anticoagulation.

Different TE risk scores have been developed to help clinicians in the decision making process regarding the prescription of oral anticoagulants for AF patients in order to reduce the risk of the catastrophic TE event. However different critical points are still on our minds as cardiologists and/or clinical investigators.

The burden of major bleeding is the downside of the anticoagulation treatment as the incidence of intracranial bleeding with VKAs ranges from 0.3 to 1.8%. Moreover, different TE risk factors like age, hypertension and prior cerebrovascular event were also found to be bleeding risk predictors. This makes prescribing oral anticoagulants to AF patients a very difficult decision. Furthermore, a sizeable subgroup of AF patients still has a significant risk of developing TE events despite being on anticoagulation. So, there is great interest to evaluate this risk and how the current TE risk scores can help us to characterize this subgroup of patients as this particular subpopulation might need

different management strategies and closer follow up in order to improve the prognosis of these patients.

The estimate that the risk of major adverse event (i.e. TE event and major bleeding) is highest in the first few months after initiation of VKAs, may point to the importance of risk assessment for those patients who are recently started on VKAs.

Several scoring systems are available to estimate TE and bleeding risk in AF patients. However, more arguments still need further investigations as many of the validation studies for these scores were not done on real life cohorts and this raises some doubts about their performance in AF patients from the real world. Moreover, given the differences in patient characteristics and medical assistance (i.e. different health systems) resulting from geographic location, when a predictive model or risk score is to be used outside the environment in which it was created, it first needs to be validated for its new context; only then can users be sure that the scores provided are not misleading. Currently, there is limited data on the usefulness of contemporary risk scores recommended to be used in anticoagulated patients with NVAF in Galicia.

Renal dysfunction and adverse events in anticoagulated patients with non-valvular atrial fibrillation*:*

In the dilemma of oral anticoagulation for patients with NVAF there is a specific issue of great concern which is the current controversy about the role of renal dysfunction — a frequent comorbidity observed in patients with AF— on the quality control of oral anticoagulation and outcomes. Patients with AF and renal dysfunction are more likely to develop TE events compared to those individuals with AF but without renal dysfunction. On the other hand, the presence of renal dysfunction is also a recognized predictor in the bleeding risk scores used commonly to estimate the hemorrhagic risk (i.e. HAS-BLED and ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation] scores). In addition, patients with NVAF are often elderly with multiple comorbidities which require pharmacotherapy of increasing complexity. All these factors make the accurate assessment of renal function to be of great importance as it will help inform the decision making process aiming to improve the management of patients with AF.

There are various equations used to calculate the estimated glomerular filtration rate (eGFR) and nowadays the two most commonly used equations are the re-expressed 4-variable Modification of Diet in Renal Disease (MDRD-4), and the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which is currently considered more accurate than the re-expressed MDRD-4. However, until now there is little information about the derived reliability from both equations in the specific area of AF and how using one equation instead of the other can affect the decision making process.

***General objectives**:*

Although the general and specific objectives proposed for each of the analyzed topics are detailed in different chapters of the thesis, they can be summarized as follows:

1- To evaluate the quality of oral anticoagulation in a real world cohort of patients with NVAF recently on VKAs. In this regard we aimed to assess the ability of the new SAMe-TT_2R_2 risk score at predicting different levels of anticoagulation control in a real world cohort of patients with NVAF recently (i.e. for a better assessment of SAMe-TT_2R_2 score) on VKAs. We also have specific objectives to examine the relation of SAMe-TT_2R_2 score with major bleeding, TE complications, and all-cause mortality; either as a composite outcome or as individual events. Additionally, we aimed to investigate some of the cardiovascular and cardinal variables that have a widely held belief as strong predictors of poor anticoagulation control.

2- To carry out a comparative validation of three contemporary risk scores for predicting TE event in patients with NVAF. In this regard we aimed to evaluate the ability of CHA_2DS_2-VASc, R_2CHADS_2, and new ATRIA scores at predicting TE events in two different real life cohorts of non-anticoagulated and anticoagulated patients with NVAF which have full spectrum of eGFR.

3- To perform a comparative validation of HAS-BLED versus ATRIA by investigating the full potential of the two bleeding prediction schemes as they were originally conceived, in a real life cohort of patients with NVAF recently on VKAs and to identify other comorbidities that would be associated with major bleeding beyond those already

included in HAS-BLED and ATRIA scores. We also interested to test the association between poor quality of INR control (i.e. labile INR) and major bleeding event.

4- To investigate the relation between renal dysfunction and adverse outcomes (i.e. poor quality control of VKAs, TE event, major bleeding and mortality) in a real life cohort of patients with NVAF who are on VKAs. We also aimed to comparatively assess the glomerular filtration rate (GFR) estimating formulas namely the re-expressed MDRD-4 and the new CKD-EPI formulas at identifying patients with renal dysfunction, and at predicting the occurrence of major adverse outcomes in a real world cohort of patients with NVAF on VKAs.

Chapter I

Introduction

***Historical review of atrial fibrillation**:*

Physicians have been fascinated by patient's pulses for over centuries. The worst prognosis associated with the irregularity of cardiac rhythm was noted and described by the ancient physicians. Hippocrates [around 460 - 370 Before Christ (B.C)] described a clinical case of a patient with poor prognosis and violent palpitation of the heart and stated in his aphorisms: "Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly" [1]. However, that palpitation could be due to another arrhythmia. Later on, in 1187 Anno Domini (A.D), Moses Maimonides wrote aphorisms that pertained to the human pulse. He described in some of his manuscripts a totally irregular pulse that was most likely atrial fibrillation [2].

Figure 1.1: Hippocrates around 460 - 370 B.C.

In 1876 A.D, when Carl Wilhelm Hermann Nothnagel, was the first to record the pulse waves in AF, and he observed that "In this form of arrhythmia the heart beats follow each other in complete irregularity. At the same time, the height and tension of the pulse waves are continuously changing" [3]. Following the first record of the pulse wave in

AF, James Mackenzie in 1904 A.D, observed that the atrial pulse waves, measured in jugular veins, disappeared at the onset of the persistent irregular arterial pulse and returned when the pulse became regular again [4]. Thereafter, there was a general consensus that the three essential features of "the absolutely irregular heart" were an absolute irregularity of the arterial pulse, the persistence of the abnormal rhythm and the absence of venous atrial pulse waves [3,5]. It is well recognized now that the development of the electrocardiogram (ECG) by Einthoven and the studies which have been done by him and Sir Thomas Lewis clearly put atrial fibrillation on the map.

Willem Einthoven, published the first ECG in a human being, showing AF in 1906 A.D, without having clear idea about its true nature [6]. Electrocardiographic studies in 1910 A.D, which were done by Thomas Lewis, highlighted that the fine oscillations between the R waves, which were thought to be disturbances, were evidence of atrial activity throughout the cardiac cycle [7]. Using the chest leads, Lewis demonstrated that these oscillations originated from the atria rather than from the atrioventricular node, and noticed that the R wave had its normal electrical vector during the irregular pulse and he concluded that the ventricular activity must therefore start from its usual point [3]. Thomas Lewis, had the chance to test and to observe the phenomenon of heart irregularity in horses, where he saw the auricles of the atria trembling, when ECG findings and venous pressure curves were consistent with AF, and he named this phenomenon "auricular fibrillation" [7].

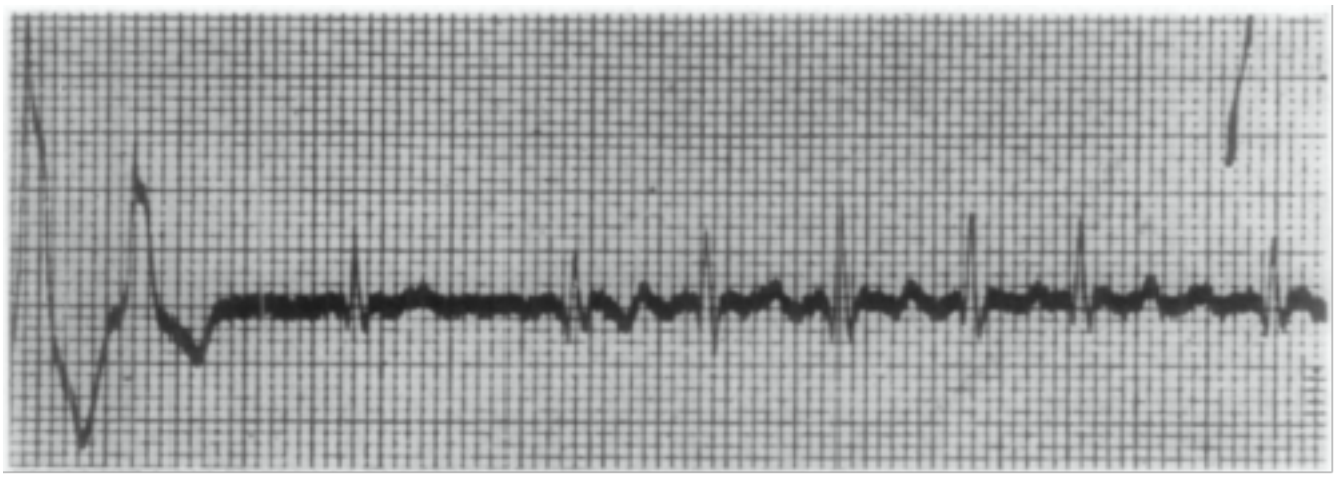


Figure 1.2: The first atrial fibrillation recorded by ECG in 1906 by Willem Einthoven [6].

Current definition of atrial fibrillation:

AF is defined as a cardiac arrhythmia with the following characteristics [8]:

(1) The surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e., RR intervals which do not follow a repetitive pattern.

(2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.

(3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 milliseconds (>300 beat per minute).

It is conventional to divide AF into cases which are described as "valvular or non-valvular" as the natural history and management of both types of AF is different.

NVAF is defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair [9].

***Mechanism and thrombogenesity of atrial fibrillation**:*

Structural heart disease like heart failure, coronary artery disease or hypertension may induce progressive structural remodeling in both the ventricles and the atria. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts with enhanced connective tissue deposition and fibrosis are the hallmarks of this process [10]. Structural remodeling leads to electrical remodeling which results in electrical dissociation between muscle bundles and local conduction heterogeneities facilitating the initiation and perpetuation of AF [10]. This electro-anatomical substrate allows multiple small re-entrant circuits that can stabilize AF. There are three types of atrial remodeling: structural, contractile and electrical. They are related to each other and contribute to maintaining the AF [11]. Factors affecting hemodynamic function in patients with AF involve loss of coordinated atrial contraction, rapid ventricular rates, irregularity of the ventricular response, and decrease in myocardial blood flow, as well as long term changes such as atrial and ventricular cardiomyopathy [10,11]. Acute loss of coordinated atrial mechanical function during an episode of AF reduces cardiac output by 5–15% [11]. This effect is more pronounced in patients with already reduced ventricular compliance in whom atrial contraction contributes significantly to ventricular filling. High ventricular rates limit ventricular filling due to the short diastolic interval. Rate-related interventricular or intraventricular conduction delay may lead to non-synchronization of the left ventricle and further reduction of cardiac output. In addition, irregularity of the ventricular rate can reduce cardiac output [11]. Because of force–interval relationships, persistent variations of the RR intervals cause significant variability in the strengths of subsequent heart beats, so resulting in pulse deficit.

Sustained elevation of ventricular rates above 130 bpm may produce ventricular tachycardiomyopathy [12].

TE risk associated with AF is linked to a number of underlying pathophysiological mechanisms which fulfill the Virchow triad of thrombogenesis. 'Flow abnormalities' in AF are evidenced by stasis within the left atrium, with reduced left atrial appendage flow velocities, and visualized as spontaneous echo-contrast on transoesophageal echocardiography [13]. Endocardial abnormalities include progressive atrial dilatation, endocardial denudation, and edematous/fibro-elastic infiltration of the extracellular matrix. The left atrial appendage is the dominant source of embolism (90%) in NVAF. Abnormalities of blood constituents are well described in AF and include haemostatic and platelet activation, as well as inflammation and growth factor abnormalities [13].

An autopsy study in patients with history of strokes demonstrated the presence of significant intracardiac thrombus in 20% of patients with atrial fibrillation [14]. Another autopsy study showed that about two thirds of patients with long-term AF had a thrombus in their left atrial appendage [15].

The dissociation of a part of the thrombus from the left atrial appendage can lead to the most feared complication in AF, ischemic stroke. The risk of stroke is increased fivefold in the presence of AF, and it is estimated that in one out of every four strokes, AF is the source of thromboembolism [16].

A meta-analysis of different trials has demonstrated an average annual stroke rate of 4.5% for patients without a previous stroke and 12% for patients with a previous history of stroke in those patients not receiving antithrombotic therapy [17]. It is clear that the most important treatment goal in atrial fibrillation is to reduce thromboembolic complications.

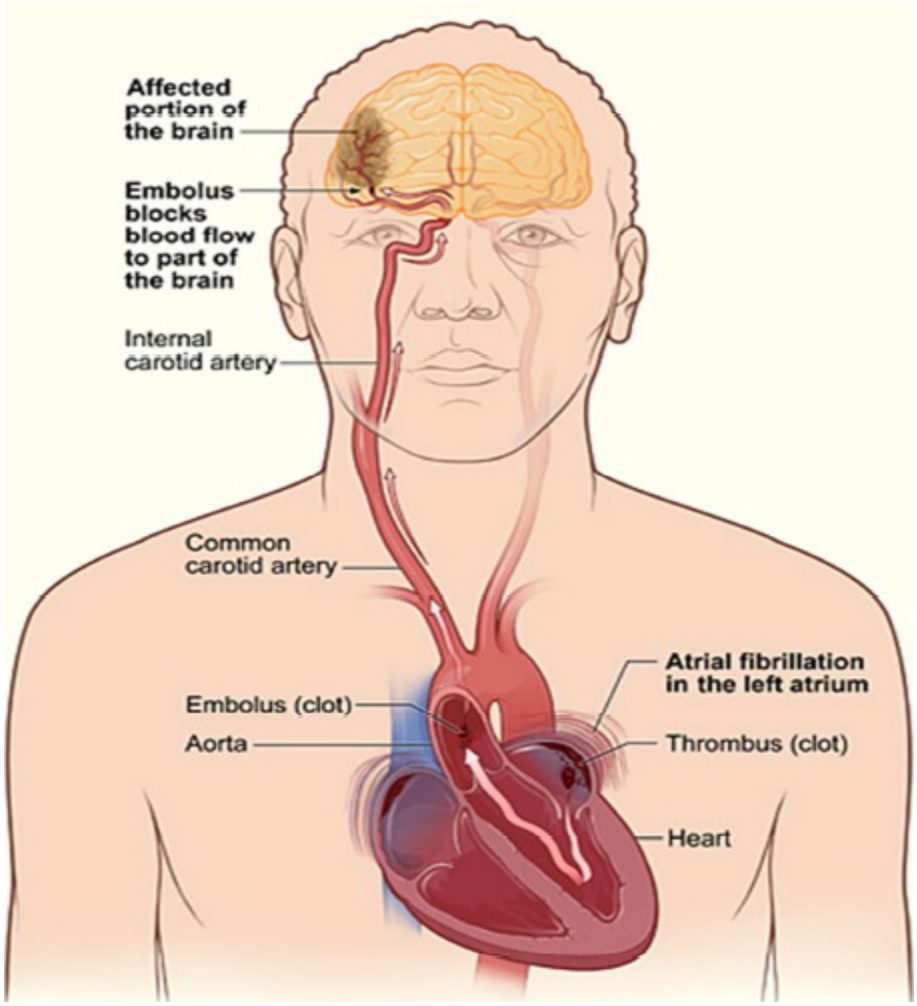


Figure 1.3: Atrial fibrillation and the risk of thromboembolic stroke. Source: National Heart, Lung, and Blood Institute, United States of America.

***Prevalence and burden of atrial fibrillation "magnitude of the problem"**:*

In the last 20 years, AF has become one of the most important public health issues and an important cause of health care expenditure in western countries. AF influences quality of life significantly as a result of its anatomic, hemodynamic, and hemocoagulative consequences. In addition, AF is frequently associated with disturbing symptoms and critical socioeconomic problems, such as permanent disability, cognitive disturbance, hospitalization, and absence from work [18].

The most common and reliable studies on the epidemiology of AF which were carried out in developed countries and published between the end of the 20th century and the first years of the 21st century estimated the prevalence of AF to be between 0.5% and 1% in the general population [19,20]. However, in the last decade, and as perceived by the number of hospitalizations, emergency room visits, and burden of outpatient visits for AF, the common opinion was that the prevalence of AF had to be markedly higher [20-22]. The most recent studies have confirmed this perception and demonstrated that the prevalence of AF in the general adult population of Europe is more than double that reported just one decade earlier, it is now ranging from 1.9% in Italy, Iceland, and England to 2.3% in Germany and 2.9% in Sweden [23].

In the United States of America, it appears that the prevalence of AF has increased by 0.3% per year in Medicare beneficiaries older than 65 years, with a real growth of 4.5% (from 4.1% to 8.6%) in the period 1993-2007[24-29]. However, despite this increase, the actual prevalence of AF is probably still underestimated because it is well known that AF, in a discrete proportion (10%–25%) of cases, occurs in the absence of symptoms [30,31]. In this regard, even if AF was detected appropriately by active screening, its true prevalence would be higher and closer to 3%, as estimated for 2015 in the United States of America [30-32]. In developing countries, AF occurs in approximately 0.6% of males and 0.4% of females. Although these rates are markedly lower than in developed nations, it appears that the burden of AF in these countries is enough to be a potential problem for health care systems [33].

In Spain, a recent study demonstrated that the prevalence of AF in the general Spanish population older than 40 years is high, at 4.4%. Actually, it is estimated that there are more than one million patients with AF in the Spanish population [34]. Another study

was held in Spain and showed that the prevalence of AF has progressively increased with age and reached 6.3% for those older than 75 years [35].

At the present time, in the European Union (estimated population of 500 million people) there are approximately 10 million patients with AF and 100,000–200,000 with new-onset AF. In the year 2030 the prevalence of AF would be 2.7%–3.3% in a European population with 516–525 million inhabitants. Therefore, within 15 years, the number of European citizens with AF will be 14-17 million and the number of new AF cases will be 120,000–215,000 per year [23]. There will be approximately 14 million AF patients among individuals aged >55 years in the year 2030 [36]. To these figures must be added a further 280,000–340,000 new ischemic strokes, 3.5-4 million hospitalizations for AF, and 100–120 million outpatient visits [23]. The magnitude of this data seems to confer an endemic dimension to this health care problem, implying not only a greater engagement of physicians but also a significant effort of health care systems to improve AF prevention and treatment and to facilitate the organization of social interventions for the cure of its consequences [23,36].

The socioeconomic burden of AF in Spain and the European Union countries is considerable [37]. A study analyzing the costs of AF in five European countries showed that AF was associated with average healthcare costs from 1010 euros per patient per year in Poland up to 3225 euros per patient per year in Italy, while in Spain the average health care cost was about 2315 euros per patient per year [38]. The total annual costs for treating AF range from 272 million euros in Greece up to 3286 million euros in Italy, while in Spain, the total annual cost for treating AF was 1545 million euros [38].

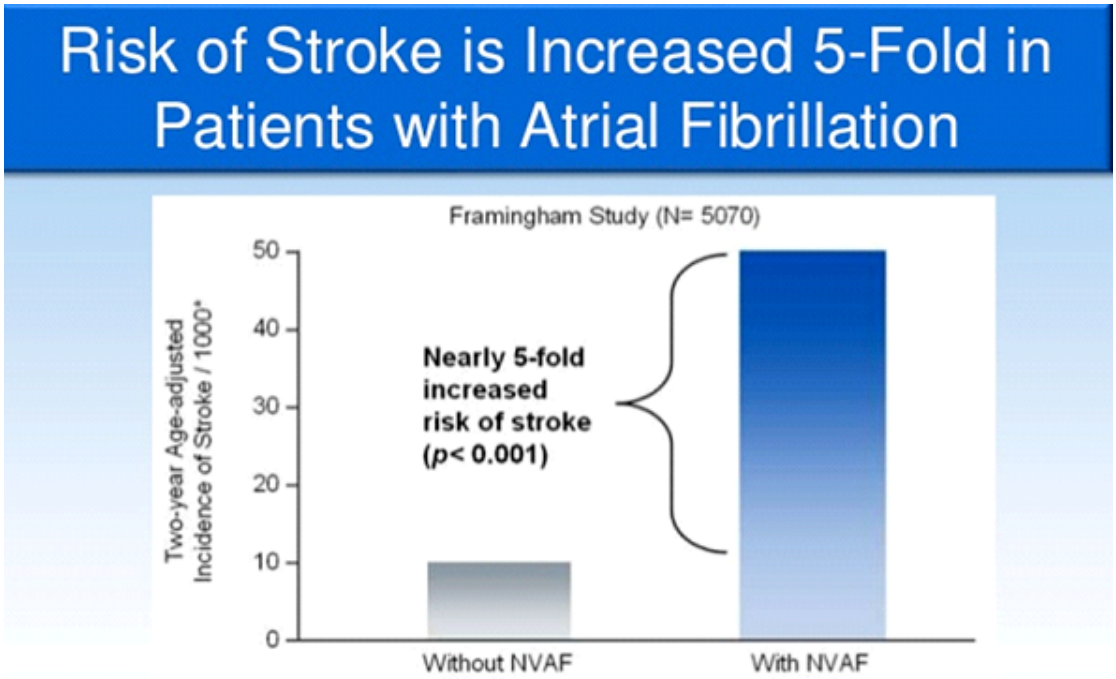


Figure 1.4: Demonstrates the significant burden of atrial fibrillation in term of high stroke risk [16]. NVAF: non-valvular atrial fibrillation.

***Atrial fibrillation in the context of cardiovascular disease**:*

AF commonly coexists with cardiovascular disease and if inappropriately treated, the presence of these factors adds to the development of new onset AF [39], and to the complications associated with AF, such as stroke [40].

Systemic arterial hypertension:

Hypertension is the most prevalent, independent, and potentially modifiable risk for atrial fibrillation [41,42]. In addition to its role as a major risk factor for the development of atrial fibrillation, the presence of hypertension increases the risk of stroke in patients with AF. Patients with AF have a 3 to 6 fold increase in stroke risk compared with the general population [16,43,44]. In patients with AF, hypertension worsens stroke rate by an additional 2 to 3 fold [45].

The prevalence of systemic arterial hypertension in patients with AF was estimated to be about 76% in Spain [34]. In a prospective study which was carried out in Galician patients with AF demonstrated that hypertension was the most prevalent risk factor (77%) [46].

Heart failure:

In Spain, a recent study demonstrated that heart failure is a common comorbidity among patients with AF with estimated prevalence of 29.4% [34]. The prevalence of heart failure in a registry of Galician patients with AF was 12.2% [46]. Recently, AF and heart failure have been recognized as the two epidemics of modern cardiovascular medicine [47]. Both conditions frequently coexist because heart failure is a strong risk factor for AF. The risk of AF increases 4.5 to 5.9 fold in presence of heart failure. AF prevalence increases as heart failure severity worsens. AF has been estimated to occur in 5% to 10% of patients with mild heart failure, 10% to 26% with moderate disease, and up to 50% with advanced heart failure [48-50]. Heart failure can be both a consequence of AF due to tachycardiomyopathy or decompensation in acute onset of uncontrolled AF and can be a cause of AF due to increased atrial pressure, volume overload and secondary valvular dysfunction with atrial dilatation or chronic neurohumoral stimulation [51,52]. An analysis of prospective registry of Galician patients with AF showed that 30.5% of AF patients with heart failure died during a mean follow up of 2.9 years compared to 14.4% of those with AF but without heart failure [53].

Coronary artery disease:

After acute myocardial infarction, development of AF is associated with a worse prognosis [54]. Coronary artery disease is common among patients with AF and may be one of its underlying etiologies [55]. Moreover, AF may be the sole manifestation of

coronary artery disease [56]. Furthermore, epidemiological data has indicated that ischemic heart disease is one of the most common underlying causes of death among patients with AF [57].

Once AF is diagnosed, the presence of coronary artery disease is shown to be related to recurrent AF episodes [58], to the presence of symptoms (including arrhythmia, heart failure, and angina symptoms), and to increased risk of death [59,60]. Therefore, coronary artery disease plays an important role in the mortality and quality of life of patients with AF.

It is estimated that about 17.9% of Spanish patients with AF have coronary artery disease [34]. A prospective registry of Galician patients with AF demonstrated that 17.7% of them had ischemic heart disease which was an independent risk factor for mortality in these patients [46].

Vitamin K antagonists in atrial fibrillation*:*

There is an extensive evidence base for the use of VKAs in AF, as this evidence has come from many randomized studies which demonstrated and proved the absolute benefit of VKAs in AF.

Anticoagulation therapy with VKAs versus control:

Between 1989 and 1993, six trials were published, five of them were large randomized trials evaluated VKAs mainly for the primary prevention of TE event in patients with NVAF [61-65]. The sixth trial focused on secondary prevention among patients who had survived non-disabling stroke or transient ischemic attack (TIA) [66]. In a large meta-analysis, the relative risk (RR) reduction with VKAs was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of

2.7% [17]. When only ischemic strokes were considered, adjusted-dose VKAs use was associated with a 67% RR reduction. This reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Of note, all-cause mortality was significantly reduced (26%) by adjusted-dose VKAs versus control [17].

VKAs versus antiplatelet therapy:

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study demonstrated that VKAs with INR in the therapeutic range of 2-3 were superior to aspirin 75 mg daily in reducing the primary endpoint of stroke, intracranial hemorrhage (ICH), or significant arterial embolism by 52%, with no difference in the risk of major hemorrhage between VKAs and aspirin [67]. Similar results were found in the small Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial, in which there were significantly more adverse events with aspirin (33%) than with warfarin (6%, p =0.002), including serious bleeding. When the trials conducted prior to BAFTA were considered, the risk for ICH was doubled with adjusted dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per year) [17].

In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events–Warfarin arm (ACTIVE W) trial, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction 40%; 95% CI 18–56), with no difference in bleeding events between treatment arms [68]. The Aspirin arm (ACTIVE A) trial found that major vascular events were reduced in patients receiving aspirin–clopidogrel, compared with aspirin monotherapy (RR 0.89; 95% CI 0.81–0.98; p =0.01), primarily due to a 28% relative reduction in the rate of stroke with combination therapy [69]. Major bleeding was significantly increased with combined aspirin-

clopidogrel therapy (2.0% per year vs. 1.3% per year; RR 1.57; 95% CI 1.29–1.92; p=0.001), broadly similar to that seen with VKAs therapy. Of note, 50% of patients had entered the trial due to 'physician's perception of being unsuitable for VKAs therapy' and 23% had a risk factor for bleeding at trial entry. Thus, double antiaggregant therapy with aspirin plus clopidogrel might be considered as an interim measure where VKAs therapy is unsuitable, but not as an alternative to VKAs in patients at high bleeding risk.

INR as an index of quality control of anticoagulation with VKAs:

The effects of VKAs on blood coagulation are measured by the INR using a prothrombin test [70]. INR is derived from the ratio between the actual prothrombin time and that of a standardized control serum and it is the world-wide standardized coagulation method used for monitoring and evaluating the effect of VKAs therapies [8]. To obtain optimal benefits of anticoagulation control, patients on treatment with VKAs therapy need to be maintained within their INR target/reference range, which requires regular monitoring and appropriate adjustment of treatment. To achieve a balance between embolic stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with NVAF on VKAs [8,18].

The efficacy and safety of VKAs therapy are closely associated to the quality of oral anticoagulation management [71,72]. The quality of anticoagulation can be measured by a number of methods and no standardized consensus exists as to which is the best measure, and as such, all of the available methods have specific advantages and disadvantages. Meta-analysis of 47 studies of patients with atrial fibrillation on oral anticoagulation treatment with VKAs demonstrated that TTR measured by the Rosendaal method and the PINRR were the most frequently reported measures to

determine the therapeutic effectiveness of oral anticoagulation proved that both method have a significant correlation (r = 0.99, p= 0.001) [73].

Several studies have shown how a high TTR translates into a lower risk of stroke and bleeding, whilst on VKAs [73-76]. A recent European consensus document recommends that an average individual TTR should be > 70 % for optimal efficacy and safety outcomes whilst on VKAs and this is also recommended in the European Guidelines [77].

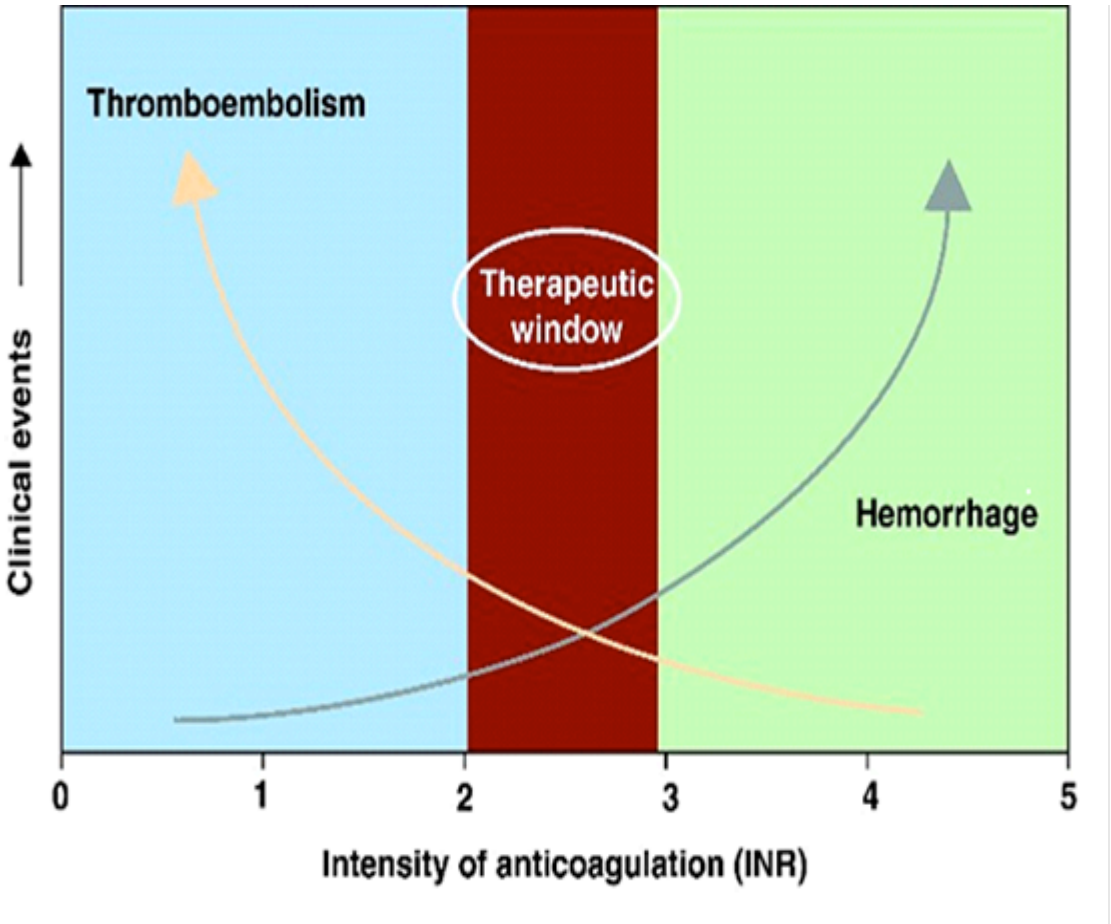


Figure 1.5: Keeping the INR in the therapeutic window reduces the adverse event. INR: international normalized ratio.

***Risk stratification in atrial fibrillation. A general overview**:*

The increasing prevalence of AF brings a high burden of its related complications, among which major TE event like ischemic stroke is the most disabling and associated with high mortality and morbidity [78,79]. Stroke prevention is necessary in the management of patients with AF. Really, appropriate TE prophylaxis essentially requires oral anticoagulants [77]. However, anticoagulant agents used for TE event prevention in AF will potentially increase the risk of minor, major and fatal bleeding events. The incidence of ICH and fatal bleeding with VKAs ranges from 0.3 to 1.8% and from 0.5 to 1.0%, respectively [80]. Among patients treated with VKAs, the risk of severe disability or death occurs in only 3% of patients with major extracranial hemorrhage whereas it can be as high as 76% in patients with ICH [81]. The quality control of oral anticoagulation is the most important risk factor for bleeding and ICH. It has been demonstrated that the risk of major bleeding is nearly two-times higher in patients with INR >3.0 compared with patients with INR between 2 and 3 [82].

The understanding of the risks and benefits of oral anticoagulation therapy is of great value in the real world clinical practice [77,83]. Although AF increases stroke risk 5-fold, this risk is not homogeneous. In a large cohort study of AF patients and over 6 years of follow up, the annual rate of TE event was 1.09 per 100 person-years in patients with no history of stroke and 3.46 per 100 person-years in patients with a history of stroke, both receiving VKAs, and in turn, this means that there are still groups of AF patients having high TE risk despite anticoagulation. However, there were 0.51 annual rates of ICH associated with VKAs therapy in patients with no history of stroke compared with 1.16 in patients with prior stroke [84].

Many TE risk factors also confer an increased risk of bleeding. Various TE and bleeding risk-stratification schemes have been developed to help inform clinical decision-making. These scores were derived and validated in different study cohorts, ranging from highly selected clinical-trial cohorts to real-world populations. Thus, the performance and classification accuracy of these scores vary depending on their derivation cohort(s) [85].

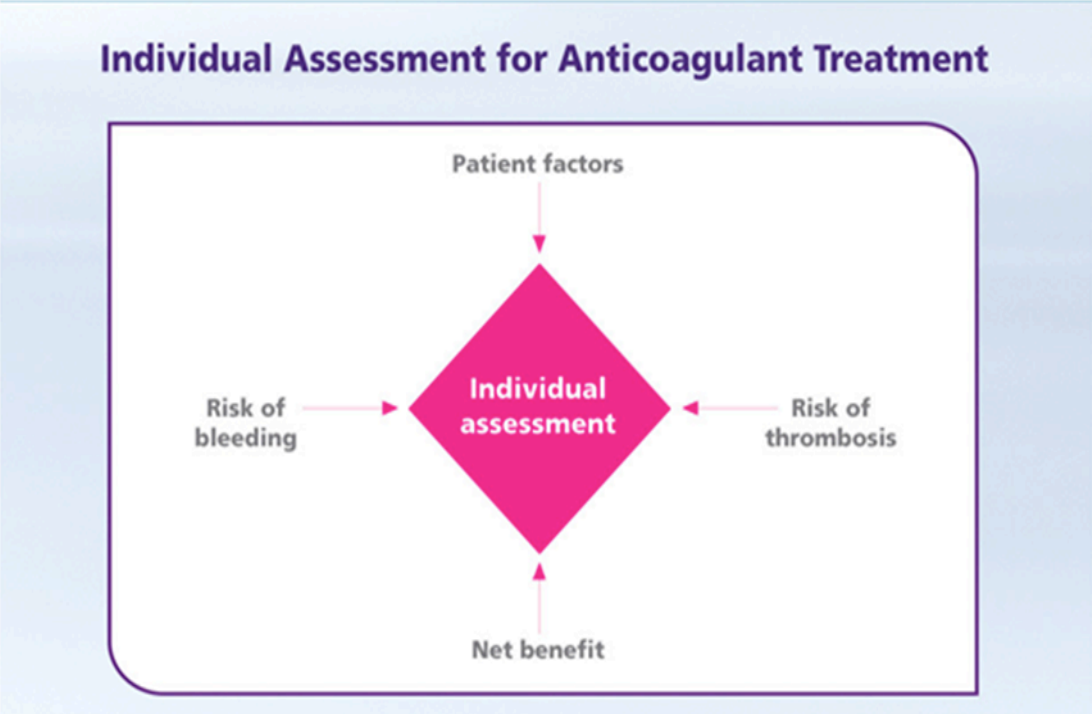


Figure 1.6: The risk of stroke or bleeding is not homogenous and the assessment is done at the individual level.

***Thromboembolic risk stratification in non-valvular atrial fibrillation**:*

Many TE risk factors have been identified among AF patients and the patient's risk will depend mainly on the combination of those risk factors, rather than from simply being an AF patient. Permutations of those risk factors have been used to design stroke risk-stratification schemes, with the initial objective of identifying high-risk patients to be targeted for oral anticoagulant [86,87]. The derivation of stroke risk-stratification schemes depends on identification of common risk factors, which already have been defined and recorded in the derivation cohort [88].

The $CHADS_2$ score with the acronym (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus and prior **S**troke or TIA) is one of the simplest and commonly used TE risk-stratification schemes. $CHADS_2$ score is a point system in which 2 points are assigned to a history of prior cerebral ischemia and 1 point is assigned for the presence of each of the cardiac failure, hypertension, age ≥75 years, diabetes mellitus with a maximum score of 6 points [89].

It is well recognized that the $CHADS_2$ score does well at identifying high-risk patients but provides less reliable results in those at low or moderate stroke risk [90]. Furthermore, the $CHADS_2$ score has been subject to more criticism as it did not include important independent TE risk factors and because of the discrepancy observed between the original validation and further applications in guidelines and real-life cohorts [91].

To overcome some of the limitations of the $CHADS_2$ score, the CHA_2DS_2-VASc score has been proposed giving extra weight to age ≥75 years, as this is a major driver of stroke risk, and including additional risk factors such as age 65 to 74 years, female sex, and vascular disease. CHA_2DS_2-VASc is calculated by adding 2 points for **A**ge ≥ 75 years; 2 points for prior **S**troke or TIA; and 1 point for each of the following factors:

Congestive heart failure\left ventricular ejection fraction ≤40%, **H**ypertension, **D**iabetes mellitus, **V**ascular disease [i.e. coronary artery disease, peripheral arterial disease or aortic plaque], **A**ge 65 to 74 and Female **S**ex, with a maximum score of 9 points [92].

CHA_2DS_2-VASc has been found to be superior to $CHADS_2$ in numerous validation studies for identifying truly low-risk patients and in minimizing the categorization of patients as moderate risk [92-94].

In a community based cohort of non-anticoagulated Galician patients with AF, CHA_2DS_2-VASc correctly identified the greatest proportion of AF patients at high risk [95].

The current consensus has now shifted the focus from identifying 'high-risk' patients to identifying those patients who are truly at low risk using the CHA_2DS_2-VASc score.

Although the current clinical practice guidelines recommend the use of $CHADS_2$ and CHA_2DS_2-VASc risk scores in the effective TE prevention strategy [77,96,97]. However, in several studies, $CHADS_2$ and CHA_2DS_2-VASc showed just a moderate discrimination ability to predict TE event [98,99], and in a recently published large cohort study, the annual ischemic stroke rate was noticeable in the group of patients classified in "the true low risk category" according to CHA_2DS_2-VASc [100]. Furthermore, there is great interest in estimating the prognosis of patients who have a level of risk outside the CHA_2DS_2-VASc (i.e. those with renal dysfunction). All this could lead to a number of questions and potential avenues for further research.

Recently, and with the aim to improve the ability to predict TE event, two new TE risk scores (i.e. R_2CHADS_2 [101] and the new ATRIA risk scores [102]) have demonstrated, in their own derivation cohorts, better performance than $CHADS_2$ and CHA_2DS_2-VASc. Really, the two recently proposed risk scores contain new risk factors (e.g. renal dysfunction) in their schemes which were not included in the most recommended

CHA_2DS_2-VASc score. This fact could qualify them to strongly capture the risk of suffering a future TE event, but little information is available in this regard in independent dataset of patients with NVAF. R_2CHADS_2 is calculated by adding 2 points for **R**enal dysfunction (i.e. creatinine clearance <60 mL/min); 2 points for prior **S**troke or TIA; and one point for each of the following factors: **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 and **D**iabetes mellitus with a maximum score of 8 points [101]. Really, the development of the R_2CHADS_2 score was driven by the knowledge that AF and kidney dysfunction coexist commonly and both increase the risk of stroke. Although, the R_2CHADS_2 score might have some limitations that may affect its performance; for example, derivation from a selected anticoagulated clinical-trial cohort that excluded patients with creatinine clearance <30 mL/min and included those with a high risk of stroke development, as the latter is contradictory to current recommendations to first identify low-risk patients [77]. However, there is still a need for further validation of the R_2CHADS_2 in a real world cohort with full spectrum of eGFR [103].

The new ATRIA risk score might be the newest TE risk stratification scheme proposed. This score was derived from the ATRIA cohort and it represents a point-based stratification scheme. The new ATRIA TE risk score is calculated by adding 1 point for each of the following factors: female sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria and renal dysfunction (i.e. eGFR < 45 mL/min/1.73 m^2 or end-stage renal disease) and by adding 0 to 9 points depending on the specific score weighting of patients age according to the presence or absence of prior ischemic stroke with a maximum score of 15 points [102]. ATRIA TE risk score looks to be more complex than the other scores.

Table 1.1: Thromboembolic risk stratification with CHA_2DS_2-VASc [92] and R_2CHADS_2 [101] scores.

CHA_2DS_2-VASc risk factor	**Score**	**R_2CHADS_2** risk factor	**Score**
Congestive heart failure/left ventricular dysfunction	1	**R**enal dysfunction (i.e. creatinine clearance <60 mL/min)	2
Hypertension	1	**C**ongestive heart failure	1
Age ≥75 years	2	**H**ypertension	1
Diabetes mellitus	1	**A**ge ≥75 years	1
Stroke/transient ischemic attack	2	**D**iabetes mellitus	1
Vascular disease (coronary artery disease, peripheral arterial disease, or aortic plaque)	1	**S**troke/transient ischemic attack	2
Age 65–74 years	1		
Sex category (female gender)	1		
Maximum score	9		8

Table 1.2: Thromboembolic risk stratification with ATRIA thromboembolic risk score [102].

ATRIA thromboembolic risk factor	**Score** without prior stroke	**Score** with prior stroke
Age, years		
≥85	6	9
75–84	5	7
65–74	3	7
<65	0	8
Female sex	1	1
Diabetes mellitus	1	1
Congestive heart failure	1	1
Hypertension	1	1
Proteinuria	1	1
Estimated glomerular filtration rate <45 mL/min/1.73m^2 or end stage renal disease	1	1
Maximum score	12	15

Bleeding risk stratification in patients with non-valvular atrial fibrillation on vitamin K antagonists*:*

The consequences of major bleeding during oral anticoagulation represent a potential fatal hazard of therapy, so we always need to recognize those patients with specific risk factors for adverse bleeding events. To some extent, estimation of the bleeding risk during AF is far more complex than the estimation of TE risk. Several clinical risk models for bleeding risk assessment have been developed to help the decision-making process when prescribing VKAs to AF patients [85].

Currently different clinical guidelines recommend the HAS-BLED [104] (**H**ypertension [uncontrolled: systolic >160 mm Hg]), **A**bnormal renal function, abnormal liver function, **S**troke, **B**leeding history or predisposition (anemia), **L**abile international normalized ratios, **E**lderly > 65 years, and **D**rugs/alcohol concomitantly) risk score for bleeding risk assessment in patients with NVAF [77,105]. HAS-BLED is calculated by adding 1 point for each of the 9 individual variables it includes [104]. Compared with other bleeding risk scores, the superiority of the HAS-BLED score was also demonstrated with a stepwise increase in rates of major bleeding with increasing HAS-BLED score ($p < 0.0001$) [106].

More recently, the ATRIA bleeding risk score was derived from the ATRIA study [107]. The ATRIA score is calculated by adding 3 points for anemia; 3 points for eGFR < 30 mL/min/1.73m2; 2 points for age ≥75 years; 1 point for prior bleeding, and 1 point for diagnosed hypertension [107]. Different studies have demonstrated that HAS-BLED score performs better than the ATRIA at predicting major bleeding in NVAF patients [108-110]. However, the results obtained by these studies might not be truly representative of the real world outpatient practice as some of these studies came from clinical trial population or from hospitalized patients [108,110]. Moreover, there is

limited information about the comparative performance of both scores at predicting ICH which is the most dreadful complication of oral anticoagulation therapy [108,109]. Furthermore, the few studies compared both scores in real world practice used "modified" versions of the original scores [109] and this brings doubts about the validity of their results.

Table 1.3: Bleeding risk stratification with HAS-BLED [104] and ATRIA [107] scores.

HAS-BLED risk factor	**Score**	**ATRIA** bleeding risk factor	**Score**
Hypertension (systolic blood pressure >160mm Hg)	1	Anemia (i.e. Hemoglobin <13 g/dL in men and <12 g/dL in women and/or thrombocytopenia	3
Abnormal renal and/or liver function	1 or 2	Severe renal disease (estimated glomerular filtration rate <30 mL/min or dialysis dependent)	3
Stroke	1	Age ≥75 years	2
Bleeding tendency or predisposition	1	Prior hemorrhage	1
Labile international normalized ratios	1	Hypertension	1
Elderly (e.g. age >65 years, frail condition)	1		
Drugs (e.g. concomitant antiplatelet or Nonsteroidal anti-inflammatory drugs) or alcohol excess/abuse	1 or 2		
Maximum score	9		10

A new score proposed to predict quality control of anticoagulation with vitamin K antagonists*:*

The peculiar characteristics of VKAs make them difficult to handle. VKAs are considered inconvenient drug as they have several limitations mainly due to their narrow therapeutic window and variable dose requirement. To maintain the dose of VKAs in the therapeutic range, many different factors should be taken into consideration like race, dietary vitamin K intake, comorbidities (e.g. liver disease) or whether the patient is taking interacting drugs [72]. Nevertheless, maintaining the therapeutic dose of VKAs is also partly influenced by genetic polymorphisms [111]. However, pharmacogenetics-guided dosing of VKAs has not yet demonstrated the ability to decrease the incidence of labile INR, and consequently, to decrease major adverse events and to be cost-effective in patients taking VKAs [112]. Really, patients in the real world clinical practice tend to be older, with associated comorbidities like cardiovascular disease with their polypharmacy regimen, which often result in weak adherence and poor quality of anticoagulation expressed as low PINRR or TTR [113].

The availability of NOACs have revolutionized the landscape of anticoagulation management and greatly increased the interest toward finding an easy clinical tool to identify those patients who would do well on VKAs or conversely, to be a good candidate for one of the NOACs. In this regard, Apostolakis et al [114], proposed the SAME-TT_2R_2 score [**S**ex, **A**ge (< 60 years), **Me**dical history (more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), **T**reatment (interacting drugs, e.g. amiodarone for rhythm control) (all 1 point), as well as **T**obacco use (2 points) and **R**ace (non-Caucasian; 2

points)]. This simple clinical score might help decision making by identifying those AF patients that would probably do well on VKAs with a high PINNR or TTR. However, the SAMe-TT_2R_2 score still need further validation in real world cohorts before being a reliable tool.

Table 1.4: Quality of anticoagulation control assessment with SAMe-TT_2R_2 score [114].

SAMe-TT_2R_2 risk factor	**Score**
Sex (i.e. female)	1
Age <60 years	1
Medical history (more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease)	1
Treatment with interacting drugs (e.g. amiodarone)	1
Tobacco use	2
Race (nonwhite)	2
Maximum score	8

The relevance of renal dysfunction in non-valvular atrial fibrillation patients on vitamin K antagonists (a special and complex concern)*:*

The frequency of AF in patients with end-stage renal failure is 10 to 20 fold higher than that of the general population, although significant variability in prevalence exists between the studies, ranging from 7% to 27% [115-117]. Moreover, chronic kidney disease (CKD) is a common comorbidity among AF patients. In Spain the prevalence of renal dysfunction in patients with AF estimated to be 31.6% [118]. CKD results in complex pathophysiological changes, involving both hypo- and hypercoagulability [119]. An intimate relationship between CKD and oral anticoagulant related hemorrhagic events is well established. As a result, severe CKD is a predictor in most oral anticoagulant related bleeding risk estimation tools [104,107]. On the other hand, patients with AF and advanced CKD have higher risk of TE events compared with AF patients and normal renal function [120,121].

All these data when taken together indicate that accurate assessment of renal function is of paramount importance as it will help inform the decision making process regarding the optimal management of patients with AF. Currently, it is recommended to estimate renal function by means of eGFR using the prediction equations instead of serum creatinine [122].

The two most commonly used equations to estimate GFR were the MDRD-4 Study [123] and the Cockcroft-Gault equation [124]. The MDRD-4 equation was re-expressed and revalidated to be used in the current era of standardized serum creatinine assay, whereas the Cockcroft-Gault equation was not updated, and its use is not recommended currently [125]. More recently, a new equation, the CKD-EPI equation [126], has been proposed as an alternative equation to replace the widely used re-expressed MDRD-4

formula in routine clinical practice. Although, the new CKD-EPI outperformed the re-expressed MDRD-4 formula at estimating the true renal function in several studies [127-129]. However, it is still unknown if the better estimates from the new CKD-EPI would be translated into better risk prediction in the particular context of patients with NVAF, as very few percentage of patients in the derivation cohort of the new CKD-EPI formula were having AF [126].

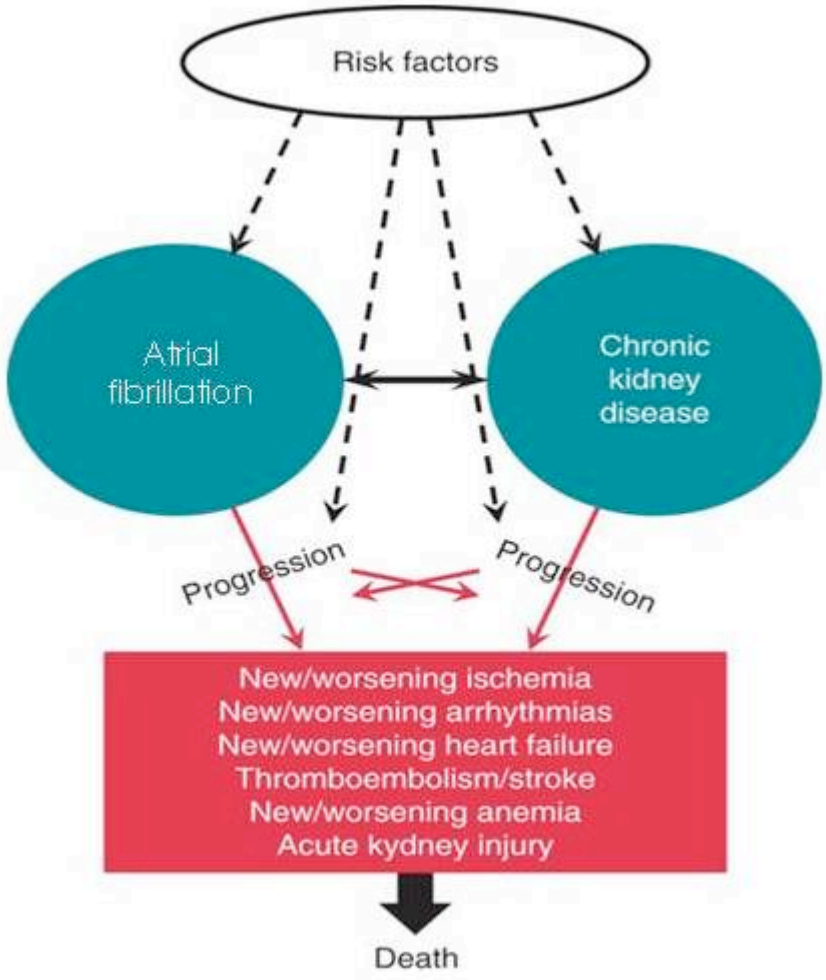


Figure 1.7: The interactions between renal dysfunction and atrial fibrillation.

Chapter II

Current challenges in the management of non-valvular atrial fibrillation with oral anticoagulation

As AF becomes more and more prevalent, there is a substantial interest to address the challenges that prevent optimal management of this condition.

Global Challenges in the real world to maintain high quality control of VKAs:

Over the last five decades, VKAs have been the mainstay of oral anticoagulation treatment and multiple clinical trials had shown that well-controlled, dose-adjusted VKAs are a safe and effective therapy to reduce the risk of TE event in AF patients. However, the practical difficulties in maintaining the therapeutic INR, understandably raise many concerns that the efficacy and safety achieved with VKAs in clinical trials might not reflect what can be observed in daily clinical practice. Clinical trials monitor patients very closely, more than might be practical or possible in routine clinical practice. Moreover, to meet trial design and ethical requirements, clinical trials often exclude patients at high risk of bleeding while also recruiting relatively few elderly patients [130,131].

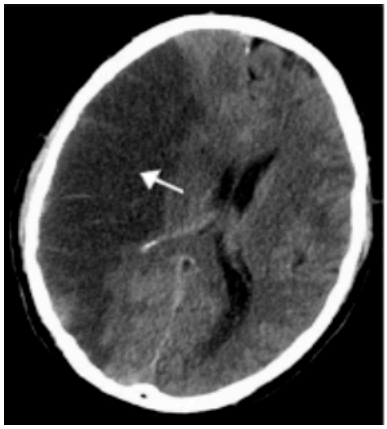
VKAs have a narrow therapeutic range and they interact with many common foods and medicines. In this regard, VKAs require close monitoring and frequent dose adjustments to ensure that patients receive a dose that consistently maintains a reduced risk of stroke without increasing the risk of bleeding. Really, maintaining therapeutic range in patients treated with VKAs has always been challenging and the potential consequences of deviating from the therapeutic range can result in a devastating event. Several indices of anticoagulation quality have been proposed, TTR and PINRR being the most widely used [132]. Both major bleeding and mortality rates have been reported to be significantly higher in patients with TTR < 60% compared to those with TTR > 75% [133].

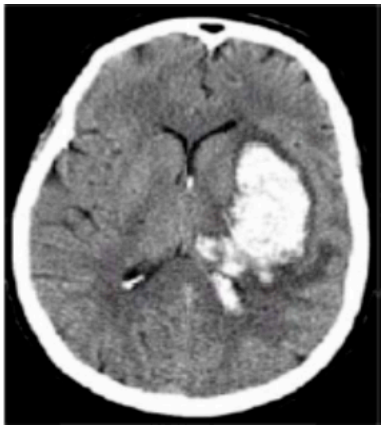
In a recent meta-analysis of AF studies performed worldwide between 1990 and 2013 they found that just only 61% of their TTR and only 56% of their PINRR were in therapeutic range [132]. Moreover, a recently published study looked at the length of time patients spend in the target range of VKAs in France, Germany, Italy and the United Kingdom. They found that more than half the patients evaluated in France (52%), Germany (56 %) and Italy (54 %) had poorly controlled treatment (defined as spending less than 70 per cent of time within the target therapeutic range). In the United Kingdom this proportion was just 35%, and this difference may be attributable to the use of specialized clinics for monitoring treatment, where patients were more closely followed and the dose of VKAs was adapted in a more responsive manner than was the case in the other countries [134].

It is clearly recognized that it's not simply prescribing VKAs as very close attention to the quality of anticoagulation control is necessary. Moreover, it is not easy to achieve a high TTR/PINRR because of the inconvenience of regular anticoagulation monitoring and the various food/drug restrictions associated with the VKAs.

More recently, we have had the NOACs [135] available, which offer efficacy, safety and relative convenience compared to the VKAs, for TE prevention in AF. When a patient is first started on a VKA, the inception period is often associated with poor TTR/PINRR, and an excess of TE event has been noted in various studies and this discourages the use of VKAs stress test in VKAs naïve patients [136,137].

A major challenge therefore is to easily identify those AF patients who are less likely to do well on VKAs (with an expected poor TTR/PINRR) who may be best switched to NOACs, rather than being exposed to suboptimal TTRs and inadequate thromboprophylaxis, exposing the patients to fatal and disabling strokes.





Ischemic stroke……..**Hemorrhagic stroke**

Figure 2.1: The estimation of risk-benefit ratio of vitamin K antagonists is a continuous challenge.

A continuous challenge to refine TE risk scores and to define truly low risk patients:

Medicine might be considered as a science of uncertainty and an art of probability [138], and this is especially true in the decision making process to prevent stroke in patients with AF. In clinical practice, the decision to initiate anticoagulation in patients with AF starts with an attempt to quantify the patient's stroke risk. It has been recognized for some time that TE risk in patients with AF depends less on the "quantity" or "severity" of their AF and more on other clinical characteristics. Epidemiological and observational studies continue to analyze these clinical variables with the aim to yield a number of risk stratification schemes to help guide anticoagulation decisions.

$CHADS_2$ score was validated and conceived in the year of 2001 with the aim of identifying patients at high risk of TE events [89]. However, patients at low risk according to $CHADS_2$ score continued to have significant annual stroke rate (i.e. 2%) [93,139], this yielded a great interest to investigate the significance of other risk factors

not included in the $CHADS_2$ score and, in turn, has led to a shift in the clinical paradigm with a new aim to identify "truly low risk" patients using CHA_2DS_2-VASc score [92]. The advantages of the CHA_2DS_2-VASc score were clearly demonstrated in a retrospective analysis performed in the Danish nationwide cohort study, which involved patients with $CHADS_2$ score 0 (i.e. low-risk patients). When their stroke risk was sub-stratified according to the CHA_2DS_2-VASc score, those with a $CHADS_2$ score of 0 had stroke rates ranging from 0.8% per year to 3.2% per year [93]. However the ability of the of the CHA_2DS_2-VASc score to define truly low risk patients might be still in question as it can be concluded from a recently published large nationwide cohort from the real world in which low risk patients according to the CHA_2DS_2-VASc were having an annual stroke rate [100] that might be considered a significant risk which may deserve anticoagulation with the NOACs [140]. This puts a continuous challenge to truly identify low risk patients in the real world practice and points to the need for directing more efforts towards improvement of the performance of the current TE risk scores and to define more new risk factors.

In this regard, two new TE risk scores (i.e. R_2CHADS_2 [101], and the ATRIA TE risk scores [102]) include new TE risk factors in their schemes (i.e. renal dysfunction and proteinuria) and where proposed to improve the ability to predict TE event.

Renal dysfunction is still one of the current challenges as it is well known that patients with renal dysfunction are at an increased risk of TE event and of (i.e. if they are anticoagulated) bleeding [120,121]. Giving the increased prevalence of aging population, hypertension, heart failure and diabetes, the associated increased incidence of renal dysfunction becomes a global challenge. This challenge extends to the dilemma of anticoagulation for patients with AF [119]. Therefore, it has been proposed that renal dysfunction should be added to the widely used stroke risk stratification schemes for AF

(i.e. $CHADS_2$ and CHA_2DS_2-VASc), as this will effectively lower the threshold for anticoagulant treatment in these patients. On the other hand, some have argued that renal dysfunction is a strong risk factor for bleeding complications in conjunction with anticoagulation, and thus, renal disease rather should invoke caution and a raised threshold for initiating anticoagulation [119, 120,121].

Deserve to mention here, the special challenge of how to avoid further TE event in anticoagulated patients. It is well known from different studies that there is annual TE rate of about 1-2% despite anticoagulation. This group of patients at high risk represents a real challenge as the identification of patients who remain at high risk of TE event despite anticoagulation may affect treatment strategies of clinical practice [94,120].

Really, the serious and continuous challenge which is facing the cardiologists in the daily clinical practice is the fact that the majority of patients with AF are often elderly and have associated comorbidities like hypertension and prior stroke which are also considered bleeding risk factors and this means that the same patient could have moderate to high risk of both stroke and bleeding at the same time [85].

However, in the real world practice, prescribing anticoagulant agents for patients with AF is ultimately a clinical decision to be made between the physician and the patient. Risk stratification schemes could aid in our clinical decision making only if we use them and it is clear that there is a continuous need to develop more accurate stroke risk estimators.

Chapter III

Future considerations in the dilemma of non-valvular atrial fibrillation and oral anticoagulation

To prescribe VKAs or NOACs, how will it be a simple decision for cardiologists?

Proper prevention of TE event with oral anticoagulants is key to modern management of AF patients [77]. Now and for many years, VKAs have been the most common oral anticoagulants used in many countries, despite our recognition that it's not simply prescribing VKAs as very close attention to quality of anticoagulation control is necessary [72]. This became more pronounced as a TTR of >70% is recommended, to maximize the efficacy and safety of the VKAs [72,76].

It is clear that VKAs continue to be inconvenient drugs as they have significant inter- and intra-patient variability, partly from diet and drug interactions, thus necessitating regular and continuous INR monitoring [72]. These concerns have led to the introduction of the NOACs, which have more efficacy, safety and convenience compared to the VKAs [135]. Thus, poorly controlled VKAs therapy patients would beneficiate from switching to anticoagulant therapy with one of the NOACs, especially if they were VKA experienced patients. But the critical question now is what about decision making in anticoagulation naïve patients to start with VKAs or NOACs?

Due to the high cost of the NOACs, many healthcare systems mandate a trial of VKAs (i.e. VKAs stress test) for the initial 6 months, to determine whether a patient can do well on a VKAs and only if the TTR/PINRR is suboptimal (e.g. <60%) then a NOACs can be prescribed. But the fact that when a patient is first started on a VKA, the inception period is often associated with poor TTR/PINRR, may make the VKAs stress test a hazard approach as an excess of TE event has been noted in various studies [136,137].

Much of the recent and current efforts are therefore directed to easily identify those AF patients who are less likely to do well on VKAs (i.e. with a poor TTR/PINRR) who may be best switched to NOACs, rather than being exposed to suboptimal TTR/PINRR that

could expose the patient to fatal and disabling major bleeding or TE event and rather than using guesswork (or budget considerations) to decide between VKAs or NOACs in a newly diagnosed anticoagulation naïve patient. It is appreciated that rather than a 'trial of VKAs' for every patient, the decision-making for cardiologists could be easier, with the availability of a simple easy clinical tool to identify those patient who would do well on VKAs (i.e. with high TTR/PINRR) or conversely, who would on probability are likely to have low TTR/PINRR.

Although, more recently a simple clinical score (i.e. $SAMeTT_2R_2$) [114], has been proposed to help decision making by identifying those AF patients that would probably do well on VKAs with a high average TTR/PINRR. However, more future efforts should be directed to further validation and improvement of the performance of this score in contemporary real world populations of AF patients who are VKAs naïve patients in order to avoid the VKAs stress test.

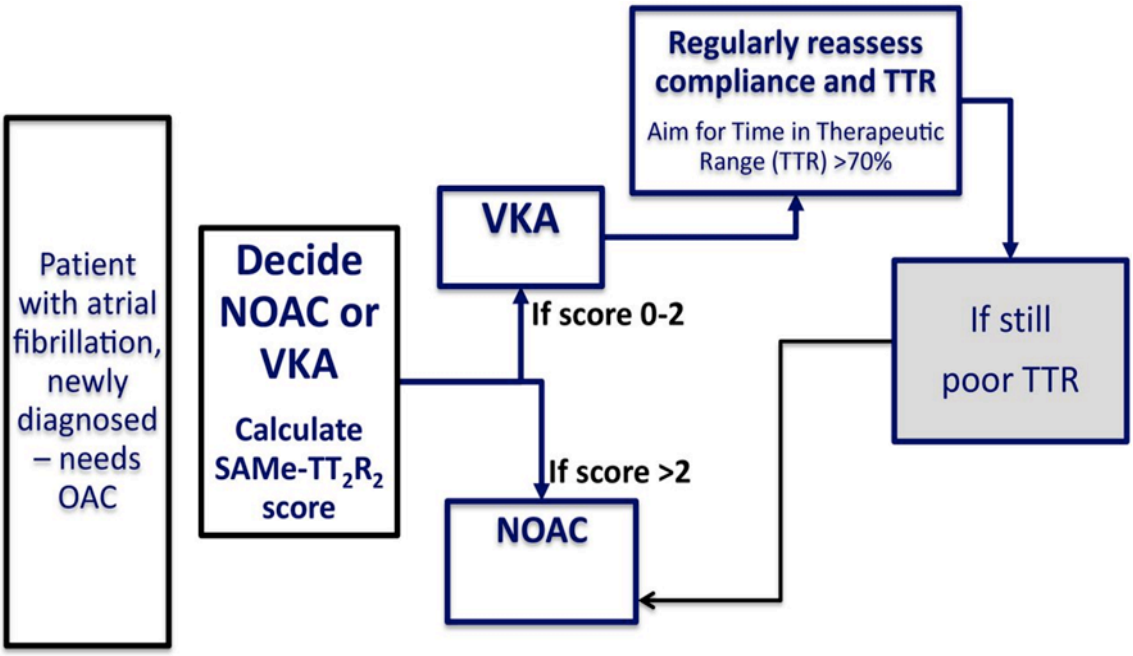


Figure 3.1: A proposed plan for using the SAMe-TT_2R_2 score and to help the decision making regarding the anticoagulation choice in naïve patients with NVAF [141]. NOAC: new oral anticoagulant; OAC: oral anticoagulation; SAMe-TT_2R_2: Sex female, Age < 60 years, Medical history [more than two comorbidities], Treatment [interacting drug, e.g. Amiodarone], Tobacco use [doubled], and Race [doubled]); TTR: time within therapeutic range; VKA: vitamin K antagonist.

In the future there is a need for continued improvement in patient risk stratification and personalization of care:

There is potential for improvement in the extent to which AF management is directed to the needs of individual patient, in terms of both biomedical and social factors, by expanding and making use of the evidence based on biomarkers, genomic factors and outcomes for a range of patients and therapies. One area that could be further developed is TE risk stratification, where our understanding of patient who should be prescribed anticoagulants for prevention of AF related TE event could be further refined. A better

understanding of that risk may make it possible to reduce the number of patients receiving anticoagulation in the future. In terms of social factors, there is also scope for patients' preference to play a larger role in the future in clinical decisions about which management options are most appropriate for them. Adapting management to patient needs and preferences can help improve compliance. For example, in terms of preferences for VKAs versus NOACs for anticoagulation, some patients may prefer the regular interaction they receive through monitoring when on VKAs. On the other hand, other patients, such as those who work full-time, may prefer the reduced burden associated with NOACs (the lack of a need for monitoring and fewer restrictions related to food and drug interactions). Ongoing clinical trials are currently gathering evidence to enable a better understanding of biomarkers, risk factors and outcomes in patient groups that have been less well studied. Biomarkers based risk scores for predicting TE event in AF could be available in the future. An example of these biomarkers is the natriuretic peptides as the previous studies described elevated levels of natriuretic peptides in patients with AF as compared to matched controls in sinus rhythm [142,143]. Moreover, it was thereafter reported that levels of natriuretic peptides fall rapidly following restoration of sinus rhythm [144]. Furthermore, a community based cohort study on elderly adults demonstrated that elevated natriuretic peptides levels predicts an increased risk for development of AF independent of other risk factors including echocardiographic parameters [145,146]. The future could carry new TE risk scores which incorporate biomarkers beside the clinical variables as such scores may provide more accurate estimates of risk than the current risk scores.

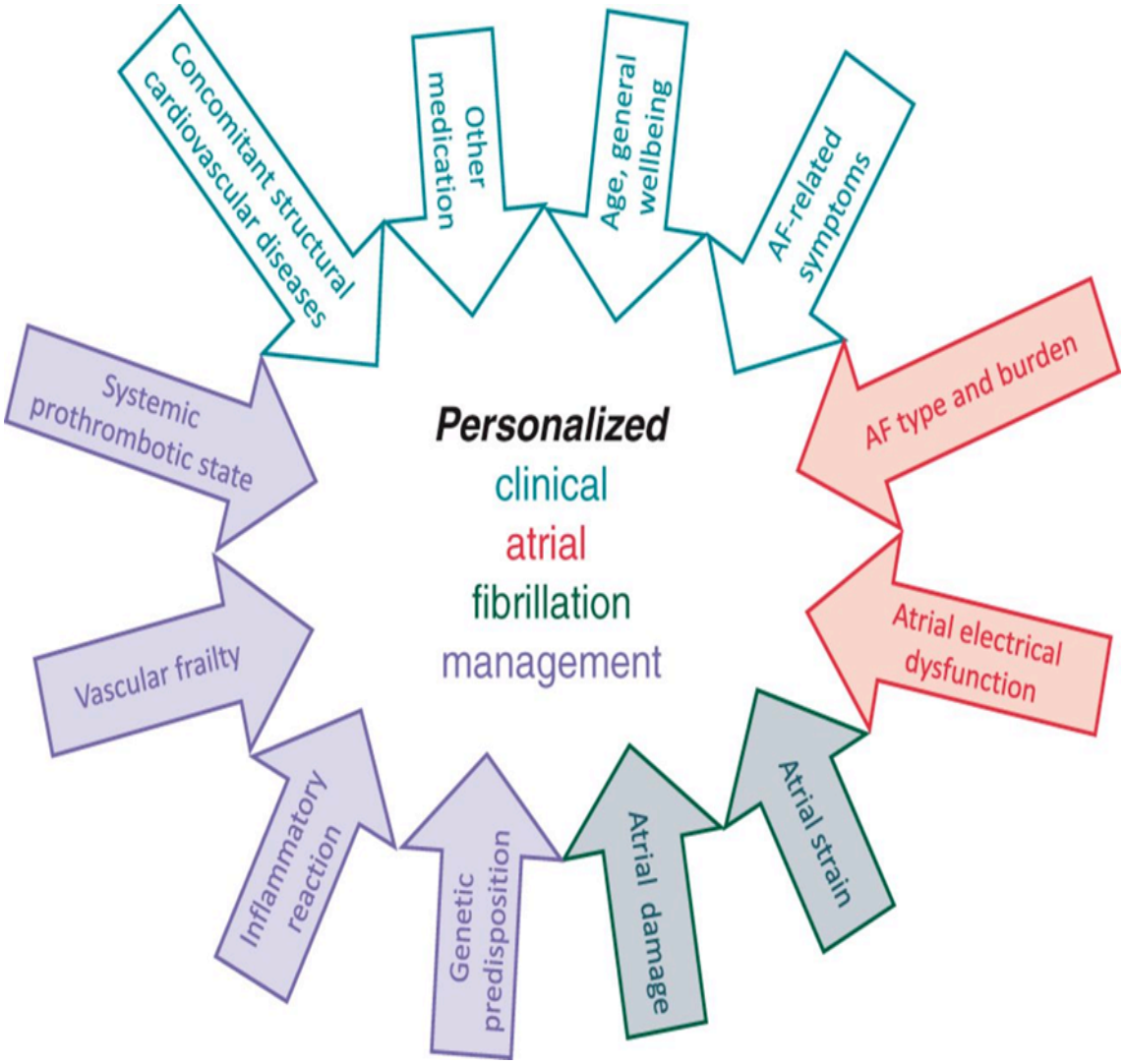


Figure 3.2: In the future every patient with atrial fibrillation may have his own management plan according to his overall clinical, laboratory, imaging and genetic characteristics [147].

Chapter IV

Evaluation of SAMe-TT_2R_2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists

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CLINICAL RESEARCH
Atrial fibrillation

Evaluation of SAMe-TT_2R_2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists

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Aims Clinicians need to get better at identifying patients who would have poor quality of anticoagulation control with vitamin-K antagonists (VKAs). We assessed the predictive ability of SAMe-TT_2R_2 score, recently conceived for the prior purpose, and examined its relationship with major bleeding, thromboembolic (TE) complications, and death.

Methods and results Retrospectively, 911 consecutive patients with non-valvular atrial fibrillation (NVAF) started on VKAs within 8 months were studied. The percentage of international normalized ratios in therapeutic range (PINRR) at different levels was used as a metric of anticoagulation quality. We also tested the SAMe-TT_2R_2 predictability for major bleeding, TE complications, and death throughout 10 ± 3 months. The PINRR decreased from 62% at zero point to 53% at ≥4 points of SAMe-TT_2R_2. 82.1% of patients who achieved PINRR ≥ 70% had 0 or 1 point of SAMe-TT_2R_2. SAMe-TT_2R_2 performed significantly better at PINRR 70% than at 65 and 60% (c-statistic = 0.60 vs. c-statistic = 0.56). The calibration of SAMe-TT_2R_2 was excellent (Hosmer–Lemeshow test *P*-values ≥ 0.6). SAMe-TT_2R_2 showed significant association with the composite outcome of major bleeding, TE complications, and death [*n* = 98; hazard ratio (HR) = 1.32; 95% confidence interval (CI) 1.08–1.60]; the c-statistic was 0.57 (95% CI: 0.51–0.62) and *P* = 0.03. As individual outcomes, SAMe-TT_2R_2 was significantly associated with death (*n* = 60; HR = 1.3; 95% CI: 1.03–1.69), but not with either major bleeding (*n* = 30; HR = 1.2; 95% CI: 0.85–1.76) or TE complications (*n* = 15; HR = 1.01; 95% CI: 0.58–1.77).

Conclusion Among NVAF patients, SAMe-TT_2R_2 could represent a useful clinical tool to identify patients who would have poor quality of anticoagulation control with VKAs. SAMe-TT_2R_2 successfully predicts the composite outcome of major bleeding, TE complications, and death.

Keywords Atrial fibrillation • SAMe-TT_2R_2 • Vitamin-K antagonists • Anticoagulation quality control

Introduction

Vitamin-K antagonists (VKAs) are highly effective for the prevention of thromboembolic (TE) complications in patients with non-valvular atrial fibrillation (NVAF),[1] and are still the most used oral anticoagulants in these patients.

However, achieving the best benefit and safety from VKAs in the clinical practice remains a major challenge mainly because of their unpredictable anticoagulant response. Several reports indicate a strong association between international normalized ratio (INR) controls out of range and the increased rates of both stroke and major haemorrhage in patients on VKAs.[2–4]

With the availability of new oral anticoagulants (NOACs), the landscape of anticoagulation management in NVAF has been revolutionized.[5] Clinicians now need to get better at identifying the patients who would do well on VKAs and those less likely to do well, for whom the use of NOACs can be considered as an alternative therapeutic option aiming to avoid stroke and bleeding.

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What's new?

- The clinicians are in continuous need to refine their judgment regarding the correct identification of patients who would do well on vitamin-K antagonists; our study provides a good and unique advancement in this regard.
- Our study shows that SAMe-TT_2R_2 appeared to be an acceptable predictor of the quality of anticoagulation control in patients with non-valvular atrial fibrillation on vitamin-K antagonists, and its prediction ability can be improved significantly if integrated with the physician judgment, which takes into account the overall patients clinical characteristics.
- The analysis of our study demonstrated that if other important risk factors of having low anticoagulation quality are added as strong independent predictors to SAMe-TT_2R_2 score, the discriminative power and its clinical utility can be improved substantially in a real-world practice.

Recently, Apostolakis *et al.*[6] proposed the SAMe-TT_2R_2 [Sex (female); Age < 60 years; Medical history (more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled)] score to help in identifying individuals who will have or not good INRs control.

In this study, we aimed to assess the ability of the new SAMe-TT_2R_2 risk score at predicting different levels of anticoagulation control in a real-world cohort of NVAF patients. We also examined the relationship of SAMe-TT_2R_2 score with major bleeding, TE complications, and all-cause mortality; either as a composite outcome or as individual events.

A secondary goal of our analysis was to investigate some of the cardinal variables that have a widely held belief as strong predictors of poor anticoagulation control.

Methods

Patient's sample

Retrospectively, we identified all consecutive patients of ≥18 years of age with a confirmed diagnosis of atrial fibrillation (AF) on VKAs attending outpatient cardiology consultations at a tertiary hospital between January 2011 and February 2013. Only patients who fulfilled the following criteria were included in this study: patients with permanent or paroxysmal AF recently started on VKAs (i.e. not more than 8 months passed since the beginning of their VKAs therapy), and who have regular visits for INR measurements. Patients with prosthetic valve ($n = 452$), rheumatic heart disease ($n = 43$), active cancer ($n = 41$), dementia ($n = 26$), and/or interrupted VKA >3 days ($n = 73$) were excluded. Thus, the final analysed cohort consisted of 911 patients. A detailed medical history was recorded for each patient, and the basal clinical characteristics at study entry together with information on follow-up were carefully gathered by cardiologists.

The vast majority of patients were on acenocoumarol (93%; and the remaining patients were on warfarin). The INRs measurements were performed at the outpatient anticoagulation clinics in our institution. The available consecutive INRs values for each patient (after excluding the INR measurements during the first month of VKAs initiation) were used to measure the quality of anticoagulation control.

We used the percentage of INRs within the therapeutic range (PINRR) as an index of the quality of oral anticoagulation control. The PINRR method utilizes the number of INRs within the target range (i.e. INR between 2 and 3) divided by the overall number of INRs during that selected time interval.

Patients were followed up to 1-year after the enrolment or until major bleeding, TE complications, or death occurred, whichever comes first. Data on major bleeding and TE complications were gathered from the cardiology clinic visits and records, and through hospital files as well as through primary care centres reports.

The study was approved by the Clinical Research Ethics Committee of our hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

SAMe-TT_2R_2 score calculation

The recently published SAMe-TT_2R_2 score[6] was applied to the database, to evaluate its performance at predicting poor anticoagulation quality controls. For each patient, the SAMe-TT_2R_2 score was calculated as the sum of points after adding one point each for female gender, age < 60 years, medical history of >2 co-morbidities (e.g. hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, prior stroke, pulmonary disease, hepatic, or renal disease), treatment (interacting drugs, e.g. Amiodarone for rhythm control), and two points each for tobacco use and non-White race.

Since all patients in our study were Whites, the maximum score will be of six points.

Patients with SAMe-TT_2R_2 score between 0 and 1 were classified as having low risk of not doing well on VKAs, and ≥2 as at high risk of not doing well with VKAs, as was early described by Apostolakis *et al.*[6]

Variables and definitions

We defined renal dysfunction as glomerular filtration rate <30 mL/min/1.73m^2, while liver disease was defined as cirrhosis or elevated liver transaminases enzymes >3 times higher than the upper limit of normal and elevated total bilirubin >2 times higher than the upper limit of normal. Alcohol abuse was defined as a daily consumption of ≥40 g of ethanol. Past history of malignant disease was assigned, if there is non-active cancer and not being under chemotherapy or radiotherapy in the 6 months previous to the study entry.

We used the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria to define major bleeding.[7] Thus, a major bleeding event was adjudicated if one of the following criteria was met: fatal bleeding and/or symptomatic bleeding in a critical area or organ (e.g. such as intracranial, intraspinal, intraocular, retroperitoneal, atraumatic intraarticular, pericardial, or intramuscular with compartment syndrome); and/or bleeding causing drop of haemoglobin of ≥2 g/dL, or leading to transfusion of ≥2 units of whole blood or packed red blood cells.

A TE complication was defined as the occurrence of ischaemic stroke, transient ischaemic attack, or peripheral embolism. Diagnosis of stroke or transient ischaemic attack required an acute neurological deficit lasting for more than or <24 h, respectively, which could not be explained by other causes and with at least one image test (CT or MRI) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism leading to an abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in the absence of another mechanism such as atherosclerosis, instrumentation, or trauma.

Statistical analysis

Qualitative data were expressed as frequencies and percentages, while quantitative data were summarized as mean and standard deviation. Comparison between qualitative data was performed using the χ^2 test or the Fisher's exact test, as appropriate. The Student's *t*-test or analysis of variance (ANOVA) test was used to compare quantitative data.

Since there is no firm global consensus on the acceptable level of anticoagulation control, and different anticoagulation control levels proved to be meaningful in different reasonable studies,[2,3,8,9] the performance of SAMe-TT_2R_2 risk score was tested regarding different meaningful levels of anticoagulation control: namely PINRR 70, 65, and 60%. This was done by entering the SAMe-TT_2R_2 score, either as a continuous or categorical variable, into separate univariate logistic regression models.

For a better understanding of the effects of the component variables on SAMe-TT_2R_2, we also entered all of the SAMe-TT_2R_2 individual variables into a logistic regression model to test their relationship with PINRR at 65%. We used this cutoff point (i.e. 65%) because it was recently advised to be used for the validation of SAMe-TT_2R_2.[6]

We also attempted to identify other variables correlated with the PINRR cutoff point at 65%. This was used by univariate logistic regression analyses. The effect of variables comprising the SAMe-TT_2R_2 as well as the effect of other variables, which were found to be correlated with PINRR at 65%, were reported as odds ratio (OR) and 95% confidence interval (CI).

All the covariables demonstrating significant association with PINRR at 65% were added to SAMe-TT_2R_2 (as a continuous variable). Thereafter, we analysed the improvement in the performance of SAMe-TT_2R_2 by comparing the c-statistic values of the original score and after adding the above-mentioned covariables. This comparison was done using the Delong method.

We also tested the ability of SAMe-TT_2R_2 to predict major bleeding, TE complications, or all-cause mortality, either as a composite outcome or as individual events, by using Cox proportional hazard models.

The discriminative capacity of the SAMe-TT_2R_2 score to distinguish between patients who will and who will not develop an event of interest was determined by calculating the c-statistic, which is equivalent to the area under the receiver-operating characteristic curve.

The calibration of the model was assessed with the Hosmer–Lemeshow goodness-of-fit test. This test is commonly used to validate models that have just been developed, but it is equally useful for validating (using an external database) the existing logistic models, such as the SAMe-TT_2R_2 model. This test determines how closely the predicted event rate approximates the observed event rate over a range of scores. A significant value of *P* indicates a lack of fit.

A two-sided $P < 0.05$ was considered statistically significant for all analyses. All the analyses were performed with SPSS 21, and by using the MedCalc statistical software version 13.

Table 1 Baseline characteristics

Age, years	73 ± 11
Men	605 (66.4%)
Systolic blood pressure at study entry	139 ± 28
Hypertension	678 (74.4%)
Current smoking	77 (8.5%)
Diabetes mellitus	220 (24.1%)
Heart failure	343 (37.7%)
Peripheral arterial disease	92 (10.1%)
History of stroke or TIA	103 (11.3%)
Coronary artery disease	127 (13.9%)
COPD	183 (20.1%)
CHA_2DS_2-VASc	
= 0	62 (6.8%)
≥ 1	849 (93.2%)
≥ 2	772 (84.7%)
History of malignancy	135 (14.8%)
HAS-BLED	
0	47 (5.2%)
1	160 (17.6%)
2	365 (40.1%)
3	261 (28.6%)
4	69 (7.6%)
5	6 (0.7%)
6	3 (0.3%)
Alcohol consumption ≥40 g/daily	81 (8.9%)
Prior bleeding	115 (12.6%)
Thyroid disorder:	
Hyperthyroidism	14 (1.5%)
Hyporthyroidism	79 (8.7%)
Anaemia	178 (19.5%)
eGFR < 30 mL/min/1.73m^2	36 (4%)
Abnormal liver function[a]	9 (1%)
PINRR	58% ± 18%

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke, vascular disease, female sex category; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HAS-BLED, uncontrolled Hypertension: systolic >160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly > 65 years, Drugs/alcohol concomitantly; TIA, transient ischaemic attack. PINRR, percentage of INRs in therapeutic range.
[a]Defined as cirrhosis or elevated liver transaminases enzymes >3 times higher than the upper limit of normal and elevated total bilirubin >2 times higher than the upper limit of normal.

Results

Baseline characteristics

Our cohort consisted of 911 patients with NVAF on VKAs. *Table 1* summarizes the baseline characteristics of the patients included in the study. Mean age was 73 ± 11 years, and 66.4% were men.

Mean PINRR of the study cohort was 58% ± 18%. Every patient had at least nine consecutive INR measurements (range: 9–15 INR measurements) with intervals <42 days.

Predictive ability of SAMe-TT_2R_2

The relation between SAMe-TT_2R_2 (either as a continuous or a categorical scale) and the anticoagulation quality in terms of mean PINRR values is presented in *Table 2*. The mean PINRR values decreased from 62% at zero point to 53% at ≥4 points of SAMe-TT_2R_2 (ANOVA *P*-value < 0.001). Moreover, the anticoagulation quality clearly decreased from 59% in the low risk to 54% in the high SAMe-TT_2R_2 risk group ($P = 0.001$).

As *Figure 1* illustrates, the majority of patients (82.1%) who achieved a high level of anticoagulation control (i.e. PINRR ≥ 70%)

Table 2 Percentage of INRs in therapeutic range across the different SAMe-TT_2R_2 scores and categories

	Number of patients	PINRR % (mean ± SD)
Continuous SAMe-TT_2R_2		
0	247	62 ± 18
1	425	58 ± 18
2	174	54 ± 19
3	46	55 ± 15
≥4	19	53 ± 18
Categorical SAMe-TT_2R_2		
Low risk: 0–1 point	672	59 ± 18
High risk: ≥2 points	239	54 ± 19

INR indicates international normalized ratio; PINRR, percentage of INRs in therapeutic range; SAMe-TT_2R_2, Sex female, Age < 60 years, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled), and Race (doubled); SD, standard deviation.

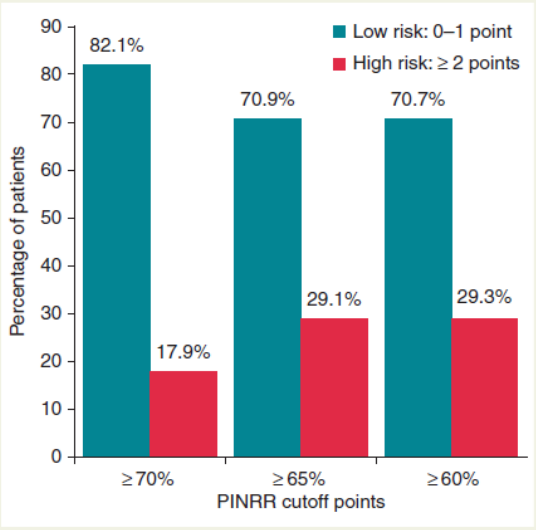

Figure 1 The rate of patients in each risk strata of the SAMe-TT_2R_2 score at different PINRR cutoff points. SAMe-TT_2R_2 indicates Sex female; Age < 60 years; Medical history [more than two comorbidities]; Treatment [interacting drug, e.g. Amiodarone]; Tobacco use [doubled], and Race [doubled]); INR, international normalized ratio; PINRR, percentage of INRs in therapeutic range.

had 0 or 1 point of SAMe-TT_2R_2. However, we found that the prior rate was significantly reduced when we set the PINRR below 70% (70.9% for PINRR ≥ 65%, and 70.7% for PINRR set at ≥60%; $P < 0.001$ for comparisons with PINRR set at ≥70%).

The performance of the SAMe-TT_2R_2 score, in terms of OR and c-statistic, at different PINRR cutoff points is represented and compared in *Table 3*. The best SAMe-TT_2R_2 performance was found at the highest PINRR cutoff point of 70%, regardless of whether it was considered as a continuous or categorical variable: OR = 1.5 and the c-statistic = 0.60 (95% CI: 0.56–0.64, $P < 0.001$) for continuous SAMe-TT_2R_2, and OR = 1.9 with the c-statistic = 0.56 (95% CI: 0.53–0.60, $P < 0.001$) for categorical SAMe-TT_2R_2.

The significant difference ($P = 0.01$), however, was found during the comparison between the continuous SAMe-TT_2R_2 at predicting PINRR ≥ 70% and continuous SAMe-TT_2R_2 for predicting PINRR < 70%.

The calibration of continuous SAMe-TT_2R_2 was excellent regardless of the cutoff points used (*P*-value of Hosmer–Lemeshow being ≥0.6).

The effect of the individual variables comprising SAMe-TT_2R_2 at predicting PINRR cutoff point of 65% (the advised cutoff point to use SAMe-TT_2R_2)[6] is summarized in *Table 4*. Three of the five variables forming SAMe-TT_2R_2, namely female sex (OR = 1.48, 95% CI: 1.12–1.96), medical comorbidities (OR = 2.19; 95% CI: 1.61–2.98), and treatment interaction (e.g. amiodarone) (OR = 1.48, 95% CI: 0.98–2.24), were independent predictors of poor quality of anticoagulation control with VKAs.

The effect of alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or left ventricular ejection fraction (LVEF) < 40%, history of malignancy, and chronic liver disease on the quality of INR control (PINRR < 65%) is presented in *Table 4*. All of these six variables except chronic liver disease were significantly associated with poor quality of INR control defined as having PINRR < 65%.

Adding all of the prior five clinical covariables—showing significant association with poor INR control—as independent predictors over the SAMe-TT_2R_2 score, resulted in a substantial and significant improvement in the score performance for predicting PINRR cutoff point of 65%: the c-statistic = 0.65 (95% CI: 0.61–0.68, $P < 0.0001$), as compared with the c-statistic value of 0.56 (95% CI: 0.53–0.60, $P = 0.001$) when using solely the original SAMe-TT_2R_2 model.

SAMe-TT_2R_2 and the composite outcome of major bleeding, thromboembolic complications, or death

During the follow-up (10 ± 3 months), 98 (10.8%) patients developed major bleeding, TE complications, or death. There was a significant association between SAMe-TT_2R_2 and the composite outcome [hazard ratio (HR) = 1.32; 95% CI: 1.08–1.60, $P = 0.006$]; the c-statistic was 0.57 (95% CI: 0.51–0.62, $P = 0.03$).

The addition of alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or left ventricular ejection fraction (LVEF) < 40%, and history of malignancy, over SAMe-TT_2R_2, significantly improved the score performance: c-statistic = 0.70 (95% CI 0.65–0.75) ($P = 0.007$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

SAMe-TT_2R_2 and major bleeding

Thirty (3.3%) patients developed major bleeding events during the follow-up. There was no significant association between SAMe-TT_2R_2 and major bleeding (HR = 1.2; 95% CI: 0.85–1.76, $P = 0.28$); the c-statistic was 0.57 (95% CI: 0.47–0.67, $P = 0.20$).

The performance of SAMe-TT_2R_2 significantly improved by adding the above-mentioned five clinical variables over the score: c-statistic = 0.68 (95% CI: 0.59–0.77) ($P < 0.001$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

Table 3 Performance of SAMe-TT_2R_2 at different PINRR cutoff points

	PINRR ≤ 70% *n* = 671	PINRR ≤ 65% *n* = 554	PINRR ≤ 60% *n* = 433
Continuous SAMe-TT_2R_2			
OR (95% CI)	1.5 (1.2–1.8)	1.3 (1.1–1.5)	1.2 (1.1–1.4)
c-statistic (95% CI)	0.60 (0.56–0.64)*	0.56 (0.53–0.60)	0.56 (0.52–0.59)
Categorical SAMe-TT_2R_2			
OR (95% CI)	1.9 (1.3–2.7)	1.5 (1.1–2.0)	1.4 (1.0–1.8)
c-statistic (95% CI)	0.56 (0.52–0.60)†	0.54 (0.50–0.57)	0.53 (0.49–0.57)

CI refers to confidence interval; OR, odds ratio; INR, international normalized ratio; PINRR, percentage of INRs in therapeutic range; SAMe-TT_2R_2, Sex female; Age < 60 years; Medical history (more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled); SD, standard deviation.
*$P = 0.01$ for the comparison of c-statistic value of continuous SAMe-TT_2R_2 at predicting PINRR ≤ 70% vs. the remaining c-statistic values.
†$P = 0.6$ for the comparison of c-statistic values of SAMe-TT_2R_2 at predicting different PINRR cutoff points.

Table 4 Individual SAMe-TT_2R_2 variables and other risk factors in relation with PINRR < 65%

	OR (95% CI)	*P*-value
Female sex	1.48 (1.12–1.96)	0.006
Age < 60 years	1.38 (0.93–2.04)	0.11
More than two medical comorbidities	2.19 (1.61–2.98)	<0.0001
Treatment interaction (e.g. Amiodarone)	1.48 (0.98–2.24)	0.06
Tobacco	1.17 (0.92–1.50)	0.21
Alcohol abuse	3.08 (1.73–5.48)	<0.0001
eGFR < 30 mL/min/1.73 m^2	1.49 (1.11–2.01)	0.008
History of malignancy	1.93 (1.29–2.91)	0.002
Diabetes mellitus	1.56 (1.13–2.16)	0.007
Heart failure or LVEF < 40%	1.66 (1.27–2.20)	<0.0001
Liver disease	1.61 (0.31–8.38)	0.57

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PINRR, percentage of INRs in therapeutic range.

SAMe-TT_2R_2 and thromboembolic complications

Fifteen (1.6%) TE events occurred during the follow-up (10 strokes, 2 transient ischaemic attacks, and 3 peripheral embolisms). The SAMe-TT_2R_2 was not significantly associated with TE complications (HR = 1.01; 95% CI: 0.58–1.77, $P = 0.90$); the c-statistic was 0.49 (95% CI: 0.35–0.63, $P = 0.94$). However, the addition of the above-mentioned five clinical variables over SAMe-TT_2R_2 significantly improved its performance: c-statistic = 0.62 (95% CI: 0.49–0.75) ($P = 0.02$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

SAMe-TT_2R_2 and all-cause mortality

During the follow-up, 60 (6.6%) patients died. The increase in the SAMe-TT_2R_2 score was significantly associated with all-cause mortality HR = 1.3 (95% CI: 1.03–1.69); the c-statistic value was 0.57 (95% CI: 0.50–0.64, $P = 0.08$).

The performance of SAMe-TT_2R_2 improved significantly by adding alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or LVEF < 40%, and history of malignancy over the score (c-statistic = 0.75 (95% CI 0.69–0.81) ($P < 0.001$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

Discussion

The VKAs represent the most commonly used oral anticoagulant therapy in patients with NVAF, but in everyday practice there are still many difficulties in reaching an optimal management with VKAs.[4] There is now a great interest in identifying those patients who are at risk of having a poor anticoagulation control with VKAs and therefore could be potential candidates for prescribing NOACs which have more predictable anticoagulant effect, and were found to be superior to VKAs, particularly as long as the level of anticoagulation control is decreasing.[8,9]

In our cohort analysis, we studied for the first time, the predictive ability of the new SAMe-TT_2R_2 at different interesting and clinically meaningful levels of anticoagulation control, in a real-world cohort of patients with NVAF. Generally, we observed that SAMe-TT_2R_2 exhibited a statistically significant ability to predict the quality of anticoagulation control with VKAs.

Since absolute difference of 5% in the level of anticoagulation control has been considered as constituting a meaningful difference in performance and probably the standard for clinically important differences,[10] we tested the performance of SAMe-TT_2R_2 at different interesting PINRR cutoff points (i.e. 60, 65, and 70%) which had shown clinical significance in various studies and in a reasonable recommendation.[2,3,8,9] Remarkably, the SAMe-TT_2R_2 predictive model showed a significantly better predictability at a relatively high PINRR cutoff point of 70%, as compared with lower PINRR cutoff points (i.e. 60 and 65%). In addition, SAMe-TT_2R_2 as a categorical scale demonstrated that patients classified as at high risk of having poor quality of INR control had significantly lower PINRR value (*Table 2*). This finding is consistent with a recent validation study of SAMe-TT_2R_2 in which there was a clear decline of the mean level of anticoagulation control from 74% in low risk to 68% in the high-risk category.[11]

The fact that in our analysis SAMe-TT_2R_2 showed incremental improvement in its performance from PINRR cutoff point of 60%

across 65–70% may partially reflect the findings described in the original SAMe-TT_2R_2 validation cohort[6] in which the best performance of SAMe-TT_2R_2 was tested at the outliers groups, and not on the average level of anticoagulation control.

On the other hand, Apostolakis *et al.*[6] advised using a mean level of anticoagulation of ~65%, given that at this value the SAMe-TT_2R_2 score could aid in the decision making by identifying patients with AF who would have high quality of anticoagulation control with VKA (score = 0–1) from those who are at risk of suboptimal anticoagulation (score ≥ 2). However, in our analysis, at PINRR cutoff point of 65%, the performance of categorical SAMe-TT_2R_2 (0–1 point vs. ≥2 points) was rather modest (c-statistic = 0.54; P = 0.06). In this regard, our results are concordant with the recent finding of Lip *et al.*,[12] who evaluated the SAMe-TT_2R_2 score at predicting labile INR and reported a modest performance with the c-statistic value of 0.58.

In the present paper, we also tested the ability of other risk factors, beyond the SAMe-TT_2R_2 variables, at predicting the PINRR cutoff point of 65% (*Table 4*). We found that five of them (history of cancer, alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, and heart failure/LVEF < 40%) were significant predictors of having TTR < 65%. Notably, these five strong prognosticators found in our study also had demonstrated a strong independent association with low level of anticoagulation control in the inception and experienced periods of the VARIA study.[13]

Moreover, in our study, it stands to reason that these five cardinal risk factors significantly improved the discriminative capacity of SAMe-TT_2R_2 (c-statistics improved from 0.56 to 0.65, P = 0.004 for comparison). This interesting finding could improve the clinical utility and accuracy of SAMe-TT_2R_2 in a real-world practice if the prior five risk factors are taken into account. Therefore, in the present analysis we provide a reasonable and logistic assumption that the SAMe-TT_2R_2 score can be improved significantly by including more variables such as the variables found in our study. In this regard, SAMe-TT_2R_2 can be improved significantly if it is integrated with the physician judgment which takes into account other clinical risk factors that had a widely held belief about their role in the dilemma of INR control.

In the present study, we found that SAMe-TT_2R_2 has a good ability to capture the baseline risk of developing the composite outcome of major bleeding, TE complications, and death. However, the ability of SAMe-TT_2R_2 for predicting major bleeding as an individual outcome was not better than chance, as was also recently reported in another study with similar sample size to our cohort.[11] Nonetheless, a recent study by Lip *et al.*[12] showed a significant association between SAMe-TT_2R_2 and major bleeding in 4637 AF patients on VKA.[12] Another study by Gallego *et al.*[14]—including 972 NVAF patients on acenocumarol—demonstrated a trend towards prediction of major bleeding (HR = 1.23; 95% CI: 0.99–1.53, P = 0.059).[14]

Similarly, we found no relationship between SAMe-TT_2R_2 and TE complications. This might be explained by the very few number of TE events in our study which could limit the capacity of the score to discriminate between patients who did and those who did not develop a TE complication. In an Italian study of about 1000 AF patients with 63 stroke/transient ischaemic attack, SAMe-TT_2R_2 was not significantly associated with stroke/transient ischaemic attack.[11] However, it is noteworthy that another recent study in which 379 stroke/TE events were recorded, a significant association was found between SAMe-TT_2R_2 and stroke/TE events. Anyhow, it should be noted that there are another specific scoring systems for predicting bleeding as well as TE complications in AF patients.[15,16]

With the availability of NOACs, the landscape of anticoagulation management in NVAF has been revolutionized,[5] and clinicians appreciate the methods and tools designed to refine their judgment regarding the correct identification of patients who would have high quality of anticoagulation control with VKAs and distinguish them from those less likely to do well on VKAs for whom the use of NOAC should be proposed as an alternative therapeutic option aiming to avoid the excess risk of stroke and bleeding.[17,18] For this purpose, SAMe-TT_2R_2 may represent an acceptable clinical tool which can facilitate the physicians decision-making process to optimize the oral anticoagulation management.

Limitations

The main limitation of our study is its retrospective design, but it has interesting strong points as it reflects real-world practice by enrolment of consecutive NVAF patients attending our outpatient cardiology clinics with the advantage of careful follow-up and data collection by cardiologists and of recording successive INR values, which give a reasonable index of the quality of anticoagulation control.

Of note, our study could be criticized by the fact that we used the PINRR method as an index of the quality of anticoagulation control. However, the quality of anticoagulation can be measured by a number of methods and no standardized consensus exists as to which is the best measure, and as such, all of the available methods have specific and known advantages and disadvantages. Additionally, the PINRR method is still a recognized method and proved to have a significant correlation with the Rosendaal method (r = 0.99, P < 0.001).[19]

Although we excluded groups of patients (i.e. believed to have poor adherence, more frequent INR measurements, and/or more dose adjustments) with active cancer, dementia, and interrupted VKAs, residual confounding is likely as we did not have enough data about the magnitude of dose adjustments in regard to the frequency of INR measurements and their specific relations to the other risk factors. Also, we were not able to collect data about other possible confounding variables such as educational level, socioeconomic status, and distance from the anticoagulation clinics, which may have an association with the overall quality of anticoagulation. The sample size is another limitation of our study that could limit the likelihood of detecting small effects or significant relationships from the data. Finally, the applicability of our findings in other populations with different races and other patient characteristics should be addressed in other studies.

Conclusions

In conclusion, the SAMe-TT_2R_2 score constitutes a user-friendly tool for predicting the quality of anticoagulation control with VKAs, especially at high level. The SAMe-TT_2R_2 score successfully predicts mortality and the composite outcome of major bleeding, TE complications, and mortality. However, SAMe-TT_2R_2 does not appear to predict major bleeding or TE complications among our NVAF patients on VKAs.

Our study also indicates that the performance of SAMe-TT_2R_2 could be improved by taking into account other cardinal risk factors related to poor INR control.

Conflict of interest: none declared.

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Chapter V

Comparison between CHA_2DS_2-VASc and the new R_2CHADS_2 and ATRIA scores at predicting thromboembolic event in non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation

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Comparison between CHA_2DS_2-VASc and the new R_2CHADS_2 and ATRIA scores at predicting thromboembolic event in non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation

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Abstract

Background: Accurate risk stratification is considered the first and most important step in the management of patients with non-valvular atrial fibrillation (NVAF). We compared the performance of the widely used CHA_2DS_2-VASc and the recently developed R_2CHADS_2 and ATRIA scores, for predicting thromboembolic (TE) event in either non-anticoagulated or anticoagulated patients with NVAF.

Methods: The non-anticoagulated cohort was comprised of 154 patients, whereas 911 patients formed the cohort of patients on vitamin-K-antagonist. The scores were computed using the criteria mentioned in their developmental cohorts. Measures of performance for the risk scores were evaluated at predicting TE event.

Results: In the non-anticoagulated cohort, 9 TE events occurred during 11 ± 2.7 months. CHA_2DS_2-VASc showed significant association with TE occurrence: hazard ratio (HR) = 1.58 (95 % confidence interval [95 % IC] 1.01–2.46), but R_2CHADS_2 and ATRIA did not (HR = 1.23 (95 % CI 0.86–1.77) and 1.20 (95 % CI 0.93–1.56), respectively.
In the anticoagulated cohort, after 10 ± 3 months of follow up, 18 TE events were developed. In that cohort, the three scores showed similar association with TE risk: HR = 1.49 (95 % CI 1.13–1.97), 1.41 (95 % CI 1.13–1.77) and 1.37 (95 % CI 1.12–1.66) for CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA, respectively.
In both cohorts, no TE event occurred in patients classified in the low risk category according to CHA_2DS_2-VASc or R_2CHADS_2.

Conclusions: In this study of NVAF patients, CHA_2DS_2-VASc has better association with TE events than the new R_2CHADS_2 and ATRIA risk scores in the non-anticoagulated cohort. CHA_2DS_2-VASc and R_2CHADS_2 can identify patients at truly low risk regardless of the anticoagulation status.

Keywords: Atrial fibrillation, Anticoagulant, Thromboembolism

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Background

Atrial fibrillation (AF) increases the risk of embolic stroke by 5-fold [1]. Effective prevention of thromboembolic events (TE) with oral anticoagulants is the cornerstone of AF management and appropriate TE risk stratification is a critical step in the decision making process regarding this vital issue [2].

The current clinical practice guidelines [3–5] recommend the use of $CHADS_2$ [6] and CHA_2DS_2-VASc [7] risk scores in the effective TE prevention strategy. $CHADS_2$ [6] score was validated and conceived in the year of 2001 with the aim of identifying patients at high risk of TE events. However, patients at low risk according to $CHADS_2$ score continued to have significant annual stroke rate [8, 9], this enhanced the motivation to investigate the significance of other risk factors not included in the $CHADS_2$ score and, in turn, has led to a clinical shift in the paradigm with a new aim to identify "truly low risk" patients using CHA_2DS_2-VASc score [7]. Anyhow, in several studies, $CHADS_2$ and CHA_2DS_2-VASc showed just a moderate discrimination ability to predict TE complications [10, 11], and at least one recently published large cohort study demonstrated an annual ischemic stroke rate of 1.06 % in the group of patients classified in "the true low risk category" according to CHA_2DS_2-VASc [12]. All this could lead to a number of questions and potential avenues for further research.

Recently, and with the aim to improve the ability to predict TE event, two new TE risk scores (i.e. R_2CHADS_2 [13] and ATRIA [14]) have been shown, in their own derivation cohorts, better performance than $CHADS_2$ and CHA_2DS_2-VASc. Really, the two recently proposed risk scores contain new risk factors in their schemes which were not included in the most recommended CHA_2DS_2-VASc score. This fact could qualify them to strongly capture the risk of suffering a future TE event, but little information is available in this regard in independent dataset of patients. A recent expert review has announced the need for further validation of the R_2CHADS_2 in a real world cohort with full spectrum of estimated glomerular filtration rate (eGFR) [15].

We aimed to evaluate the ability of CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA scores at predicting TE events in contemporary two different real world cohorts of non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation (NVAF) which have full spectrum of eGFR.

Methods

This retrospective study is composed of two separate and different cohorts: for the first cohort, we screened all the consultations which were registered in the emergency department of our tertiary hospital between January 2008 and June 2010, by this we were able to identify all consecutive patients ≥18 years of age with AF documented by electrocardiographic records ($n = 1873$). After excluding patients with prosthetic valve ($n = 473$), rheumatic heart disease ($n = 46$) and/or patients with active cancer ($n = 61$), there were 1293 patients with NVAF. We also excluded patients on anticoagulation ($n = 1135$) and those patients lost to follow up ($n = 4$). Thus, the non-anticoagulated cohort consisted of 154 consecutive patients with NVAF.

The second cohort of the present study was constituted by 911 patients with NVAF on vitamin K antagonists (VKAs), as was previously described [16].

For both cohorts, a detailed medical history was recorded for each patient, and the basal clinical characteristics at study entry together with information on follow up were carefully gathered by cardiologists.

The study was approved by the Clinical Research Ethics Committee of the University Clinical Hospital of Santiago de Compostela. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

TE risk calculation

CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA scores for predicting TE complications were calculated in each patient from the original corresponding prognostic variables scores used in their derivation cohorts. CHA_2DS_2-VASc was calculated by adding 2 points for age ≥ 75 years; 2 points for prior stroke or transient ischemic attack (TIA); and 1 point for each of the following factors: congestive heart failure\left ventricular ejection fraction ≤40 %, hypertension, diabetes mellitus, vascular disease, age 65–74 and female sex, with a maximum score of 9 points.

R_2CHADS_2 was calculated by adding 2 points for renal dysfunction (i.e. estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2); 2 points for prior stroke or TIA; and one point for each of the following factors: congestive heart failure, hypertension, age ≥ 75 and diabetes mellitus with a maximum score of 8 points.

For CHA_2DS-VA_2Sc and R_2CHADS_2, patients with 0 point were defined as being in the low risk category and patients with 1 point were at intermediated risk, while patients with ≥2 points were in the high risk stratum.

The ATRIA TE risk score was calculated by adding 1 point for each of the following factors: female sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria and renal dysfunction (i.e. eGFR < 45 ml/min/1.73 m^2 or end-stage renal disease) and by adding 0–9 points depending on the specific score weighting of patients age according to the presence or absence of prior ischemic stroke [14]. We did not have data about proteinuria, so the maximum score of the ATRIA risk score will be 14 points. Patients with ≤ 5 points were defined as low

risk category and patients with 6 points were at intermediated risk, while patients with ≥7 points were in the high risk stratum.

eGFR was estimated at study entry for every patient in both cohorts using the 4 variable Modification of Diet in Renal Disease (MDRD-4) [17].

End point definition

The primary endpoint for the present study was the development of TE event during follow-up. A TE complication was defined as the occurrence of ischemic stroke, TIA or peripheral embolism (including fatal TE events). Diagnosis of stroke or transient ischemic attack required an acute neurological deficit lasting for more or less than 24 h, respectively, which could not be explained by other causes and with at least 1 image test (computed tomography or magnetic resonance) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism leading to an abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in absence of another mechanism such as atherosclerosis, instrumentation or trauma.

For both cohorts, patients were followed up for 1-year after the enrolment or until TE event or death occurred. Data on TE event were gathered from the cardiology clinic visits and records, and through hospital files as well as through primary care centers reports. Data regarding death during the follow up period was also recorded.

Statistical analysis

Qualitative data were expressed as frequencies and percentages while quantitative data were summarized as mean and standard deviation. Each risk score was entered into separate Cox regression models to test their association with TE complication. Thereafter, we calculated the c-statistic as a measure of the predictive ability of the scores and tested the hypothesis that these schemes performed significantly better than chance (indicated by a c-statistic 0.50). We calculated and reported the p-values and hazard ratios (HR) with their 95 % confidence interval (95 % CI). P-value < 0.05 was considered statistically significant. The data was performed using the SPSS v.18 software.

Results

Baseline characteristics

Our study enrolled a total of 1065 patients, distributed in two different cohorts. The non-anticoagulated cohort had 154 patients with NVAF and the anticoagulated cohort consisted of 911 patients with NVAF on VKAs.

Table 1 summarizes the baseline characteristics of the patients in each cohort. For the non-anticoagulated cohort the mean age was 74 ± 12 and 52.6 % were females. For the anticoagulated cohort, the mean age was 73 ± 11 and 33.6 % were females.

Table 1 Baseline characteristics of patients with nonvalvular atrial fibrillation in the non-anticoagulated and the anticoagulated cohorts

	Non-anticoagulated cohort	Anticoagulated cohort
	N = 154	*N* = 911
Age (years)	74 ± 12	73 ± 11
Age ≥65 years, %	127 (82.5)	707 (77.6)
Age ≥75 years, %	75 (40.5)	445 (48.8)
Female sex, %	81 (52.6)	306 (33.6)
Systolic blood pressure at study entry (mmHg)	129 ± 15	139 ± 28
Current smoking, %	53 (30.4)	77 (8.5)
Hypertension, %	110 (71.4)	678 (74.4)
Diabetes mellitus, %	33 (21.4)	220 (24.1)
Peripheral arterial disease, %	20 (12.9)	92 (10.1)
Heart failure, %	10 (6.5)	343 (35.5)
History of stroke or TIA, %	9 (5.8)	103 (11.3)
Coronary artery disease, %	23 (14.9)	127 (13.9)
COPD, %	31 (20.1)	183 (20.1)
Hyperthyroidism, %	2 (1.3)	14 (1.5)
Anemia, %	27 (17.4)	178 (19.5)
Alcohol consumption ≥ 40 gr/daily, %	9 (5.8)	81 (8.9)
Antiplatelets, %	150 (97.4)	23 (2.5)
PINRR (%)	–	58 ± 18
eGFR < 60 ml/min/ 1.73 m^2, %	44 (28.6)	311 (34.1)
CHA_2DS_2-VASc		
0 point, %	5 (3.2)	62 (6.8)
1 point, %	18 (11.7)	77 (8.4)
≥ 2 points, %	131 (85.1)	772 (84.7)
R_2CHADS_2		
0 points, %	22 (14.3)	98 (10.8)
1 points, %	43 (27.9)	142 (15.6)
≥ 2 points, %	89 (57.8)	671 (73.7)
ATRIA		
≤ 5 points, %	79 (51.3)	389 (42.7)
6 points, %	14 (9.1)	115 (12.6)
≥ 7 points, %	61 (39.6)	407 (44.7)

ATRIA the anticoagulation and risk factors in atrial fibrillation score, *CHA2DS2-VASc* congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *PINNR* proportion of international normalized ratio within therapeutic range, R_2CHADS_2 renal dysfunction, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, *TIA* transient ischemic attack

Outcomes during follow up

During follow up (11 ± 2.7 months) of the non-anticoagulated cohort, 8 (5.2 %) patients died and 9 (5.8 %) patients developed TE events, 8 of them were ischemic strokes and one event was a peripheral embolic event. For the anticoagulated cohort, 60 (6.6 %) patients died and 18 (2 %) patients developed TE events during the follow up (10 ± 3 months): 13 events were ischemic strokes, 2 events were TIAs and 3 were peripheral embolic events.

Risk scores performance

Risk scores performance in the non-anticoagulated cohort

CHA_2DS_2-VASc score classified 85.1 % of patients in the high risk category, while R_2CHADS_2 classified 57.8 % as high risk patients; ATRIA classified just 39.6 % of patients in the high risk category (Table 1).

The distribution of the TE events rates in the different risk categories of the three risk scores, demonstrated the absence of occurrence of TE event in the subgroups of patients classified as low risk (i.e. patients with 0 point) according to CHA_2DS_2-VASc and R_2CHADS_2. However, TE events occurred in 6.3 % of patients classified as at low risk according to ATRIA (Table 2).

CHA_2DS_2-VASc was the only score to show significant association with TE events: HR = 1.58 (95 % CI; 1.01–2.46). R_2CHADS_2 and ATRIA did not show significant association with TE event: HR = 1.23 (95 % CI; 0.86–1.77) and 1.20 (95 % CI; 0.93–1.56) for both scores, respectively (Table 3).

The discriminative capacity of the three risk scores at predicting TE event are shown in Table 4. CHA_2DS_2-VASc and R_2CHADS_2 had moderate discriminative capacity with c-statistics of 0.69 (95 % CI; 0.53–0.85) and 0.65 (95 % CI; 0.53–0.78), respectively. The ATRIA score showed a weaker discriminative ability at predicting TE events: c- statistics = 0.64 (95 % CI; 0.49–0.80).

Table 2 Distribution of thromboembolic events according to the different risk category of each risk score

	Non-anticoagulated cohort *N* = 9	Anticoagulated cohort *N* = 18
CHA_2DS_2-VASc		
0 point, %	0 (0)	0 (0)
1 point, %	0 (0)	1 (1.3)
≥ 2 points, %	9 (6.9)	17 (2.2)
R_2CHADS_2		
0 point, %	0 (0)	0 (0)
1 point, %	1 (2.3)	0 (0)
≥ 2 points, %	8 (9)	18 (2.7)
ATRIA		
≤ 5 points, %	5 (6.3)	2 (0.5)
6 points, %	0 (0)	1 (0.9)
≥ 7 points, %	4 (6.6)	15 (3.7)

ATRIA the anticoagulation and risk factors in atrial fibrillation score, *CHA2DS2-VASc* congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female, *R_2CHADS_2* renal dysfunction, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack

Table 3 Association between each risk score as continuous variables and thromboembolic event in both cohorts

	Non anticoagulated cohort HR (95 % CI)	Anticoagulated cohort HR (95 % CI)
CHA_2DS_2-VASc	1.58 (1.01–2.46)	1.49 (1.13–1.97)
	$p = 0.044$	$p = 0.005$
R_2CHADS_2	1.23 (0.86–1.77)	1.41 (1.13–1.77)
	$p = 0.25$	$p = 0.03$
ATRIA	1.20 (0.93–1.56)	1.37 (1.12–1.66)
	$p = 0.17$	$p = 0.002$

ATRIA the anticoagulation and risk factors in atrial fibrillation score, *CHA2DS2-VASc* congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female, *CI* confidence interval, *HR* hazard ratio, *NVAF* nonvalvular atrial fibrillation, *p*; *p* value, *R_2CHADS_2* renal dysfunction, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack

Risk scores performance in the anticoagulated cohort

CHA_2DS_2-VASc score classified 84.7 % of patients in the high risk category, while R_2CHADS_2 classified 73.7 % and ATRIA classified just 44.7 % of patients in the high risk category (Table 1).

The distribution of the TE events rates in the different risk categories showed the absence of TE event in patients classified in the low risk category according to CHA_2DS_2-VASc and R_2CHADS_2. However, two TE events occurred among patients belonged to the low risk category by ATRIA (Table 2).

In terms of hazard ratios, as a measure of association between each risk score and TE events, all the studied scores demonstrated similar and significant association with TE events: HR = 1.49 (95 % CI; 1.13–1.97), 1.41 (95 % CI; 1.13–1.77) and 1.37 (95 % CI; 1.12–1.66) for CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA, respectively (Table 3).

Table 4 Discriminatory capacity of risk scores as continuous variables at predicting thromboembolic event in both cohorts

	Non anticoagulated cohort c-statistics (95 % CI)	Anticoagulated cohort c-statistics (95 % CI)
CHA_2DS_2-VASc	0.69 (0.53–0.85)	0.72 (0.63–0.82)
R_2CHADS_2	0.65 (0.53–0.78)	0.70 (0.61–0.79)
ATRIA	0.64 (0.49–0.80)	0.72 (0.62–0.83)

ATRIA the anticoagulation and risk factors in atrial fibrillation score, *CHA2DS2-VASc* congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female, *CI* confidence interval, *HR* hazard ratio, *R_2CHADS_2* renal dysfunction, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack

The three risk scores showed good discriminative ability at predicting TE event: c-statistics = 0.72 (95 % CI; 0.63–0.82) for CHA_2DS_2-VASc; 0.70 (95 % CI; 0.61–0.79) for R_2CHADS_2 and 0.72 (95 % CI; 0.62-0.83) for ATRIA (Table 4).

Discussion

In this study comparing three contemporary TE risk scores in non-anticoagulated and anticoagulated real world cohorts of patients with NVAF which have full spectrum of eGFR, CHA_2DS_2-VASc was the only score to show significant association in terms of hazard ratio at predicting TE events in the non-anticoagulated cohort.

In the anticoagulated cohort of this study, the three TE risk scores had similar and significant association and discrimination at predicting TE event. On note, only the CHA_2DS_2-VASc and R_2CHADS_2 were accurate at defining patients at truly low risk to develop TE event in both cohorts.

Oral anticoagulants are highly effective in preventing TE event in patients with AF. However, risk of major bleeding is the downside of oral anticoagulants therapy, so accurate risk estimation of TE event is of paramount importance to help decision making process regarding this issue [2]. Up to our knowledge, this is the first study to compare the most recommended CHA_2DS_2-VASc and the recently developed and more sophistically derived R_2CHADS_2 and ATRIA scores in real world non-anticoagulated and anticoagulated patients with NVAF.

It is clearly recognized that TE risk scores are best tested in a non-anticoagulated cohort from a real world [15]. In this regard, although R_2CHADS_2 and ATRIA contained new risk factors believed to have strong association with TE event like renal dysfunction [13, 14, 18]. However, CHA_2DS_2-VASc was the best score to have strong association with TE event in the non-anticoagulated cohort of our study, this may be explained by the fact that factors like renal dysfunction may coexist with advancing age, hypertension, diabetes, heart failure and vascular disease which are already individual components comprising the CHA_2DS_2-VASc score. Moreover, our results can be explained and supported if we take into account that R_2CHADS_2 score [13] was mainly derived and validated from the ROCKET AF trial of anticoagulated patients which excluded patients with creatinine clearance < 30 ml/min and this may limit its predictability in non-anticoagulated AF patients from the real world with full range of eGFR. Furthermore, similar to our findings in which CHA_2DS_2-VASc clearly outperformed ATRIA score in non-anticoagulated cohort of patients with AF, were found in a recent nationwide study [12].

The analysis of the anticoagulated cohort of the current study showed that the three TE risk scores have demonstrated similar association and discrimination at predicting thromboembolism. The improvement we have seen in the performance of the R_2CHADS_2 and ATRIA in the anticoagulated cohort may be explained by the fact that factors like renal dysfunction —which is involved in the R_2CHADS_2 and ATRIA— is a strong independent predictor of poor anticoagulation control and hence for more TE complications [16, 19]. Furthermore, these findings, in turn, may reflect that the non-anticoagulated and the anticoagulated cohorts of patients with NVAF are completely different groups of patients and re-emphasized the belief and strong hypothesis that TE risk scores are best tested in a non-anticoagulated cohort.

In our analysis, CHA_2DS_2-VASc and R_2CHADS_2 were accurate at identifying truly low risk patients in both cohorts. In previous studies, CHA_2DS_2-VASc had identified accurately patients at low risk in non-anticoagulated and anticoagulated patients with NVAF [7, 20]. Similar to our results regarding the reasonable ability of R_2CHADS_2 at identifying patients at low risk, were found in the external validation of R_2CHADS_2 in which the rates of TE event in the low risk patients at 3-years of follow up were as low as 0.36 % and 0.5 % in the non-anticoagulated and anticoagulated subgroups of the ATRIA study cohort, respectively [13].

In the two different cohorts of current study, ATRIA classified about half of patients in the low risk category, and this may limit its ability to correctly classify patients at truly low risk. Similar performance of the ATRIA risk score was found in a recent study enrolled large cohort of patients [12].

Similar to our findings in which CHA_2DS_2-VASc classified the greatest number of patients as being at high risk (85.1 %) and (84.7 %) in the non-anticoagulated and anticoagulated cohorts, respectively, were reported previously [12, 20]. This may aid and reflect the accuracy of CHA_2DS_2-VASc at classifying a small group of patients who are truly at low risk of TE event.

Finally, our analysis of the anticoagulated cohort showed that those patients in the high risk category according to CHA_2DS_2-VASc and the R_2CHADS_2 are still at high risk of developing TE event despite anticoagulation. Really, the identification of patients who remain at high risk of TE event despite anticoagulation could be of great importance in daily clinical practice as this high risk group of patients may need specific treatment strategy with close follow up and more efforts to improve the quality of anticoagulation control and to achieve the best management of their risk factors like hypertension, diabetes and heart failure.

Although this is the first study aimed to compare the CHA2DS2-VASc and the new R2CHADS2 and ATRIA scores in real world non-anticoagulated and anticoagulated cohorts of patients with NVAF. However, the

relatively small number of patients enrolled in the current study - when compared with several previous studies [12–14] - might limit the validity of our results. This might reflect the need for future studies with large cohorts of patients for further validation of the interesting results obtained from our analysis.

Our overall results when taken together might indicate that the CHA_2DS_2-VASc still the best user friendly tool at predicting TE event as well as at identifying patients at truly low risk particularly in the non-anticoagulated patients who are actually need accurate TE risk stratification.

Limitations

The main limitation of our study is its retrospective design, but it has interesting strong points as it reflects real world practice by enrolment of two contemporary separate and different cohorts of non-anticoagulated and anticoagulated patients with NVAF consulted the emergency department or the outpatient cardiology clinics of a tertiary hospital with the advantage of careful follow-up and data collection by cardiologists. Nevertheless, in this regard prospective studies in the future may be needed for better assessment of the clinical validity of our results.

The sample size of the non-anticoagulated cohort of the current study might be another limitation of our study that could limit the likelihood of detecting small effects or significant relationships from the data. However, the availability of a contemporary large non-anticoagulated cohort of patients with NVAF is challenging and increasingly unlikely. Furthermore, the findings in our study might need to be enhanced by further studies with large real world cohorts of patients with NVAF. In the non-anticoagulated cohort, the vast majority of patients were taking antiplatelet therapy during follow up. However, antiplatelet therapy alone is not a substitute for thromboembolic prevention in AF and could not reduce significantly the TE risk [21], so patients in the non-anticoagulated cohorts continue to have high TE risk during the follow up.

Really, most patients in the non-anticoagulated cohort were at risk of TE event and despite this, the anticoagulation was underused in these patients. This may be mainly due to the effect of advance age, associated comorbidities and/or patient preference on the medical decisions taken by the emergency department doctors and the reluctance to change the medication regime.

Conclusions

CHA_2DS_2-VASc has better association with TE events than R_2CHADS_2 or ATRIA in non-anticoagulated patients with NVAF, and represents in this study the more accurate clinical tool for TE risk stratification in these patients. The CHA_2DS_2-VASc and the R_2CHADS_2 scores may accurately identify patients at truly low risk of developing future TE events regardless of the anticoagulation status.

Availability of supporting data

The database is available in the department of Cardiology-University Clinical Hospital of Santiago de Compostela and needs authorized access. The original dataset is available on request from the corresponding author at drrami2012@hotmail.com.

Abbreviations

AF: atrial fibrillation; eGFR: estimated glomerular filtration; HR: hazard ratio; MDRD-4: 4 variable modification of diet in renal disease; NVAF: nonvalvular atrial fibrillation; TE: thromboembolic event; TIA: transient ischemic attack; VKAs: vitamin k antagonists.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

RRA is the principal investigator who participated substantially in the acquisition of data, design of the study, interpretation of data and drafting the manuscript. EAA participated significantly in the design of the study, statistical analysis and drafting the manuscript. ALL participated in the acquisition of data and drafting the manuscript. SRR participated in the interpretation of data and drafting the manuscript. MRM participated in the interpretation of data and critically revised the manuscript. JGS participated in the interpretation of data and drafting the manuscript. CPG participated in the design of the study and reviewed critically the manuscript. LMS participated in the interpretation of data and reviewed critically the manuscript. XFL participated in the interpretation of data and drafting the manuscript. JGJ participated in the design of the study and reviewed critically the manuscript. All authors read and approved the final manuscript.

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Chapter VI

Comparative evaluation of HAS-BLED and ATRIA scores by investigating the full potential of their bleeding prediction schemes in non-valvular atrial fibrillation patients on vitamin-K antagonists

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Letter to the Editor

Comparative evaluation of HAS-BLED and ATRIA scores by investigating the full potential of their bleeding prediction schemes in non-valvular atrial fibrillation patients on vitamin-K antagonists

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Although vitamin K antagonists (VKAs) greatly reduce the risk of stroke in non-valvular atrial fibrillation (NVAF), the risk of bleeding with this therapy remains challenging [1]. HAS-BLED [2,3] and ATRIA [4] are currently the most popular scoring systems for bleeding risk assessment in NVAF. Until now, the main studies [5–7] comparing both scores used "modified" versions of the original scores, while the current recommendation [3] is to use HAS-BLED as it was originally conceived. Furthermore, most of these studies came from a trial population or hospitalized patients [5,7].

We compared for the first time the performance of HAS-BLED and ATRIA by investigating the full potential of these prediction schemes as they were originally conceived in a real-world practice. We also aimed to identify risk factors for bleeding beyond those already included in HAS-BLED and ATRIA.

Retrospectively, we enrolled 911 consecutive NVAF patients (excluded were patients with prosthetic valve, rheumatic heart disease, active cancer and/or dementia) recently on VKAs (within 8 months) attending outpatient cardiology consultations between January 2011 and February 2013. 93% of the patients were on acenocoumarol. The international normalized ratio (INR) measurements were performed in our anticoagulation clinics.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

HAS-BLED and ATRIA scores were calculated the same as the original corresponding prognostic variables scores used in their derivation cohorts [2,4]. Patients with either ≥3 points using HAS-BLED or ≥5 points using ATRIA were categorized as high risk [2,4].

Our primary endpoint was major bleeding – using the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria – during follow-up. The effects of HAS-BLED and ATRIA, as continuous or categorical variables, on either major bleeding or intracranial hemorrhage (ICH) were tested using separate Cox regression models. We also entered the individual variables forming each of both scores into separate Cox models to determine which variables were independent predictors of major bleeding. We also used a multivariate Cox regression analysis to identify major bleeding-related factors beyond those already included in the scores being studied.

Median age was 75 years (interquartile range 66–81), and 66.4% were men. After 11 (interquartile range 9–12) months, 3.3% of patients developed major bleeding; 1% developed ICH, and 6.6% died.

There was a strong gradient of risk from the lowest to the highest risk scores delineated by HAS-BLED, as compared with ATRIA (Fig. 1).

Three of the 9 prognosticators composing HAS-BLED were independent predictors of major bleeding (Table 1). In the Cox multivariable analysis, chronic obstructive pulmonary disease (COPD) was independently associated with major bleeding (Table 1).

In Table 2, for ICH, HAS-BLED was a robust independent predictor, while ATRIA showed a marginal association with ICH.

Our study shows better performance of HAS-BLED versus ATRIA especially in the prediction of ICH in NVAF patients on VKAs. Diabetes mellitus and COPD should be taken into account at bleeding risk assessment in those patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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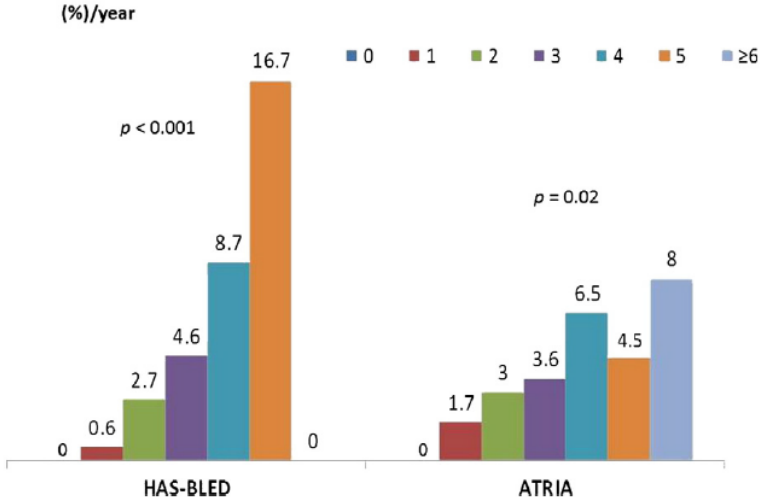

Fig. 1. Major bleeding rate according to HAS-BLED and ATRIA.

Table 1
Effect of the individual components of HAS-BLED and ATRIA on major bleeding and independent predictors of major bleeding identified in this study.

		Hazard ratio	95% confidence interval	p
HAS-BLED	Hypertension (uncontrolled: systolic pressure >160 mm Hg)	1.1	0.29–4.53	0.69
	Abnormal liver function	12.9	3.02–55.4	0.001
	Abnormal renal function	1.9	0.24–14.8	0.56
	Stroke	1.1	0.67–1.96	0.63
	Bleeding or predisposition	4.1	1.83–9.3	0.001
	Labile INR	2.6	1.17–5.67	0.02
	Elderly (>65 years)	1.4	0.38–4.85	0.65
	Drugs	0.9	0.12–6.7	0.9
	Alcohol abuse	0.5	0.03–5.8	0.54
ATRIA	Hypertension	1.6	0.54–4.75	0.39
	Age ≥75 years	1.2	0.81–1.88	0.32
	Anemia	1.2	0.94–1.63	0.19
	Prior bleeding	4.8	2.25–10.42	<0.001
	Glomerular filtration rate <30 ml/min/1.73 m^2	1.0	0.614–1.67	0.96
The present study multivariate model[a]	Prior bleeding	4.1	1.91–8.86	<0.001
	Abnormal liver and/or renal function	2.5	8.02–26.20	0.001
	Time within therapeutic range <60%	2.6	1.21–5.52	0.01
	Chronic obstructive pulmonary disease	2.9	1.37–6.21	0.005
	Diabetes mellitus	2.8	1.28–5.92	0.01

[a] Adjusted for: age (continuous), hypertension, prior bleeding, anemia, abnormal liver and/or renal function, prior heart failure, gender, diabetes mellitus, chronic obstructive pulmonary disease, prior malignancy, and time within therapeutic range <60%.

Table 2
Effect of HAS-BLED and ATRIA, either as continuous or categorical variables, on major bleeding and intracranial hemorrhage.

		Continuous			Categorical		
		Hazard ratio	95% confidence interval	p	Hazard ratio	95% confidence interval	p
HAS-BLED risk score	Major bleeding (n = 30; 3.3%)	2.8	1.90–4.01	<0.001	5.2	2.5–11.08	<0.001
	Intracranial hemorrhage (n = 9; 1%)	2.7	1.34–5.29	0.005	6.9	1.78–28.03	0.007
ATRIA risk score	Major bleeding (n = 30; 3.3%)	1.4	1.18–154	<0.001	4.2	2.00–8.89	<0.001
	Intracranial hemorrhage (n = 9; 1%)	1.3	0.99–1.65	0.06	3.9	0.96–15.5	0.06

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Chapter VII

Renal function assessment in atrial fibrillation: Usefulness of chronic kidney disease epidemiology collaboration vs re-expressed 4 variable modification of diet in renal disease

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Retrospective Cohort Study

Renal function assessment in atrial fibrillation: Usefulness of chronic kidney disease epidemiology collaboration *vs* re-expressed 4 variable modification of diet in renal disease

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Author contributions: All the authors solely contributed to this paper.

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Informed consent statement: This retrospective cohort study does not have any risk to the enrolled patients, and was approved by the Research Ethics Committee of our institution according to the Helsinki declaration.

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Data sharing statement: The original anonymous dataset is available on request from the corresponding author at drrami2012@hotmail.com

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Abstract

AIM: To compare the performance of the re-expressed Modification of Diet in Renal Disease equation *vs* the new Chronic Kidney Disease Epidemiology Collaboration equation in patients with non-valvular atrial fibrillation.

METHODS: We studied 911 consecutive patients with non-valvular atrial fibrillation on vitamin-K antagonist. The performance of the re-expressed Modification of Diet in Renal Disease equation *vs* the new Chronic Kidney Disease Epidemiology Collaboration equation in patients with non-valvular atrial fibrillation with respect to either a composite endpoint of major bleeding, thromboembolic events and all-cause mortality or each individual component of the composite endpoint was assessed using continuous and categorical $\geqslant$ 60, 59-30, and < 30 mL/min per 1.73 m^2 estimated glomerular filtration rate.

RESULTS: During 10 ± 3 mo, the composite endpoint occurred in 98 (10.8%) patients: 30 patients developed major bleeding, 18 had thromboembolic events, and 60 died. The new equation provided lower prevalence of renal dysfunction < 60 mL/min per 1.73 m^2 (32.9%),

compared with the re-expressed equation (34.1%). Estimated glomerular filtration rate from both equations was independent predictor of composite endpoint (HR = 0.98 and 0.97 for the re-expressed and the new equation, respectively; $P < 0.0001$) and all-cause mortality (HR = 0.98 for both equations, $P < 0.01$). Strong association with thromboembolic events was observed only when estimated glomerular filtration rate was < 30 mL/min per 1.73 m^2: HR is 5.1 for the re-expressed equation, and HR = 5.0 for the new equation. No significant association with major bleeding was observed for both equations.

CONCLUSION: The new equation reduced the prevalence of renal dysfunction. Both equations performed similarly in predicting major adverse outcomes.

Key words: Atrial fibrillation; Anticoagulants; Follow-up studies; Kidney; Prognosis

Core tip: In atrial fibrillation, renal dysfunction entails more adverse events. Limited data exist on the performance and prognostic value of the re-expressed Modification of Diet in Renal Disease equation *vs* the new Chronic Kidney Disease Epidemiology Collaboration equation in atrial fibrillation. We compared the performance of both equations at predicting major outcomes in patients with non-valvular atrial fibrillation. The study encouraged the use of the new equation as it decreased the prevalence of patients with renal dysfunction, in a real world cohort of patients with non-valvular atrial fibrillation and at the same time showed similar prognostic impact like the re-expressed equation.

Abumuaileq RRY, Abu-Assi E, López-López A, Raposeiras-Roubin S, Rodríguez-Mañero M, Martínez-Sande L, García-Seara FJ, Fernandez-López XA, González-Juanatey JR. Renal function assessment in atrial fibrillation: Usefulness of chronic kidney disease epidemiology collaboration *vs* re-expressed 4 variable modification of diet in renal disease. *World J Cardiol* 2015; 7(10): 685-694 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i10/685.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i10.685

INTRODUCTION

Renal dysfunction is a common comorbidity observed in patients with atrial fibrillation (AF). Patients with AF and renal dysfunction are more likely to develop thromboembolic (TE) events compared to those with AF and normal renal function[1,2]. The presence and severity of renal dysfunction is also a recognized predictor in the bleeding risk scores used commonly to estimate the hemorrhagic risk in anticoagulated patients with AF[3,4].

Therefore, accurate assessment of renal function is of paramount importance as it will help inform the decision making process aiming for optimizing the management of patients with AF. Current recommendations advocate the estimation of renal function by means of estimated glomerular filtration rate (eGFR) using the validating prediction equations instead of serum creatinine[5].

Until recently, the two most commonly used creatinine based equations estimating GFR were the 4 variable Modification of Diet in Renal Disease (MDRD-4) Study[6] and the Cockcroft-Gault (C-G) equation[7]. The MDRD-4 equation was re-expressed to be used in the current era of standardized serum creatinine assay, whereas the C-G equation was not updated, and its use is not recommended currently[8]. More recently, a new equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[9], has been proposed as an alternative equation to replace the widely used re-expressed MDRD-4 formula in routine clinical use, on the basis that it estimates measures of GFR more accurate than the re-expressed MDRD-4 equation.

Several studies have demonstrated the higher accuracy of the new CKD-EPI at estimating the true renal function, thus enabling it to provide better clinical risk prediction in different disease contexts[10-12]. However, it is currently unknown if the better estimates from the new CKD-EPI would be translated into better risk prediction in the particular context of patients with AF, since very few patients in the derivation cohort of the new CKD-EPI formula had AF[9].

In this study, we aimed to comparatively evaluate the re- expressed MDRD-4 and the new CKD-EPI formulas at predicting the occurrence of major adverse outcomes in a real world cohort of patients with non-valvular AF (NVAF) who are recently on vitamin K antagonists (VKA).

MATERIALS AND METHODS

Patient's sample

Retrospectively, we identified all consecutive patients of ⩾ 18 years of age with a confirmed diagnosis of AF on VKAs attending outpatient cardiology consultations of a tertiary hospital between January 2011 and February 2013. Only patients who fulfilled the following criteria were included in this study: Patients with permanent or paroxysmal AF recently started on VKAs (*i.e.*, not more than 8 mo passed since the beginning of their VKAs therapy), and who have regular visits for INR measurements. Patients with prosthetic valve (n = 452), rheumatic heart disease (n = 43), active cancer (n = 41), dementia (n = 26), and/or interrupted vitamin K antagonist > 3 d (n = 73) were excluded. Thus, the final analyzed cohort consisted of 911 patients. A detailed medical history was recorded for each patient, and the basal clinical characteristics at study entry together with information on follow up were carefully

gathered by cardiologists.

The vast majority of patients were on acenocoumarol (93%; and the remaining patients were on warfarin).

The study was approved by the Clinical Research Ethics Committee of our hospital.

Calculation of eGFR

For each patient, Serum creatinine was measured by the modified kinetic Jaffe method in a single clinical laboratory in our institution. All creatinine measurements were performed with an isotope dilution mass spectroscopy (IDMS)-traceable enzymatic assay that has previously been shown to provide very reliable eGFR results compared with the measured GFR[13]; these measurements were analyzed automatically using the ADVIA 2400 Chemistry System (Siemens Diagnostics, Tarrytown, NY, United States).

We calculated the eGFR using the IDMS-traceable version of the MDRD-4 equation[8]: 175 × [standardized serum creatinine (mg/dL)]$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.212 if black).

The new CKD-EPI equation was also used[9]: 141 × (minimum of standardized serum creatinine (mg/dL)/κ or 1)$^{\alpha}$ × [maximum of standardized serum creatinine (mg/dL)/κ or 1]$^{-1.209}$ × 0.993^{age} × (1.018 if female) × (1.159 if black). Where κ is 0.7 for females and 0.9 for males and α is -0.329 for females and -0.411 for males.

We categorized the eGFR obtained from each formula into three categories: ⩾ 60 mL/min per 1.73 m^2 (normal or mild renal dysfunction), 30-59 mL/min per 1.73 m^2 (moderate renal dysfunction) and < 30 mL/min per 1.73 m^2 (severe renal dysfunction). No patients were on renal replacement therapy.

Endpoints and definitions

Patients were followed up to 1-year after the enrolment. The primary endpoint of the present study was a composite endpoint of major bleeding, TE complications, or death; whichever comes first. The secondary endpoint was each individual component of the composite endpoint.

Data on major bleeding, and TE complications were gathered from the cardiology clinic visits and records, and through hospital files as well as through primary care centers reports.

We used the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria to define major bleeding[14]. Thus, a major bleeding event was adjudicated if one of the following criteria was met: fatal bleeding and/or symptomatic bleeding in a critical area or organ (*e.g.,* such as intracranial, intraspinal, intraocular, retroperitoneal, atraumatic intraarticular, pericardial, or intramuscular with compartment syndrome); and/or bleeding causing drop of hemoglobin of ⩾ 2 g/dL, or leading to transfusion of ⩾ 2 units of whole blood or packed red blood cells.

A TE complication was defined as the occurrence of ischemic stroke, transient ischemic attack, or peripheral embolism (including fatal TE events). Diagnosis of stroke or transient ischemic attack required an acute neurological deficit lasting for more or less than 24 h, respectively, which could not be explained by other causes and with at least 1 image test (computed tomography or magnetic resonance) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism leading to an abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in absence of another mechanism such as atherosclerosis, instrumentation, or trauma.

Statistical analysis

Qualitative data were expressed as frequencies and percentages while quantitative data were summarized as mean and standard deviation. Comparison between qualitative data was performed using the χ^2 test or the Fisher exact test, as appropriate. The *t*-Student test was used to compare quantitative data.

The relationship between the primary endpoint and eGFR according to both formulas was evaluated using separate Cox proportional hazard regression models. The candidate variables to construct the multivariate Cox models were those variables presented $P < 0.10$ in the univariate Cox analysis, or those co-variables of recognized prognostic value in the medical literature. Once the initial Cox models had been established, they were simplified by stepdown elimination. Thus, the final Cox models to determine the adjusted effect of eGFR on the composite endpoint, included: age, sex, previous stroke, basal hemoglobin, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure or left ventricular ejection fraction ⩽ 40%, history of malignant disease and coronary artery disease.

The association between eGFR formulas and the individual endpoints of either major bleeding or TE events was determined using competing-risks regression based on Fine and Gray's proportional subhazards models. The Fine and Gray models were adjusted for HAS-BLED score[4] in the case of testing the relationship between eGFR formulas and major bleeding, and for CHA_2DS_2-VASc score[15] in the case of testing the relationship between eGFR formulas and TE events. For all-cause mortality, we used a Cox regression model. Once the initial Cox model for predicting all-cause mortality had been established, it was simplified by stepdown elimination; and finally included the following covariables: age, sex, diabetes mellitus, and history of malignant disease, previous stroke, basal hemoglobin, and congestive heart failure or ejection fraction ⩽ 40%.

The discriminatory capacity of each formula at predicting either the primary or secondary endpoint was determined by calculating the c- statistic. We used

Table 1 Baseline characteristics *n* (%)

Age (yr)	73 ± 11
Men	605 (66.4)
Systolic blood pressure at study entry	139 ± 28
Hypertension	678 (74.4)
Current smoking	77 (8.5)
Diabetes mellitus	220 (24.1)
Heart failure	343 (37.7)
Peripheral arterial disease	92 (10.1)
History of stroke or TIA	103 (11.3)
Coronary artery disease	127 (13.9)
COPD	183 (20.1)
CHA2DS2-VASc:	
= 0	62 (6.8)
⩾ 1	849 (93.2)
⩾ 2	772 (84.7)
History of malignancy	135 (14.8)
HAS-BLED	
0	47 (5.2)
1	160 (17.6)
2	365 (40.1)
3	261 (28.6)
4	69 (7.6)
5	6 (0.7)
6	3 (0.3)
Alcohol consumption ⩾ 40 g/daily	81 (8.9)
Prior bleeding	115 (12.6)
Anemia	178 (19.5)
Abnormal liver function[1]	9 (1)
PINRR	58% ± 18%

[1]Defined as cirrhosis or elevated liver transaminases enzymes > 3 times higher than the upper limit of normal and elevated total billirubin > 2 times higher than the upper limit of normal. CHA2DS2-VASc: Congestive heart failure, hypertension, age ⩾ 75, diabetes mellitus, stroke, vascular disease, female sex category; COPD: Chronic obstructive pulmonary disease; HAS-BLED: Uncontrolled Hypertension: systolic > 160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, elderly > 65 years, drugs/alcohol concomitantly; TIA: Transient ischemic attack; PINRR: Percentage of INRs in therapeutic range.

the Delong test to compare the c-statistic values from each formula.

The calibration of the model was assessed with the Grønnesby and Borgan goodness-of-fit test. This test determines how closely the predicted event rate approximates the observed event rate over a range of scores. A significant value of *P* indicates a lack of fit.

The estimated coefficients were expressed as the hazard ratio (HR) with the respective 95%CI. A 2-sided $P < 0.05$ was considered statistically significant for all analyses.

Finally, we also assessed the incremental prognostic value of using one equation over another; using the concept of net reclassification improvement (NRI) as described by Pencina *et al*[16], to determine whether the reclassification of patients by one of the formulas regarding to each other, would result in a more accurate risk estimation.

All the analyses were performed with STATA 13, and by using the MedCalc statistical software version 12.2.1.

The study was reviewed by our expert Biostatistic Emad Abu-Assi, MD, PhD.

RESULTS

Mean age was of 73 ± 11 years, male patients constitute 66.4% of the studied population. Baseline characteristics are summarized in Table 1.

Assessment of renal function according to the formula used

The mean eGFR was higher when computed by the new CKD-EPI than with the re-expressed MDRD-4 (69.8 ± 23, 67.2 ± 19 mL/min per 1.73 m^2), respectively ($P < 0.0001$ for comparison).

There was lower prevalence of eGFR < 60 mL/min per 1.73 m^2 with the new CKD-EPI than with the re-expressed MDRD-4 (32.9% *vs* 34.1%).

Events throughout the follow-up

During a follow up of 10 ± 3 mo, the composite endpoint occurred in 98 (10.8%) patients: 30 (3.3%) patients developed major bleeding, 18 (2%) had TE events, and 60 (6.6%) patients died.

Relation with the composite endpoint

The rate of the composite endpoint increased monotonically from the higher to the lower eGFR categories for both formulas (Figure 1).

Significant association was observed between the eGFR using both formulas as continuous variables and the composite endpoint. The adjusted hazard ratios of eGFR by each formula on the composite endpoint were: 0.98 (95%CI: 0.967-0.988) and 0.97 (95%CI: 0.963-0.987) for the re-expressed MDRD-4 and the new CKD-EPI, respectively (Table 2).

Similarly, the eGFR as a categorical variable was a strong independent predictor of the occurrence of the composite endpoint regardless of the formula used (Table 3).

The discriminative capacity of both formulas at predicting the composite endpoint, were quite similar, regardless of the eGFR was used as continuous (0.683 *vs* 0.695 for the re-expressed MDRD-4 and the new CKD-EPI, respectively; $P = 0.748$) or categorical variable (0.632 *vs* 0.639 for the re-expressed MDRD-4 and the new CKD-EPI, respectively; $P = 0.45$) (Table 4).

Relation with major bleeding

There was a step increase in the major bleeding rate, as the eGFR declines, independently of the formula used to calculate the eGFR (Figure 1).

After adjusting for HAS-BLED bleeding risk score, the re-expressed MDRD-4 eGFR as well as the new CKD-EPI eGFR, as continuous variables, showed a tendency to predict major bleeding: HR for both formulas = 0.98 (95%CI: 0.965-1.000; $P = 0.07$) (Table 2).

No significant association was observed between

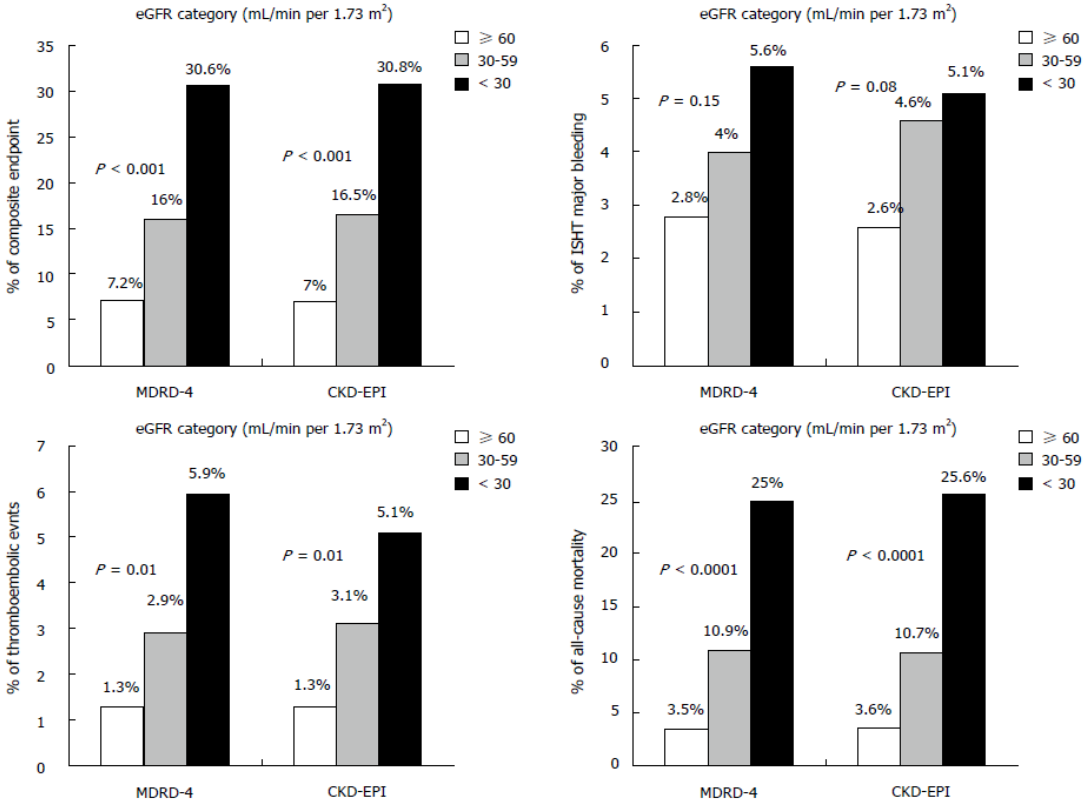

Figure 1 Distribution of major cardiovascular events according to the categories of estimated glomerular filtration rate using the re-expressed Modification of Diet in Renal Disease-4 and the new Chronic Kidney Disease Epidemiology Collaboration equations. eGFR: Estimated glomerular filtration rate; MDRD-4 indicates: Four variables Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Table 2 Unadjusted and adjusted effect (HR) on outcomes of continuous estimated glomerular filtration determined by the re-expressed Four variables Modification of Diet in Renal Disease and the new Chronic Kidney Disease Epidemiology Collaboration equations

	MDRD-4		CKD-EPI	
n (%)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Composite endpoint, 98 (10.8)	0.97 (0.958-0.977)	0.98[1] (0.967-0.988)	0.96 (0.955-0.975)	0.97[1] (0.963-0.987)
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Major bleeding, 30 (3.3)	0.97 (0.951-0.985)	0.98[2] (0.965-1.000)	0.97 (0.949-0.984)	0.98[2] (0.965-1.000)
P value	< 0.0001	0.07	< 0.0001	0.07
Thromboembolism, 18 (2)	0.98 (0.959-1.003)	0.98[3] (0.965-1.000)	0.97 (0.948-0.996)	0.98[3] (0.965-1.001)
P value	0.09	0.15	< 0.0001	0.22
All-cause mortality, 60 (6.6)	0.96 (0.948-0.973)	0.98[4] (0.965-0.995)	0.96 (0.947-0.971)	0.98[4] (0.965-0.995)
P value	< 0.0001	< 0.0001	0.02	0.001

[1]Adjusted for age, sex, previous stroke, basal hemoglobin, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure or left ventricular ejection fraction ⩽ 40%, history of malignant disease and coronary artery disease; [2]Adjusted for HAS-BLED risk score [Hypertension (uncontrolled: systolic >160 mmHg)], abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition (anemia), labile international normalized ration (INR), elderly > 65 years, and Drugs/alcohol concomitantly); [3]Adjusted for CHA2DS2-VAScscore [Cardiac failure or dysfunction, Hypertension, Age ⩾ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74 years, and Sex category (female)]; [4]Adjusted for age, sex, diabetes mellitus, history of malignant disease, previous stroke, basal hemoglobin and congestive heart failure or ejection fraction ⩽ 40%. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD-4: 4-variable Modification of Diet in Renal Disease Study equation.

categorical eGFR from both formulas and major bleeding, either in the unadjusted or by using the adjusted competing-risk models (Table 3).

At predicting major bleeding, the discriminative ability of the continuous re-expressed MDRD-4 eGFR was modest: 0.666; quite similar to that obtained from

Table 3 Unadjusted and adjusted effect (HR) on outcomes of categorical estimated glomerular filtration rate determined by the re-expressed four variables Modification of Diet in Renal Disease and the new Chronic Kidney Disease Epidemiology Collaboration equations

		MDRD-4		CKD-EPI	
n (%)		Unadjusted HR (95%CI)	Adjusted HR (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Composite endpoint, 98 (10.8)	≥ 60		1.00 (Reference)		
	30-59	2.43 (1.592-3.703)	1.7[1] (1.11-2.78)	2.51 (1.642-3.827)	1.8[1] (1.1-2.8)
		P < 0.0001	*P* = 0.02	*P* < 0.0001	*P* = 0.02
	< 30	6.99 (3.585-13.649)	3.3 (1.6-6.9)	7.4 (3.871-14.125)	3.6 (1.8-7.4)
		P < 0.0001	*P* = 0.001	*P* < 0.0001	*P* < 0.0001
Major bleeding, 30 (3.3)	≥ 60		1.00 (Reference)		
	30-59	1.53 (0.715-3.260)	1.01[2] (0.46-2.25)	1.87 (0.883-3.948)	1.2[2] (0.58-2.75)
		P = 0.30	*P* = 0.95	*P* = 0.1	*P* = 0.58
	< 30	3.56 (0.811-15.580)	1.03 (0.22-4.95)	3.65 (0.827-16.074)	1.1 (0.25-5.35)
		P = 0.09	*P* = 0.93	*P* = 0.08	*P* = 0.9
Thromboembolism, 18 (2)	≥ 60		1.00 (Reference)		
	30-59	2.04 (0.734-5.649)	1.4[3] (0.49-4.15)	2.13 (0.767-5.917)	1.4[3] (0.50-4.25)
		P = 0.17	*P* = 0.15	*P* = 0.15	*P* = 0.50
	< 30	8.01 (1.664-38.555)	5.1 (1.04-25.4)	7.84 (1.625-37.825)	5 (1.0-24.9)
		P = 0.009	*P* = 0.045	*P* = 0.01	*P* = 0.04
All-cause mortality, 60 (6.6)	≥ 60		1.00 (Reference)		
	30-59	3.34 (1.909-5.827)	2.6[4] (1.4-2.7)	3.14 (1.793-5.481)	2.4[4] (1.3-4.5)
		P < 0.0001	*P* = 0.002	*P* < 0.0001	*P* = 0.005
	< 30	10.64 (4.843-23.359)	4.9 (2.0-11.9)	10.89 (5.122-23.166)	5.2 (2.2-12.3)
		P < 0.0001	*P* < 0.0001	*P* < 0.0001	*P* < 0.0001

[1]Adjusted for age, sex, previous stroke, basal hemoglobin, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure or ejection fraction ≤ 40%, history of malignant disease and coronary artery disease; [2]Adjusted for HAS-BLED risk score [Hypertension (uncontrolled: systolic > 160 mmHg)], Abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition (anemia), labile international normalized ration (INR), elderly > 65 years, and drugs/alcohol concomitantly); [3]Adjusted for CHA2DS2-VAScscore [Cardiac failure or dysfunction, Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74 years, and Sex category (female)]; [4]Adjusted for age, sex, diabetes mellitus, history of malignant disease, previous stroke, basal hemoglobin and congestive heart failure or ejection fraction ≤ 40%. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD-4: 4-variable Modification of Diet in Renal Disease Study equation.

Table 4 Calibration and discrimination abilities of the re-expressed four variables Modification of Diet in Renal Disease and the new Chronic Kidney Disease Epidemiology Collaboration equations

			MDRD-4	CKD-EPI	*P* value
Composite endpoint	Calibration, χ^2 (*P* value)		1.7 (0.79)	3.5 (0.48)	
	c-statistic (95%CI)	eGFR continuous	0.683 (0.629-0.737)	0.695 (0.643-0.747)	0.748
		eGFR categorical	0.632 (0.600-0.664)	0.639 (0.607-0.670)	0.452
Major bleeding	Calibration, χ^2 (*P* value)		5.9 (0.20)	5.4 (0.25)	
	c-statistic (95%CI)	eGFR continuous	0.666 (0.581-0.751)	0.677 (0.596-0.759)	0.8548
		eGFR categorical	0.550 (0.443-0.658)	0.571 (0.465-0.679)	0.7872
Thromboembolism	Calibration, χ^2 (*P* value)		0.13 (0.99)	1.9 (0.76)	
	c-statistic (95%CI)	eGFR continuous	0.616 (0.584-0.648)	0.644 (0.612-0.675)	0.2736
		eGFR categorical	0.617 (0.585-0.649)	0.622 (0.590-0.654)	0.7582
All-cause mortality	Calibration, χ^2 (*P* value)		0.83 (0.94)	1.5 (0.82)	
	c-statistic (95%CI)	eGFR continuous	0.715 (0.684-0.744)	0.722 (0.691-0.750)	0.5227
		eGFR categorical	0.679 (0.647-0. 709)	0.678 (0.646-0.708)	0.911

eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD-4: 4-variable Modification of Diet in Renal Disease Study equation.

using the continuous new CKD-EPI eGFR: c-statistic = 0.677 (*P* = 0.85).

When eGFR was considered as a categorical variable, the discriminative capacity of each formula at predicting major bleeding was of 0.550 and of 0.571 for the re-expressed MDRD-4 and the new CKD-EPI, respectively (*P* = 0.79) (Table 4).

Relation with thromboembolic event

As shown in Figure 1, the distribution of the TE event rate in the different eGFR categories, demonstrated a consistent gradient of risk, regardless of the formula used.

After adjusting for the CHA_2DS_2-VASc risk score, no significant association was observed between eGFR as a continuous variable and TE events: HR = 0.98 (95%CI: 0.965-1.000) and 0.98 (95%CI: 0.965-1.001), for the re-expressed MDRD-4 and the new CKD-EPI, respectively (Table 2).

When eGFR was considered as a categorical variable, only significant association existed between eGFR < 30 mL/min per 1.73 m^2 and the TE complications, after

controlling for CHA_2DS_2-VASc score: HR = 5.1 (95%CI: 1.04-25.4) for the re-expressed MDRD-4, and HR = 5.0 (95%CI: 1.0-24.9) for the new CKD-EPI (Table 3).

The discriminative power of GFR estimates determined by both formulas was also modest. For continuous eGFR, the c-statistic values were of 0.616 and 0.644 for the re-expressed MDRD-4 and the new CKD-EPI, respectively, (P = 0.27), and for categorical eGFR, the c-statistic values were 0.617 and 0.622 when using the re-expressed MDRD-4 and the new CKD-EPI, respectively, (P = 0.76) (Table 4).

Relation with all-cause mortality

The rate of all-cause mortality increased progressively from the higher to the lower eGFR values for both formulas (Figure 1).

Continuous eGFR calculated by either the reexpressed MDRD-4 or the new CKD-EPI was an independent predictor of all-cause mortality; adjusted HR = 0.98; (P < 0.01) (Table 2).

A strong association was also found between categorical eGFR and all-cause mortality after adjusting for several confounders (Table 3).

Good discrimination was obtained from continuous eGFR: c-statistic = 0.715 for the re-expressed MDRD-4 and 0.722 for the new CKD-EPI (P = 0.52).

The discriminative power of eGFR as a categorical variable in terms of c-statistic was: 0.679 and 0.678 when using the re-expressed MDRD-4 and the new CKD-EPI, respectively, (P = 0.91) (Table 4).

Estimated GFR from both formulas demonstrated good calibration for the major cardiovascular events with P value > 0.1 (Table 4).

The NRI analysis did not significantly favor the new CKD-EPI over the re-expressed MDRD-4 whether for predicting the composite endpoint, major bleeding and all-cause mortality (NRI = 2.13%, 4.35%, and 0.9%, with P = 0.27, 0.19, and 0.7, respectively).

However, at predicting the TE event, the NRI favored the new CKD-EPI formula with NRI of 1% (95%CI: -0.08 to +2.0, P = 0.07) indicating a strong tendency to reclassify better the patients according to their risk of developing TE event, compared with the re-expressed MDRD-4.

DISCUSSION

In this real world cohort of patients with NVAF on VKAs, the new CKD-EPI formula classified lower percentage of patients as having eGFR < 60 mL/min per 1.73 m^2 than the re-expressed MDRD-4 equation did. This means that the use of the new CKD-EPI formula results in lower prevalence of renal dysfunction. We also found that renal dysfunction assessed either by the re-expressed MDRD-4 or the new CKD-EPI was strongly associated with the composite endpoint of major bleeding, TE event and all-cause mortality, and with all-cause mortality, as well.

Patients with NVAF are often elderly with multiple comorbidities which require pharmacotherapy of growing complexity, and this makes the reliable estimation of renal function to be undeniably a critical issue. Moreover, the availability of the new oral anticoagulants have renewed the great interest toward the accurate evaluation of renal function in patients with NVAF[17,18].

Up to our knowledge, this is the first study comparing the prognostic performance of the re-expressed MDRD-4 and the new CKD-EPI formulas used for estimating GFR in a real world population of patients with NVAF on VKAs who have a full range of eGFR.

In this cohort, the new CKD-EPI formula classified lower percentage of patients as having eGFR < 60 mL/min per 1.73 m^2 (32.9% with new CKD-EPI *vs* 34.1% with re-expressed MDRD-4). This reasonable ability of the new CKD-EPI formula to reduce the rate of patients with renal dysfunction could be highly appreciated by the clinicians in daily clinical practice which usually needs close attention to the status of renal function to reach the optimal management, and more safe use of renally excreted medications and nephrotoxic contrast agents, in patients with NVAF. Our finding is consistent with that found in the derivation cohort of the new CKD-EPI[9] and to the findings obtained from multiple studies in different clinical settings[12,19-21].

In our analysis, renal dysfunction determined by GFR estimates using both formulas was a significant predictor of the composite endpoint and all-cause mortality. Similar findings have been shown in previous study used the MDRD-4[22], but until now, no study has compared the prognostic usefulness of these formulas in a real world patients with NVAF. In this study, we did not find any significant difference in the prognostic impact between the new CKD-EPI and the re-expressed MDRD-4 at predicting major adverse cardiovascular outcomes.

In our analysis, we found that both formulas with the eGFR as a continuous variable and after controlling for HAS-BLED risk score[4], showed a tendency to predict major bleeding. Previous association between renal dysfunction and major bleeding were found in AF studies[22,23]. However, the prior tendency was lost when the eGFR using both formulas was tested as categorical variables; this may be explained by the small number of events (30 events, 3.3%) that could limit the detection of significant relationship from the data.

TE prevention remains the primary cornerstone in the management of patients with NVAF. In dealing with this great aim, there are conflicting data about the ability of renal dysfunction to predict this major catastrophe. Several studies demonstrated significant association between reduced eGFR and TE event[22-24], conversely, in other studies, decreased eGFR did not show significant relationship with TE event[25,26]. These differences could be explained by the differences in the formula used to estimate GFR, sample size, patients

characteristics (*i.e.,* from a real world or clinical trial population), and/or the disparities in duration of follow up between the studies. Therefore, there is a strong need for further evaluation of that uncertainty in a real world population. Regarding this important issue, in our real world cohort of patients with NVAF, and after adjusting for the CHA_2DS_2-VASc risk score[15] there was a significant association between eGFR as categorical variable and TE event only when the eGFR was < 30 mL/min per 1.73 m^2 (*i.e.,* severe renal dysfunction category) with similar prognostic impact of both the re-expressed MDRD-4 and the new CKD-EPI. Furthermore, the NRI analysis showed a tendency of the new CKD-EPI to reclassify better the patients according to their risk of developing TE event, compared with the re-expressed MDRD-4.

It should be kept in mind that the eGFR formulas were designed to most accurately estimate renal function and not to predict major adverse outcomes. Indeed, the relative performance of the two different GFR estimating equations in our study can be explained by their respective compositions (*i.e.,* the difference of mathematical modeling and how specific variables are coded and weighted by each equation). Also, the relative variance in performance between both formulas can be explained by the differences in their respective derivation populations. The MDRD-4 formula was originally developed in patients with established renal dysfunction[6]; for this, the re-expressed MDRD-4 formula may be less applicable to patients from the real world with full range of GFR. In contrast, the new CKD-EPI equation could be more precise in our community-based cohort of patients with NVAF, as the new CKD-EPI was developed in population with and without renal dysfunction[9].

Although, many laboratories are preparing their installation to use the new CKD-EPI equation instead of the re-expressed MDRD-4 formula according to the current guideline[27] and a consensus document[28], however, old habits die hard. Our assessment of the prognostic performance of both formulas in the particular clinical context of AF might be of great importance as it could help convince the clinicians and mitigate the doubts and obstacles regarding the adoption of the new CKD-EPI.

Really, patients with NVAF and renal dysfunction continue to represent a complex management problem in relation to decision making for thromboprophylaxis. With respect to the overall concept, the data obtained from our analysis, state that the new CKD-EPI formula reduced the prevalence of patients with renal dysfunction (*i.e.,* eGFR < 60 mL/min per 1.73 m^2), and at the same time continued to have prognostic impact similar to that of the re-expressed MDRD-4 equation at predicting the major adverse events. Taken together, our notable results from a real world cohort encourage the use of the new CKD-EPI equation to assess renal function in patients with NVAF and reinforce the current recommendation[9,27,28] for the use of the new CKD-EPI formula in all clinical situations.

It is clear that our study presents an analysis of a modest sized cohort of patients with NVAF on VKAs from the real world, and the prevalence of patients with eGFR < 60 ml/min/1.73 m^2 was just reduced by 1.2% when using the new CKD-EPI formula. However, our cohort might give a good reflection of the general population with millions of patients having NVAF, in whom the percentage of 1.2% would be highly significant.

Limitations

The main limitation of our study is its retrospective design, but it has interesting strong points as it reflects real world practice by enrolment of consecutive patients with NVAF who have full range of eGFR and were attending our outpatient cardiology clinics with the advantage of careful follow up and data collection by cardiologists.

The sample size might be another limitation of our study that could limit the likelihood of detecting small effects or significant relationships from the data. Important to mention here that we did not have the direct measured GFR, so we cannot determine the extent to which the two formulas reflect the GFR as determined by the gold standard method. However, eGFR is the practical way to estimate renal function which has been used in several patient populations. The fact that we have only one serum creatinine measure for every patient could limit the verification of the acute *vs* chronic nature of the renal dysfunction in some patients, but this limitation was present in several related studies[23-25]. The lack of cystatin C data might be considered a limitation of our study. However, it should be taken into account that all the creatinine measurements in our study cohort were performed with the IDMS-traceable enzymatic assay method, which has been shown to provide very reliable eGFR results[13] and is considered the standard method to assess renal function[29].

Finally, all of the enrolled patients in our cohort have Caucasian race, so the applicability of our findings in other populations with different races should be addressed in other studies.

The new CKD-EPI reduced the prevalence of patients with renal dysfunction, in a real world cohort of patients with NVAF on VKAs. Renal dysfunction reflected by GFR estimates from the re-expressed MDRD-4 or the new CKD-EPI was an independent predictor of the composite endpoint and all-cause mortality. Both formulas had similar prognostic impacts regarding the prediction of composite endpoint, major bleeding, TE events and all-cause mortality. Our analysis indicates that the more widespread adoption of the new CKD-EPI instead of the re-expressed MDRD-4 may improve the management of patients with NVAF.

COMMENTS

Background

Renal dysfunction is a frequent comorbidity seen in patients with atrial fibrillation. Moreover, renal dysfunction is a strong predictor of thromboembolic event and also of bleeding event (when the patients are anticoagulated). This reflects the need for more accurate estimate of renal function to guarantee the optimal management of patients with atrial fibrillation. The standard way to assess renal function is the glomerular filtration rate. Among the available equations to estimate the glomerular filtration rate are: the re-expressed Modification of Diet in Renal Disease equation which is still the commonly used equation by many laboratories all over the world and the new Chronic Kidney Disease Epidemiology Collaboration equation which has been recently proposed to be used instead of previous equation in daily practice as the new equation has an assumed ability to reduce the prevalence of patients with renal dysfunction and better reclassification of patients. There is limited information about the performance of both equations in patients with atrial fibrillation.

Research frontiers

The authors think that the new Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate must have a wide diffusion as an alternative to the re-expressed Modification of Diet in Renal Disease equation. In this paper the authors provide support to the hypothesis, reporting the superiority of the new Chronic Kidney Disease Epidemiology Collaboration equation over the re-expressed Modification of Diet in Renal Disease equation in the clinical context of patients with atrial fibrillation on anticoagulation.

Innovations and breakthroughs

The results derived from our analysis, state that the new Chronic Kidney Disease Epidemiology Collaboration equation reduced the prevalence of patients with renal dysfunction (*i.e.*, estimated glomerular filtration rate < 60 ml/min per 1.73 m^2), and at the same time continued to have the prognostic impact similar to the re-expressed Modification of Diet in Renal Disease equation at predicting the major adverse events. Although there are still some concerns about the performance of the new equation in subgroups of elderly and obese patients, the study from a real world cohort encourages the cardiologists to use of the new Chronic Kidney Disease Epidemiology Collaboration equation to assess renal function in patients with atrial fibrillation and increase the confidence to use it in all clinical situations.

Applications

The millions of patients with atrial fibrillation will get benefit and better management if there is wide spread adoption of the new Chronic Kidney Disease Epidemiology Collaboration equation instead of the re-expressed Modification of Diet in Renal Disease equation, giving the ability of the new equation to correctly reclassify patients in comparison with the re-expressed equation.

Terminology

The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was published in May 2009 as a reliable tool to estimate glomerular filtration rate. It was developed in an effort to create an equation more accurate than the re-expressed Modification of Diet in Renal Disease equation. Researchers pooled data from multiple studies to develop and validate this new equation. They used 10 studies that included 8254 participants, randomly using 2/3 of the data sets for development and the other 1/3 for internal validation. Sixteen additional studies, which included 3896 participants, were used for external validation. The CKD-EPI equation performed better than the Modification of Diet in Renal Disease equation, as the prevalence of chronic kidney disease was 11.5% *vs* 13.1% according to the National Health and Nutrition Examination Survey data in the United States of America.

Peer-review

First of all I would like to congratulate the authors with their achievement. In this retrospective study including relatively limited sample size of Caucasian subjects, the findings encourage the use and application of the new CKD-EPI equation for assessment not only of renal function in patients with non-valvular atrial fibrillation but also in all clinical situations. For the first time, Abumuaileq RRY *et al* evaluated the re- expressed MDRD-4 and the new CKD-EPI formulas at predicting the occurrence of major adverse outcomes in a real world cohort of patients with non-valvular atrial fibrillation on anticoagulation. The study was well conducted and clinically relevant.

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Chapter VIII

Clinical implications

A way of improving the ability to predict the quality control of vitamin K antagonists in naïve patients with non-valvular atrial fibrillation*:*

In the real world clinical practice and in the dilemma of anticoagulation in NVAF, cardiologists are still facing substantial difficulties in dealing with anticoagulants naïve NVAF patients when different critical decisions need to be carried out quickly regarding to start or not the anticoagulation?; with which agent to start, one of VKAs or one of NOACs?. Usually, the precautions of anticoagulation derived from patients clinical variables make the decision to start anticoagulation in those patients greatly challenging. Moreover, patients with NVAF, are frequently old, with several comorbidities (e.g. cardiovascular disease and/or renal dysfunction), and complex pharmacotherapy which can include antiplatelet therapy, all these factors add great obstacles to the decision making process, to the plan of follow up and to the accurate estimation of the thromboembolic and hemorrhagic risk.

In the real world practice, maintaining the therapeutic range in patients treated with VKAs had always been challenging whilst the potential consequences of deviating from the optimal control of VKAs are deleterious in patients with NVAF, given the increased risk for thromboembolic and bleeding events [73-76].

Various clinical decision making tools have been developed to help decision making in the management of patients with NVAF. In 2013, the new score - SAMe-TT_2R_2 - was proposed to help identify those patients who were likely to have a propensity to poor INR control. This simple score based on clinical features may help identify those AF patients who would do well on VKAs (i.e. SAMe-TT_2R_2 score = 0–1), or conversely, those who might require additional interventions to achieve acceptable anticoagulation control (i.e. SAMe-TT_2R_2 score ≥2) [114]. This score was derived from a trial cohort

and thus independent validation in 'real-world' AF cohorts would be needed. We performed a retrospective analysis of a cohort of outpatients with NVAF recently (i.e. not who were on VKAs for long time and for a better assessment of SAMe-TT_2R_2 score) on VKAs and found that SAMe-TT_2R_2 score could indeed represent a useful clinical tool to identify poor quality of anticoagulation control with VKAs. The predictive ability of SAMe-TT_2R_2 is acceptable for identifying poor PINRR and its ability has been improved when integrated with other clinical characteristics. Really, our research demonstrates that SAMe-TT_2R_2 can be used as a reliable score to refine the clinician judgment regarding the correct identification of patients who would have high quality of anticoagulation control with VKAs and distinguish them from those less likely to do well on VKAs for whom close follow up or the use of NOACs should be proposed as an alternative therapeutic option aiming to avoid the excess risk of stroke and bleeding. For this purpose, SAMe-TT_2R_2 may represent a good clinical tool which can facilitate the physician decision making process to optimize the oral anticoagulation management. Moreover, our study gives more attention to cardinal risk factors such as heart failure, eGFR less than 30 mL/min/1.73 m^2, diabetes mellitus and history of malignancy which should seriously be taken into account by the clinicians when they prescribe VKAs in daily clinical practice as these risk factors are common in patients with NVAF and show strong and independent association with poor quality control of VKAs.

***Insights at assessment of thromboembolic and bleeding risk in patients with non-valvular atrial fibrillation**:*

Although, the most commonly used risk score for the prediction of TE event is the CHA_2DS_2-VASc [92]. However, the continuous refinement of risk scores is a never ending process, and as such two new TE risk scores (i.e. R_2CHADS_2 [101] and ATRIA [102]) has been proposed for this purpose as they -in their own derivation- outperformed the CHA_2DS_2-VASc. Really, these recently proposed scores contain new risk factors in their schemes (e.g. renal dysfunction) which were not included in the most popular CHA_2DS_2-VASc score. One can assume that the integration of new risk factors might qualify them to more accurately capture the risk of suffering a TE event. However, limited information is available about the comparative abilities of these three risk scores in independent real world cohorts of patients with NVAF. Our study compares these three contemporary TE risk scores in non-anticoagulated and anticoagulated different real world cohorts of patients with NVAF, and shows that despite similar association and discrimination of the three scores in the anticoagulated cohort. However, CHA_2DS_2-VASc was the only score to show significant association in terms of hazard ratio at predicting TE events in the non-anticoagulated cohort. Thus, our research demonstrates clearly that CHA_2DS_2-VASc is still the best score to be used by the cardiologists in the real world practice at predicting TE event and at defining truly low risk patient. One of the interesting findings of our research shows that those patients in the high risk category (i.e. with high points of risk) according to CHA_2DS_2-VASc and the R_2CHADS_2 are still at high risk of developing TE event despite being on uninterrupted VKAs. This point would need further research, as the identification of patients who remain at high risk of TE event despite anticoagulation could be of great

value and highly appreciated by the physicians in daily clinical practice as by this approach the clinicians might identify early these patients who need specific treatment strategy with more frequent follow up visits and more efforts directed to improve the quality control of anticoagulation and to achieve the best management of their partially modifiable risk factors like hypertension, diabetes and heart failure. Really, several reports demonstrated that the risk of major adverse event (i.e. TE event and major bleeding) is greatest in the first few months after starting VKAs, this might indicate the importance of risk assessment for those patients who are recently on VKAs [80,148].

Oral anticoagulants carry the risk of major bleeding events among which is ICH that constitutes the most dreadful complication of oral anticoagulation. In real world practice, clinicians highly appreciate tools which are proposed to predict the occurrence of major bleeding event especially ICH as by this they can minimize the chance of suffering from these catastrophic events. In our study, the HAS-BLED [104] score provides a more useful tool than ATRIA [107] for prediction of major bleeding particularly ICH, and the results of our analysis increase the confidence to use HAS-BLED score in the real world practice. Moreover, our study provides new insight on the importance of certain comorbidities like diabetes mellitus and chronic obstructive pulmonary disease which were identified as independent predictors of major bleeding and the need to take these new risk factors into consideration when prescribing VKAs as these factors when taken into account beside the HAS-BLED score might improve the ability of estimating major bleeding risk. Furthermore, poor quality of anticoagulation control with VKAs (i.e. labile INR) is a significant predictor of major bleeding in our population of patients with NVAF recently on VKAs. This may point to the critical need of having a valid clinical tool to predict the quality of anticoagulation control before prescribing VKAs.

***Advance in renal function assessment in patients with non-valvular atrial fibrillation**:*

In daily clinical practice, when dealing with patients having NVAF, renal function assessment is frequently requested by the cardiologists to optimize the management plan, mainly because renal dysfunction is associated with TE and bleeding event, and can have negative effects on the pharmacotherapy regime. Thus, accurate renal function assessment could be of great help in daily practice. The re-expressed MDRD-4 [125] and CKD-EPI [126] are the two equations available to be used in the current era of standardized serum creatinine. However, little data is available about their values in the population of patients with NVAF. Our study tries to uncover this area of uncertainty with the goal to define the best clinically justifiable and reliable equation to be used in the context of NVAF. Although, the analysis of our study demonstrates that eGFR values derived from both equations have the same prognostic impact. However, the results of our study show that the new CKD-EPI formula has a reasonable ability to reduce the rate of patients with renal dysfunction. When taken together, these results could be highly appreciated by clinicians in real world practice which usually needs close attention to status of renal function to reach optimal management, and for safer use of renally excreted medications, in patients with NVAF. Thus, our study increases the confidence to use CKD-EPI by the laboratories and cardiologists in the particular context of NVAF. Our analysis demonstrates that severe renal dysfunction (i.e. eGFR less than 30 mL/min/1.73 m^2) is significantly associated with poor quality of VKAs and TE event in patients with NVAF on VKAs, this may reflect the need for more follow-up visits and measures to improve the quality control of VKAs in this group of patients.

***Cardiovascular disease and non-valvular atrial fibrillation, a way to improve the outcome**:*

Our study demonstrates high prevalence of cardiovascular disease among anticoagulated patients with NVAF mainly hypertension, heart failure and coronary artery disease as it showed that their prevalence was 74.4%, 37.7% and 13.9%, respectively. Moreover, our analysis shows that heart failure is strongly associated with poor quality control of VKAs and hence more adverse outcomes. The combination of heart failure and AF constitutes an epidemic in modern cardiology. Furthermore, the analysis reflects that the presence of multiple cardiovascular diseases (i.e. more than two medical comorbidities according to SAMe-TT_2R_2 score) is strongly associated with poor quality control of anticoagulation with VKAs. All these findings reflect the critical need to put more efforts toward optimal management of all associated cardiovascular morbidities and risk factors in patients with NVAF in order to improve the outcomes and not to treat NVAF as a separate entity. Further studies are needed to clarify this dilemma. On the other hand, among cardiovascular drugs, amiodarone shows significant association with poor quality control of VKAs, and this may point to the need to give more attention to the possible interaction between VKAs and amiodarone in daily clinical practice.

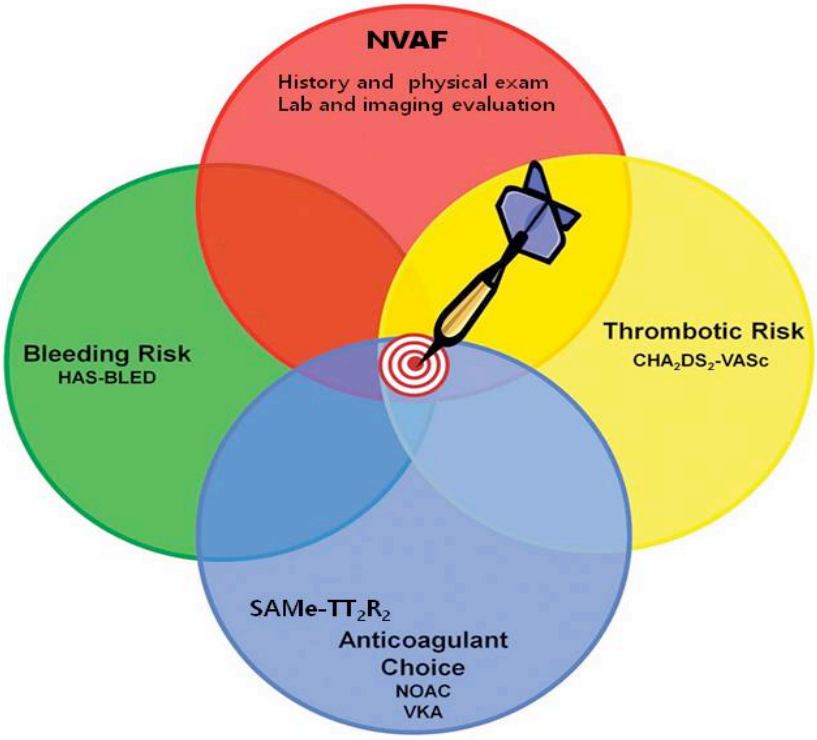

Figure 8.1: Targeting the optimal therapy in the setting of non-valvular atrial fibrillation, requires balancing considerations of the patient risk scores. CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke, vascular disease, female sex category; HAS-BLED: uncontrolled Hypertension: systolic >160 mm Hg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly >65 years, Drugs/alcohol concomitantly; NOAC; new oral anticoagulant; NVAF; non-valvular atrial fibrillation; SAMe-TT_2R_2: Sex female, Age < 60 years, Medical history [more than two comorbidities], Treatment [interacting drug, e.g. Amiodarone], Tobacco use [doubled], and Race [doubled]); VKA: vitamin K antagonist.

Chapter IX

Conclusions

Although specific conclusions are detailed in each chapter, those presented below can reflect the overall objectives of this research.

***In relation to objective 1**:*

1- The anticoagulation quality control of VKAs in Galician patients with NVAF is still below the optimal level as the mean PINRR in this real world cohort was 58% ±18 indicating the need for more efforts toward the improvement of the quality control of VKAs in our population.

2- In patients with NVAF recently on VKAs, the SAMe-TT_2R_2 score constitutes a user-friendly tool for predicting the quality of anticoagulation control with VKAs. Moreover, the SAMe-TT_2R_2 score successfully predicts mortality and the composite outcome of major bleeding, TE complications, and mortality in our population.

3- Cardiovascular diseases are highly prevalent in patients with NVAF. Heart failure deserves great attention as it commonly accompanied AF and demonstrated a strong association with poor quality control of VKAs. Moreover, among cardiovascular drugs, amiodarone shows significant association with poor quality control of VKAs.

4- The performance of SAMe-TT_2R_2 could be improved by taking into account other cardinal risk factors related to poor INR control like eGFR less than 30 mL/min/1.73 m^2, history of malignancy, diabetes mellitus, heart failure and alcohol abuse. These factors should be taken into account before prescribing VKAs.

***In relation to objective 2**:*

1- The annual rate of TE event is noticeable (i.e. about 2%) in a real world cohort of Galician patients with NVAF despite being on uninterrupted anticoagulation with VKAs. The CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA TE risk scores show significant association at predicting TE event in these patients. This finding sets an alarm for further research to define this category of patients as the management plan for them could be different and with intensive follow up visits toward minimizing their TE risk.

2- The CHA_2DS_2-VASc demonstrates better association with TE event than R_2CHADS_2 or ATRIA TE scores in non-anticoagulated patients with NVAF, and represents a more accurate clinical tool for TE risk stratification in these patients.

3- Regarding the identification of patients with low TE risk, the CHA_2DS_2-VASc and the R_2CHADS_2 scores accurately identify patients at truly low risk of developing future TE events while the new ATRIA score fails to show similar ability in this regard.

***In relation to objective 3**:*

1- The annual rate of major bleeding event is nearly 3.3% in a real world cohort of Galician patients with NVAF recently on VKAs. The HAS-BLED bleeding risk score demonstrates better performance than the ATRIA bleeding score especially in prediction of the most catastrophic ICH event in our population. Our study encourages the use of HAS-BLED score in the management of patients with NVAF in the daily clinical practice.

2- Poor quality of anticoagulation control with VKAs (i.e. labile INR) is a significant predictor of major bleeding in our population of patients with NVAF recently on VKAs. This may indicate the importance of having proper risk assessment tools to predict the quality of anticoagulation control before prescribing VKAs.

3- The analysis highlights diabetes mellitus and chronic obstructive pulmonary disease as strong predictors of major bleeding which might be useful to be taken into account when estimating the bleeding risk in patients with NVAF before prescribing VKAs. Further research should be encouraged in this regard.

***In relation to objective 4**:*

1- Renal dysfunction is strongly associated with all cause mortality and shows a tendency to predict major bleeding event in patients with NVAF on VKAs. Moreover, the analysis indicates that patients with NVAF and eGFR less than 30 mL/min/1.73 m^2 may be at high risk of having poor quality control of VKAs and major adverse events (i.e. TE event, mortality) compared to those with NVAF and normal renal function.

2- Renal dysfunction reflected by GFR estimates either from the re-expressed MDRD-4 or the new CKD-EPI equations is an independent predictor of the composite endpoint (i.e. major bleeding, TE complications, or death) and all cause mortality. In this regard, both formulas show similar prognostic impacts regarding the prediction of composite endpoint, major bleeding, TE events and all cause mortality.

3- The analysis might indicate that the use of the new CKD-EPI equation to estimate GFR can reduce the prevalence of patients with renal dysfunction compared with the re-expressed MDRD-4 equation, in a real world cohort of patients with NVAF.

4- The findings indicate that the most widespread adoption of the new CKD-EPI instead of the re-expressed MDRD-4 may result in modifying the overall management of patients with NVAF, particularly in regard to the use of renally excreted medications.

Resumen

Está bien establecido que la fibrilación auricular (FA) aumenta unas 5 veces el riesgo de ictus isquémico. Los antagonistas de vitamina K (AVK) continúan siendo los anticoagulantes orales más ampliamente usados en los pacientes con FA no valvular (FANV), y son considerados muy efectivos para la prevención de complicaciones trombeoembólicas (TE) en esos pacientes. Sin embrago, optimizar el beneficio terapéutico en el uso de los AVK en la práctica clínica, siguen siendo el principal reto debido a lo impredecible de la respuesta anticoagulante.

La asociación entre la mala calidad de los controles del international normalized ratio (INR) y el aumento tanto de la tasa de hemorragias serias como de ictus, está bien establecida.

El tiempo en rango terapéutico (TRT) o el porcentaje en rango terapéutico de los controles del INR (PRINR), son metidos usados medir la calidad de los controles de anticoagulación con los AVK.

En la práctica clínica diaria, los registros de los valores de INR son el mejor indicador de la calidad de anticoagulación in pacientes tratados durante largo periodo de tiempo con AVK. En contraste, en los pacientes sin tratamiento previo con AVK o aquellos con inicio reciente de AVK, existe un interés creciente en encontrar una herramienta que pueda ayudar a predecir de antemano si esos pacientes presentarán o no una adecuada respuesta terapéutica una vez prescrito un AVK.

Por otra parte, con la disponibilidad de los nuevos anticoagulantes orales (NACO), el manejo de la anticoagulación en FANV se ha revolucionado ya que estos nuevos fármacos son más seguros que los AVK. De este modo, hay una fuerte necesidad de caracterizar los pacientes con FANV con indicación de anticoagulación pero que podrían tener pobre calidad de respuesta anticoagulantes con los AVK, por lo cual

serían candidatos adecuados para recibir los NACO con el fin de evitar complicaciones hemorrágicas graves, así como complicaciones isquémicas.

El objetivo de nuestro estudio fue evaluar el riesgo de intermedios (es decir, controles pobres de INR) y los eventos adversos en pacientes contemporáneos con FANV recientemente tratados con AVK. Por otra parte, se evalúan los predictores de presentar eventos adversos en estos pacientes, y evaluar la validez de los scores de riesgo contemporáneos desarrolladas y recomendadas para su uso en el contexto de FANV.

Retrospectivamente, se identificaron todos los pacientes consecutivos de ≥ 18 años de edad con un diagnóstico confirmado de la FA en AVK, asistiendo a las consultas de cardiología ambulatoria en un hospital de tercer nivel entre enero de 2011 y febrero de 2013.

Sólo los pacientes que cumplían los siguientes criterios se incluyeron en el estudio: pacientes con FA permanente o paroxística recientemente tratados con AVK (es decir, no más de 8 meses transcurridos desde el inicio del AVK), y que tienen visitas regulares para medidas de INR.

Se excluyeron los pacientes con prótesis valvular, enfermedad cardíacas reumáticas, cáncer activo, demencia y/o interrupción de los AVK. Los pacientes fueron seguidos hasta 1 año después de la inclusión en este estudio o hasta el desarrollo de hemorragia grave, complicaciones TE, o la muerte.

En total, se incluyó a 911 pacientes en la cohorte anticoagulada. Por otra parte, se incluyeron 154 pacientes consecutivos con FANV que no recibían ningún tratamiento anticoagulante.

La historia clínica se recogió de forma detallada para cada paciente y las características clínicas basales, junto con la información sobre eventos durante el seguimiento.

- El control de calidad de la anticoagulación con AVK en pacientes gallegos con FANV es aún por debajo del nivel óptimo como el PRINR en esta cohorte del mundo real fue 58% indicando la necesidad de más esfuerzos hacia la mejora del control de calidad de la anticoagulación con AVK en nuestra población.

- Las enfermedades cardiovasculares son muy prevalentes en pacientes con FANV y la insuficiencia cardíaca merece gran atención, ya que comúnmente acompaña AF, y demostró una fuerte asociación con el mal control de la calidad de AVK, y los resultados adversos. Por otra parte, entre los fármacos cardiovasculares, la amiodarona se asocia con un mal control de calidad de anticoagulación con AVK.

- El score SAMe-T_2R_2 constituye una herramienta fácil de usar para la predicción de la calidad del control de la anticoagulación con AVK. El rendimiento de SAMe-TT2R2 podría mejorarse teniendo en cuenta otros factores de riesgo relacionados con un mal control de INR como: disfunción renal, antecedentes de cáncer, diabetes mellitus, insuficiencia cardíaca y el abuso del alcohol. Estos factores deben tenerse en cuenta antes de prescribir AVK.

- La tasa de evento TE a pesar de la anticoagulación es notable (aproximadamente de 2%). En cuanto a la identificación de los pacientes con bajo riesgo de TE, los scores CHA_2DS_2-VASc y R_2-$CHADS_2$ identifican con mayor precisión a los pacientes en verdadero bajo riesgo de desarrollar futuros eventos TE, mientras que el score ATRIA no alcanzó habilidad similar.

- La incidencia de hemorragias graves fue del 3,3%. La puntuación de riesgo HAS-BLED sangrado demuestra mejor rendimiento que el ATRIA sangrado puntuación especialmente en la predicción de la hemorragia intracraneal, en una cohorte contemporánea de pacientes gallegos afectos de FANV y anticoagulados con AVK.

- Nuestro estudio alienta el uso de HAS-BLED, en el manejo de pacientes con FANV en la práctica clínica diaria. Además, la diabetes mellitus y la enfermedad pulmonar obstructiva crónica son fuertes predictores de hemorragia mayor, que deben tenerse en cuenta en la estimación del riesgo de hemorragia en pacientes con FANV antes de prescribir AVK. Son necesarios más estudios en esta área.

- La disfunción renal estimada por la tasa de filtración glomerular, ya sea calculado por la ecuación MDRD-4 re-expresada o la fórmula CKD-EPI, es un predictor independiente de hemorragia grave, TE o muerte, así como de mortalidad por cualquier causa. En este sentido, ambas fórmulas muestran impactos pronósticos similares en cuanto a la predicción de la variable combinada (hemorragia grave, TE y mortalidad por cualquier causa). Sin embargo, en este estudio se encontró que el uso de la nueva ecuación CKD-EPI reduce la prevalencia de pacientes con disfunción renal en comparación con la ecuación MDRD-4 re-expresada. Todo esto podría indicar que la adopción más generalizada de la nueva CKD-EPI en lugar de la MDRD-4 re-expresada puede dar lugar a la modificación del manejo general de los pacientes con FANV, en particular con respecto a los medicamentos a base de excreción renal.

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Title : Usefulness of the SAMe-TT2R2 risk score in identifying patients who will do well with vitamin K antagonist therapy in a community-based cohort of patients with non-valvular atrial fibrillation

Topic : 01.06 - Atrial fibrillation (AF)

Category : Bedside

Option : Young Investigator Award (YIA) Thrombosis

RAMI. Riziq Yousef Abumuaileq1, EMAD. Abu Assi1, SERGIO. Raposeiras Roubin1, ANDREA. Lopez Lopez1, NOELIA. Bouzas Cruz1, MARIA. Castineira Busto1, A. Redondo Dieguez1, V. Gonzalez Salvado1, JR. Gonzalez Juanatey1 - (1) University Hospital of Santiago de Compostela, Cardiology, Santiago De Compostela, Spain

Background. Oral anticoagulant therapy (OAC) is the cornerstone treatment in atrial fibrillation (AF) patients at risk of thromboembolic events. However, time in therapeutic range (TTR) for OAC therapy is critical to prevent the devastating consequences of AF-related thromboembolic complications. There is now a great interest in identifying patients at risk of having a poorer TTR and therefore could be potential candidates for prescribing a new OAC. Recently, a new predictive model, the SAMe-TT2R2 was conceived for this purpose. However, the performance of this risk score in an independent datasets is poorly known.

Aim. To examine the validity of the new SAMe-TT2-R2 score at predicting the quality of anticoagulation, in a sample of outpatients with non-valvular AF.

Methods. Retrospectively, Between June, 2012 and December 2013, all consecutive patients with non-valvular AF on a vitamin-K antagonist who were attending the outpatient Cardiology clinics of a tertiary hospital were recruited. We calculated the SAMe-TT2R2 score in 534 ambulatory patients with non-valvular AF who had > 12 months of uninterrupted VKA and more than 9 consecutives INR values. The performance of the SAMe-TT2R2 was evaluated by checking its discriminative power (c-index) and calibration ability (Hosmer-Lemeshow goodness-of-fit test) with regard to the 25th, 10th, and 5th percentile as the TTR cut off points.

Results. Mean INR values was 13.9 (SD 1.8); 342 (64%) patients had 15 INR values. The mean TTR (% in Range) was 60% (SD 18). The 25th, 10th, and 5th percentile of the TTR was of 46.7%, 33.3% and 26.7%, respectively. The SAMe-TT2R2 score values ranged from 0 to 5 (201 [39% patients had ≥2 points]). The c-index values for the 25th, 10th, and 5th percentiles of the TTR were 0.58 (95%CI 0.52-0.63), 0.65 (95% CI 0.57-0.74), and 0.66 (95%CI 0.58-0.75), respectively. The risk score performed well in terms of calibration as all the p-values of the Hosmer-Lemeshow goodness-of-fit test were ≥ 0.20.

Conclusions. The new SAMe-TTR2 score predicts acceptably poor INR control and could potentially aid decision-making in the management of patients with non-valvular AF.

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Title : CHA2DS2-VASc vs. CHADS2 at predicting the risk of stroke and death in a community-based cohort of patients with non-valvular atrial fibrillation who are on anticoagulation.

Topic : 01.06 - Atrial fibrillation (AF)

Category : Bedside

Option : Young Investigator Award (YIA) Thrombosis

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Background: CHA2DS2-VASc risk score was seen to be more reliable than the CHADS2 score for identifying patients with non valvular atrial fibrillation (AF) who are at risk of stroke. The predictive superiority of the CHA2DS2-VASc over the CHADS2 in anticoagulated patients with non valvular AF is not well known.

Aim: To assess the predictive ability of CHA2DS2-VASc and CHADS2 in predicting the composite endpoint of stroke and death in non valvular AF patients on vitamin K antagonist.

Methods. Retrospectively, from June/2012 to December/2013, 534 patients with non-valvular AF on vitamin-K antagonist who were attending the outpatient Cardiology clinics of a tertiary hospital in Spain were recruited. We calculated CHA2DS2-VASc and CHADS2 from the variables they include. The Cox regression analyses were used to assess the association (in terms of hazard ratio *HR*) between each of the two risk schemes and the study endpoint. Data regarding stroke and death was collected at 10 (SD=3) months. The performance of both risk

scores was computed by using area under the ROC (receiver operating characteristics) curves [AURc].

Results. Mean age was 74 (SD 11) years, and 216 (40.4%) were women. CHADS ranged from 0 to 6 points, while CHADS-VASc ranged form 0 to 8 points. According to CHADS scheme there were 8.8% at low risk (0 points), 20% at intermediate risk (1 point), and 71.2% at high risk (≥2 points) of non fatal stroke and death at 10 (SD 3) months. However, according to CHA2DS2-VASc, 5.4%, 5.6%, and 89% of patients were classified as having low, intermediate and high risk, respectively. At 10 (SD 3) months, 14 events were recorded: 5 patients suffered a non fatal stroke and 9 patients died. 13 out of the 14 events were found in the high risk category of the CHA2DS2-VASc (one event in the intermediate risk category). In contrast, using the CHADS2 classification system, 11 of 14 events occurred in the high risk strata, 2 of 14 in the intermediate risk strata, and 1 of 14 in the low-risk category. HR for the association between the CHA2DS2-VASc (as a continuous category) and stroke/death during follow-up was 1.4 (95%CI 1.007-2.041; p=0.046), similar to the HR obtained by using the CHADS2 score (HR 1.4 [95%CI: 1.001-2.248]; p=0.049). CHA2DS2-VASc exhibited a better predictability than did CHADS2 as was seen by the AURc: 0.67 [95%CI 0.52 to 0.80; p=0.03] vs. 0.63 [0.46 to 0.79; p=0.11].

Conclusion. In our study the rate of stroke in patients with non valvular AF was nearly 1% despite anticoagulation. CHA2DS2-VASc outperformed the old CHADS2 in predicting the risk of stroke and death in these patients

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Title : Characterizing patients who do not do well on a vitamin-K antagonist therapy in a community based cohort of patients with non valvular atrial fibrillation

Topic : 01.06 - Atrial fibrillation (AF)

Category : Bedside

Option : Young Investigator Award (YIA) Thrombosis

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Background and Aim: In atrial fibrillation (AF) the risk of complications increases when INR (International normalized ratio) values are out of therapeutic range. Mean time in therapeutic range (TTR) below 60% indicates that vitamin-K antagonist (VKA) is inefficient. We aimed to determine TTR values in patients who were on VKA treatment and had non-valvular AF and to identify the factors affecting TTR in these patients.

Method: Retrospectively, between June 2012 and December 2013, 534 consecutive patients with non-valvular AF who were attending the out-patient Cardiology clinics of a tertiary hospital were enrolled. For the purpose of the present study, only patients who were on uninterrupted AVK in at least > 12 months and had more than 9 consecutives INR values were included. TTR values were determined using the fraction of INR´s in range (the number of INR´s within target range [2 to 3] divided by the total number of INR´s). A cut off value of 60% was used to assess efficiency of TTR. Thereafter, patients were classified into two groups according to their TTR values (≥60% vs. <60%) and the characteristic features of these groups

were compared. Independent predictors of having TTR < 60% were identified using a binary logistic regression analysis.

Results: The mean age of the patients was 73 ± 11 years and 40.4% were female. 64% of the patients had 15 INR´s consecutive tests, and the average number of INR´s tests was 13.9±1.8. Mean TTR value was 59±16%, and 44.8% (n=239) had TTR values below 60%. In the univariate analysis, patients with TTR < 60% were younger (72±12 vs. 74±11 years; p=0.03) and more commonly women (65% vs. 34%; p=0.01) than those patients with TTR ≥60%. History of congestive heart failure, chronic obstructive pulmonary disease, moderate with alcohol consumption, being on home amiodarone, hyperuricemia, and a history of prior malignant disease, were significantly associated ($p<0.05$) with TTR < 60%. Prior coronary artery disease and smoking status showed a tendency to be associated with TTR < 60% ($p<0.10$). After a multivariate adjustment, the independent predictor of having a TTR < 60%, were moderate alcoholism consumption (odds ratio 5.3 [95%CI 1.1-24.8]), history of malignant disease (odds ratio 2 [95%CI 1.2-4.0]), on home amiodarone (odds ratio 1.6 [95%CI 1.1-3.1]), and age < 65 years (odds ratio 1.5 [95%CI 1.1-1.8]).

Conclusions: We found that about 45% of our study patients had inefficient TTR values and that TTR values were associated with some potentially modifiable factors such as alcohol

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Title : HAS-BLED versus ATRIA at predicting the risk of major bleeding in a real world cohort of patients with non-valvular atrial fibrillation on vitamin K antagonists

Topic : 01.06 - Atrial fibrillation (AF)

Category : Bedside

Option : No Options

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Background. Vitamin K antagonists (VKAs) greatly reduce the risk of stroke and still is the most commonly used therapy for this purpose in atrial fibrillation. However, this therapy also conveys a risk of bleeding complications, and the risk-benefit evaluation of oral anticoagulants therapy remains challenging. HAS-BLED and ATRIA are contemporary scoring systems used to predict hemorrhagic complications in patients with non-valvular atrial fibrillation (NVAF).

Purpose. We compared the predictability of both scores in a community based cohort of patients with NVAF on VKAs.

Methods. Retrospectively, we identified 911 consecutive patients with NVAF recently on VKAs who were attending the outpatient cardiology consultation of a tertiary hospital between January 2011 and February 2013. HAS-BLED and ATRIA were computed using the original criteria used in their development cohorts. Measures of performance for the risk scores were evaluated

at predicting major bleeding (2005 International Society on Thrombosis and Haemostasis criteria) and intracranial hemorrhage (ICH).

Results. During 10 ± 3 months of follow up, 30 (3.3%) developed major bleeding; 9 (1%) were ICH. Although both scores predicted major bleeding and ICH better than chance, their discriminative capacity was rather modest and did not differ significantly between each other regardless if they were considered as continuous (c-statistic ≤0.71) or categorical (c-statistic ≤0.65) variables. While as categorical variables, the HAS-BLED score was strongly associated with ICH (hazard ratio = 6.9; 95%CI: 1.8-28.1; p= 0.007), the ATRIA risk score was not significantly associated with ICH (hazard ratio= 3.9; 95%CI: 0.96-15.5; P= 0.06). The net reclassification improvement index numerically favored HAS-BLED for predicting major bleeding and ICH (+5.9% and +12%, respectively). In this cohort, diabetes mellitus (hazard ratio= 2.8, p= 0.01)and chronic obstructive pulmonary disease (hazard ratio= 2.9, p= 0.005) were also identified as independent predictors of major bleeding.

Conclusions. In this study, HAS-BLED outperformed ATRIA scoring system especially at predicting ICH in a real world cohort of patients with NVAF on VKAs. Diabetes mellitus and chronic obstructive pulmonary disease should be considered at bleeding risk stratification in these patients.

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Title : Prognostic usefulness of the glomerular filtration rate estimation equations in patients with non-valvular atrial fibrillation on vitamin K antagonists: the new CKD-EPI versus the re-expressed MDRD-4

Topic : 01.06 - Atrial fibrillation (AF)

Category : Bedside

Option : No Options

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Background. In atrial fibrillation, renal dysfunction entails more adverse events. Limited data exist on the prognostic value of the re-expressed Modification of Diet in Renal Disease equation (MDRD-4) versus the new Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) in atrial fibrillation.

Purpose. We compared the performance of the re-expressed MDRD-4 equation versus the new CKD-EPI equation at predicting major adverse outcomes in a real world cohort of patients with non-valvular atrial fibrillation (NVAF) on vitamin K antagonists (VKAs).

Methods: Retrospectively, we identified 911 consecutive patients with NVAF on VKAs who were attending the outpatient Cardiology consultation of a tertiary hospital between January

2011 and February 2013. The performance of each equation with respect to either a composite endpoint of major bleeding, thromboembolic events and all-cause mortality or each individual component of the composite endpoint was assessed using continuous and categorical ≥60, 59–30, and <30 ml/min/1.73 m2 estimated glomerular filtration rate.

Results: During 10±3 months of follow up, the composite endpoint occurred in 98 (10.8%) patients: 30 patients developed major bleeding, 18 had thromboembolic events, and 60 died. The new CKD-EPI equation provided lower prevalence of renal dysfunction <60 ml/min/1.73m2 (32.9%), compared with the re-expressed MDRD-4 equation (34.1%)

Estimated glomerular filtration rate from both equations was an independent predictor of the composite endpoint (hazard ratio=0.98 and 0.97 for the re-expressed MDRD-4 and the new CKD-EPI, respectively; p<0.0001) and all-cause mortality (hazard ratio=0.98 for both equations, p<0.01). Strong association with thromboembolic events was observed only when estimated glomerular filtration rate was < 30 ml/min/1.73m2: hazard ratio=5.1 for the re-expressed MDRD-4 equation, and hazard ratio=5.0 for the new CKD-EPI.

No significant association with major bleeding was observed for both equations.

Conclusions: The new CKD-EPI equation reduced the prevalence of renal dysfunction in a community based cohort of patients with NVAF on VKAs. Both equations performed similarly in predicting major adverse outcomes.

Rev Esp Cardiol. 2014;67 Supl 1:368

REVISTA ESPAÑOLA DE CARDIOLOGIA

6002-32 - UTILIDAD DEL SISTEMA DE PUNTUACIÓN SAME-TT2R2 EN LA IDENTIFICACIÓN DE PACIENTES CON FA NO VALVULAR QUE PRESENTARÁN POBRE CALIDAD DE ANTICOAGULACIÓN CON ANTAGONISTAS DE VITAMINA K

Rami Riziq-Yousef Abumuaileq, Emad ABU-ASSI, Sergio Raposeiras-Roubin, Andrea López-López, Alfredo Redondo Diéguez, Violeta González Salvado y J.R. González-Juanatey del Complexo Hospitalario Universitario de Santiago de Compostela (A Coruña).

Resumen

Introducción: La terapia con un anticoagulante oral (ACO) es la piedra angular del tratamiento en fibrilación auricular (FA) y riesgo tromboembólico. El tiempo en rango terapéutico (TTR: INR 2-3) para la terapia de la OAC es fundamental para prevenir las tromboembolias relacionadas con la FA. Actualmente, existe un gran interés en identificar que pacientes tendrán un pobre TTR, por lo que, serían candidatos a ser tratados con un nuevo OAC. Recientemente, un nuevo modelo predictivo, SAMe-TT2R2 fue concebido para este fin. Pretendemos examinar la validez de la nueva puntuación SAMe-TT2-R2 en la predicción de la calidad de la anticoagulación, en una muestra de pacientes ambulatorios con FA no valvular.

Métodos: Retrospectivamente, entre 6/2012 y 12/2013, se incluyó a todos los pacientes consecutivos con FA no valvular tratados con un antagonista de la vitamina K (AVK), que asistían a las consultas externas de cardiología de nuestro hospital. Se calculó la puntuación de SAMe- TT2R2 en 534 pacientes ambulatorios con FA no valvular que tenían > 12 meses de de tratamiento ininterrumpido con un AVK y que tenían ≥ 9 valores consecutivos INR. El rendimiento de la SAM-TT2R2 se evaluó mediante la comprobación de su poder discriminativo (índice c) y la capacidad de calibración (prueba de Hosmer-Lemeshow) en relación con los percentiles 5º, 10º, y 25º como puntos de corte del TTR. La media de los valores de INR fue de 13,9 (DE 1,8). La media del TTR (% en el rango) fue de 60% (DE 18%).

Resultados: Los valores de SAMe-TT2R2 oscilaron entre 0 y 5 (201 [39% tenían ≥ 2 puntos]). Los valores del índice c para los percentiles 5º, 10º y 25 º del TTR fueron: 0,58 (IC95%: 0,52-0,63), 0,65 (IC95%: 0,57-0,74) y 0,66 (IC95%: 0,58-0,75), respectivamente. La calibración del modelo fue buena (p de Hosmer-Lemeshow ≥ 0,20).

Conclusiones: La escala SAMe-TT2R2 predice aceptablemente que pacientes presentarán mal control de INR y podría ayudar a la toma de decisiones en el manejo de los pacientes con FA no valvular.

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REVISTA ESPAÑOLA DE CARDIOLOGIA

5010-7 - CHA_2DS_2-VASC VS $CHADS_2$ PARA PREDECIR EL RIESGO DE ACCIDENTE CEREBROVASCULAR Y MUERTE EN UNA COHORTE COMUNITARIA DE PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR TRATADOS CON ANTICOAGULACIÓN ORAL

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Resumen

Introducción: La escala CHA_2DS_2-VASc es más fiable que $CHADS_2$ en la identificación de que pacientes con fibrilación auricular no valvular (FANV) están en riesgo de accidente cerebrovascular. La superioridad de CHA_2DS_2-VASc respecto a $CHADS_2$ en pacientes con FA tratados con anticoagulación no es bien conocida. Evaluamos la capacidad de CHA_2DS_2-VASc y $CHADS_2$ en la predicción del riesgo "ictus o muerte por cualquier causa" en pacientes con FANV tratados con un antagonista de vitamina K.

Métodos: Retrospectivamente, entre junio/2012 a 12/2013, se reclutaron 534 pacientes con FANV anticoagulados con un antagonista de vitamina K, que asistieron a las consultas externas de cardiología de nuestro hospital. Después de calcular CHA_2DS_2-VASc y $CHADS_2$, se utilizaron modelos de regresión de Cox para evaluar la asociación (en términos de *Hazard ratio* [HR]) entre cada uno de los dos esquemas y el evento "ictus o muerte". El rendimiento de ambas puntuaciones de riesgo se calcula utilizando el área bajo la curva (AUR-ROC). La edad media fue de 74 ± 11 años; 40,4% eran mujeres. Según el esquema $CHADS_2$, un 8,8% de los pacientes tenían 0 puntos, 20% riesgo tenían 1 punto, y 71,2% tenían ≥ 2 puntos. Según el sistema CHA_2DS_2-VASc: 5,4%, 5,6%, y el 89% se clasificaron en bajo, intermedio y alto riesgo, respectivamente.

Resultados: A los 10 ± 3 meses, se registraron 14 eventos: 5 pacientes sufrieron un accidente cerebrovascular no mortal y otros 9 murieron. Trece de los 14 eventos fueron encontrados en la categoría de alto riesgo de la CHA_2DS_2-VASc (un evento en la categoría de riesgo intermedio). Por el contrario, utilizando el sistema de clasificación $CHADS_2$, 11/14 de los eventos ocurrieron en la categoría de riesgo alto; 2/14 en la categoría de riesgo intermedio; y 1/14 en la categoría de bajo riesgo. La asociación (HR) entre la CHA_2DS_2-VASc (como variable continua) y el evento "ictus o muerte" fue de 1,4 (IC95%: 1,007-2,041), similar a la obtenida de la puntuación $CHADS_2$ (HR [IC95%: 1,001-2,248]). CHA_2DS_2-VASc exhibió mejor discriminación que $CHADS_2$: AUR-ROC = 0,67 [IC95%: 0,52-0,80; p = 0,03] frente a 0,63 [0,46-0,79; p = 0,1].

Conclusiones: En nuestro estudio la tasa de accidente cerebrovascular en pacientes con FA no valvular fue de casi un 1% a pesar de la anticoagulación. CHA_2DS_2-VASc superó el viejo $CHADS_2$ en la predicción del riesgo de accidente cerebrovascular y muerte en estos pacientes.

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REVISTA ESPAÑOLA DE CARDIOLOGIA

6002-33 - CARACTERÍSTICAS DE LOS PACIENTES QUE PRESENTAN POBRE CALIDAD DE LA ANTICOAGULACIÓN CON UN ANTAGONISTA DE LA VITAMINA K EN UNA COHORTE COMUNITARIA DE PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR

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Resumen

Introducción: En la fibrilación auricular (FA) el riesgo de complicaciones aumenta cuando los valores de INR están fuera del rango terapéutico. El tiempo medio en rango terapéutico (TTR) < 60% indica ineficiencia de la anticoagulación. Determinamos los valores de TTR en pacientes con FA no valvular (FANV) tratados con un antagonista de vitamina K (AVK), e identificamos los factores asociados a TTR < 60%.

Métodos: Retrospectivamente, entre 6/2012 y 12/2013, se incluyeron a 534 pacientes consecutivos con FANV que asistieron a las clínicas ambulatorias de cardiología de un hospital terciario. Solo se incluyeron a aquellos que se encontraban en terapia ininterrumpida con un AVK durante ≥ 12 meses y que tenían ≥ 9 determinaciones consecutivos de INR. Los valores de TTR se determinaron utilizando la fracción de INR en rango. Se utilizó un valor de corte de 60% para evaluar la eficiencia del TTR. Los pacientes fueron clasificados en 2 grupos según los valores de TTR (≥ 60% vs < 60%). Se identificaron los predictores independientes de tener TTR < 60% mediante un análisis de regresión logística.

Resultados: La edad media fue de 73 ± 11 años; 40,4% eran mujeres. La media de las determinaciones de INR fue 13,9 ± 1,8. La media del valor del TTR fue 59 ± 16%. 239 (44,8%) tenían valores de TTR < 60%. En el análisis univariado, los pacientes con TTR < 60% eran más jóvenes (72 ± 12 vs 74 ± 11 años, p = 0,03) y más frecuentemente mujeres (65% vs 34%, p = 0,01) que los pacientes con TTR ≥ 60%. Los antecedentes de insuficiencia cardiaca, enfermedad pulmonar obstructiva crónica, consumo moderado de alcohol, tratamiento previo con amiodarona, la hiperuricemia, y una historia previa de enfermedad maligna, se asociaron de forma significativa (p < 0,05) con TTR < 60%. La cardiopatía isquémica y el tabaquismo mostraron una tendencia a asociarse con TTR < 60% (p < 0,10). Después de un ajuste multivariado, los predictores de tener un TTR < 60%, fueron consumo moderado de alcohol (*odds ratio* (OR) 5,3 [IC95%: 1,1-24,8]), antecedentes de enfermedad maligna (OR 2 [IC95%: 1,2-4,0]), tratamiento con amiodarona (OR 1,6 [IC95% 1.1-3.1]), y edad < 65 años (OR 1,5 [IC95%: 1.01-1.08]).

Conclusiones: Alrededor del 45% de nuestros pacientes tenían valores ineficientes de TTR. INR < 60% se asoció con algunos factores potencialmente modificables, como el consumo de alcohol y el tratamiento con amiodarona.

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REVISTA ESPAÑOLA DE CARDIOLOGIA

7001-8 - COMPARACIÓN ENTRE CHA_2DS_2-VASC Y LOS NUEVOS *SCORES* R_2CHADS_2 Y ATRIA EN LA PREDICCIÓN DE EVENTOS TROMBOEMBÓLICOS EN PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR

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Resumen

Introducción y objetivos: La precisa estratificación del riesgo de eventos tromboboembólicos (TE) es el primer y más importante paso en el manejo de los pacientes con fibrilación auricular no valvular (FANV). Se comparó el desempeño del *score* CHA_2DS_2-VASc y los recientemente desarrollados R_2CHADS_2 y ATRIA, para la predicción de TE en pacientes no anticoagulados o anticoagulados con FANV.

Métodos: Incluimos a 154 pacientes no anticoagulados con FANV que asistieron al departamento de Urgencias entre enero de 2008 y junio del 2010. Además, se estudió una segunda cohorte de 911 pacientes con FANV anticoaguados con antagonistas de la vitamina K que asistieron a la consulta externa de cardiología entre enero de 2011 y febrero de 2013. Las puntuaciones de los distintos scores se calcularon utilizando los criterios mencionados en sus cohortes de desarrollo. Las medidas de rendimiento para las puntuaciones de riesgo fueron evaluados en la predicción de eventos TE.

Resultados: En la cohorte no anticoagulada hubo 9 eventos TE durante su seguimiento (11 ± 2,7 meses). El *score* CHA_2DS_2-VASc mostró una asociación significativa con la ocurrencia TE: hazard ratio (HR) = 1,58 (95% intervalo de confianza [IC95%] 1,01-2,46), pero R_2CHADS_2 y ATRIA no presentaron asociación significativa (HR = 1,23 (IC95% 0,86-1,77) y 1,20 (IC95% 0,93 a 1,56), respectivamente. En la cohorte anticoagulada, después de 10 ± 3 meses de seguimiento, se desarrollaron 18 eventos TE. En esa cohorte, las tres puntuaciones mostraron asociación similar con el riesgo TE: HR = 1,49 (IC95% 1,13-1,97), 1,41 (IC95% 1,13-1,77) y 1,37 (IC95%: 1,12 a 1,66) para CHA_2DS_2-VASc, R_2CHADS_2 y ATRIA, respectivamente. En ambas cohortes, ningún evento TE ocurrió en pacientes clasificados en la categoría de bajo riesgo según CHA_2DS_2-VASc o R_2CHADS_2.

Conclusiones: El *score* CHA_2DS_2-VASc tiene una mejor asociación con eventos TE que las nuevas puntuaciones de riesgo R_2CHADS_2 y ATRIA en la cohorte no anticoagulada. Los scores CHA_2DS_2-VASc y R_2CHADS_2 permiten identificar a los pacientes con riesgo bajo.

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REVISTA ESPAÑOLA DE CARDIOLOGIA

6002-29 - HAS-BLED FRENTE ATRIA PARA PREDECIR EL RIESGO DE HEMORRAGIA MAYOR EN UNA COHORTE CONTEMPORÁNEA DE LOS PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR TRATADOS CON ANTAGONISTAS DE LA VITAMINA K

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Resumen

Introducción y objetivos: Los antagonistas de la vitamina K (AVK) reducen el riesgo de accidente cerebrovascular en la fibrilación auricular. Sin embargo, esta terapia también aumenta el riesgo de complicaciones hemorrágicas. La evaluación de riesgos y beneficios de la terapia con anticoagulantes orales sigue siendo un reto. HAS-BLED y ATRIA son sistemas de puntuación contemporáneos utilizados para predecir complicaciones hemorrágicas en pacientes con fibrilación auricular no valvular (FANV). Se comparó la capacidad predictiva de las dos puntuaciones en una cohorte basada en la comunidad de pacientes con FANV y AVK.

Métodos: Retrospectivamente, se identificaron 911 pacientes consecutivos con FANV y AVK que asistían a la consulta externa de cardiología entre enero de 2011 y febrero de 2013. HAS-BLED y ATRIA fueron calculados utilizando los criterios originales. Las medidas de rendimiento para las puntuaciones de riesgo fueron evaluados en la predicción de sangrado mayor (2005 Sociedad Internacional de Trombosis y Hemostasia criterios) y hemorragia intracraneal (HIC).

Resultados: Durante 10 ± 3 meses de seguimiento, 30 pacientes (3,3%) presentaron hemorragia grave; de ellas 9 casos fueron HIC (1%). Aunque ambas puntuaciones predijeron hemorragia mayor y HIC mejor que el azar, su capacidad discriminativa fue más bien modesta y no hugo diferencias significativas entre ambas sin importar si se consideraron como variables continuas (c-estadístico ≤ 0,71) o categóricas (c-estadístico ≤ 0,65). Como variables categóricas, la puntuación HAS-BLED se asocio fuertemente a la HIC (*hazard ratio* (HR) = 6,9; intervalo de confianza (IC) del 95%: 1,8 a 28,1; p = 0,007), la puntuación de riesgo ATRIA no se asoció significativamente con la HIC (HR = 3,9; IC del 95%: 0,96 a 15,5; p = 0,06). El índice de mejora reclasificación neta favorecida HAS-BLED para predecir la hemorragia mayor y HIC fue del + 5,9% y + 12%, respectivamente. En esta cohorte, la diabetes mellitus (HR = 2,8; p = 0,01) y la enfermedad pulmonar obstructiva crónica (HR = 2,9; p = 0,005) fueron también identificados como predictores independientes de sangrado mayor.

Conclusiones: El *score* HAS-BLED mostró una mayor asociación con hemorragias mayores que el *score* ATRIA, en especial con las hemorragias intracraneales.

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REVISTA ESPAÑOLA DE CARDIOLOGIA

6002-28 - UTILIDAD PRONÓSTICA DE LAS ECUACIONES DE ESTIMACIÓN DE FILTRADO GLOMERULAR EN PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR: LA NUEVA CKD-EPI FRENTE A LA REEXPRESADA MDRD-4

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Resumen

Introducción y objetivos: En la fibrilación auricular la disfunción renal implica más eventos adversos. Existen datos limitados sobre el valor pronóstico de la reexpresada Modificación de la Dieta en la ecuación Enfermedad Renal (MDRD-4) frente a la ecuacion CKD-EPI (*Chronic Kidney Disease-Epidemiology Collaboration*) en la fibrilación auricular. Se comparó el desempeño de la reexpresada MDRD-4 ecuación contra la nueva ecuación CKD-EPI en la predicción de los principales resultados adversos en un verdadero mundo de la cohorte de pacientes con fibrilación auricular no valvular (FANV) tratados con antagonistas de la vitamina K (AVK).

Métodos: Retrospectivamente, se incluyeron 911 pacientes consecutivos con FANV y AVK que asistían a la consulta externa de Cardiología entre enero de 2011 y febrero de 2013. El rendimiento de cada ecuación con respecto a cualquiera de una variable combinada de hemorragia mayor, eventos tromboembólicos y mortalidad por cualquier causa o de cada componente individual de la variable combinada se evaluó usando continua y categórica ≥ 60, 59-30, y < 30 ml/min/1,73 m² tasa de filtración glomerular (TFG) estimada.

Resultados: Durante 10 ± 3 meses de seguimiento, la variable combinada se produjo en 98 (10,8%) pacientes: 30 pacientes desarrollaron hemorragia mayor, 18 tuvieron episodios tromboembólicos, y 60 murieron. La nueva ecuación CKD-EPI proporciona una menor prevalencia de disfunción renal < 60 ml/min/1,73 m² (32,9%), en comparación con la ecuación reexpresada MDRD-4 (34,1%). La TFG estimada de ambas ecuaciones fue un predictor independiente de la variable combinada (hazard ratio = 0,98 y 0,97 para la reexpresada MDRD-4 y el nuevo CKD-EPI, respectivamente; p < 0,0001) y la mortalidad por cualquier causa (hazard ratio = 0,98 para ambas ecuaciones, p < 0,01). Se observó una fuerte asociación con eventos tromboembólicos solo cuando la TFG estimada fue < 30 ml/min/1,73 m²: hazard ratio = 5,1 para la ecuación reexpresada MDRD-4, razón de riesgo = 5,0 para la nueva fórmula CKD-EPI. No se observó una asociación significativa con la hemorragia mayor para ambas ecuaciones.

Conclusiones: La nueva ecuación CKD-EPI reduce la prevalencia de la disfunción renal en una cohorte basada en la comunidad de pacientes que tienen FANV con AVK. Ambas ecuaciones realizan de manera similar en la predicción de los principales resultados adversos.