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Anticoagulation in the elderly patient with atrial fibrillation

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Summary

Increasing age stands out as one of the most powerful risk factors for stroke in patients with atrial fibrillation. With the steadily increasing age of the global population, questions regarding the optimal anticoagulation strategy in the elderly are pervasive and often present highly complex clinical dilemmas. This group of patients is at increased risk of bleeding related to multiple other comorbidities, higher rates of falling, and polypharmacy – especially the anti-platelet agents. The elderly patient is more sensitive to warfarin, and coupled with higher rates of intracranial bleeding, the newer anti-coagulants present an attractive alternative in selected subgroups. This review is aimed at contextualizing the problem, and providing a practical, balanced approach to managing the inescapable predicament of bleeding versus thromboembolic stroke in this high-risk group.

Key words: ELDERLY
ANTICOAGULATION
ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, and it is most common in the elderly (>75 years old). This sector of the population is growing rapidly as global societies continue to age, and the scope of the problem is vast – affecting over 10% of all patients over the age of 80 years of age[1,2]. Moreover the incidence and prevalence of atrial fibrillation is also continuing to increase, and there is no indication that the epidemic of AF has reached its plateau[3-6]. In parallel, risk factors for stroke appear to be following a parallel trend in growth[7] –obesity, type 2 diabetes, hypertension, and obstructive sleep apnea– and the relationship is likely to be causal (Figure 1).

Almost half of all thromboembolic strokes in the United States are thought to be caused by atrial fibrillation – and this rate is probably similar across developed countries[8,9]. The presence of atrial fibrillation alone in this age-group increases the risk of stroke five-fold, and yet other risk factors for stroke such as diabetes, heart failure, hypertension, and vascular disease frequently co-exist in this group of patients[10]. The primary conundrum is that the very same risk factors (and especially advanced-age itself) that increase their risk of stroke – also increase the risk of hemorrhage[11,12]. And, perhaps, the actual difficulty in negotiating this specific decision is no better illustrated than by the obvious metric of the marked underutilization of anticoagulation in the elderly – in whom anticoagulation is recommended and in whom greatest benefit is known (Figure 2). Repeated studies have demonstrated that approx. half of those with atrial fibrillation over the age of 75 years with a history of cerebral thromboembolism were prescribed warfarin[13,14]. Aspirin does seem to be commonly prescribed as monotherapy in this group, and disturbingly this appears to be associated with increased risks of stroke in the elderly[15]. Importantly, the misperception that aspirin is an effective agent probably contributes to the underutilization of anticoagulation in this population[16].

Advancing age and stroke

The pathophysiology underlying the development of thrombus and cardioembolic stroke in the elderly is likely similar to that in other age groups, and involves multiple contributing risk factors. In the context of atrial fibrillation, the lack of consistent atrial contraction and emptying results in the primary element of relative blood stasis within the left atrium and left atrial appendage. And although atrial fibrillation per se is a fundamental step to-

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wards stroke, other risk factors conspire to varying degrees to effect thrombus formation - with age itself being key. In the young patient without comorbidities, stroke is rare: occurring in less than 1% of patients[17].

The prognosis after an ischemic stroke in the elderly is also worse, with a higher morbidity and mortality[18,19].

Comorbidities and polypharmacy in the elderly

Comorbidities in the elderly, including hypertension, diabetes, left ventricular systolic and diastolic dysfunction and vascular disease directly impact the atrial substrate, with resultant stretch and enlargement of the atria (predominantly the left) leading to the development of atrial fibrillation and probable fibrosis and perhaps atrial endothelial dysfunction. Obesity in its own right interestingly also appears to indirectly damage the atrial tissue at a transcriptional and translational level resulting in conduction abnormalities. Fractionated electrograms, lower atrial voltage, increased profibrotic TGF-β1 expression and interstitial atrial fibrosis with an increased propensity for AF is concurrently found[20]. Where these changes affect arrhythmogenesis, the associated increase in the left atrial size also predisposes towards the development of thrombus[21-25]. Stretch-induced mechanisms conspire to result in endothelial dysfunction, and a potentially a pro-coagulable state, while several hemostatic factors also appear to be dysregulated by AF itself[26]. It appears that this paradigm exists in both paroxysmal and persistent atrial fibrillation syndromes, yet our understanding of the underlying mechanisms of a hyper-coagulable state of AF remains elusive to a large degree[26-29] (Figure 3). Platelet activation is noted to be upregulated, in addition to higher levels of thrombin–antithrombin complex formation, together with acute endothelial dysfunction and higher von Willebrand factor levels[29,30]. It is well-known that the inflammatory cascade is upregulated in AF, with higher levels of C-reactive protein, heat shock proteins and other pro-inflammatory cytokines acting in concert towards or with the infiltration of lymphomononuclear cells into the atrial tissue of AF patients compare to those who are in sinus rhythm[31]. These processes are also substantially upregulated in certain well-known clinical conditions that are associated with the precipitation of AF, namely: cardiac surgery[32], myocardial infarction[33], obesity[32] and potentially even hypertension[34]. Exactly why inflammation would trigger arrhythmia is not entirely clear, yet this mediator and precipitant are common in the elderly, and is also recognized to affect clotting in a prothrombotic manner[35].

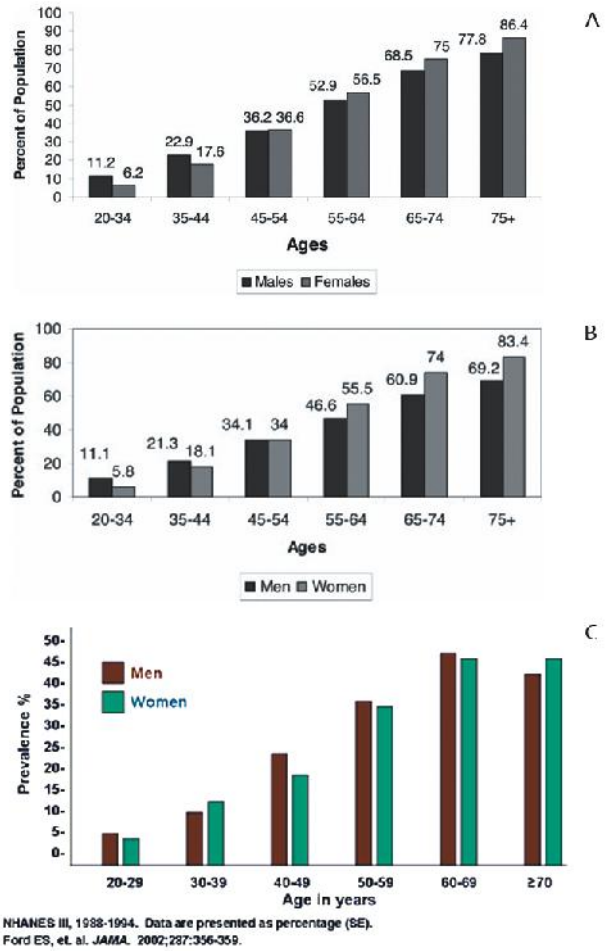

Figure 1. A) Prevalence of cardiovascular diseases in Americans age 20 and older by age and sex (NHANES: 1999-2002). Source: CDC/NCHS and NHLBI. B) Prevalence of high blood pressure in Americans by age and sex (NHANES: 1999-2002). Source: CDC/NCHS and NHLBI. C) Prevalence of the metabolic syndrome in Americans by age and sex (NHANES: 1988-1994). Source: CDC/NCHS and NHLBI.

It is also important to recognize that concomitant pathologies such as aortic stiffness, diffuse atherosclerosis, cerebrovascular disease and vascular disease are common in the elderly, and in this context, stroke and systemic embolism may be directly related to the arterial disease and perhaps requires the catalytic influence of an inflammatory "milieu" [36]. Recently high sensitivity Troponin I levels, a sensitive indicator of myocardial damage, were independently and significantly associated with an increased risk of stroke, systemic embolism, and all-cause mortality[37].

Polypharmacy -most common in the elderly more than any other group[38]- is especially consequential in the management of anticoagulation.

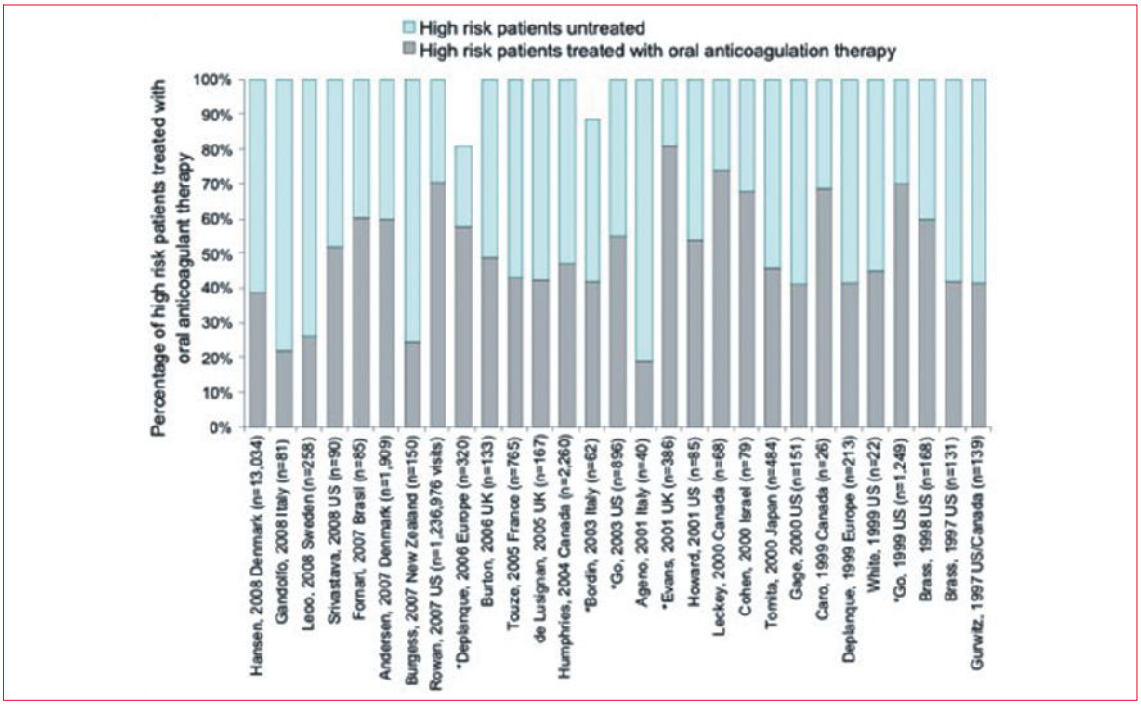

Figura 2. Patients with atrial fibrillation and prior stroke/transient ischemic attack: oral anticoagulation treatment levels as a proportion of patients eligible for oral anticoagulation therapy.
* Contraindications taken into account.
The American Journal of Medicine, Volume 123, Issue 7, 2010, 638-645.e4 Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review Isla M. Ogilvie, Nick Newton, Sharon A. Welner, Warren Cowell, Gregory Y.H. Lip

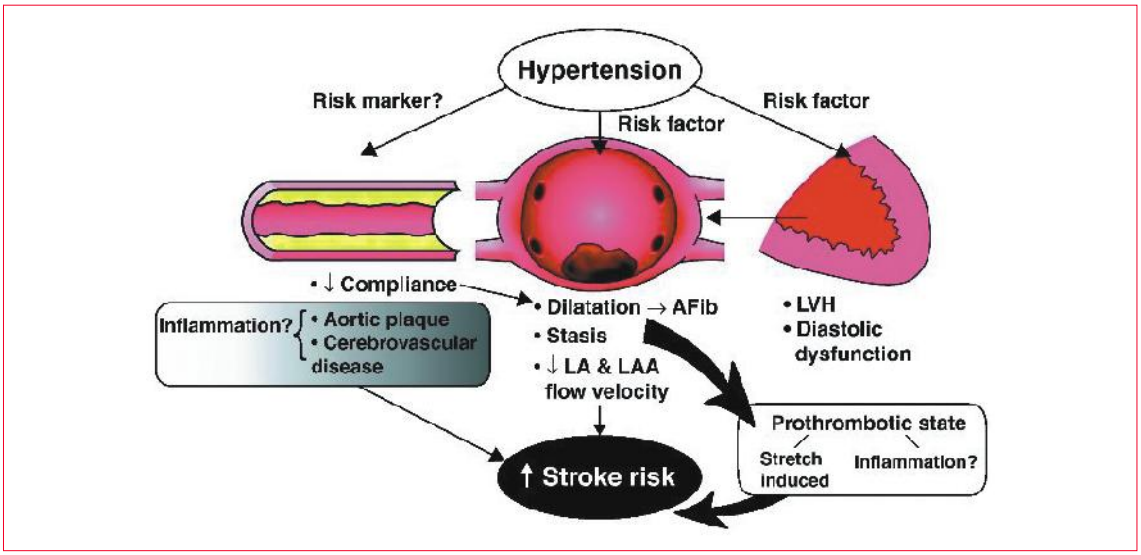

Figure 3. The development of a prothrombotic environment that supports the risk of stroke in nonvalvular hypertension. Untreated hypertension, vascular disease and increased arterial stiffness can result in left ventricular hypertrophy, diastolic dysfunction, and left atrial volume overload with stasis and thrombus formation. Atrial fibrillation and atrial stretch contributes to stasis and a hypercoagulable state.
Afib: atrial fibrillation; LA: left atrial; LAA: left atrial appendage; LVH: left ventricular hypertrophy.
Modified with permission from Rev Esp Cardiol. 2011; 64:260-8.

Well-known interactions of other drugs with the hepatic metabolism of warfarin by the cytochrome p-450 system result in pro- thrombotic sub-therapeutic INR's and conversely bleeding related to inhibition of metabolism of the same system. Furthermore, and frequently as difficult to manage and predict, is the interaction of the anti-platelet drugs on overall hemostasis. There are very little data to

guide co-prescription of these agents with warfarin or with the newer anticoagulants, and it is not uncommon that this subset of patients is also taking aspirin in addition to clopidogrel, prasugrel or ticagrelor[39].

Important comorbidities that also affect the anticoagulation status of the elderly patient include renal and hepatic dysfunction. Renal function declines consistently with advancing age[40] and the majority of the newer anticoagulants are cleared by the kidney. It does also appear that renal dysfunction is itself a risk factor for stroke in patients with AF[41], yet unfortunately bleeding is also a major issue in patients with advanced renal disease[42]. In essence, with and without the use of anticoagulation, the elderly patient is more likely to bleed. Complicating management, and discussed in more detail below - the novel anticoagulants (NOAC's) should be avoided if the creatinine clearance is below <15 mL/minute. Common to many chronic conditions is a fluctuating course - something the clinician needs to remain acutely aware of when prescribing renally-excreted medications.

Fear of falls

Many clinicians involved in the management of anticoagulation in the elderly have witnessed the catastrophic event of intracranial bleeding in a patient on warfarin. These anecdotal experiences may be fundamental to magnifying the perception of the potential risk of falls, and it is imperative that the prescriber recognize that the risk of traumatic intracranial hemorrhage from a fall is in fact fairly low[43,44]. Striking modeling data suggests that patients with AF at higher risk of stroke would have to fall in excess of 295 times per year before the risk of a traumatic intracranial bleed would outweigh the risk of ischemic stroke[45-47]. Furthermore, it is also important to note that in reality, if one looks specifically at older persons in a high fall risk category, the mean number of falls is around 2 falls per annum[45-47]. Nonetheless there are elderly subsets at higher risk including patients with severe orthostatic hypotension, peripheral neuropathy, gait instability requiring the use of a walker etc and this need to be taken into account when prescribing anticoagulation.

Nutritional status

The patients dietary habits do not need to be changed whether anticoagulation should be prescribed or not, but rather needs to be considered in the selection of the type of anticoagulation. Poor nutritional status –more common in the frail, elderly[48]– must be recognized by the clinician, and it is likely a novel anticoagulant would be the better choice, given the significant and unpredictable interactions that warfarin has with food.

Risk stratification

Based on comorbidities, the risk of stroke and bleeding varies significantly from patient to patient, thereby providing a central role for risk-stratification, and who should receive anticoagulation and who can forego it[49]. Although several large studies suggest that the $CHADS_2$ and CHA_2DS_2-VASc models had the best predictive value in elderly patients[50,51], regrettably, the ability of these or any other risk schema to predict stroke is less than ideal - identifying those patients who will sustain a stroke with approximately a 60% - 70% accuracy. Nevertheless, these risk-estimation schemas have proved vital in clinical care and do form the basis for anticoagulation prescription. Both European and American societal guidelines now identify the CHA_2DS_2Vasc risk scoring system as the primary method for considering the potential benefits of anticoagulation. This more contemporary scheme does appear to do better at risk stratifying those at lowest risk, thereby helping to identify those who can avoid anticoagulation. Given that age > 75 years provides two points using this scheme - all elderly patients are recommended to be treated with oral anticoagulation. This recommendation, however, does need to be tempered against the concerns for bleeding in each patient, taking into account that an increased risk of bleeding is not a contraindication for anticoagulation but a warning signal that mandates careful attention to anticoagulation dosing. Bleeding score schemas are available for easy bedside computation of risk/benefit. Although the HAS-BLED scoring system is simple and facile to use (predicated on hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), age greater than 65, and concomitant drugs and alcohol use) [52] – the true net clinical benefit is more complicated to derive. Based on the difference between the potential benefits of stroke prevention weighed against the risk of bleeding, a quick system to analyze this complex interplay is not available. However, the net clinical benefit of warfarin improves progressively with advancing age and is greatest for patients with AF 85 years and older[53]. The net clinical benefit for the newer anticoagulants remains to be established in the elderly.

A significant limitation of all risk-schema is that non-valvular atrial fibrillation was not included in the substantiation of these tools[54]. It may well be that a 75 year old patient with severe aortic stenosis and significant diastolic dysfunction, is at much

higher risk than the counterpart with a normal aortic valve, and until more data is available for these groups - it is the authors' contention that these patients be more carefully considered, as there is likely a higher incidence of stroke.

More recently, cardiovascular biomarkers (such as highly sensitive troponin T) are emerging as exciting and perhaps more reliable predictors of thromboembolic risk – reflecting the prothrombotic state of the individual. Further studies are, however, necessary to establish these as dependable assays in this regard, and perhaps utilization of these biomarkers may augment or replace the current risk schemas. Similar to the advent of brain natriuretic peptide monitoring, and before clinical use, the underlying pathophysiology of stroke and systemic embolism in its relationship to these biomarkers needs to be better understood.

What is the evidence for the benefit of anticoagulation in atrial fibrillation?

Current ESC and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, insist on an individualized approach to recommending anticoagulation for stroke and peripheral thromboembolism prevention[9,55]. And with a CHA_2DS_2-VASc score of 2 or higher there is agreement that anticoagulation be recommended[9,56]. Anticoagulation options are summarized below.

Aspirin

Although used for many years, and still prescribed widely for thromboembolic prophylaxis in atrial fibrillation, aspirin is now felt to be ineffective in this endeavor, and potentially harmful in the elderly[9]. Driven by the results of a single trial, the putative benefit of aspirin has perpetuated – yet close review of this particular study (Stroke Prevention in Atrial Fibrillation (SPAF-1)[57], questions this inference. Reporting a 42% reduction in stroke using aspirin 325 mg/day compared with placebo, aspirin's effect varied disparately – reducing stroke by 94 versus 8%, in warfarin eligible and ineligible patients respectively. Particularly germane to this review, aspirin did not reduce strokes in those aged 75 or older, and nor did it prevent severe strokes. From a safety point of view, the Birmingham Atrial Fibrillation Treatment of the Aged Study[58] identified a similar risk of major bleeding and intracranial hemorrhage when compared with warfarin.

Dual antiplatelet therapy

In the large ACTIVE study[59], clopidogrel plus aspirin significantly reduced the rate of the combined endpoint of first occurrence of stroke, systemic embolism, myocardial infarction, and vascular death; yet this benefit came at a price of a 50% increase in major bleeding. The mean age of patients within this trial was 71 ± 10 years, and hence the majority was in the "elderly sub-group". On the basis of this trial, we feel it is difficult to consider this approach of dual-antiplatelet therapy as a viable alternative to warfarin, when contrasted against the novel anticoagulants which provide similar protection – but with less bleeding than warfarin.

Warfarin compared to antiplatelet therapy

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study compared warfarin (target INR 2 to 3) with aspirin in patients with atrial fibrillation who were 75 years of age or older (mean age, 82 years). The results of this study echo the other trials, which typically have demonstrated a relative risk reduction in stroke and mortality by around 60% and 25% respectively, when compared with placebo or antiplatelet agents[58].

Despite these indisputable clinical benefits for the elderly patient with AF, the clinician and patient are acutely aware of the multiple caveats associated with warfarin therapy. The drug action has a delayed onset of action – thereby often needing bridging with l a form of heparin post-cardioversion or in high-risk patients. It has a very narrow therapeutic range, requiring constant vigilance and monitoring with regards to dose adjusting. It has multiple interactions with medications, foods and diet, and also an unpredictable effect related to specific genetic polymorphisms encoding for the metabolic pathways that manage the drug. These are critical limitations, given that the time in the therapeutic range (ideally 65% or greater), is intimately linked to who benefits from warfarin[60], and also who sustains a bleeding event[61,62] (Figure 4). This need for constant and frequent monitoring also introduces an element of inconvenience – which not uncommonly is linked to non-compliance. Time in the therapeutic range is unfortunately poor in the large trials and also in practice – varying tremendously and typically around 50 to 60% in the United States[63-65]. Home INR monitoring is however associated with less stroke and less bleeding – yet the benefit at this stage appears to be small[66].

Dabigatran etexilate

Dabigatran Etexilate (Pradaxa®) is an oral direct thrombin inhibitor that has multiple effects on the

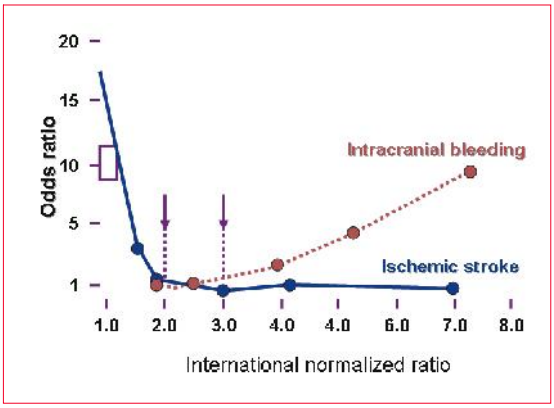

Figure 4. The narrow therapeutic window of warfarin. Less time in the therapeutic range is associated with an annual risk increase of major hemorrhage and thromboembolism. Modified from Ann Intern Med 1994;120(11):897-902.

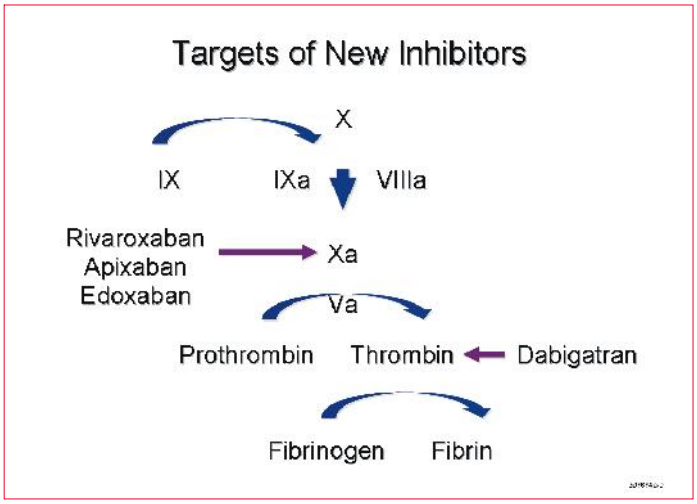

Figure 5. Targets of the novel oral anticoagulants.

clotting cascade.(Figure 5) The medication is taken twice daily to inhibit the conversion of fibrinogen to fibrin, block the activation of platelets, and to stabilize clot[67,68]. Like the other novel oral anticoagulants (NOACs), it has a rapid onset of action, and INR testing is not required. The key atrial fibrillation trial (RE-LY) randomized over 18 thousand patients to either the trial drug or warfarin, and 150 mg twice daily of dabigatran was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to warfarin[69]. At a dose of 110mg twice per day, rates of stroke and systemic embolism were similar to those associated with warfarin, but rates of major hemorrhage were around 60% lower. Importantly, this clinical difference was found regardless of the time spent in the therapeutic range for those patients taking warfarin[70].

Rivaroxaban

Rivaroxaban, apixaban and edoxaban are all factor Xa inhibitors, and block the central protease which is common to both the intrinsic and extrinsic coagulation cascades[67,68].

Rivaroxaban has a rapid onset of action, and is dosed once daily. It is cleared by predominantly via a hepatic mechanism and also by the kidney, and does not require INR monitoring. The ROCKET-AF trial evaluated over fourteen thousand patients with atrial fibrillation and a mean $CHADS_2$ risk score of 3.5. Compared against warfarin therapy, rivaroxaban was found to be non-inferior and patients sustained a significantly lower incidence of bleeding – especially intracranial bleeding.

Apixaban

The Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial — compared apixaban to aspirin in 5600 patients who were deemed by their physician to be “unsuitable” for warfarin[71]. This study was terminated early because apixaban significantly reduced the risk of stroke and systemic emboli without increasing the incidence of bleeding[72]. The ARISTOTLE TRIAL (Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation) which compared apixaban to warfarin in in around eighteen thousand patients with atrial fibrillation and a $CHADS_2$ score of 2.1. The results confirmed the superiority of apixaban over warfarin in reducing stroke or systemic thromboembolism, again with significantly less bleeding, especially intracranial. Importantly, apixaban was not noted to be associated with any increase in gastro-intestinal (GI) bleeding, whereas dabigatran and all other factor Xa inhibitors were seen to increase the likelihood of GI hemorrhage. All-cause mortality was also reduced in the apixaban group.

Edoxaban

The Effective Anticoagulation with Factor Xa Generation in Atrial Fibrillation Trial (ENGAGE AF-TIMI 48) evaluated over twenty one thousand patients with atrial fibrillation and a mean $CHADS_2$ score of 2.8[73]. Edoxaban was found to be non-inferior to warfarin, and was associated with less major bleeding, including less intracranial hemorrhage but there is a concern about the benefit of

edoxaban in patients with a creatinine clearance greater than 95[74].

Practical issues to consider when prescribing NOACs

As is evident from the NOAC vs. warfarin trial data summarized above, these new agents provide very encouraging clinical data. The mean age of trial participants in the studies referred to above varies from 70 to 73 years, so even though more data is still needed in the elderly patient group – a large percentage of participants were actually in the over 75 range.

1. It is widely known that warfarin metabolism is significantly affected by diet, genetics and concurrent use of other medications – and although the dietary limitations and genetic issue is avoided by using a NOAC, it is important to note that the NOACs do exhibit significant drug interactions. Those agents that affect both the CYP3A4 and p-glycoprotein system provide most concern: inhibitors (e.g. ketoconazole, ritonavir, clarithromycin) and inducers (e.g. rifampin, phenytoin, carbamazepine). These are specific to each drug, and not entirely consistent across the class. It behooves the clinician to learn the specific details for the NOACs they most commonly prescribe.
2. Dose reductions or avoidance of the NOACs are necessary in the context of chronic kidney disease – based on the level of dysfunction and specific to each drug.
3. Although as a class the NOACs are associated with less intracranial bleeding, dabigatran 150 mg twice daily was associated with an increased risk of major extra-cranial bleeding in elderly patients compared with warfarin.
4. Cost is a major difference; with the price of the NOACs being up to 50 fold more in the Unites States (depending upon insurance). Frequently the cost of INR testing is not born by the patient, and the actual cost to the medical system needs to be evaluated for each provider/patient system.
5. Dyspepsia is a common side effect with dabigatran, and GI bleeding is recognized to be more common with all NOACs except for apixaban[75]. This is especially true in the elderly[76].
6. Although the NOACs are associated with significantly less bleeding, the lack of reversibility in the context of trauma or emergency surgery is a concern. Reversal agents are currently being evaluated and should be clinically available in the near future

Decision-making in the elderly

Warfarin is frequently a stigmatized medication - favored or avoided by the patient or the physician. Despite the excellent evidence for its benefit against stroke in selected elderly patients, the decision remains difficult from a physician's perspective and often more so for the patient and family. Cognitive impairment in this age-group complicates the decision-making process, and often the ultimate conclusion is decided on by the caregiver or family member. Cognitive issues are also commonly associated with medication non-compliance - further thwarting the deliberation and care of these patients. Decision-aids have been utilized with clear benefit in AF[77], and although not yet not specifically studied in the elderly, this group may stand to potentially benefit more.

Conclusions

The incoming demographic tide in the growth of elderly populations is a crucial global health problem, and for diseases such as atrial fibrillation which are enriched in this age-group. Long-awaited, yet timely arrivals of multiple new anticoagulants have ushered in a new era, and also allowed for vast numbers of elderly patients with atrial fibrillation to be studied in the context of their risk of stroke and bleeding. More data is still needed, and registries will continue to play a critical role in evaluating the true clinical risks and benefits.

Conflicts of interest: none declared.

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