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Oral Anticoagulants in Older Adults with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in adults and contributes directly to adverse clinical events, ranging from ischemic stroke to heart failure and cardiovascular death. Because the incidence of AF and its attendant complications increase with age, there is a strong and growing need to develop safe, effective and widely available therapies. The following review summarizes the use of oral anticoagulants in older adults with AF, focusing on practical topics such as drug metabolism, drug- drug interactions, co-morbidities and cost considerations in a complex payer environment.

Keywords

Atrial fibrillation; novel oral anticoagulant; older adult

AGE AND ATRIAL FIBRILLATION

Defining Old Age

There is no general agreement on the age at which a person becomes old [1]. The use of a calendar age to mark the threshold of old age assumes “equivalence” with biological age, yet it is generally accepted that these are not necessarily synonymous [1]. In many societies, old age is precipitated by a change in social role or physical status. If one considers the self-definition of “old age”, as people grow older, it seems their self-definitions of old age become decreasingly multifaceted and increasingly related to health status [2,3]. Yet others consider an adult old when one has surpassed the average life span of human beings [4].

According to a 2004 report by the *Centers for Disease Control Prevention* (CDC), *The Merck Institute of Aging and Health*, and the *Gerontological Society of America* (GSA), Americans are living longer due to declines in heart disease and stroke mortality, but chronic diseases such as diabetes and high blood pressure are becoming more prevalent among older adults. The proportion of those aged 65–74 reporting very good- to- excellent health rose to 42% in 1999, which is an increase of 7% since 1982. Those age 75 years and older, however, reported little improvement or a decline in health status (34% and 28% of those aged 75–84 and aged 85+, respectively, reported themselves in very good- to -excellent health) [5].

Accordingly, health care providers now identify subgroups of older adults as “younger old” (ages 65–74), “older old” (ages 75–85) and “oldest old” (ages 85 and older) [4]. The number of “younger old” increased when the first of 77 million “Baby Boomers” turned 65 years old in 2011. Presently, nearly 10,000 Americans turn 65 years old daily [5].

For the purpose of our review, we will define “older adults” as age 75 and older. Patients who are 75 years old often present a complex clinical picture with coexisting conditions and frailty [6].

Atrial Fibrillation (AF) in an Aging Population

The mean age in phase 3 clinical trials of novel oral anticoagulants (NOAC) among patients with non- valvular atrial fibrillation (AF) exceeds 70 years of age. This is not unexpected given that the incidence of AF increases with age and nearly half of all patients with AF are 75 or older [7]. In addition, stroke as a complication of AF increases with age: the attributable risk of stroke from AF is estimated at 1.5% for those aged 50 to 59 years, and 23.5% for those aged 80–89 years [8]. While older adults with AF are at higher risk of thromboembolic stroke compared to their younger counterparts, they are also less likely to be anticoagulated largely due to greater propensity for bleeding and, at times, an unfounded perception of prohibitive risk [9].

The available data show that anticoagulant and platelet-directed therapy reduce stroke risk by approximately 60% and 20%, respectively, in patients with AF [10]. Yet just over half of eligible patients receive vitamin K antagonists (VKAs) [11]. Factors that limit the use of VKAs include: their narrow therapeutic index; requirement for frequent coagulation monitoring; complex dosing; prolonged pharmacodynamic effects; and numerous food-drug and drug-drug interactions.

Accordingly, NOACs should represent an attractive alternative to VKAs in older adults with AF. To assure optimal utilization, clinicians must be familiar with: NOAC pharmacology; clinical trial methodology, including entry and exclusion criteria; and several factors specific to older patients that impact drug metabolism and clearance, toxicity and effectiveness.

DRUG METABOLISM AND EFFECTS OF AGING

Drug metabolism is altered with aging, in ways that may not be readily apparent (or easily quantitated). Inter-individual variability in response to drug effects is noticeable among older adults and far more prominent compared to young adults.

Pharmacokinetic Considerations

Bioavailability—The bioavailability of any drug after oral administration depends upon many factors, including the fraction of the administered dose absorbed through the gastrointestinal mucosa, the fraction of the absorbed dose that passes through the gastrointestinal tract into the hepatic portal blood unmetabolized, and the hepatic first-pass availability [12]. Gut absorption typically declines and first pass metabolism slows with aging, often producing a clinically insignificant net effect on drug bioavailability compared to young adults. Bioavailability can be increased, however, if the hepatic first-pass effect of

highly cleared drugs is greatly reduced, due to decreases in liver mass and perfusion with aging [13]. Accordingly, the conclusions of studies on old age and the bioavailability of orally administered drugs are variable: the absolute bioavailability of labetalol and lidocaine, for example, nearly doubles with age, whereas no differences have been reported for metoprolol and morphine [12]. No specific effect of aging on the efflux pump, P-glycoprotein, in the gastrointestinal tract has been reported [12].

Volume of Distribution—Alterations in protein binding that occur with aging do not typically affect orally administered medications. Body fat increases and body water decreases with aging; this may affect peak plasma concentrations and other pharmacokinetic parameters following loading doses [12].

Renal Aging—There have been many studies of the pharmacokinetics of renally excreted drugs with aging, although few have attempted to define the specific relationship among normal aging, renal function, and altered pharmacokinetics [12]. The incidence of hypertension increases with age as peripheral blood vessels calcify and stiffen. The presence of small vessel pathology in older adults without apparent renal disease or hypertension suggests that even in healthy older adults, renal changes may be secondary to vascular disease and altered vascular responsiveness [12]. In addition, glomerulosclerosis has been associated with aging and disease (including hypertension) [14]. Regardless of etiology, most adults demonstrate a decline in renal function over time [15]. When subjects with “possible renal or urinary tract disease” and subjects on diuretics and antihypertensives were excluded from the Baltimore Longitudinal Study of Aging, the mean decrease in creatinine clearance was 0.75 ml/min/year. However, one-third had no decrease in creatinine clearance over a 23 year period [16].

Serum creatinine does not provide an accurate assessment of renal function, making methods used to calculate function based on creatinine imperfect. In older adults, the daily production of creatinine is reduced as result of decreased muscle mass. Figure 1 demonstrates the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) simplified algorithm (left) and estimated creatinine clearance using the Cockcroft-Gault formula (right) for a serum creatinine of 1.0 mg/dL. Renal dysfunction in older adults (especially white women) calculated using the Cockcroft-Gault formula may be underestimated, while it may be overestimated using the MDRD formula [17,12]. As a consequence, careful examination of the safety and efficacy of renally-cleared drugs in older adults is particularly important in drug development.

Hepatic Aging—Aging is associated with a decrease in hepatic blood flow and hepatocyte mass as well as pseudo-capillarization [12]. In general, the inter-individual variation in metabolic drug clearance by cytochrome (CYP) P450 enzymes or phase I reactions exceeds the decline caused by aging [18]. Phase II pathways (e.g., glucuronidation, acetylation, sulfation) are well preserved in older adults [13].

In addition to the enzymatic processing of drugs within the hepatocytes, various transporter proteins accomplishing the hepatic uptake of drugs and the biliary and hepatic extrusion of metabolites are indirectly involved in drug metabolism. During recent years, the importance

of drug transporters for absorption, distribution, and elimination processes has been increasingly recognized. Such transport processes and the oxygen supply for phase I reactions to the hepatocytes might demonstrate age- dependencies yet to be fully delineated [13].

Epigenetic influences have potentially important implications for hepatic clearance and variability in response to drugs in older adults [19]; however, age-related changes in the liver itself may have a greater impact on overall hepatic clearance [20].

Pharmacodynamic Considerations

The effects of age on the activity and expression of many receptors have been reported. However, the impact of age on pharmacodynamic effects of drugs acting on specific receptors is less well established [12]. Altered responses to drugs in older adults could be due to several factors, including age-related changes in drug-receptor interactions, receptor-membrane interactions, post-receptor events, structural changes in organs or tissues, and altered homeostatic functions [21].

Pharmacodynamic studies have focused primarily on relatively healthy older adults, yet the pathophysiology of human diseases themselves may alter the pharmacodynamic response and therapeutic outcome [12]. Therefore, in sicker older adults, dose-response relationships may be more difficult to characterize with medications including NOAC.

Adverse Drug Reactions

When adverse drug reactions occur in older adults, they are more likely to be severe and less likely to be recognized or reported by the patient [12]. Although age-related changes in pharmacokinetics and pharmacodynamics may contribute, adverse drug reactions appear more strongly associated with comorbidity and polypharmacy [22,23]. Polypharmacy has been associated with frailty in older adults independent of medical diagnoses [24,25]. How drug metabolism is altered in the presence of frailty is not well established: frailty may produce a general impairment of conjugation pathways, and possibly reduced drug clearance through CYP3A4 [26].

Inflammation is a component of both frailty and aging that has the capacity to down-regulate drug metabolism and transporter pathways, reducing systemic clearance and possibly leading to adverse drug effects [27]. Inflammation can also increase the chance of adverse drug effects, both on- and off-target, through activation of the coagulation system: IL-6 plays a major role in synthesis and release of fibrinogen, tissue factor and factor VIII from multiple tissues [28].

Many coagulation proteins that increase with aging are also acute phase reactants, raising the possibility that age-related thrombosis could be secondary to inflammation. This seems plausible when considering that regular physical activity in older adults has been associated with reductions in fibrinogen, factor XIII and factor IX [28].

Inter-individual Variability in Drug Response among Older Adults

Chronological age is recognized as a poor predictor of variability in response to medications [20]. Variability is a likely consequence of age-associated changes in organ function and body composition, declining homeostatic reserve, and comorbid disease, all of which alter drug pharmacokinetics and pharmacodynamics [20].

Frailty is a confounding factor when considering the impact of aging on drug disposition [13]. Inflammation associated with frailty has the potential to significantly alter drug transporter and metabolizing enzyme expression and thereby contribute to variability in drug clearance (and therefore response) in frail older people [20].

PHARMACOLOGICAL PROFILE OF NOVEL ORAL ANTICOAGULANTS FOR STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION

Dabigatran

As the first NOAC approved for non-valvular AF in adults, dabigatran was received by the medical community with high expectations. Unlike the vitamin K antagonist (VKA) warfarin, dabigatran has a low propensity to interact with other drugs, which is critical for older adults at risk for adverse drug effects. With predominantly (80%) renal clearance and a lack of an antidote, dabigatran has not been fully embraced by practicing clinicians. To better understand the potential reasons for its relatively slow uptake in clinical practice, dabigatran's pharmacology, performance in clinical trials, and the *U.S. Food and Drug Administration* (FDA) approval process will be detailed in the following section.

Dabigatran etexilate, a pro-drug, is converted to the active metabolite dabigatran which directly inhibits free thrombin (factor IIa) and clot-bound thrombin. Dabigatran does not exert direct inhibitory activity against factor Xa, trypsin, plasmin, tissue plasminogen activator, and activated protein C [29] (Table 1). Two doses of dabigatran (110 mg, 150 mg) given twice daily were studied in the RE-LY trial [30]. The 150 mg dose was superior to warfarin in reducing the primary endpoint of stroke (comprised of both ischemic and hemorrhagic stroke) and systemic embolism by 34% with no significant difference in major bleeding. The incidence of intracranial hemorrhage (ICH), a composite comprised of intraparenchymal, subarachnoid and sub-dural hemorrhage was much less common with dabigatran than with warfarin; however, major gastrointestinal bleeding was more common. By comparison, the 110 mg dose was non-inferior to warfarin in preventing ischemic stroke and systemic embolism, and was associated with a 20% relative risk reduction in major bleeding compared with warfarin.

According to the methods paper for RE-LY [31]:

The decision to test 2 doses of dabigatran in a large phase 3 trial is unusual. Identifying the correct dose was considered critical. The dose of 150 mg BID was tested in the phase 2 PETRO study, whereas 110 mg twice a day had not been directly tested. The choice of this lower dose was based on interpolations of phase 2 data, considerations of the peak and time course of anticoagulant effect of dabigatran, and the observation that a total daily dose of 220 mg was effective in

orthopedic surgery patients for deep venous thrombosis prevention. The identification of a lower dabigatran etexilate dose [for non-valvular atrial fibrillation] that might potentially have similar efficacy to adjusted-dose warfarin with less bleeding was considered important. Having 2 doses might allow tailoring of dosing to optimize the benefit against risk.

To date, the FDA has approved two dosing regimens, a 150 mg twice-daily regimen for those with normal, mildly impaired and moderately impaired kidney function (CrCl 30 to 50 ml/min) and a 75 mg twice-daily regimen for those with severely impaired kidney function (CrCl 15 to 30 ml/min). No age or weight-based recommendations have been made.

A rationale for the FDA's disapproval of the 110 mg dose appeared in the *New England Journal of Medicine* [32]:

Among the 40% of patients in RE-LY who were 75 years of age or older (n = 7238), the rate of stroke or systemic embolism was lower with 150 mg of dabigatran (1.4 per 100 patient years) than with 110 mg (1.9 per 100 patient-years), but the rate of major bleeding was higher (5.1 vs. 4.4 per 100 patient-years). If stroke or systemic embolism and major hemorrhage were considered equally undesirable, these rates would indicate similar benefit–risk assessments for the two doses. Most people would agree, however, that the irreversible effects of strokes and systemic emboli have greater clinical significance than nonfatal bleeding.

Subsequent sub-group analyses by age support this position for non-central nervous system major bleeding, but not for intracranial hemorrhage [33]. It is of interest that the FDA's approval of 75 mg twice daily dosing in patients with severe renal insufficiency was based entirely on small pharmacokinetic studies [34] and simulations [35] including a population pharmacokinetic analysis performed by Liesenfeld *et al.* using RE-LY data [36]. They analyzed 27,706 plasma concentrates from 9,522 patients who received 110 mg or 150 mg dabigatran using non-linear mixed-effects modeling; of those studied 3,505 had severe renal insufficiency. Simulations included a 6-hour delay in dosing (e.g., dose 1 at 0:00, dose 2 at 18:00, dose 3 at 24:00 hours). Statistically significant factors (CrCl, age, sex, heart failure, South Asian race, body weight and hemoglobin), except for renal function status, showed only small- to- moderate effects on the apparent clearance of dabigatran (<26% change in exposure at steady state).

Renal function in RE-LY was approximated using estimated creatinine clearance (CrCl), not estimated glomerular filtration rate (eGFR). In essence, any effect of age on dabigatran clearance might have been taken into account by using the formula for CrCl. Interestingly, curves of renal function calculated by CrCl and eGFR (Figure 1) seem to deviate most dramatically for white women 75 years of age, a common demographic for AF with a recognized unmet need for anticoagulation. Moreover, the majority of patients in RE-LY were classified as having mild chronic kidney disease, highlighting the relevance of accurately accounting for age in the determination of renal insufficiency.

One must recognize that age lies on a continuum, as does renal dysfunction. Therefore, two disparate doses (one half of the other) may seem restrictive to the prescribing clinician treating a patient with 'borderline' or fluctuating renal function. As a result, dabigatran has

been prescribed at a dose of 150 mg q12h every other day and 150 mg q day every other day; other possible dosing regimens are likely prescribed in daily clinical practice. This practice pattern is reminiscent of dosing VKA to a low target International Normalized Ratio (INR) in patients believed or known to be at risk for bleeding. Given the non-linear relationship between renal dysfunction and drug exposure, and varying peaks and troughs with regimens similar to those described, 'mix and match dosing' based upon most recent measurement of patient's renal function may ultimately carry greater risk than likelihood of benefit.

According to *Health Canada's Health Products and Food Branch* (HPFB) prescribing information, patients aged 80 years and older with AF should be treated with dabigatran 110 mg BID for prevention of thromboembolic events [37]. This recommendation is based, in part, on the pharmacokinetic study showing exposure to dabigatran increased 1.7 to 2-fold in 36 participants ≥ 65 years (compared with young participants in earlier studies); this finding was attributed to slightly decreased renal function of older patients ($\text{CrCl } 77 \pm 13.4 \text{ mL/min}$) [38]. In patients with increased risk of bleeding (including those with moderate renal impairment; using concomitant medications that inhibit P-glycoprotein; receiving aspirin, NSAIDs, or clopidogrel; with concurrent disease; or undergoing procedures with special hemorrhagic risk), Canadian prescribing information also recommends 110 mg BID. Lastly, according to the *European Medicines Agency* (EMA) [39] and *Health Canada's HPBP* prescribing information, dabigatran is not recommended for patients with liver enzymes >2 times the upper limit of normal.

While it may be difficult to completely reconcile different prescribing patterns in North America, it is easy to understand how existing evidence fails to provide completely clear guidance on how to optimally prescribe dabigatran to an older adult with AF.

Rivaroxaban

Rivaroxaban was approved for the treatment of non-valvular AF on November 4, 2011, approximately a year after dabigatran received FDA approval on October 19, 2010. Rivaroxaban has a dual mode of elimination; one-third is eliminated unchanged by the kidneys and two-thirds is metabolized by the liver. Approximately half of the fraction metabolized by the liver is eliminated through the hepatobiliary route; the other half is eliminated renally. As a NOAC with predominantly hepatic metabolism and once daily dosing, rivaroxaban was expected to overcome dabigatran's shortcomings related to dosing and renal clearance in older adults. To understand why rivaroxaban might not always be an optimal choice for older adults, its pharmacology and clinical trials will be summarized (Table 1).

Rivaroxaban is a direct, specific and competitive active site factor Xa inhibitor [40]. In ROCKET-AF [41], 20 mg of daily rivaroxaban (and 15 mg in patients with moderate renal impairment defined as a CrCl of 30–49 mL/min) was non-inferior to warfarin for the prevention of stroke or non-CNS systemic embolism. Overall, there was no significant difference in major bleeding compared to warfarin; however, in the rivaroxaban group, intracranial and fatal bleeding occurred less frequently, and non-fatal gastrointestinal bleeding occurred more frequently. There was no evidence of heterogeneity in treatment

effect across dosing groups [42]. Dosing was based on simulation and prior study of rivaroxaban in deep venous thrombosis [43].

Despite its predominantly hepatic metabolism, rivaroxaban has not been tested in, or approved for, patients with severe renal impairment. Within the liver, rivaroxaban is metabolized primarily via cytochrome P450 CYP3A4/5 and to a lesser extent CYP2J2; P-glycoprotein transporters are also involved. With a systemic clearance of approximately 10L/h, rivaroxaban can be classified as a low-clearance drug, making it less likely to be susceptible to altered metabolism due to hepatic aging (from diminished hepatic blood flow).

The maximum concentration (C_{max}) of rivaroxaban is unaffected by age; however, *exposure* is 41% higher in subjects > 75 years of age compared with those age 18 to 45 years [44]. Elimination occurs with mean terminal half-life of 5 to 9 hours in young individuals, and 11 to 13 hours in the elderly [45]. These findings are attributed to decreased renal function in the elderly [45,44]. Kubitz *et al.* performed a dose-escalation study of 48 healthy elderly subjects, age 60 to 76 years; they found no significant impact of age or gender on rivaroxaban exposure [45]. Simulations of data taken from two phase IIb studies of patients undergoing major orthopedic surgery indicate that only in case of 90-year-old patient with lean body mass of 30 kg would predicted rivaroxaban plasma concentration exceed a 90% confidence interval of the average (mean) younger, heavier patient [46]. Nevertheless, physiologically-based pharmacokinetic simulations suggest that drug-drug-disease interactions with rivaroxaban are possible, which could significantly increase rivaroxaban exposure and increase bleeding risk. Depending on severity of renal impairment, rivaroxaban exposure with the P-gp inhibitor erythromycin increases 1.9 to 2.6-fold in subjects 20–45 years and 2.5 to 3.0-fold in subjects 55–65 years [47].

Preliminary ROCKET-AF sub-group analyses show a greater benefit in stroke reduction in those ≥ 75 years (HR 0.67, 95% CI 0.51–0.88, in on-treatment analysis of patients ≥ 75 years vs. HR 0.91, 95% CI 0.70–1.19, <75 years) [48]. Though confidence intervals span 1.0, a relative risk reduction in ischemic stroke relative to warfarin in patients ≥ 75 years was also seen (HR 0.88, 95% CI 0.67–1.66); this advantage was not apparent in patients <75 (HR 1.10, 95% CI 0.84–1.44) [48].

Major bleeding was greater in those ≥ 75 years compared to the younger group (4.86 vs. 2.69 events per 100 patient years in those ≥ 75 years vs. <75 years, respectively; however, unlike dabigatran there was not an age-by-bleeding interaction); a trend toward more major bleeding in those ≥ 75 years versus warfarin was also seen (4.86 vs. 4.40 events per 100 patient years in those ≥ 75 years on rivaroxaban vs. warfarin, respectively) [48]. Hemorrhagic stroke risk was lower versus warfarin regardless of age (0.41 vs. 0.20 events per 100 patient years in those < 75 years on warfarin and rivaroxaban, respectively; 0.49 vs. 0.34 events per 100 patient years in those ≥ 75 years on warfarin and rivaroxaban, respectively). The Hazard Ratio for major bleeding on rivaroxaban vs. warfarin was 1.11 (95% CI 0.92–1.34) in patients ≥ 75 years vs. 0.96 (95% CI 0.78–1.19) in patients < 75 years [48].

Like dabigatran, rivaroxaban does not penetrate the blood-brain barrier [49] which could explain, at least in part, the lower rate of ICH compared with warfarin which is known to cross. ICH rates appeared lower regardless of stroke history [50]. Further study is warranted to determine what mechanism explains this observation with NOACs, and whether age plays an important role.

Apixaban

Apixaban is the third promising NOAC studied in phase 3 clinical trials for non-valvular AF. With EMA approval for non-valvular AF on November 20, 2012, followed shortly thereafter by *Health Canada*, FDA approval for non-valvular AF occurred on Friday, December 28, 2012. With very few drug interactions identified and mixed renal-hepatic clearance, it may be a particularly attractive treatment option for older adults (Table 1).

Apixaban, like rivaroxaban, is a direct, selective and competitive active site factor Xa inhibitor, but has a lower K_i (inhibitory constant) than rivaroxaban, indicating it has a higher potency; this is likely due to a better complementary “fit” for apixaban in the FXa protein’s active site. Whether this property will impact drug reversibility is unknown. Apixaban is metabolized by the liver (primarily by CYP3A4, CYP3A5 and sulfotransferases 1A1), kidneys and intestine, and excreted through the hepatobiliary system (75%) and kidneys (25%).

In ARISTOTLE [51], apixaban was associated with a 31% relative risk reduction in major bleeding (including a 48% relative risk reduction in hemorrhagic stroke), a 21% relative risk reduction in the combined endpoint of stroke or systemic embolism, and an 11% relative risk reduction in mortality relative to warfarin. Similar to AVERROES [52], 2.5 mg twice daily rather than 5 mg twice daily was given to patients with at least two of the following: age 80 years; weight 60 kg; serum Cr 1.5 mg/dL. Per protocol, apixaban dosing was based primarily on the phase 2 dose-ranging study in venous thromboembolism prevention [53], the study in deep venous thrombosis treatment [43], and “experiences with other anticoagulants studied in this patient population.” Outcomes for the sub-group receiving the lower dose of apixaban have not been published to date.

In a sub-study of AVERROES, moderate renal impairment (CrCl 30–49 mL/min) was found to be an independent predictor of stroke in AF patients. Among these patients, 2.5 mg twice daily apixaban significantly reduced the incidence of stroke relative to aspirin without increasing the risk for major hemorrhage. An ARISTOTLE sub-study supported these results: both the annual rates of stroke or systemic embolism and ischemic strokes were more than doubled in patients with moderate/severe renal impairment when compared with patients with normal renal function. With a consistent relative reduction in the rate of stroke or systemic embolism, apixaban provided the largest absolute benefits in patients with renal impairment [54]. Renal function was determined using two creatinine-based estimates of GFR namely, Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration, and using cystatin C, possibly a more reliable marker of renal function than serum creatinine [54]. Of the three formulas, only the one using cystatin C excludes age. Cystatin serum levels have been shown to depend upon body composition though which may affect cystatin-based measurement of GFR in those who are frail [55].

As an agent with primarily hepatic metabolism, apixaban may ultimately outperform dabigatran in patients with renal dysfunction. Whether apixaban will outperform dabigatran in older adults is less clear. Like rivaroxaban and dabigatran (110 mg), apixaban did not show a significant overall reduction in ischemic stroke compared to warfarin. In an adjusted indirect comparison, apixaban did lower the risk of overall major and gastrointestinal bleeding versus dabigatran and rivaroxaban [56]. Additionally, with multiple clearance pathways, apixaban carries a comparatively modest potential for drug-drug interactions [57].

Several months prior to FDA approval, the *American Heart Association / American Stroke Association* incorporated apixaban into its AF management guidelines [58].

BLEEDING RISK IN OLDER ADULTS WITH AF

The complexity of atherothrombosis in older adults is heightened by a concomitant bleeding tendency—conceivably an age-related vasculopathy involving small, hemostasis-maintaining vessels that is characterized by impaired vascular healing, loss of anatomic vasoreactivity, and immune incompetence [59]. Apart from age-associated remodeling of the vascular wall, which includes luminal enlargement, intimal and medial thickening, and increased vascular stiffness, endothelial function declines with age [60].

In the review by Puca *et al.*, the authors report endothelial dysfunction appears to be the hallmark of vascular damage in advancing age [61]. Many functions of the vascular endothelium are modulated by nitric oxide which is able to: induce smooth muscle relaxation; inhibit platelet aggregation and leukocyte adhesion to endothelial cells; and preserve endothelial progenitor cell function. Oxidative stress reduces nitric oxide bioavailability, contributing to endothelial dysfunction and vascular aging [61]. How vessel wall integrity and repair processes change with aging is a fundamental question in vascular biology that is under active investigation.

WHEN DOES THE RISK OF COMPLICATIONS FROM NOVEL ORAL ANTICOAGULANT THERAPY OUTWEIGH ITS BENEFIT?

Overestimation of the risk of bleeding by physicians is a key barrier to oral anticoagulant prescription, particularly among elderly patients [62]. The concept of “net clinical benefit” has been used to quantify the balance between risk of ischemic stroke and risk of ICH for oral anticoagulant therapy in the setting of non-valvular AF. Modeling of NOAC has shown that each agent offers net clinical benefit over warfarin therapy in patients with a CHADS₂ score ≥ 1 or CHA₂DS₂-VASc score ≥ 2, regardless of bleeding risk [63]. By definition, net clinical benefit excludes major gastrointestinal and nuisance bleeding, both of which may be important aspects of older adults’ quality of life. Nonetheless, the analysis incorporated CHADS₂, CHA₂DS₂-VASc and HAS-BLED scoring systems, highlighting the inherent trade-off between thromboembolism and bleeding. Many risk factors for bleeding in older adults are also risk factors for stroke (e.g., prior stroke, kidney disease, malignancy), some of which are incorporated into these scoring systems. When older adults prioritize quality of life over longevity, the likelihood of surviving a severe stroke must be considered in relation to the likelihood of major gastrointestinal and/or nuisance bleeding. Further investigation,

development and validation of scoring systems that take all factors into consideration are needed.

PRACTICAL ISSUES: NOAC IN OLDER ADULTS

NOAC have been shown to be non-inferior to warfarin for stroke prevention in non-valvular AF, and significantly decrease ICH compared to warfarin. In older adults, decreased hemorrhagic stroke risk is particularly important. Yet in this \$10 billion industry, adoption of NOAC in younger and older adults alike has been more modest than anticipated. Some have suggested that a lack of reversibility is, at least in part, responsible. Additional concerns among older adults may also play a part.

Age, creatinine and weight may poorly reflect underlying practical concerns such as comorbidity, renal insufficiency and frailty. Although no universally accepted definition of frailty exists, most agree that the “frailty phenotype” is highlighted by decreased physiologic reserve and diminished resilience. The pathophysiology of frailty appears to be rooted in the dysregulation of immune, metabolic, vascular, inflammatory and neuroendocrine systems. Increased inflammatory markers (CRP, IL-6, TNF- α) have been associated with frailty in numerous studies [64–66].

No studies of frailty and NOAC have been published to date. One study of frailty and warfarin use underscored several practical limitations for the use of NOAC. Using the Edmonton Frail Scale, Perera *et al.* found that frail older inpatients with AF were significantly less likely to receive warfarin than non-frail patients upon hospital admission and discharge [67]. During hospitalization, the proportion of frail patients prescribed warfarin decreased by 10.7% and the proportion of non-frail patients prescribed warfarin increased by 6.3%. In this study, the association between frailty and prescription of warfarin was consistent across three distinct clinical services: geriatric medicine, general medicine and cardiology. The study was not powered to detect differences in outcomes between frail and non-frail patients, though the frail appeared more vulnerable to worse clinical outcomes with and without antithrombotic therapies.

Besides frailty, certain factors that limit use of warfarin may similarly restrict the use of NOAC in older adults: cognitive impairment; terminal illness; and patient values and preferences. In a systematic review by Pugh *et al.*, fall risk was noted to be a disproportionate barrier to warfarin prescription [68]. Frequent falls should not deter one from considering a NOAC unless the risk of morbidity secondary to falls outweighs concern of stroke-related morbidity and mortality.

Table 2 offers a practical guide to prescribing NOAC. Given that rivaroxaban is approved for use in the prevention of venous thromboembolism, it could be the novel agent of choice for an older adult at high risk of venous thromboembolism (e.g., certain active malignancies) and non-valvular AF. Further, rivaroxaban was recently approved by the FDA for the treatment of deep vein thrombosis and pulmonary embolism; however, one must be cognizant of dosing differences if treating for both conditions.

Rivaroxaban may also be the best option for a NOAC in an older adult with mild cognitive impairment, given that it is the only agent studied as once daily dosing and can be placed in a pill box (unlike dabigatran). Apixaban and dabigatran are alternatives to consider in those who can reliably take medication twice daily. Assistance with dosing from family members and/or skilled care providers may be necessary regardless of agent selected. In older adults who are thin or frail, or with history of renal insufficiency, dabigatran should be used with extreme caution, and possibly even avoided; rivaroxaban and apixaban may be safer alternatives.

Given that ROCKET-AF included a high proportion of patients with history of prior stroke, rivaroxaban may be considered safe in patients with history of prior stroke. Preliminary ROCKET-AF sub-group analysis shows that those ≥ 75 years in ROCKET-AF had *lower* incidence of prior stroke compared to those < 75 years (42% vs. 65% in patients ≥ 75 years vs. < 75 years, respectively), but that the incidence of ischemic stroke in ROCKET-AF was lower among those ≥ 75 years versus warfarin (see rivaroxaban discussion above) [48]. Regardless, dabigatran is the only NOAC that achieved an overall reduction in ischemic stroke compared to warfarin. Ischemic stroke was not a primary outcome in any of these trials, making it difficult to draw any firm conclusions.

Next, inflammatory osteoarthritis is common in older adults, and over-the-counter NSAIDs are a mainstay of therapy. While short-term perioperative use of NSAIDs has not been shown to increase the risk of bleeding when given concomitantly with dabigatran [69], the chronic use of NSAIDs increases the bleeding risk by 50% [70]. The safety of long-term use of concomitant NSAIDs with rivaroxaban or apixaban has not been studied.

Finally, dabigatran may be less well-tolerated in patients with history of dyspepsia. Unlike rivaroxaban and apixaban, dabigatran is acid sensitive and has a tartaric acid core to improve bioavailability. Higher rates of dyspepsia observed with dabigatran (versus warfarin) may be related to its formulation.

Even when one or more factors favor prescribing a NOAC to older adults, practical concerns may ultimately prevail in some patients. The cost of NOACs is a major consideration in the current healthcare environment. Presently, dabigatran and rivaroxaban cost out-of-pocket consumers approximately \$3,500 yearly. At least half of 2010 Medicare beneficiaries were living below 200% of the federal poverty level ($< \$11,000$ for an individual) [71], making affordability of NOAC largely dependent on insurance coverage.

As of September 2012, 63% of Medicare beneficiaries (or 32 million) were enrolled in Medicare Part D plans, with traditional plans charging 25% coinsurance to the initial coverage limit of $\leq \$3,000$. Given that the 2013 Medicare Part D coverage gap spans \$2,970-\$6,955 of total drug costs, NOAC prescription alone would place most beneficiaries in “the gap”.

Under *The Patient Protection and Affordable Care Act*, pharmaceutical manufacturers began providing a 50% discount on brand name prescriptions filled in the Medicare Part D coverage gap in 2011; in addition beginning in 2013, federal subsidies will account for 25% of the brand name drug cost by 2020 [72].

Of the 30% of Part D plans offering gap coverage in 2013, approximately half of these will limit gap coverage to generics only. Among plans offering gap coverage for brand-name drugs, only 10–65% of medications on formulary will be eligible for some coverage (note: this is more than double 2012) [73]. Part D enrollment is highly concentrated, with five firms –UnitedHealth, Humana, CVS Caremark, Coventry Health Care, and Express Scripts– accounting for 59% of enrollees in 2012. Clearly, Medicare Part D NOAC payment structure could heavily influence prescriber patterns of these agents in the future.

CONCLUSION

Older adults have a high prevalence of AF, and they are more likely than young adults to experience AF- related stroke. In addition, older adults have a greater incidence of comorbid conditions, and both polypharmacy and adverse drug effects are more common. Despite their high and well-known risk, older adults receive thromboprophylaxis far less often than their younger counterparts. Lack of need for routine coagulation monitoring, few drug-drug interactions and excellent performance in phase 3 clinical trials favorably position NOACs for use in older adults with non-valvular AF. With careful recognition of risks and benefits of NOACs, older adults can receive thromboprophylaxis to a greater extent than in the past.

To optimize drug selection, older adults need be carefully assessed for likelihood of stroke and bleeding-related complications of NOAC. We believe that initial and at least quarterly evaluation of renal function and face-to-face assessment of comorbidities, concurrent medications, and signs or symptoms of bleeding is vital to quality patient care. Fall risk must be carefully assessed and minimized. Cognitive impairment should be assessed and treated whenever possible. The potential cost burden of NOAC in older adults warrants consideration on a case-by-case basis. Prescribing physicians may need to consult with other providers, pharmacists and healthcare administrators to coordinate care and assure safe prescribing of NOACs.

A commonsense approach to prescribing NOAC in older adults will ultimately provide clinicians and researchers with valuable experience that may be relied upon to guide future therapeutic decision-making. Until clinical registries can provide us with experiential data, providers must rely on understanding the available drugs, their pharmacologic properties and how each was studied in phase 3 clinical trials. NOACs represent an advance in the management of older adults with AF when prescribed to the right patient at the right dose in one whom the benefit of treatment outweighs potential risk.

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Figure 1:

eGFR for Americans aged 45–85 years using the modification of diet in renal disease simplified algorithm [74] is presented in the left panel, and estimated creatinine clearance using the Cockcroft and Gault formula [75] is presented in the right panel. For calculations, mean weight and height by decade were obtained from US survey data (NHANES, <http://www.cdc.gov>), with serum creatinine designated as 1.0 mg/dl. Pink lines and circles represent estimates for women; blue lines and triangles are estimates for men; white, open symbols are estimates for Caucasians; and solid black symbols represent estimates for African Americans. The dotted red line indicates a GFR of 60 ml/min/1.73m², demarcating the level below which there is at least a moderate decrease in GFR. The brackets enclose GFRs of 30–59 ml/min/m² classified as stage 3 renal disease or moderate GFR decrease (adapted from Schwartz) [17].

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Table 1:

Novel Oral Anticoagulant Properties and Trial Data

Novel Oral Anticoagulant	Dabigatran Etexilate	Rivaroxaban	Apixaban
Mechanism of Action	Direct thrombin inhibitor	Competitive factor Xa inhibitor	Competitive factor Xa inhibitor
Manufacturer	Boehringer Ingelheim	Bayer/Johnson & Johnson	Bristol-Meyers Squibb/Pfizer
FDA approval	October 19, 2010	November 4, 2011	Pending
Half-life (hours)	12–17	5–13	9–14
Bioavailability	3.5–6.5%	70–80%	>50%
Hepatic clearance	20% (glucuronidation)	28%–35%	75%
Renal clearance	80%	65%	25%
Protein binding	35%	92–95%	87%
P-gp inhibition/induction	Yes	Yes	yes
CYP3A4 inhibition/induction	No	Yes	yes
Food interference	Acidic milieu needed for absorption; food and drugs increasing stomach / intestine pH may reduce absorption	Absorption increased by food	Possibly no effect
Phase III Clinical Trial	RE-LY	ROCKET-AF	ARISTOTLE
Study size	n=18,113	n=14,264	n=18,206
Age	71.4 years (mean)	71.2 years (mean)	70 years (median)
Study design	intention to treat	on treatment	intention to treat
Dose(s) studied	110 mg bid, 150 mg bid	15 mg daily (CrCl 30–49 mL/min), 20 mg daily	5 mg bid, 2.5 mg bid (CrCl 30–49 mL/min)
Time in Therapeutic Range	67%	57%	66%
% VKA Naïve	50%	38%	43%
CHADS₂ score	CHADS ₂ 1 (mean 2.1)	CHADS ₂ 2 (mean 3.5)	CHADS ₂ 1 (mean 2.1)
Creatinine Clearance (mL/min)	69 (median)	67 (median)	>80 (41%); 50–80 (42%); 30–50 (15%); 30 (2%)

Table 2:

Suggested NOAC by patient condition

CONDITION	Suggested NOAC	RATIONALE
Kidney Disease:		
Mild	rivaroxaban, apixaban (or dabigatran)	See discussion under 'Dabigatran Etexilate'
Moderate	rivaroxaban, apixaban	
Severe	none (use warfarin instead)	
History of:		
Dyspepsia	rivaroxaban or apixaban	Dabigatran not well tolerated
Cerebrovascular disease	rivaroxaban, dabigatran	See discussion under 'Practical Issues'
Myocardial infarction (MI)	rivaroxaban, or possibly apixaban	MI rate numerically higher with dabigatran in RE- LY; no increase in fatal bleeding with rivaroxaban in recent ACS [76]; APPRAISE-2 terminated early secondary to increased bleeding with apixaban after acute coronary syndrome [77]
Mild cognitive impairment	case-by-case basis	See discussion under 'Practical Issues'
Frequent falls	dabigatran, rivaroxaban or apixaban	Unless risk of morbidity secondary to falls outweighs concern of stroke-related morbidity and mortality, NOACs suggested [68,9]
Remote major bleeding	apixaban, none	31% risk reduction in major bleeding with apixaban vs. warfarin [51]; nonetheless, apixaban increases bleeding risk relative to placebo
Intracranial hemorrhage	None	NOACs decrease intracranial hemorrhage relative to warfarin, not placebo
Deep venous thrombosis	rivaroxaban	Rivaroxaban FDA approved for treatment of deep venous thrombosis (not AF dose) [78]; other agents under review in USA
Pulmonary embolism	rivaroxaban	Rivaroxaban FDA approved for treatment of pulmonary embolism (not AF dose) [78]; other agents under review in USA
Venous thromboembolism risk	Rivaroxaban (or apixaban)	Rivaroxaban FDA approved to reduce risk of recurrence of venous thromboembolism (not AF dose) [78]; other agents under review in USA
Ischemic stroke risk	rivaroxaban, dabigatran (or apixaban)	See discussion under 'Practical Issues'
Low body weight	rivaroxaban, apixaban	See 'Dabigatran Etexilate' and 'Practical Issues' sections; apixaban dose-adjusted for low body weight
Frail	rivaroxaban, apixaban	May be more prone to fluctuations in renal function affecting bleeding risk with dabigatran
Needs to use pill box	rivaroxaban, apixaban	Dabigatran cannot be placed in a pill box
Needs once daily dosing	rivaroxaban	Dabigatran and apixaban are dosed twice daily
Chronic NSAID use	reconsider chronic NSAID use before prescribing NOAC	Rivaroxaban and apixaban not well-studied with chronic NSAID use; chronic NSAID use with dabigatran increases bleeding risk by 50% [70]