The importance of adherence and persistence in the elderly atrial fibrillation patient

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Older adults with atrial fibrillation are at the highest risk of ischaemic stroke yet are the least likely to be prescribed anticoagulant therapy, adhere to this therapy, and maintain long-term persistence with this therapy. The reasons for this under-treatment are multifactorial and include patient-driven factors, physician-driven factors, medical system complexities, and current unknowns regarding the biology and natural history of AF. Understanding these challenges to stroke prevention and addressing identified barriers to medication adherence and persistence in this vulnerable age group will improve outcomes related to AF.

Older adults with atrial fibrillation are at the highest risk of ischaemic stroke. Without anticoagulation, the average incidence of ischaemic stroke in this age group is ~8-10% per year. The 30-day mortality from an AF-related stroke is ~24% and those who survive often have life-altering neurological disability.

The most convincing early evidence supporting the use of anticoagulant therapy for older adults came from the 2007 Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) wherein individuals aged 75 years or older were randomized to receive either warfarin or aspirin (75 mg per day). The primary endpoint was fatal or disabling stroke, intracranial haemorrhage, or systemic embolus. The trial enrolled 973 individuals with a mean age of 81.5 years. Among those treated with warfarin, there were 24 primary events (21 strokes, 2 other intracranial haemorrhages, and 1 systemic embolus) and 48 primary events (44 strokes, 1 other intracranial haemorrhage, and 3 systemic emboli) among those participants randomized to aspirin. The annual risk of extracranial haemorrhage was 1.4% (warfarin) vs. 1.6% (aspirin) (relative risk 0.87, 0.43-1.73). This seminal trial demonstrated the superior efficacy of anticoagulation therapy for stroke prevention compared to aspirin and the underappreciated hazards of aspirin in this older age group.

Further validation of these findings ultimately led to changes in clinical practice guidelines which no longer included aspirin as a treatment option for stroke prevention in AF.

Despite the heightened risk for stroke, elderly individuals with AF are least likely to receive anticoagulant therapy. Among 429,417 individuals with AF prospectively enrolled in the Practice Innovation and Clinical Excellence Registry (PINNACLE), ~50% received oral anticoagulant therapy including the highest risk patients. Similar findings were reported from the Global Anticoagulant Registry in the FIELD (GARFIELD) study. Among 10,614 patients with newly diagnosed AF, 59% of higher risk patients defined as having a CHA2DS2-VASc score of 2 or greater received anticoagulant therapy.

Once initiated, persistence with anticoagulant therapy remains a challenge. A recent study of 66,090 individuals with AF newly starting a non-vitamin K oral anticoagulant (NOAC) and naive to anticoagulation found that 59% persisted in taking the medication at 6 months and subsequently further declined to 31.6% at 12 months. Rates of adherence and persistence were considerably higher in a Danish study, perhaps in part attributable to different methodologies to assess exposure. Importantly, this study documented wide gaps in drug refills of 7-89 days that were common across treatment groups. Incidence rates for medication-specific gaps per 1000 person-years were 339.1
for apixaban, 306.3 for dabigatran, 199.7 for rivaroxaban, and 424.3 for vitamin K antagonists (VKA). Medication gaps exceeding 90 or more days were 27.6, 37.2, 25.8, and 57.5, respectively. These data attest to the frequent interruptions in therapy that occur in clinical practice that render patients vulnerable to thrombotic events. The association of medication nonadherence with stroke outcomes was demonstrated in a study of 64,661 individuals with AF initiating oral anticoagulant therapy identified within a US commercial insurance database. The investigators used the proportion of days covered (PDC) as the metric to determine drug exposure. During a median follow-up of 1.1 years, 47.5% of patients prescribed a NOAC (apixaban, dabigatran, or rivaroxaban) achieved the benchmark of adherence, a PDC of 80% or greater. For patients taking warfarin, this percentage was even lower, 40.2%. For patients with a CHA2DS2-VASc score >3, the risk of stroke increased according to duration of time off therapy: hazard ratio, 1.96 (95% CI 1.48–2.60) for gaps of 1 to 3 months, 2.64 (95% CI 1.93–3.61) for 3–6 months, and 3.66 (95% CI 2.68–5.01) for 6 months or longer compared with not taking oral anticoagulants <1 week. In a study of primary care practices in Germany, adherence and treatment persistence were measured for new users of rivaroxaban, dabigatran, and VKA among 7265 individuals with AF. The mean age of patients included was 74 years. At 6 months, the percentage of patients still taking the drug was 66.0%, 60.3%, and 58.1%, respectively. At 1 year, these proportions further declined to 53.1%, 47.3%, and 25.5%, respectively. Older age, renal dysfunction, and concomitant use of antiplatelet drugs were significantly associated with a lower likelihood of anticoagulant drug persistence of >180 days.

Factors associated with medication adherence and long-term persistence

Adherence and long-term persistence of drug therapy among elderly individuals are challenging for many reasons including patient-driven factors, physician-driven factors, and factors related to the medical system (Figure 1). From a patient perspective, complex regimens, competing priorities, cost, polypharmacy, and lack of information on drug benefit and side effects often lead to cessation of treatment or omission of doses. Understanding the indication and belief of personal vulnerability are integral to adherence and persistence. Perhaps the most critical step is the initial discussion of AF, the risks related to AF, and the benefits and risks of anticoagulant therapy with a trusted physician. Key messages are revisited and reinforced at each subsequent episode of care. Physician judgement on what constitutes drug candidacy and personal interpretation of ‘do no harm’ are key components of the initial and refill prescription decisions. As shown in the GARFIELD registry, physician perceptions about bleeding risk, fall risk, ability to adhere to treatment, among others, constituted 48% of the reasons for not prescribing anticoagulant therapy. In addition, the increasingly complex patterns of care and process barriers within complicated medical systems lead to fragmentation and breakdowns in communication. Seamless delivery of care with consistent management is difficult across multiple surgical and medical disciplines and care settings particularly amid changes in a patient’s health status. When a hospitalization occurs, medication reconciliation spans four stages of care and needs to account for drug-relevant changes in the patient’s health status: home to hospital, medical or surgical discharge to rehabilitation facility, discharge to home, and post-discharge outpatient physicians’ follow-up and evaluation. Communication of these changes throughout this continuum and ultimately to the physician responsible for the patient’s long-term management is paramount.

Lastly, uncertainties related to the biology and natural history of AF itself constitute a grey area in patient management that inevitably leads to practice variation in long-term prescription persistence. Debates and individual physician beliefs regarding burden of AF and stroke risk, in addition to mechanistic uncertainty regarding the relative contribution of atrial substrate vs. rhythm, create different thresholds for long-term anticoagulation therapy for patients with paroxysmal AF and for those patients after cardioversion or ablation. Among patients with a documented history of AF presenting with an acute ischaemic stroke, Aronis et al. found that having been diagnosed with paroxysmal AF and being age 80 years or older were the most potent factors associated with not taking an anticoagulant at the time of the stroke. Rigorous studies to define the efficacy and safety of ‘triggered’ intermittent anticoagulant therapy based on smartphone alerts, patient pulse taking, or other AF detection modalities are also direly needed before these strategies permeate clinical practice. The extent to which the concept of intermittent definable risk affects patients’ long-term commitment to anticoagulation therapy also warrants study.

Bleeding and fall risk

Bleeding events are the most common reason for stopping anticoagulant treatment and perception of bleeding risk is pivotal in the decision to start therapy. The most feared complication of anticoagulant therapy is intracranial haemorrhage with resultant morbidity and mortality of 76% among individuals taking warfarin. The incidence of intracranial haemorrhage among patients randomized to warfarin in the AF trials was 0.7–0.8% per year. Importantly, the hazard of this complication was reduced on average by ~50% with the use of the factor Xa and direct thrombin inhibitors. To further mitigate, the risk of intracranial haemorrhage in the older age group, concomitant aspirin should be avoided, and blood pressure control maintained. Resumption of anticoagulant therapy following an intracranial bleed is often a therapeutic dilemma given different risks of recurrence depending on location, lobar vs. deep, and aetiology. Few data exist on risks of recurrence with resumption or initiation of NOACs in these settings.

The gastrointestinal tract is the most common site of bleeding in the elderly with peptic ulcer disease the most frequent aetiology followed by diverticular disease. The risk of upper and lower gastrointestinal haemorrhage is substantially increased by antiplatelet therapy and nonsteroidal anti-inflammatory drugs with some gastric
protection provided by proton pump inhibitors.\textsuperscript{31,32} Although the NOACs significantly reduced the risk of intracranial bleeding, gastrointestinal bleeding was either increased or comparable to warfarin. In contrast to intracranial hemorrhage, the morbidity and mortality associated with gastrointestinal bleeding was found to be 3\% among patients taking warfarin.\textsuperscript{24}

Major bleeds often result in permanent discontinuation of treatment. Physician and patient thresholds to resume treatment following a major or minor bleed often diverge. Multiple studies have demonstrated that patients most value avoidance of a disabling stroke and would trade-off multiple major bleeds to avoid one ischaemic stroke.\textsuperscript{33–36} Resumption of anticoagulant therapy following gastrointestinal haemorrhage has been shown to lower mortality and reduce thromboembolic events without a significant increase in recurrent haemorrhage.\textsuperscript{37} Selection bias was a considered limitation of this nonrandomized study in that healthier patients may have been chosen to resume treatment. These findings were subsequently confirmed in a large meta-analysis that showed resumption of warfarin therapy was associated with a reduction in thromboembolic events and mortality without a statistically significant increase in recurrent gastrointestinal bleeding.\textsuperscript{38} The risk of recurrence depends on aetiology and success of remedial intervention. Optimal timing of resumption across the spectrum of patient stroke risk and underlying cause is largely unstudied. Given the documented risk of increased thromboembolic events with larger gaps in treatment, the interval off therapy is best kept to a minimum of a few days, if possible, especially for those at highest risk of stroke.

Older adults at risk for falls constitute a particularly vulnerable group as the risk for both stroke and bleeding are significantly increased compared to peers without this risk. For most patients, the net clinical benefit still weighs in favour of anticoagulation because of the morbidity and mortality associated with ischaemic stroke.\textsuperscript{39} However, more data are needed on the effectiveness of NOACs in routine clinical practice outside of randomized trials.\textsuperscript{40,41} Measures to reduce fall risk should be vigorously sought at the time of initiation and throughout the course of anticoagulant therapy. Balance training, core strengthening, removal of environmental hazards, improved lighting, and avoidance of medications that induce or exacerbate orthostasis and autonomic dysfunction are a few strategies to mitigate the risk of serious falls.

**Summary**

Anticoagulant therapy is highly effective in preventing stroke in AF. For elderly individuals, this is a particularly germane issue given their heightened risk of ischaemic stroke. The weight of current evidence favours anticoagulation in this age group while actively seeking interventions to reduce risk of harm.\textsuperscript{42–47} Clinicians and patients need further and continuing education regarding the relative

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### Figure 1

Medication adherence and persistence are driven by patient, physician, and system specific factors, which are all interrelated.

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| Factors Affecting Adherence and Persistence of Drug Therapy |
|------------------------------------------------------------|
| **Patient Perspective** |
| - Complex regimens |
| - Competing priorities |
| - Cost |
| - Polypharmacy |
| - Lack of understanding of drug benefits and side effects |
| - Misconceptions of personal vulnerability |
| **Physician Perspective** |
| - Judgment of drug candidacy |
| - Interpretation of “do no harm” |
| - Perceptions about bleeding risk, fall risk, and ability to adhere to treatment |
| - Burden of AF-substrate versus rhythm |
| - Clinical context of AF |
| **System Complexity** |
| - Complex patterns of care |
| - Multiple sites of care |
| - Drug-relevant changes in health status |
| - Process barriers |
| - Fragmentation and multiple hand-offs |
| - Breakdowns in communication |

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**Cessation of treatment or omission of doses**

**Not prescribing therapy or discontinuation of therapy**

**Inconsistencies in drug therapy management**

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risks of morbidity from ischaemic events and that of minor and major haemorrhagic complications related to therapy. Identifying the barriers to adherence and implementation of strategies to promote medication persistence will lead to more effective therapy.

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