Anticoagulation in Long-Term Care
How Can We Improve Medication Monitoring?

Mikel L. Holley, BA; Nicole J. Brandt, PharmD, CGP, BCPP, FASCP; and Kristin Watson, PharmD, BCPS AQ Cardiology

ABSTRACT
Thromboembolic diseases affect a significant proportion of older adults; however, due to the risks and associated adverse events with anticoagulation therapy, this population may be less likely to receive the best care. Among anticoagulant-related events within the nursing home, most involve oral anticoagulant agents and occur due to deficiencies in monitoring. With the recent approvals of new oral anticoagulant agents dabigatran, rivaroxaban, and apixaban, more options are now available for treating thrombotic disorders. Ensuring that all members of the health care team are aware of the risks and benefits of these agents is paramount to improving the monitoring as well as safety in older adults who are at greatest risk for adverse events. [Journal of Gerontological Nursing, 40(7), 10-15.]

ABOUT THE AUTHORS
Mr. Holley is PharmD Candidate, Dr. Brandt is Associate Professor, Geriatric Pharmacotherapy, Pharmacy Practice and Science, and Dr. Watson is Associate Professor, Cardiology, Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland.

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Address correspondence to Nicole J. Brandt, PharmD, CGP, BCPP, FASCP, Associate Professor, Geriatric Pharmacotherapy, Pharmacy Practice and Science, University of Maryland School of Pharmacy, 20 North Pine Street NS29, Baltimore, MD 21201; e-mail: nbrandt@rx.umaryland.edu.

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Recently, the U.S. Department of Health and Human Services (USDHHS, 2014) Office of Inspector General released its report, “Adverse Events in Skilled Nursing Facilities: National Incidence Among Medicare Beneficiaries.” It was noted that 22% of Medicare beneficiaries experience an adverse event during a short skilled nursing facility stay, and 37% of these events are related to medications. The majority (66%) of these adverse events and temporary harm related to medications were preventable, according to case reviewers (USDHHS, 2014). Many of the events were attributed to medications that cause hypoglycemia, bleeds, falls, or changes in mental status (USDHHS, 2014).

Anticoagulant agents, which are the primary offender with respect to bleeds, are the mainstay of therapy for the acute and long-term prevention and treatment of thromboembolic disorders. Anticoagulant agents refer to the following:
- Vitamin K antagonists (warfarin [Coumadin®]);
• unfractionated heparin;
• low-molecular weight heparins (e.g., enoxaparin [Lovenox®], dalteparin [Fragmin®]);
• thrombin inhibitors (e.g., argatroban, dabigatran [Pradaxa®]); and
• factor Xa inhibitors (e.g., apixaban [Eliquis®], fondaparinux [Arixtra], rivaroxaban [Xarelto®]).

The primary indications for anticoagulation therapy are treatment and prophylaxis of venous thrombotic embolism (VTE) and stroke prophylaxis in patients with atrial fibrillation (AF). Approximately 60% of thrombosis cases are diagnosed in patients older than 70. This is secondary to reduced mobility and a number of medical conditions that increase one’s risk of embolic events, including cancer, heart failure, and respiratory diseases (Bauersachs, 2012).

The most common reason for stroke in older adults is AF, which affects as many as 2.6 million people in the United States (Centers for Disease Control and Prevention [CDC], 2013). The incidence of AF increases with age, with a median age range of 66 to 75 (CDC, 2013). Additionally, age is an independent risk factor for stroke in patients with AF; other risk factors include comorbid conditions that increase in prevalence with age (e.g., hypertension, heart failure, vascular disease). Despite the increased prevalence of AF in older adults, therapy to reduce the risk of stroke is inadequate (Quilliam & Lapane, 2001).

Among the aging population, it is an ongoing challenge to prevent thromboembolic disorders while managing bleeding risks. In an analysis of the North Carolina Medication Error Quality Initiative, nursing home data between the years 2010-2011 found 1,270 errors involving oral anticoagulant agents (Desai, Williams, Greene, Pierson, & Hansen, 2013). These errors were more common (69% vs. 31%) in residents older than 75 (Desai et al., 2013). They were most likely to be due to wrong dose (45%), wrong follow up (35%), or wrong drug (13%). The majority of anticoagulation errors originated in documentation (51%), administration (35%), or monitoring (11%) (Desai et al., 2013). Similar results were found in a retrospective cohort of 25 Connecticut nursing homes where 490 residents were identified to be taking warfarin primarily for stroke prevention in AF, treatment/prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE), and general stroke prevention without AF (Gurwitz et al., 2007). There were 720 adverse warfarin-related events and 253 potential adverse events. Of these adverse events, 29% were determined to be preventable and the majority originated in prescribing (70%) and monitoring (92%) or both (62%) (Gurwitz et al., 2007).

With nursing at the intersection of these domains, nurses play a pivotal role in the communication among members of the health care team and are instrumental in monitoring and preventing adverse events (ADEs). Numerous medications have been implicated in causing ADEs; however, this article will only discuss new oral anticoagulant agents that are increasingly used to prevent and treat thromboembolic disease in older adults.

**WARFARIN**

Warfarin has been the standard of care for treatment and prophylaxis of thrombotic disorders. Dosing is individualized, titrating to a goal international normalized ratio (INR) of 2 to 3 for most indications; however, a higher range of 2.5 to 3.5 may be indicated for certain conditions, such as the presence of a mechanical heart valve (Bristol-Myers Squibb Company, 2011). The INR should be monitored every 1 to 4 weeks, depending on the patient’s regimen and therapeutic stability (January et al., 2014).

It is important to recognize that warfarin has a number of food/drug interactions that may alter the dosing requirements. The most common offenders for potentiation of warfarin effects include fluoroquinolones such as ciprofloxacin (Cipro®) and levofloxacin (Levaquin®), amiodarone (Cordarone®), sulfamethoxazole (Gantanol®), and azoles antifungal agents (e.g., fluconazole [Diflucan®]) (Holbrook et al., 2005). Warfarin efficacy is decreased by an increased dietary intake of vitamin K (notably present in leafy vegetables), as well as the concomitant use of barbiturate drugs, cholestyramine (Questran®), and some antiepileptic medications (e.g., carbamazepine [Tegretol®]).

**ALTERNATIVES TO WARFARIN**

Due to the challenges with managing warfarin, namely laboratory monitoring and numerous drug interactions, several new oral anticoagulant agents have been approved recently. With the goal of improving medication safety, this article will focus on the monitoring of oral anticoagulant therapy that is increasingly being prescribed in older adults.

**Direct Thrombin Inhibitors**

Currently, the only U.S. Food and Drug Administration approved oral direct thrombin inhibitor is dabigatran. Dosing is generally 150 mg twice per day, but should be decreased to 75 mg twice per day in those with nonvalvular AF with a creatinine clearance (CrCL) of 15 to 30 mL/min. This reduced dose is also recommended in those with AF and a CrCL <15 mL/min or on hemodialysis or those with a CrCL <30 mL/min who are receiving a P-glycoprotein inhibitor (Boehringer Ingelheim Pharmaceuticals, Inc., 2014). Additionally, dabigatran should not be used for the treatment of DVT or PE if CrCL is <30 mL/min or in patients on hemodialysis. This agent should
not be prescribed to those receiving rifampin (Rifadin®); concomitant use would lead to significant reductions in dabigatran concentrations. Furthermore, dabigatran capsules should always be kept in the original bottle; once opened, the medication must be used within 4 months. This agent may also be dispensed from pharmacy blister packs; each dose should be left in the blister pack until administered. Capsules in the blister pack can be used, if left unopened, until the expiration date provided by the manufacturer. When administering the medications, the capsules must be given whole and should not be opened or mixed with other substances (e.g., applesauce, pudding).

**Factor Xa Inhibitors**

Rivaroxaban is approved for use in individuals with nonvalvular AF, treatment and prevention of recurrent DVT/PE, and prevention of VTE in patients undergoing orthopedic surgery. When using rivaroxaban for AF, the dose is 20 mg orally per day and should be given with the evening meal (Janssen Pharmaceuticals, 2014). The dose is decreased to 15 mg for CrCl between 15 and 50 mL/min and contraindicated for CrCl <15 mL/min or in patients on hemodialysis. For treatment of DVT or PE, the dose is initially 15 mg twice per day for 3 weeks then decreased to 20 mg once per day, and should be administered with food. This agent should not be used for treatment of DVT/PE in individuals with a CrCl <30 mL/min. Prophylactic doses for knee and hip replacement are only 10 mg once per day, with or without food, for 12 or 35 days, respectively. This agent should be avoided for this indication in patients with a CrCl <30 mL/min, and those with a CrCl of 30 to 50 mL/min should be monitored closely.

It is recommended to avoid use of rivaroxaban in combination with medications that are strong 3A4 and P-glycoprotein inhibitor agents (e.g., ketoconazole, erythromycin [Benza-}

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**Antiplatelet Therapy**

When a patient is not a candidate for stroke prophylaxis using oral anticoagulant agents, providers should consider an antiplatelet regimen, which is last line in those with risk factors for stroke therapy due to their limited efficacy in AF (January et al., 2014). Aspirin (Bayer®) may be used at doses of 75 to 325 mg per day, or a dose of 81 mg per day when combined with clopidogrel (Plavix®) 75 mg per day. Metabolism of clopidogrel to its active metabolite is mediated by CYP2C19, and use with strong inhibitor agents such as omeprazole (Prilosec®), fluoxetine (Prozac®), and azole antifungal agents should be avoided (Bristol Myers Squibb Company, 2013).

**COMPARATIVE SAFETY AND EFFICACY**

**Stroke Prevention in Nonvalvular Atrial Fibrillation**

Connolly et al. (2009), in their trial of dabigatran versus warfarin, demonstrated superiority of dabigatran at a dose of 150 mg twice per day to INR-adjusted warfarin (1.11% vs. 1.69%; p < 0.001) in the incidence of stroke or systemic embolism per year. Differences in major bleeds were nonsignificant for the 150-mg dose (3.11% vs. 3.36%; p = 0.31); however, rates for hem-
orrhagic stroke (0.10% vs. 0.38%; \( p < 0.001 \)) and intracranial hemorrhage (0.30% vs. 0.74%; \( p < 0.001 \)) were lower in patients receiving dabigatran. Dyspepsia and gastrointestinal bleeding were reported more frequently in patients receiving dabigatran.

Patel et al. (2011) compared rivaroxaban to warfarin for the prevention of stroke in nonvalvular AF patients. There was no difference in the rate of stroke or systemic embolism between the rivaroxaban (1.7% per year) and warfarin groups (2.2% per year; \( p < 0.001 \), for noninferiority). Major and non-major bleeding rates were similar at 14.9% for rivaroxaban and 14.5% for warfarin. The rate of intracranial hemorrhage (0.5% vs. 0.7%; \( p = 0.02 \)) and fatal bleeding (0.2% vs. 0.7%; \( p = 0.003 \)) was lower in the rivaroxaban group; gastrointestinal bleeding was lower
in the warfarin group (3.2% vs. 2.2%; p < 0.001).

Connolly et al. (2011) reported a reduced incidence of stroke in patients receiving apixaban versus aspirin (1.6% vs. 3.7%; p < 0.001) per year. This trial enrolled patients with AF who were at an elevated risk of stroke but deemed ineligible for an oral anticoagulant agent. There was no difference in bleeding between groups. In a study by Granger et al. (2011), apixaban was shown to be superior to warfarin in preventing stroke or systemic embolism in patients with nonvalvular AF (1.3% vs. 1.6%; p = 0.01). The rate of major bleeding was lower in patients receiving apixaban (2.13% vs. 3.09%; p < 0.001). The rate of hemorrhagic stroke was lower in the apixaban group (0.24% vs. 0.47%; p < 0.001); there was no difference in the rate of gastrointestinal bleeding.

Antiplatelet therapies, such as aspirin and clopidogrel, have been shown to be less effective than warfarin in reducing the incidence of stroke. A study comparing clopidogrel plus aspirin versus aspirin alone was found to have a 28% risk reduction (17% vs. 38%; p < 0.0002) (Connolly et al., 2009).

### Treatment of Venous Thrombotic Embolism and Pulmonary Embolism

Schulman et al. (2009) compared dabigatran at a dose of 150 mg twice per day to dose-adjusted warfarin for treatment of acute VTE. In this trial, dabigatran was initiated 5 to 10 days after treatment with a parenteral anticoagulant agent. Recurrent VTE with dabigatran was shown to be noninferior to warfarin (2.4% vs. 1.9%; p < 0.001). Incidence of major or clinically relevant non-major bleeding with dabigatran was lower than warfarin (5.6% vs. 8.8%; p = 0.002).

Rivaroxaban was evaluated for DVT treatment versus warfarin with enoxaparin bridging at a dose of 15 mg twice per day for 3 weeks followed by 20 mg per day for 3 to 12 months (Bauersachs et al., 2010). Rivaroxaban demonstrated noninferiority in the incidence of recurrent, symptomatic VTE (2.1% vs. 3.0%; p < 0.001) (Bauersachs et al., 2010). There was no difference between rivaroxaban and warfarin in the incidence of clinical bleeds (8.1% vs. 8.1%; p = 0.77). The use of rivaroxaban 10 mg versus enoxaparin 40 mg was evaluated for prophylaxis of DVT following total hip arthroplasty (THA) and total knee arthroplasty (TKA). Rates of composite VTE and mortality showed superiority of rivaroxaban for THA (1.1% vs. 3.7%; p < 0.001) (Eriksson et al., 2008). Superiority for rivaroxaban was also demonstrated after TKA (9.6% vs. 18.9%; p < 0.001) (Lassen et al. 2008).

### NEW ORAL ANTICOAGULANT AGENTS IN META-ANALYSIS OF OLDER ADULTS

Recently, Sardar, Chatterjee, Chaudhari, and Lip (2014) published a meta-analysis of the safety and efficacy of new oral anticoagulant agents (NOACs). The key findings based on 10 randomized control clinical trials including more than 25,000 adults 75 and older noted:

- In AF, NOACs were more effective than conventional therapy in the prevention of stroke or systemic embolism.
- NOACs had a significantly lower risk of VTE or VTE-related death compared to conventional therapy.
- NOACs did not cause greater major or clinically relevant bleeding than conventional therapy in individuals ages 75 and older (6.4% with NOACs vs. 6.3% with conventional therapy; odds ratio = 1.02, 95% CI [0.73, 1.43]).

This meta-analysis suggests that old age per se should not be a rea-
Implications for Gerontological Nurses

It is imperative that all providers (e.g., RNs, certified nursing assistants, direct care aides) involved in the direct care of patients be aware of the use of anticoagulant agents. Ongoing pharmacovigilance is needed to ensure that patients are receiving the proper dose as well as adequate monitoring for evidence of bleeding.

Whenever there is a question of falls, patients should be thoroughly examined for the possibility of head trauma and monitored for excessive headaches or loss of consciousness, which may indicate cerebral hemorrhage (Bagli, Ergenoglu, Akin, & Aribogan, 2014). A baseline complete blood count should be obtained for all agents and monitored at least biennially or as clinically indicated. For dabigatran and the factor Xa inhibitors, renal function should be evaluated at baseline, whenever there is a suspected change, and annually thereafter (January et al., 2014). It should be noted that all newer agents carry a boxed warning regarding the discontinuation or interruption in therapy. There is an increased risk of thrombotic events when these agents are discontinued for reasons other than pathological bleeding or completion of therapy. Appropriate measures should be taken to provide alternative anticoagulation when an interruption in therapy is indicated. The Table highlights certain clinical considerations when using these oral anticoagulant agents.

Conclusion

Moving forward, a systematic and coordinated approach to managing anticoagulant agents across long-term care and transitions in care is needed to prevent ADEs. Understanding the differences among the treatment choices is imperative (Ogbonna & Clifford, 2013). Practitioners need to work as a team to overcome the challenges of managing anticoagulant agents.

References


