Up to 17% of residents in long term care facilities are receiving anticoagulant medication.\(^1\) Disease states such as atrial fibrillation, venous thromboembolism (VTE) prevention and treatment, and mechanical heart valves necessitate the use of anticoagulation therapy for prevention of thromboembolic events.

Warfarin therapy contributes to many adverse effects in long-term care (LTC) patients. Warfarin is associated with emergency department visits, hospitalizations and death. Between 2007 and 2009 warfarin accounted for 33% of hospitalizations caused by an adverse drug event, and over 50% of warfarin’s serious adverse events were considered to be a preventable.\(^2\)

Many studies assessing warfarin therapy in LTC facility residents have found that warfarin management is suboptimal, and that these patients frequently fall outside of the therapeutic range for their condition.\(^3\) Managing warfarin therapy can be challenging in LTC residents due to a wide variety of factors. The article that follows will discuss several of these factors, as well as potential strategies to improve the management of anticoagulation in LTC patients.

**Medication Errors**
Medication errors can occur in any setting including LTC facilities. One study analyzing warfarin therapy in a nursing home setting found that medication errors were most prevalent at the prescribing and monitoring stages of warfarin management.\(^3\) Strategies for decreasing medication errors and improving warfarin therapy management in a LTC setting include standardizing processes used to make therapeutic decisions, including prescribing and monitoring. This may include following site specific guidelines or developing protocols for the health care team to use. It may also be beneficial to identify a single provider to manage warfarin therapies in residents, which may help eliminate communication barriers experienced between multiple providers.\(^4\)

**Drug-Drug Interactions**
There is an extensive list of drug interactions that can impact warfarin dosing requirements, which affect warfarin therapy in all patients. An abbreviated list of several common drug-drug interactions is...
presented in Table 1. Due to concomitant disease states and conditions often experienced by residents, these interactions may be frequently encountered in LTC patients. One study found that LTC residents receiving medications that interact with warfarin spent less time within the therapeutic INR range compared to those who did not receive medications with known interactions.\(^5\) Initiating one of these therapies for treatment of an infection or comorbid disease without adjusting warfarin doses is likely to result in supratherapeutic INR levels. Delays or lack of communication between health care team members about these therapies may contribute to uncontrolled INR levels in these patients. It is reasonable to check the INR one week after initiating a medication with a known or possible interaction with warfarin to ensure that levels are therapeutic, and to make adjustments if needed.\(^6\)

Table 1. Common interactions with warfarin in the LTC setting

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Increased bleeding risk; unclear mechanism</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Variable mechanisms; inhibition of warfarin metabolism; increased bleeding risk</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Increased bleeding risk due to antiplatelet effects</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Increased bleeding risk due to antiplatelet effects</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Inhibition of warfarin metabolism; increased bleeding risk</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Inhibition of warfarin metabolism; increased bleeding risk</td>
</tr>
</tbody>
</table>

**Diet**

Warfarin’s interaction with vitamin K also has the potential to impact INR levels in LTC residents, especially in those residents that have poor dietary habits and appetites. A decreased or inconsistent consumption and absorption of vitamin K can lead to non-therapeutic INR levels. Malnourished patients may be more sensitive to warfarin and may be more difficult to control.\(^7\) Dietary supplements may frequently be used in this population to help with nutritional status. It is important to be aware of the vitamin K content in supplements, as it can impact INR values.\(^8\)

**Advancing age**

One study found that patients aged 75 years or older had a 50% lower warfarin dosage requirement for equivalent anticoagulation levels than patients who were less than 35 years of age. The mechanisms leading to increased sensitivity to warfarin are unclear, but this can be a contributing factor leading to over-
anticoagulation in LTC residents. More cautious dose adjustments are advised when managing warfarin therapy in this population.

**Comorbid Conditions**

Elderly patients often have multiple comorbid disease states, some of which may have an impact on warfarin therapy. The liver is the prominent site of warfarin metabolism; therefore, hepatic disease can impact the rate at which the drug is metabolized and lead to increased drug and INR levels. Warfarin is partially excreted by the kidney. Consequently, renal dysfunction can also affect INR control and potentially increase the risk of bleeding.

Exacerbations of heart failure or chronic obstructive pulmonary disease (COPD) can also interfere with INR control. In a case control study, it was found that exacerbations of both disease states lead to increased sensitivity to warfarin, with decompensated heart failure having a bigger impact on sensitivity than COPD exacerbations. It is hypothesized that these exacerbations lead to decreased hepatic oxygenation levels, via decreased hepatic blood flow in heart failure and through overall oxygen deprivation in COPD. Oxygen is needed by the hepatic enzymes that metabolize warfarin. Lower oxygen levels lead to decreased metabolism of warfarin and increased INRs.

Acute illnesses have been associated with decreased oral dietary intake and increased diarrhea. Both of these lead to decreased vitamin K levels and contribute to increased INR levels.

Metastatic cancer, diabetes and uncontrolled hyperthyroidism can also impact anticoagulation control. Hyperthyroidism produces a hypermetabolic state, which leads to catabolism of vitamin-K dependent clotting factors, increasing the response to warfarin. Cancer cells can activate the coagulation cascade, leading to a hypercoagulable state. Diabetes is also a hypercoagulable state due to increased clotting factors and decreased fibrinogen. Patients with these comorbidities should be monitored more closely.

**Novel Oral Anticoagulants**

In recent years, multiple non-vitamin K antagonist oral anticoagulants have become available for VTE prevention and treatment and stroke prophylaxis in patients with nonvalvular atrial fibrillation. These agents have gained some interest as being less complicated, easier to manage therapies compared to warfarin. See Table 2 for an overview of the FDA-approved indications of these agents.
Novel oral anticoagulants (NOACs) have more predictable pharmacodynamics and fewer drug-drug and drug-diet interactions than warfarin, allowing for a fixed dose regimen without routine monitoring. These agents also have a faster onset and offset of action when compared to warfarin. This may be beneficial when bleeding complications occur and when managing therapy around procedures.

Pooled analyses of NOACs versus warfarin for VTE treatment and stroke prophylaxis in nonvalvular atrial fibrillation patients found that in patients over 75 years old, NOACs were favorable over warfarin for preventing thromboembolism. The analysis assessing VTE treatment found that patients with reduced renal function (CrCl <50mL/min) had no significant difference in efficacy between NOACs and warfarin. However, patients with reduced renal function anticoagulated for stroke prevention in nonvalvular atrial fibrillation favored NOACs over warfarin for prevention of stroke or systemic embolic event. Overall, NOACs had a favorable safety profile but were associated with an increased risk of bleeding in elderly patients compared to those less than 75 years of age. Rivaroxaban and apixaban were shown to have a greater safety benefit than dabigatran, which has been associated with an increased risk of gastrointestinal (GI) bleeding.15,16

While the outcomes show that these agents may be beneficial for use in patients requiring anticoagulation treatment, there are some challenges associated with this therapy as well. Lack of long term safety and efficacy data with these drugs, especially in the geriatric population, is a concern that should be considered when initiating therapy. Many patients were excluded from trials due to high risk of bleeding and severe renal dysfunction; therefore, the frailest of patients were underrepresented in studies. The overall cost of the newer agents is much higher than warfarin treatment, even
after accounting for costs associated with warfarin management. All of the NOACs require dose adjustments based on renal function, which would need to be assessed in residents on this therapy. Another issue with these drugs is the lack of reversal agents. There is a specific reversal agent for dabigatran, but it is a very costly therapy intended for use in emergency situations only.

**When Should NOACs Be Used Over Warfarin in LTC Residents?**

It may be reasonable to consider using a new oral anticoagulant instead of warfarin in certain residents. Patients initiating anticoagulation therapy or already on warfarin therapy with consistently unstable INR values may be good candidates for therapy with a newer agent. To be considered for NOAC therapy, a number of factors should be considered. The patient must have adequate renal function in order for these newer medications to be indicated. Absence of any interacting medications would also be preferred for patients on this therapy. Medications used for HIV and epilepsy treatment often interact with NOACs, and patients on this therapy might be better treated with warfarin. Residents with a history of bleeding or GI problems may not be well suited for newer agents, as many of the agents have higher bleeding risk when compared to warfarin. Dabigatran has been associated with a higher rate of GI bleeds and should be avoided in patients with a significant history. Because the NOACs have a faster onset and offset of action, they would not be ideal for patients that often refuse doses of their medication.

**Discussion**

Among the aging population in LTC facilities on anticoagulant therapy, it is challenging to prevent thromboembolic disease while concurrently managing the risk of bleeding. Risks versus benefits of anticoagulation must be assessed in all patients before initiating therapy with any anticoagulant. Treatment with warfarin poses many challenges, especially in the elderly population. Enhancing warfarin monitoring by maximizing communication between health care team members and developing a standard practice for warfarin management may help improve control of patients on warfarin therapy.

Newer oral anticoagulants offer additional options for patients needing anticoagulation therapy for nonvalvular atrial fibrillation and VTE prophylaxis and treatment. These agents are currently not approved for use in patients with valvular heart disease. They require less monitoring than warfarin but have other challenges that should be considered before initiating therapy. They may be an appropriate alternative for select patients, especially those whose warfarin therapy is most difficult to manage.
References


