Fidaxomicin: A New Oral Macrolide Antibiotic for Treatment of *Clostridium difficile*-associated Diarrhea

Heang Suy Siek, PharmD Candidate

*Clostridium difficile* (C. difficile) accounts for 20-30% of cases of antibiotic-associated diarrhea and is the most commonly recognized cause of infectious diarrhea in healthcare settings.\(^1\) Based upon surveys of Canadian hospitals conducted in 1997 and 2005, incidence rates range from 3.8 to 9.5 cases per 10,000 patient days, or 3.4 to 8.4 cases per 1,000 admissions, in acute care hospitals.\(^2\) In the United States the incidence of *C. difficile* has more than doubled since 1996 with some estimates suggesting that up to 3 million cases each year making *C. difficile* infection the most common bacterial cause of diarrhea in the United States.\(^3\) As the incidence rises, mortality associated with disease also increases due to increasing virulence of the *C. difficile* strains and increasing host vulnerability.\(^3\)

*C. difficile* is associated with increased health-care costs, prolonged hospitalizations, and increased patient morbidity. Previous antimicrobial use, especially use of clindamycin or ciprofloxacin, is the primary risk factor for development of *C. difficile*-associated diarrhea (CDAD) because it disrupts normal bowel flora and promotes *C. difficile* overgrowth. Historically, CDAD has been associated with elderly hospital in-patients or long-term-care facility residents. Since 2000, a hyper-virulent strain of *C. difficile* identified as North American pulsed-field type 1 (NAP1) that produces an extra toxin (binary toxin) and increased amounts of toxins A and B, has caused increased morbidity and mortality among hospitalized patients.\(^4\) According to the 2006 Connecticut surveillance, related strains caused severe CDAD in healthy residents in the community at a rate of 7.6 cases per 100,000 residents, suggesting the presence of non-traditional risk factors in development of community-associated CDAD.\(^4\) A six-month surveillance program for laboratory-diagnosed *C. difficile* infection (CDI) in Monroe County, New York found that out of 366 incident CDI cases studied, 67 cases (18%) were classified as community-associated CDI.\(^5\) Community-associated CDI case-patients were younger and healthier than health care-associated case-patients.

Clinical practice guidelines for CDI recommend metronidazole for the initial episode of mild-to-moderate CDI and oral vancomycin for an initial episode of severe CDI or initially if patients are unable to take metronidazole. Metronidazole is not approved for can pulsed-field type 1 (NAP1) that produces an extra toxin (binary toxin) and increased amounts of toxins A and B, has caused increased morbidity and mortality among hospitalized patients.\(^4\) According to the 2006 Connecticut surveillance, related strains caused severe CDAD in healthy residents in the community at a rate of 7.6 cases per 100,000 residents, suggesting the presence of non-traditional risk factors in development of community-associated CDAD.\(^4\) A six-month surveillance program for laboratory-diagnosed *C. difficile* infection (CDI) in Monroe County, New York found that out of 366 incident CDI cases studied, 67 cases (18%) were classified as community-associated CDI.\(^5\) Community-associated CDI case-patients were younger and healthier than health care-associated case-patients.

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**Editor’s Summary: Fidaxomicin (Dificid®)**

**Description & Indication**
- Oral macrolide antibiotic approved for the treatment of *Clostridium-difficile*-associated diarrhea (CDAD) in adults

**Dosing**
- 200 mg orally twice daily for 10 days
- No dose-adjustments for renal or hepatic impairment

**Efficacy**
- Two phase III non-inferiority trials comparing fidaxomicin vs. oral vancomycin in adults (≥ 16 years) found no significant difference in clinical cure rates (85-88% in both groups in both trials)
- Clinical recurrence of CDAD lower after fidaxomicin

**Safety**
- Generally similar safety profile; however, fidaxomicin may have a higher incidence of GI hemorrhage compared with vancomycin
this indication by the U.S. Food and Drug Administration (FDA), but most patients with mild-to-moderate illness respond to 500 mg given by mouth three times a day for 10 days; extension of the treatment period to 14 days may be needed for slow responders.\textsuperscript{2} Metronidazole should be used with caution after the first recurrence due to potential for cumulative neurotoxicity.\textsuperscript{2,6} Because metronidazole is almost completely absorbed in the gut, there is very low drug levels in the colon, resulting in a high rate of treatment failure.\textsuperscript{3} A lack of response to treatment and recurrence of CDI happen with approximately equal frequency after both metronidazole and oral vancomycin treatments.\textsuperscript{3} The recurrence is seen in 20\% to 30\% of cases within 30 days of initial treatment; regardless of which of these two drugs is used.\textsuperscript{3}

On May 27, 2011, the FDA approved fidaxomicin for the treatment of CDAD in adults 18 years of age and older.\textsuperscript{7,8} Fidaxomicin is made by Optimer Pharmaceuticals, Inc. under the trade name Dificid\textsuperscript{®}.\textsuperscript{7} The objectives of this article are to discuss the pharmacology, pharmacokinetics, safety, tolerability, relevant clinical studies, and cost of fidaxomicin.

### Pharmacology & Pharmacokinetics

Fidaxomicin is a narrow-spectrum, nonabsorbed, macrocyclic oral antibacterial drug (macrolide) with bactericidal activity that inhibits RNA polymerase sigma subunit resulting in inhibition of protein synthesis and cell death in susceptible organisms. The drug is active against certain gram-positive aerobes and anaerobes, including \textit{C. difficile} NAP1/B1/027 strain. Fidaxomicin has only limited or no activity against gram-negative bacteria and \textit{Candida albicans}.\textsuperscript{7,9,10}

Fidaxomicin seems to have greater \textit{in vitro} activity against \textit{C. difficile} and may also have a more minimal impact \textit{in vivo} on normal intestinal flora than some other antibiotics such as vancomycin used for treatment of \textit{C. difficile} infection.\textsuperscript{3,9} However, additional studies are needed to further evaluate fidaxomicin’s effect on the normal intestinal flora.\textsuperscript{3} Fidaxomicin has \textit{in vitro} activity against gram-positive anaerobes such as \textit{C. perfringens}, other \textit{Clostridium} species, and \textit{Peptostreptococcus}. The drug only possesses limited \textit{in vitro} activity against gram-positive cocci such as \textit{Staphylococcus aureus}, \textit{Enterococcus faecalis}, and \textit{E. faecium}. Treatment of systemic infections with fidaxomicin is not effective because of its poor systemic absorption.\textsuperscript{7,9,11,12} In a dose-ranging trial (N=48) of fidaxomicin using 50 mg, 100 mg, and 200 mg twice daily for 10 days, a dose-response relationship was observed for efficacy.\textsuperscript{7} The minimum inhibitory concentration (MIC\textsubscript{90}) of fidaxomicin for \textit{C. difficile} generally ranges from 0.125–0.5 mcg/mL.\textsuperscript{9}

#### Absorption

Fidaxomicin has minimal systemic absorption following oral administration, with plasma concentrations of fidaxomicin and its active metabolite (OP-1118) in the ng/mL range at the therapeutic dose in healthy volunteers as well as in patients with CDAD (Table 1).\textsuperscript{7} In a food-effect study involving administration of fidaxomicin to healthy adults (N=28) with a high-fat meal versus under fasting conditions, C\textsubscript{max} of fidaxomicin and OP-1118 decreased by 21.5\% and 33.4\%, respectively, while AUC\textsubscript{0-1118} remained unchanged. This decrease in C\textsubscript{max} is not considered clinically significant, and thus, fidaxomicin may be administered with or without food.\textsuperscript{7,10}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Absorption</td>
<td>Minimal systemic absorption</td>
</tr>
<tr>
<td>Effect of food on absorption</td>
<td>Not clinically significant</td>
</tr>
<tr>
<td>C\textsubscript{max} (ng/mL)</td>
<td>5.20 ± 2.81</td>
</tr>
<tr>
<td>Distribution</td>
<td>Confined to GI tract</td>
</tr>
<tr>
<td>Serum concentration</td>
<td>Minimally detectable to undetectable</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hydrolysis in intestine, active metabolite (OP-1118)</td>
</tr>
<tr>
<td>T\textsubscript{1/2}</td>
<td>~12 hours for fidaxomicin; ~11 hours for OP-1118</td>
</tr>
<tr>
<td>Excretion</td>
<td>&gt; 92% in feces as fidaxomicin &amp; OP-1118; &lt; 1% in urine as metabolite</td>
</tr>
<tr>
<td>MIC\textsubscript{90} of fidaxomicin for \textit{C. difficile}</td>
<td>0.125–0.5 mcg/mL</td>
</tr>
<tr>
<td>Renal impairment dose</td>
<td>Same as adult dose</td>
</tr>
<tr>
<td>Hepatic impairment dose</td>
<td>Same as adult dose</td>
</tr>
<tr>
<td>Geriatric dose</td>
<td>Same as adult dose</td>
</tr>
</tbody>
</table>
Fidaxomicin is largely confined to the gastrointestinal tract; in single- and multiple-dose studies, fecal concentrations of fidaxomicin and OP-1118 are very high while serum concentrations vary from minimally detectable to undetectable levels.\textsuperscript{7,10}

**Metabolism**

Metabolism of fidaxomicin and formation of OP-1118 through intestinal hydrolysis are not dependent on cytochrome P-450 (CYP) isoenzymes.\textsuperscript{7,10} The plasma elimination half-lives of fidaxomicin and OP-1118 in adults are approximately 12 and 11 hours, respectively. The post-antibiotic effect of fidaxomicin is 6-10 hours. OP-1118 has less antibacterial activity against *C. difficile* than does fidaxomicin.\textsuperscript{7,10}

**Excretion**

More than 92% of an oral dose is recovered in feces as fidaxomicin and its main active metabolite OP-1118; less than 1% of a dose is recovered in urine as OP-1118.\textsuperscript{7,10} In patients treated with fidaxomicin (200 mg by mouth twice daily for 10 days), concentrations of fidaxomicin and OP-1118 in feces obtained within 24 hours of the last dose have ranged from 639–2710 mcg/g and 213–1210 mcg/g, respectively.\textsuperscript{7}

### CLINICAL TRIALS

The efficacy and safety of fidaxomicin in CDAD were established through two phase-3 clinical studies. Louie, et al.\textsuperscript{13,14} carried out the first study in Canada and the US in 2011 while Cornely et al.\textsuperscript{15} carried out the second study in Canada, USA, and Europe (Table 2). Both studies are non-inferiority studies carried out in multiple centers in different countries. The primary endpoints were clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy) while the secondary endpoints were recurrence of CDI (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure (i.e., cure with no recurrence).

Both studies were randomized and double-blinded non-inferiority trials with allocation concealment. In both studies the effectiveness for fidaxomicin and vancomycin with respect to the clinical resolution of acute diarrheal disease due to CDI was similar. No significant differences in the rates of adverse events or serious adverse events existed between the fidaxomicin group and the vancomycin group. No microbiological data were published with regard to drug effects on nor-

**Table 2 | Fidaxomicin efficacy and safety in clinical trials.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Treatment</th>
<th>Cure (%)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louie, et al.\textsuperscript{13,14}</td>
<td>Randomized, double-blinded, N=599\textsuperscript{a}</td>
<td>1. &gt;= 16 years old with acute symptoms of <em>C. difficile</em> infection, defined by &gt; 3 unformed bowel movements in the 24 h before randomization and either toxin A, B, or both in a stool specimen obtained within 48 h before randomization.</td>
<td>Fidaxomycin: 200 mg PO BID for 10 days. Vancomycin: 125 mg PO QID for 10 days.</td>
<td>87.7%</td>
<td>Fidaxomicin: 221 (87.7%) vs Vancomycin: 223 (86.8%) more sustained resolution of disease.</td>
</tr>
<tr>
<td>Cornely et al.\textsuperscript{15}</td>
<td>Randomized, double-blinded, N=509</td>
<td>1. &gt;= 16 years old with acute <em>C. difficile</em> infection defined by &gt; 3 unformed bowel movement in the 24 h before randomization and either toxin A, B, or both in a stool specimen obtained within 48 h before randomization; 2. Patients had no or one previous episode of <em>C. difficile</em> infection in the 3 months before randomization.</td>
<td>Fidaxomycin: 200 mg PO q12h for 10 days. Vancomycin: 125 mg PO q6h for 10 days.</td>
<td>87.7%</td>
<td>Fidaxomicin: 281 (87.7%) vs Vancomycin: 283 (86.8%) more sustained resolution of disease.</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Number used in the modified intention-to-treat (mITT) analysis; \textsuperscript{b}Clinical cure, clinical recurrence, and global cure in the modified intention-to-treat (mITT) analyses.
nal flora following therapy in either study. Both studies were funded by Optimer Pharmaceuticals.

**SAFETY & TOLERABILITY**

The overall combined incidence of serious adverse events (GI hemorrhage, megacolon, or decrease in WBC count) in the two Phase 3 trials did not differ significantly between the fidaxomicin group (25.7%) and the vancomycin group (23.2%). Overall, 20 (3.5%) fidaxomicin-treated vs. 12 (2.1%) vancomycin-treated subjects experienced a GI bleed in the two phase 3 trials; it is unknown whether the difference was statistically significant (Table 3). The FDA’s review of the actual events did not show any particular consistent pattern, though lower GI bleeds were more frequent for the fidaxomicin group overall. FDA has recommended postmarketing surveillance for this event.

The following adverse reactions were reported in <2% of patients taking fidaxomicin in controlled trials: abdominal distension, abdominal tenderness, dyspepsia, dysphagia, flatulence, intestinal obstruction, megacolon, increased blood alkaline phosphatase, decreased blood bicarbonate, increased hepatic enzymes, decreased platelet count, hyperglycemia, metabolic acidosis, drug eruption, pruritus, rash. The manufacturer states that there are no known contraindications to the use of fidaxomicin. Fidaxomicin should be used only in patients with proven or strongly suspected C. difficile infections. In animal reproduction studies, fidaxomicin did not cause adverse events to the fetus. Moreover, exposure to the fetus is likely low given that fidaxomicin is poorly absorbed following oral administration. There are no adequate and well controlled studies in pregnant women. The manufacturer recommends cautious use in women who intend to breastfeed since the amount of fidaxomicin excreted in breast milk is unknown.

**DOSING**

The recommended dose for fidaxomicin is 200 mg by mouth twice daily for 10 days. Fidaxomicin can be administered with or without food. Because fidaxomicin has minimal systemic absorption, patients with mild, moderate, or severe renal impairment do not need renally-adjusted doses. Likewise, patients with hepatic impairment should not need a dose adjustment, although fidaxomicin has not been studied specifically in patients with hepatic impairment. Patients 65 years of age and older can use the same dose as younger adults.

**DRUG INTERACTIONS**

Drug interaction studies using a CYP3A4 substrate (midazolam), CYP2C9 substrate (warfarin), or CYP2C19 substrate (omeprazole) indicate that fidaxomicin has no clinically important effect on the pharmacokinetics of these drugs. Based on these results, the manufacturer states that dosage adjustments are not warranted if fidaxomicin is used concomitantly with drugs that are CYP isoenzyme substrates.

**COSTS**

A cost comparison of fidaxomicin, vancomycin, and metronidazole for the treatment of CDAD is provided in Table 4. In general, a single course of fidaxomicin costs substantially more than similar courses of vancomycin and metronidazole.

**CONCLUSIONS**

The results of both phase 3 clinical trials indicate that oral fidaxomicin is noninferior to oral vancomycin for treatment of CDAD including C. difficile NAP1/B1/027 strain in adults. The trials also demonstrate that recurrence of CDAD occurs less frequently when CDAD is treated with fidaxomicin and that fidaxomicin is superior to vancomycin in terms of sustained clinical response after treatment. Overall the trials demonstrate fidaxomicin efficacy in the treatment of CDAD in adults 18 years of age and older. Fidaxomicin is not for the treatment of systemic infections and is not recommended for severe and complicated CDAD. Presence of CDAD must be con-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Most common treatment-emergent adverse effects during phase 3 trials.</th>
<th>Adverse Effect, n (%)</th>
<th>Fidaxomicin (n=564)</th>
<th>Vancomycin (n=583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>62 (11)</td>
<td>66 (11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>41 (7.3)</td>
<td>37 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (5.0)</td>
<td>39 (6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (4.4)</td>
<td>12 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>33 (5.9)</td>
<td>23 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>20 (3.5)</td>
<td>12 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (2.5)</td>
<td>12 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (2.5)</td>
<td>6 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>37 (6.6)</td>
<td>27 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24 (4.3)</td>
<td>31 (5.3)</td>
<td></td>
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</table>
firmed by laboratory testing before fidaxomicin is used. The dose for CDAD is 200 mg by mouth twice daily for 10 days with or without food and no dosage adjustment is required in geriatrics, renally-, or hepati-
cally-impaired patients. Nausea, vomiting, abdominal pain, and headache are the most common adverse
events with fidaxomicin. Further studies are needed to
compare fidaxomicin directly to metronidazole and
vancomycin, especially in severe cases of CDAD in
order to define more clearly the role of each agent. For
now, fidaxomicin can be a useful, but expensive alter-
native agent for patients who cannot tolerate metroni-
dazole and vancomycin and those who have frequent
recurrent CDAD infection.

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**Table 4 | Cost comparison for 10-day course of CDAD pharmacotherapy.**

<table>
<thead>
<tr>
<th>Drug &amp; Daily dosage</th>
<th>UCH Pharmacy</th>
<th>Walgreens</th>
<th><a href="http://www.drugstore.com">www.drugstore.com</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin 200 mg po bid x 10 days</td>
<td>$3029.00</td>
<td>$3260.00</td>
<td>$3150.98</td>
</tr>
<tr>
<td>Vancocin® 125 mg po qid x 10 days</td>
<td>$1258.63</td>
<td>$1359.00</td>
<td>$1373.98</td>
</tr>
<tr>
<td>Vancocin® 250 mg po qid x 10 days</td>
<td>$2117.63</td>
<td>$2587.00</td>
<td>$2389.26</td>
</tr>
<tr>
<td>Vancomycin 125 mg po qid x 10 days</td>
<td>$1132.70</td>
<td>$1233.00</td>
<td>not available</td>
</tr>
<tr>
<td>Vancomycin 250 mg po qid x 10 days</td>
<td>$2084.54</td>
<td>$2264.00</td>
<td>not available</td>
</tr>
<tr>
<td>Metronidazole 500 mg po tid x 10 days</td>
<td>$24.66</td>
<td>$31.69</td>
<td>$25.99</td>
</tr>
</tbody>
</table>
Timing of Warfarin Monitoring and Efficacy of Vitamin K as a Reversal Agent

Thoai Nguyen, PharmD Candidate

The incidence of venous thromboembolism in US adults is projected to double from nearly one million in 2006 to almost 2 million in 2050. Thromboemboli are largely preventable and associated with serious morbidity and mortality if not treated properly. Oral anticoagulants, such as warfarin, are often initiated to prevent thrombi formation and stroke in high risk persons. Unfortunately, anticoagulation increases the risk of bleeding and there are many factors that interact with warfarin therapy, often making it difficult to manage warfarin therapy. The effective and safe dose of warfarin is patient specific and dependent on many factors, including diet, exercise, renal and liver function, as well as concurrent medications and supplements. To ensure that patients are on safe and therapeutic doses, frequent laboratory monitoring is often needed. If laboratory values indicate warfarin is supratherapeutic, an antidote is needed to prevent bleeding. Recommendations for appropriate antidote are controversial, as are the timing of warfarin monitoring. Here, we discuss the efficacy of vitamin K as a reversal agent and appropriate frequency of INR monitoring.

INR Monitoring

Warfarin inhibits vitamin K epoxide reductase, which in turn leads to clearance of clotting factors II, VII, IX and X. Within the first 24-36 hours of administration, warfarin produces an anticoagulant effect, as a result of clearing factors VII and IX. However, the ultimate goal of warfarin therapy is to achieve antithrombotic effects that occur only with clearance of clotting factor II (prothrombin), which typically happens within 5 days of administration. To ensure adequate antithrombotic effects, the international normalized ratio (INR) is used to gauge warfarin’s efficacy at a given dose. Warfarin is most commonly titrated to an INR goal range of 2 to 3. Because it takes 5 days for factor II to be cleared and reflected in the INR, dose adjustments are typically not made sooner than 5 days after a previous dose adjustment or drug initiation.

Because of the many interactions with warfarin (e.g., lifestyle, drugs, diet), all persons require frequent INR monitoring, regardless of whether they achieve a therapeutic INR. The 2008 Chest Guidelines for vitamin K antagonist treatment recommend INR monitoring be performed at intervals not exceeding every four weeks; however, the 2012 guidelines now recommend less frequent monitoring of up to 12 weeks for persons who have been on stable doses of warfarin. The new CHEST recommendations for less frequent INR monitoring are based on three studies.

The first study enrolled 135 patients who had a therapeutic INR for at least two months to determine whether INR testing at intervals of six weeks was safe and would decrease cost versus the usual four week intervals. After a two year follow up, there was no significant difference in the combined endpoint of hemorrhagic or thromboembolic event when comparing the six week versus four week groups (3.27% vs. 3.09%; p=0.81). The mean time between INR measurements in the 6 week group was 24.9 ± 18.1 days and 22.5 ± 9.5 days in the four week group. The shortened time between INR measurements in the six week group may be partly because the time was shortened to between one and three weeks when the INR was outside of the therapeutic range.

The second study was a prospective, randomized trial comparing usual INR follow-up intervals to computer-generated follow-up intervals. The computer-generated intervals were based on the INR that day, the goal INR, number of clinic visits, historical INR variability, and cost of an INR monitoring visit. Providers were allowed to use their clinical judgment to modify the computer generated follow-up intervals. A total of 619 patients completed the study. After a mean total follow-up of eight months, the mean interval between INR monitoring was significantly longer in the intervention group compared to the usual care group (4.4 vs. 3.5 weeks; p<0.001). In the intervention group, the recommended monitoring interval was adjusted by the provider 40% of the time; mean recommended monitoring interval was 5.5 weeks compared to the actual interval of 4.4 weeks. Comparing the intervention and control groups, there were no significant differences in maintaining INR within therapeutic range, clinically important bleeding events (13 vs. 15; p=0.74), or thromboembolic events (6 vs 3 serious or life-threatening; p=0.28).

The third study was also a prospective, randomized trial that compared INR monitoring intervals of 12 and four weeks. All patients had therapeutic INRs for at least six months prior to randomization. Regardless of randomization, all patients had their INR checked at four week intervals; however, the provider was not giv-
Warfarin Reversal with Vitamin K

An elevated INR is an independent risk factor for major bleeding, and the risk of bleeding doubles with every 1-point increase in INR. Reversal agents for warfarin and warfarin-induced bleeding include vitamin K, fresh frozen plasma, prothrombin complex concentrates, and recombinant VIIa. For patients with supratherapeutic INRs, recommendations include administering a reversal agent, withholding warfarin, or decreasing the warfarin dose to prevent or stop a bleeding event. Administration of vitamin K decreases the INR by counteracting the effect of warfarin; vitamin K activates clotting factors II, VII, IX, and X and proteins C and S. For patients requiring vitamin K for a supratherapeutic INR, the lowest effective dose is desired, given the effects of vitamin K can persist for days and result in “warfarin resistance.” Because vitamin K deposits in adipose tissues, achieving and maintaining a therapeutic INR can be difficult after administration of vitamin K. Despite its long-lasting residual effects, vitamin K produces a decrease in the INR within approximately 2 hours after administration and a “normal” INR can be achieved within 24 hours in most patients.

In theory, reducing the INR from a supratherapeutic to a therapeutic range should decrease the risk of bleeding; however, the clinical efficacy of vitamin K at reducing bleeding risk is not well established. One study comparing administration of vitamin K to no reversal in persons with supratherapeutic INRs found the frequency of bleeding events to be similar. This randomized, placebo-controlled trial of 724 nonbleeding patients with INRs between 4.5-10 (INR goal 2-3.5) were given either oral vitamin K or placebo. Vitamin K decreased INR values more rapidly than placebo (mean decrease in INR = 2.8 vs. 1.5, respectively; p<0.001), but it did not reduce the incidence of bleeding events during the 90-day follow-up period (15.8% vs. 16.3%; p=0.86).

Further studies of larger populations are needed to determine whether vitamin K reduces clinically significant bleeding events attributable to excessive anticoagulation secondary to warfarin. However, at present, vitamin K, given via the oral route, is the preferred reversal agent for reducing elevated INRs in patients without clinically significant or life-threatening bleeding.

References

2. Horton, J, Bushwick, B. Warfarin therapy: Evolv-