Systematic Overview of Warfarin and Its Drug and Food Interactions

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Background: Warfarin is a highly efficacious oral anticoagulant, but its use is limited by a well-founded fear of bleeding. Drug and food interactions are frequently cited as causes of adverse events with warfarin. We provide an updated systematic overview of the quality, clinical effect, and importance of these reported interactions.

Data Sources: MEDLINE, TOXLINE, IPA, and EMBASE databases from October 1993 to March 2004. Database searches combined the keyword warfarin with drug interactions, herbal medicines, Chinese herbal drugs, and food-drug interactions.

Study Selection: Eligible articles contained original reports of warfarin drug or food interactions in human subjects. Non-English articles were included if sufficient information could be abstracted.

Data Extraction: Reports were rated independently by 2 investigators for interaction direction, clinical severity, and quality of evidence. Quality of evidence was based on previously validated causation criteria and study design.

Data Synthesis: Of 642 citations retrieved, 181 eligible articles contained original reports on 120 drugs or foods. Inter-rater agreement was excellent, with weighted κ values of 0.84 to 1.00. Of all reports, 72% described a potentiation of warfarin’s effect and 84% were of poor quality, 86% of which were single case reports. The 31 incidents of clinically significant bleeding were all single case reports. Newly reported interactions included celecoxib, rofecoxib, and herbal substances, such as green tea and danshen.

Conclusions: The number of drugs reported to interact with warfarin continues to expand. While most reports are of poor quality and present potentially misleading conclusions, the consistency of reports of interactions withazole antibiotics, macrolides, quinolones, nonsteroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, selective serotonin reuptake inhibitors, omeprazole, lipid-lowering agents, amiodarone, and fluorouracil, suggests that coadministration with warfarin should be avoided or closely monitored. More systematic study of warfarin drug interactions in patients is urgently needed.

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WARFARIN IS THE MOST commonly used oral anticoagulant in North America and has established efficacy for the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves, venous thromboembolism, and coronary artery disease. The drug is a racemic mixture of 2 optically active isomers, though the S-enantiomer is approximately 5 times more potent than the R-enantiomer. Warfarin exerts its effect by lowering the amount of active vitamin K available for the activation of clotting factors II, VII, IX, and X. Both effectiveness and safety (primarily risk of bleeding) are related to blood international normalized ratio (INR) values. Monitoring of INR and dose adjustments of warfarin are frequently required, influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors.

See also page 1185

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Despite the frequency and importance of warfarin’s drug and food interactions, the first systematic overview on the topic did not appear until 1994. For that review, we developed an interaction assessment tool that combined a “levels of evi-
METHODS

Relevant literature was identified by searching MEDLINE, TOXLINE, IPA, EMBASE databases, Health Canada and Food and Drug Administration Web sites and personal files from October 1993 to the end of March 2004. The MeSH headings and keywords used for the search were warfarin and drug interactions. Non-English articles were included if they included an English abstract with sufficient information. To retrieve warfarin/herbal drug interactions and warfarin-food interactions, 2 additional searches were conducted using the MeSH headings and keywords warfarin and herbal medicines or Chinese herbal drugs, and MeSH headings food-drug interactions and warfarin, limited to English only. The bibliographies of the retrieved articles were checked for any additional pertinent studies. Articles were considered eligible for evaluation if they contained original data involving drug or food interactions with warfarin in human subjects. Interacting drugs had to be available in the United States or Canada. Eligible studies were evaluated independently by 2 authors according to the following 4 main categories.

INTERACTION CLASSIFICATION AND SEVERITY

The drug affected and the type of interaction (potentiation, inhibition, or no effect) were noted. Interactions that potentiated or inhibited the effect of warfarin were further rated as major, moderate, minor, or nonclinical.

Major potentiation was defined by death, major bleeding, or necessity to stop warfarin therapy entirely. Major bleeding episodes included those that were life-threatening as well as those that led to the loss of at least 2 units of blood in 7 days or less. Moderate potentiation meant that (1) there was an INR change requiring an adjustment in warfarin dosage or (2) the INR increased to greater than 5.0 or (3) there was an increase in INR by greater than 1.5. Minor potentiation interactions were defined as an INR increase in which (1) no change in warfarin dosage was required and (2) the ratio remained less than 5 and (3) the increase was less than 1.5. Potentiation interactions were classified as nonclinical if the only evidence of warfarin augmentation was a statistically significant increase in warfarin levels without change in INR or clinical status.

Major inhibition interactions were defined by the occurrence of thrombosis. Moderate inhibition (clinically relevant but less than major) indicated (1) a change in INR requiring an adjustment in warfarin dosage or (2) an INR decrease to less than 1.5 or (3) a decrease in INR by greater than 1.5 units. Minor inhibition interactions were defined by (1) an INR decrease requiring no change in warfarin dosage and (2) an INR decrease to a ratio that remained more than 1.5 and (3) a decrease in INR by less than 1.5. Inhibition interactions were classified as nonclinical if the only evidence of warfarin inhibition was a statistically significant decrease in warfarin levels.

An interaction was defined as having no effect if the interacting drug neither potentiated nor inhibited warfarin’s effect in any way described herein.

QUALITY OF STUDY

Reports were classified into 1 of 4 categories based on the quality of study design. As shown in Table 1, randomized controlled trials (RCTs) were subdivided into fair to excellent quality, with those involving more than 100 subjects arbitrarily given the highest rating. Poor quality reports included non-randomized study designs, observational studies, pharmacokinetic studies, and case reports.

CAUSATION CRITERIA

For each report, the probability of the proposed interaction was rated from level I (highly probable) to level IV (highly improbable). Definitive evidence of an interaction required a level I causation rating from both healthy volunteer and patient-based reports in which both described identical interaction direction and severity. Level designation was based on how the article fulfilled 7 standard causation criteria.

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Causation Criteria Required</th>
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<tbody>
<tr>
<td>I (Highly probable)</td>
<td>A, B, C, and ≥1 of D to G</td>
</tr>
<tr>
<td>II (Possible)</td>
<td>A, B, and ≥1 of C to G</td>
</tr>
<tr>
<td>III (Probable)</td>
<td>A and ≥1 of B to G</td>
</tr>
<tr>
<td>IV (Highly improbable)</td>
<td>A alone or any combination of B to G</td>
</tr>
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</table>

A. Is the timing correct for an interaction to be pharmacologically plausible?

In patient-based studies, warfarin must have been taken at a stabilized dose common to usual practice and prior to initiation of the interacting drug or food. For volunteer-based studies, subjects had to have received warfarin, both alone as well as with the interacting drug. In addition, we required that the potentially interacting drug had to be consumed (1) long enough to attain a significant plasma level and (2) in doses common to usual practice.

B. Do laboratory tests (eg, international normalized ratio/prothrombin time/thrombotest) support the contention of an interaction?

In patient-based articles, the post-coadministration coagulation variable
had to be out of therapeutic range, whereas for volunteer studies, a 20% change in coagulation parameters for volunteer studies was required. For articles concluding “no interaction,” the absence of a statistically significant change in coagulation variables was required.

C. Are other potential factors affecting warfarin pharmacokinetics/pharmacodynamics ruled out satisfactorily? Factors such as diet, other medications, as well as certain medical conditions (hepatic dysfunction and hyperthyroidism) had to have been declared to be ruled out as possible causes of the outcome.

D. Has the patient had a similar result with previous exposure to the same drug?

The patient had to have been taking the interacting drug in addition to warfarin at a time prior to that reported with a similar outcome.

E. Was a dose-response relationship demonstrated for the interacting drug? The alterations in the dose of the implicated interacting drug or food being administered with warfarin correlated with subsequent changes in coagulation variables, inferring a dose-response relationship.

F. Was the subject rechallenged and, if so, did a similar response occur? The interacting drug had to have been administered simultaneously with warfarin in 2 or more separate courses (the second course conducted to confirm the results of the first), with similar results each time.

G. Are the authors’ conclusions supported by other objective evidence? Other objective evidence such as plasma levels of warfarin or coagulation factors supported the authors’ conclusions.

RELIABILITY AND VALIDITY

The criteria and rating scheme were evaluated and approved a priori by a panel of experts in the fields of thromboembolism, clinical pharmacology, and clinical epidemiology to assure face validity. Interrater agreement for interaction direction and severity, quality of study, and level of causation was assessed using a weighted κ statistic.

CONFLICTING EVIDENCE

If ratings differed among articles for the same interacting drug or food, a hierarchy was implemented (type of subject > quality of study > level of causation > severity of clinical outcome). For example, a case report involving a patient was considered to be superior to an RCT using healthy volunteers as subjects. If 2 or more articles had the same subject type, the result of the highest quality study was listed—a patient-based RCT was considered superior to a patient case report. If 2 or more articles with the same subject type and quality of study varied in level of causation and clinical outcome, the clinical outcome associated with the highest level of evidence was listed. For example, the case report describing moderate potentiation of warfarin by celecoxib, with a level II causation rating, outweighed the level III case report describing a similar interaction.

A total of 642 citations were identified, of which 205 contained original data on drug or food interactions with warfarin. Of these 205 articles, 181 were retrievable and available for review. The reviewed articles contained 187 separate reports of interactions involving 120 drugs or foods. The weighted κ statistic for the interaction direction and severity rating, level of causation evaluation, and quality of study rating among the reviewers were 0.98, 0.84, and 1.0 respectively. All rating disagreements were resolved by repeated review and consensus.

No study met our definition of excellent quality. Thirty-three small RCTs were rated fair or good quality, of which 28 involved healthy subjects and 26 concluded a lack of interaction between warfarin and the drug or food studied. Olestra, vitamin E, clopidogrel, coenzyme Q10/ginkgo biloba, ciprofloxacin, and celecoxib, ciprofloxacin, and fluoxetine/diazepam coadministration. Only 2 of all 34 reports were level I, describing inhibition involving mesalamine and trazodone. Several herbal drugs, foods rich in vitamin K, and carbamazepine were reported to decrease warfarin’s effect as were other anti-infective agents, including griseofulvin, rifampin, and penicillamine-resistant penicillins, such as nafcillin, dicloxacillin, and cloxacinil.

There were 3 drugs—terbinafine, ritonavir, and influenza vaccine—for which conflicting evidence of an interaction with warfarin was presented. A cumulative
summarized, combining evaluations from our original review with those of the update is presented in Table 2. Although few interactions met level 1 causation requirements, the recurrent reports on non-steroidal anti-inflammatory drugs (NSAIDs), \textsuperscript{230} antibiotics (particularly macrolides—azithromycin, \textsuperscript{124} erythromycin, \textsuperscript{11} and clarithromycin, \textsuperscript{126} azoles (fluconazole\textsuperscript{231} and miconazole\textsuperscript{25}), amoxicillin, and quinolones (ciprofloxacin\textsuperscript{10} and levofloxacin\textsuperscript{139}) continue. New alerts regarding the potential for major bleeding when warfarin is taken with cyclooxygenase-2 (COX-2) selective NSAIDs\textsuperscript{9,10,232} or herbal drugs are raised.\textsuperscript{127,233} Table 3 presents a summary of all clinically significant potentiation and inhibition interactions with warfarin, based on drug family and level of causation. The most commonly cited mechanisms for interactions with warfarin involved stereoselective clearance due to S-enantiomer (ritodrine) and terbinafine or the vitamin K pathway (green tea). However, most of the interactions reported have no documented mechanism.

This updated review indicates that the number of reports of interactions between warfarin and drugs or foods is increasing, reaffirming both the anticoagulant’s widespread use and its use with concomitant medications. Although the true mechanisms of drug interactions almost always remain unknown, there are several pharmacokinetic and pharmacodynamic factors that could influence warfarin’s effect. Cholestyramine is thought to reduce the gastrointestinal absorption of warfarin.\textsuperscript{97,234} The more potent warfarin S-isomer is metabolized by cytochrome P-450 (CYP) 2C9. Many of the drugs identified as potentiating warfarin’s effect are known inhibitors of CYP 2C9, including amiodarone, fluconazole, fluvoxamine, isoniazid, lovastatin, phenylbutazone, and sertraline.\textsuperscript{235} Rifampin and secobarbital are both known inducers of CYP 2C9.\textsuperscript{91,102}

The R-isomer of warfarin is metabolized by CYP 1A2 and CYP 3A4, and quinolones\textsuperscript{56,139} inhibit CYP 1A2, and macrolides\textsuperscript{11,124,126} inhibit CYP 3A4. The azoles (several reports involving metronidazole, fluconazole, trimethoprim-sulfamethoxazole, miconazole, and voriconazole\textsuperscript{25,28,70,81,83,236}) are also considered to inhibit CYP 1A2 or CYP 3A4. The pharmacodynamics of warfarin may be influenced by medications that affect either vitamin K or the coagulation factors.\textsuperscript{237} Sudden changes in dietary sources of vitamin K such as leafy greens or a supplemented diet followed by a change in warfarin’s effect are relatively easy to understand.\textsuperscript{100,238-240} However, for several drugs, including cephalosporins, levofloxoxine, and clofibrate, their supposed pharmacodynamic interactions with warfarin are very poorly understood.\textsuperscript{70,234,241}

Although understanding a drug’s pharmacology helps predict its potential for interaction with warfarin, the translation of these predictions into clinical reality is far from certain. We also found no evidence that specific factors might identify patient subgroups most at risk of pharmacokinetic drug interactions. Regular monitoring of INR remains the best protection against major harm due to these pharmacokinetic and pharmacodynamic interactions.

The most difficult groups of drugs to deal with are those that potentiate bleeding on their own. The risk of bleeding is then greater when taken with warfarin, and INR monitoring is of no help. This is an issue with other anticoagulants (such as heparin), antiplatelet drugs (eg, acetylsalicylic acid, clopidogrel, dipyridamole, sulfipyrazone, and ticlopidine) and all NSAIDs including COX-2 selective NSAIDs. All of these drugs should be avoided in combination with warfarin unless proven to provide benefit that outweighs the risk of bleeding—for example, for artificial heart valves.\textsuperscript{237} Contrary to the early theories of safety of COX-2 selective NSAIDs, we do not consider them safe in combination with warfarin. Both celecoxib (10 cases moderate\textsuperscript{69,232} to major\textsuperscript{9,10}) and rofecoxib (2 cases moderate\textsuperscript{6}) are reported to potentiate anticoagulation. Acetami-
### Table 2. Drug and Food Interactions With Warfarin by Level of Causation and Direction of Interaction

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Potentiation</th>
<th>Inhibition</th>
<th>No Effect</th>
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<td><strong>I (Highly probable)</strong></td>
<td>Barbituates&lt;sup&gt;93,94&lt;/sup&gt;</td>
<td>Carbamazepine&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Alcohol†&lt;sup&gt;99,100&lt;/sup&gt;</td>
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<td></td>
<td>Alcohol (if concomitant liver disease)†&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Carbamazepine&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Anticoagulant†&lt;sup&gt;102,103&lt;/sup&gt;</td>
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<td>Amiodarone†&lt;sup&gt;65-67&lt;/sup&gt;</td>
<td>Chlordiazepoxide&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Argatroban†&lt;sup&gt;96&lt;/sup&gt;</td>
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<td></td>
<td>Anabolic steroids†&lt;sup&gt;68,69&lt;/sup&gt;</td>
<td>Cholestyramine†&lt;sup&gt;97,98&lt;/sup&gt;</td>
<td>Atenolol†&lt;sup&gt;97&lt;/sup&gt;</td>
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<td></td>
<td>Barbituates&lt;sup&gt;93,94&lt;/sup&gt;</td>
<td>Clofibrate†&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Barbituates&lt;sup&gt;93,94&lt;/sup&gt;</td>
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<td>Balzamine†&lt;sup&gt;91&lt;/sup&gt;</td>
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<td>Boldo-fenugreek&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Citalopram‡ (n = 12)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Cotrimoxazole†&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Carbonic anhydrase inhibitors†&lt;sup&gt;101&lt;/sup&gt;</td>
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<td>Diltiazem‡ (n = 20)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Carbonic anhydrase inhibitors†&lt;sup&gt;101&lt;/sup&gt;</td>
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<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Fish oil&lt;sup&gt;23&lt;/sup&gt;</td>
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<td>Phenylbutazone†&lt;sup&gt;84,85&lt;/sup&gt;</td>
<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Clofibrate†&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Sulfinpyrazone (biphasic with later inhibition)†&lt;sup&gt;99,100&lt;/sup&gt;</td>
<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Clofibrate†&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Vitamin K content foods/enteral feeds†&lt;sup&gt;106,107&lt;/sup&gt;</td>
<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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<td>Carbamazepine†&lt;sup&gt;95&lt;/sup&gt;</td>
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</table>

| **II (Probable)** | Acetylsalicylic acid†<sup>122</sup> | Azathioprine†<sup>136</sup> | Alcohol†<sup>93,94</sup> | Alcohol†<sup>93,94</sup> |
| | Azithromycin<sup>24</sup> | Atenolol†<sup>89</sup> | Anastrozole (N = 16)<sup>36</sup> | Anastrozole (N = 16)<sup>36</sup> |
| | Azithromycin<sup>24</sup> | Atorvastatin†<sup>167</sup> | Anastrozole (N = 16)<sup>36</sup> | Anastrozole (N = 16)<sup>36</sup> |
| | Cefmetazole†<sup>133</sup> | Azithromycin<sup>24</sup> | Anastrozole (N = 16)<sup>36</sup> | Anastrozole (N = 16)<sup>36</sup> |
| | Cefmetazole†<sup>133</sup> | Azithromycin<sup>24</sup> | Anastrozole (N = 16)<sup>36</sup> | Anastrozole (N = 16)<sup>36</sup> |
| | Cefmetazole†<sup>133</sup> | Azithromycin<sup>24</sup> | Anastrozole (N = 16)<sup>36</sup> | Anastrozole (N = 16)<sup>36</sup> |

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Health Canada’s Canadian Adverse Drug Reaction Monitoring Program and Food and Drug Administration’s MedWatch were solicited for cases. We also were unable to review all non-English publications. The handling of conflicting evidence, while sensible, could have led to a mistaken conclusion. Others may not agree with our multidimensional, hierarchical evaluation methods.

In the extreme, no drug can be deemed “safe” based on our summary chart because the absence of proof of a severe interaction does not mean proof of absence. Idiosyncratic reactions can always be expected. We therefore continue to recommend careful monitoring of warfarin therapy at the time of introduction of any new medication, herbal product, or food. Herbal products are particularly problematic given the lack of quality control on their contents and the failure of clinicians to ask about their use.

How can clinicians use this information? To prescribe safely, there are 3 choices: one is to never prescribe or allow another medicine to be given with warfarin. This is clearly impractical for most patients requiring warfarin. The second is to use an electronic medical record or prescribing system that will evaluate interactions among the patient’s entire profile of therapies. Because these systems are not available to most physicians and are frequently incomplete and sometimes inaccurate, a third approach is required. The third option is to group the majority of offending interacting drugs.

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Potentiation</th>
<th>Inhibition</th>
<th>No Effect</th>
</tr>
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<tbody>
<tr>
<td>III (Possible)</td>
<td>Acarbose174</td>
<td>Amiodarone-induced toxicosis175</td>
<td>Cyclosporine172</td>
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<tr>
<td></td>
<td>Amoxicillin12</td>
<td>Amoxicillin/tranexamic rinse13</td>
<td>Eretinate179</td>
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<td>Amoxicillin12</td>
<td>CMF (cycloglobosomide/methotrexate/fluorouracil)177</td>
<td>Sulfasalazine164</td>
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<td>Chloramphenicol178</td>
<td>Cranberry juice179</td>
<td>Sushi containing seaweed175</td>
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<td>Danazol178</td>
<td>Curcumin178</td>
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<td>Quetiapine190</td>
<td>Sulfisoxazole190</td>
<td>Vancomycin190</td>
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*Interaction key: major interaction (bold/italics); moderate interaction (bold); minor interaction (italics); nonclinical interaction (regular).
†Data from 1994 review.6
‡Drugs and foods for which evidence is based on fair- to good-quality randomized controlled trials; numbers in parentheses indicate number of subjects in trial.
into easier-to-remember families or therapeutic groups, as we have done in Table 3. We recommend exercise caution when adding any antibiotic to warfarin therapy, especially for macrolides, quinolones, and “azoles.” Many common cardiovascular drugs, including statins, fibrates, heparin, aspirin, and amiodarone, are problematic. Also, NSAIDs, including COX-2 selective NSAIDs, should be avoided, as should omeprazole, alcohol, chloral hydrate, anabolic steroids, and a wide variety of, if not all, herbal supplements. New oral anticoagu-

lants may soon be available but have not demonstrated superior long-term efficacy, safety, or drug interaction profile compared with warfarin.

### CONCLUSIONS

In summary, there is an abundance of medications and foods for which an adverse interaction with warfarin, generally potentiation of warfarin’s effect, has been reported. While the drug interaction literature is generally of poor quality, relatively consistent reporting of interactions between warfarin and certain commonly used drugs and drug families (mainly anti-infective agents, lipid-lowering drugs, NSAIDs including COX-2 selective NSAIDs, selective serotonin reuptake inhibitors, amiodarone, omeprazole, fluorouracil, and cimetidine) is cause for concern. In patients who are starting therapy with one of these medicines, consideration should be given to using an alternative medication with less potential for warfarin interactions (eg, rabeprazole instead of omeprazole and acetaminophen in-
Table 3. Clinically Significant Interactions With Warfarin by Level of Causation and Drug Group (cont)

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>GI Drugs and Food</th>
<th>Potential Potentiation</th>
<th>Herbal Supplements</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Highly probable)</td>
<td>Cimetidine&lt;sup&gt;10-75&lt;/sup&gt; Fish oil&lt;sup&gt;77&lt;/sup&gt; Mango&lt;sup&gt;24&lt;/sup&gt; Omeprazole&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Boldo-fenugreek&lt;sup&gt;18&lt;/sup&gt; Quillinggao&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Anabolic steroids&lt;sup&gt;60,63&lt;/sup&gt; Zileuton&lt;sup&gt;59&lt;/sup&gt;</td>
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<tr>
<td>II (Probable)</td>
<td>Grapefruit juice&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Danshen&lt;sup&gt;127&lt;/sup&gt; Dong quai&lt;sup&gt;140&lt;/sup&gt; Lycium barbarum L&lt;sup&gt;140&lt;/sup&gt; PC-SPES&lt;sup&gt;141&lt;/sup&gt;</td>
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<tr>
<td>III (Possible)</td>
<td>Cranberry juice&lt;sup&gt;156&lt;/sup&gt; Orlistat&lt;sup&gt;158&lt;/sup&gt;</td>
<td>Danshen/methyl salicylate&lt;sup&gt;162&lt;/sup&gt;</td>
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<td>Etoposide/carboplatin&lt;sup&gt;215&lt;/sup&gt; Levonorgestrel&lt;sup&gt;218&lt;/sup&gt;</td>
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Abbreviations: CNS, central nervous system; GI, gastrointestinal.

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