

2014

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### Recommended Citation

Kho R, Kim S, Lee S, Tsu LV. A Review of Common Drug-drug and Food-drug Interactions Associated with Cardiovascular Medications. *Arizona Journal of Pharmacy* 2014;36-43.

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### Comments

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# A Review of Common Drug-drug and Food-drug Interactions Associated with Cardiovascular Medications

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## Goal:

This home-study CPE activity has been developed to educate pharmacists on the common drug-drug and food-drug interactions associated with cardiovascular medications.

## Objectives

1. Identify the uses of various over-the-counter (OTC) products of interest in cardiovascular patients
2. Describe the mechanism of action (MOA) of various food-drug/drug-drug interactions involving cardiovascular medications (statins, antiplatelet therapies, warfarin, red yeast rice)
3. Explain the clinical significance of these interactions in medication therapy
4. Relate recommendations with current clinical evidence
5. Formulate an appropriate treatment plan given a possible drug interaction scenario for cardiovascular patients

## Clopidogrel and PPIs

Clopidogrel (Plavix®) is an antiplatelet medication used to lower the risk of ischemic events in patients who suffer from coronary artery disease (CAD), peripheral artery disease (PAD), or who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). As a hepatically activated prodrug, it must first be metabolized via CYP2C19 before it can take effect.<sup>1</sup> Once activated, clopidogrel prevents the activation of platelets by inhibiting adenosine diphosphate (ADP) receptors, specifically P2Y<sub>12</sub> receptors, on the platelet surface.<sup>2</sup> ADP is an endogenous prothrombic molecule that is crucial for the initiation of clot formation. As shown in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, clopidogrel with aspirin in dual-antiplatelet therapy has shown added benefits in the prevention of ischemic events in patients who suffered recent transient ischemic attack (TIA) or minor stroke, compared to these medications alone.<sup>3</sup> The Clopidogrel for the Reduction of Events During Observation (CREDO) trial found an increase in thromboembolic protection with dual-antiplatelet therapy in patients who had recently undergone PCI.<sup>4</sup> Studies have also shown a trend toward fewer ischemic strokes and heart failure in those with non-ST elevation acute coronary syndrome taking dual-antiplatelet therapy, as well as a decreased occurrence of stent thrombosis compared to warfarin-aspirin therapy.<sup>5,6</sup>

## Interaction

Due to the inherent bleeding concerns that accompany the use of antiplatelet drugs and aspirin, there is legitimate controversy over the concomitant use of these agents. Studies have shown that there may be an increased risk of gastrointestinal (GI) bleeding associated with clopidogrel-aspirin dual therapy and

that proton-pump inhibitors (PPI) may be beneficial in reducing these events.<sup>7</sup> PPIs are known inhibitors of CYP2C19 with differing degrees of inhibition attributed to each PPI; therefore, new concerns arise regarding PPIs decreasing the conversion of clopidogrel to its active form and the subsequent increased risk of thromboembolic events. Recent studies have been performed to more clearly elucidate the risk versus benefit of concomitant use of PPIs in patients undergoing clopidogrel-aspirin therapy, which have important implications for pharmacists who may encounter this regimen in practice.

There are studies that suggest PPIs like omeprazole may have an effect on the activation of clopidogrel<sup>8</sup> and lead to increased platelet reactivity in patients who are at risk for clots. These findings are supported by studies that have shown that patients using PPIs with clopidogrel suffer worse outcomes<sup>9,10</sup> versus those not using PPIs or PPIs that are only slightly metabolized by CYP2C19, like pantoprazole. From these studies, it was believed that alternatives for CYP2C19-metabolized PPIs, such as histamine-2-receptor antagonists or differently metabolized PPIs would provide more benefit to patients on clopidogrel-aspirin therapy.

However, conflicting research suggests that the pharmacodynamic interactions observed between PPIs and clopidogrel are not universal among PPIs and are mostly limited to omeprazole.<sup>11,12</sup> This is supported by the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), a randomized controlled trial that sought to investigate the efficacy and safety of clopidogrel with PPIs in patients receiving aspirin. Bhatt et al. found that PPI use significantly reduced bleeding risks in these patients and concluded that the use of omeprazole and clopidogrel did not result in clinically significant cardiovascular interactions<sup>7</sup>. Recent retrospective observational reviews also paint a contradictory picture. In their analysis, Dunn et al. found that PPI-use in the CAPRIE study correlated with reduced effects of clopidogrel, at least in patients who were not also receiving aspirin, while data from the CREDO trial showed no increase in cardiovascular events in the PPI group.<sup>13</sup> Currently, there is no consensus regarding the effect PPI-use has on outcomes in patients on dual-antiplatelet therapy and further studies are needed to more clearly

understand their relationship.

**Recommendation**

In 2010, the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA) issued a consensus document to address the controversy regarding PPIs and drugs like clopidogrel. The document acknowledged the pharmacokinetic plausibility of a drug-drug interaction involving CYP2C19 and the need for further research into its clinical significance. For healthcare professionals, these organizations suggest careful discretion for patients on GI prophylaxis and antiplatelet therapies. Although PPIs are considered appropriate in patients undergoing antiplatelet therapy, the risks and benefits associated with cardiovascular (CV) and GI complications must be considered as well.<sup>14</sup> Risk factors for GI bleed such as history of GI bleed, advanced age, and use of corticosteroids must be assessed, and PPI use should be reserved for those who are at highest risk. A patient's physician should be consulted if concerns of negative CV outcomes outweigh the risk of developing a GI bleed.

**Niacin**

Nicotinic acid (niacin) is recommended as a therapeutic option for the treatment of dyslipidemia due to its effectiveness in favorably affecting all lipid parameters: it increases high density lipoprotein (HDL) cholesterol by 15-35%, decreases low density lipoprotein (LDL) cholesterol by 5-25%, and additionally decreases triglycerides (TGs) by 20-50% with doses of 2-3 g/day.<sup>15</sup> It is thought that niacin achieves this by working on multiple tissues, proteins, and enzymes.<sup>16</sup> In the liver, niacin has three functions: decrease TG synthesis to ultimately decrease very low density lipoproteins (VLDL) and LDL secretion, inhibit removal of HDL from circulation, and increase HDL biogenesis. Lipid-independent effects include decreased monocyte adhesion and infiltration, increased HDL function, and decreased foam cell formation. These effects, however, have not been conclusively shown to translate into improved clinical outcomes in clinical trials.<sup>17, 18</sup> In particular, the recent HPS2-THRIVE randomized-controlled trial confirmed the results of the AIM-HIGH trial, demonstrating no additional benefit of adding extended release (ER) niacin and laropiprant (to decrease flushing) to first-line therapy.<sup>19</sup> Newly released hyperlipidemia guidelines include this information and recognize that lowering non-HDL-C when LDL-C is at target levels yields no additional benefit in reducing atherosclerotic cardiovascular disease (ASCVD) events.<sup>20</sup> These new guidelines focus on statin therapy, finding no data supporting the efficacy of adjunct non-statin agents in reducing ASCVD events. Adjunct therapy with agents shown to reduce ASCVD risk in RCTs is only recommended for high-risk individuals who have insufficient response to statins, who cannot tolerate recommended higher statin doses, or can-

not tolerate statins at all. Given the results of the HPS2-THRIVE and AIM-HIGH trials, niacin may not qualify as a non-statin alternative under these new guidelines.

**Interaction**

Some of niacin's side effects stem from how its different formulations are metabolized by the liver with first-pass metabolism.<sup>21</sup> Niacin is metabolized by two pathways that result in either conjugation or amidation. The conjugative pathway, a low-affinity and high-capacity pathway, is only utilized when the amidation pathway (high-affinity and low-capacity) is saturated. It is these glycine conjugated products, such as nicotinuric acid, that lead to prostaglandin-mediated vasodilation and flushing. Tolerance to flushing may develop but not before many discontinue therapy due to the discomfort. The high-affinity and low-capacity amidation pathway generates nicotinamide and pyrimidine metabolites that are associated with hepatotoxicity. Hepatotoxicity caused by niacin has been described to have an onset of 1 week to 48 months.<sup>22</sup> This usually presents with elevated aminotransferase levels, but there are mixed reports of patterns of hepatocellular and cholestatic injury. Other effects include nausea and vomiting and a sharp decrease in serum lipid levels, which is reversible, with a recovery period of 1-2 months following discontinuation. Although fulminant hepatic failure is rare, hepatotoxicity is a concern with doses exceeding 2-3 g/day.

Niacin is available in many formulations: immediate-release (IR), extended-release (ER) and sustained-release (SR). Most formulations are available as OTC supplements that have not been reviewed by the FDA for safety and efficacy as agents for dyslipidemia, with only a few that have FDA approval.<sup>23</sup> Since IR products will quickly saturate the amidation pathway, most of the IR dose will be metabolized by the conjugative pathway such that the primary side effect will be flushing. In contrast, SR products slowly release niacin over time which is continuously metabolized by the amidation pathway, resulting in increased risk of hepatotoxicity. Thus, IR use is limited by extreme flushing while SR use is limited by risk of hepatotoxicity. Patients who take IR niacin products at therapeutic doses almost never experience hepatotoxicity, but half of those who take SR niacin will have elevated transaminases. Niaspan<sup>®</sup>, the only available ER product, seems to be equally metabolized by the two pathways such that it has relatively moderate levels of flushing and hepatotoxicity. In a clinical trial, only 5% of patients stopped therapy due to flushing and it has not been shown to cause an increase in aminotransferase levels at doses of 2 g/day or lower. This middle-of-the-road product is preferable, but currently, it is only available prescription-only.

## Food-Drug Interactions

### Recommendation

Due to the wide availability and range of niacin products on the market, any patient taking these products should be advised about the side effects specific to the formulation that they are taking. Patients might readily purchase OTC niacin products without knowledge of the risks of flushing and hepatotoxicity. Given the moderate side effect profile of Niaspan<sup>®</sup>, it would be the preferred niacin product; however, there may be an associated increase in cost. In addition to flushing and hepatotoxicity, niacin is known to cause hyperglycemia so caution must also be taken with diabetic patients. Pharmacists and physicians should monitor for these side effects and start with lower doses. With the recent results from clinical trials and hyperlipidemia guidelines, it is even debatable whether adding niacin is beneficial for decreasing clinical outcomes in patients with dyslipidemia.

### Fish Oil and Warfarin

Therapy with fish oil supplements is indicated for those with CAD and high-dose fish oil supplements are indicated for use in hypertriglyceridemia (AHA). Fish oils contain the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have potent anti-inflammatory effects stemming from their ability to inhibit cyclooxygenase, an essential enzyme required for the formation of prostaglandins and thromboxane.<sup>24</sup> Reducing inflammation, coupled with the inhibition of pro-atherosclerotic mediators<sup>25</sup>, likely account for EPA and DHA's potent plaque stabilization characteristics. These fatty acids are also believed to reduce triglyceride levels through numerous mechanisms including the modulation of nuclear transcription factors associated with lipogenesis.<sup>26</sup> Studies are underway to further elaborate on the benefits of omega-3 fatty acids on other conditions including rheumatoid arthritis, hypertension and depression.

### Interaction

A study by Shahar et al. regarding atherosclerosis risk and omega-3 fatty acids showed that fish oils may decrease fibrinogen, factor VIII, and Von Willebrand factor (vWF), as well as increase protein C.<sup>27</sup> Fish oil's possible interaction with platelets and clotting factors raises concern over their potential to increase bleeding risk in patients. This concern is further compounded when fish oils are taken by patients who are already on antiplatelets or anticoagulants, as this may lead to severe bleeding events. In addition to the additive anti-atherothrombotic actions of fish oils with warfarin, EPA and DHA may cause increased bleeding due to interactions that result in decreased platelet aggregation<sup>28</sup>, decreased platelet derived growth factor-like proteins<sup>29</sup>, and decreased platelet activating factor.<sup>30</sup> In fact, increases in baseline INR have been reported in patients who have significantly increased their

doses of fish oil to ~2g/day while taking warfarin.<sup>31</sup> One randomized-controlled trial that included 610 subjects showed no difference in bleeding in patients using high-dose (4g) fish oil therapy versus control.<sup>32</sup> The study also found no increase in bleeding time between the two groups, though it did acknowledge that investigation of larger doses may be warranted. The researchers also measured plasma beta-thromboglobulin levels among the participants, which increases with platelet activation, and found no difference between the study and control groups. Another randomized-controlled trial, which included patients on chronic warfarin therapy, showed no difference in lead-in INR and treatment INR among study groups.<sup>33</sup> As the participants were stratified into groups that received placebo, 3g fish oil, or 6g fish oil, no differences in INR were noted among the different groups. In this study, Bender et al. conclude that fish oil supplementation of up to 3-6g/day does not significantly affect the safety of patients taking warfarin.

### Recommendation

In spite of these studies, there is not enough definitive evidence that validates the relationship between the use of fish oils and increased bleeding time. So how are healthcare professionals to respond when faced with patients taking fish oil supplements along with their antithrombotic therapy? One proposed approach is to follow the guidelines that are applicable to other anticoagulants.<sup>34</sup> This entails the reduction of fish oil consumption or discontinuation of fish oils supplementations when the patient is suffering from acute bleeding illnesses like hemorrhagic stroke. Also, the discontinuation of fish oils before surgical procedures (to decrease the risk of bleeding) and restarting these therapies following major operations (for its antithrombotic effects) should be considered. For all cases, it is the duty of healthcare professionals to weigh the risks and benefits of fish oils in patients who are at increased risk for bleeding complications.

### Red Yeast Rice

Red yeast rice (RYR) has been consumed for thousands of years since its use as a food spice in Asia. It is prepared by fermenting rice with the mold *Monascus purpureus* (*M. purpureus*) under sterile and controlled conditions. The ultimate product contains starch, sugar, sterols, iso-flavones, pigments, fatty acids and, most notably, yeast polyketides.<sup>35</sup> These polyketides consist of monacolins that include monacolin K, a compound that is identical in structure to lovastatin, an HMG-CoA reductase inhibitor; hence there was a controversy over its status as an OTC product, since it contains an FDA regulated drug. In May 1998, the FDA took the stance that RYR supplements containing lovastatin are unapproved drugs.<sup>36</sup> This

was upheld by several courts and the FDA began enforcing this edict. Currently, labels of RYR products do not contain information on levels of lovastatin and many do not contain lovastatin at all. Those that do are considered illegal, as emphasized by a consumer warning issued in 2007.<sup>37</sup> The clinical efficacy of RYR products containing lovastatin has been demonstrated by several groups.<sup>38</sup> In addition to reducing total cholesterol and LDL levels, it decreases the frequency of major coronary events. Studies have found that RYR products containing 2-5 mg of lovastatin have similar efficacy to 20 mg of lovastatin.<sup>39</sup> This suggests that there are additive and/or synergistic effects of the various components of RYR such as isoflavonoids, monounsaturated fats, and sterols.<sup>38</sup> There is no specified role for RYR in updated hyperlipidemia guidelines,<sup>20</sup> and it is briefly mentioned as alternative or adjunct therapy in ESC/EAS guidelines.<sup>40</sup> Sales of RYR increased 80% between 2005 and 2008 to \$20 million,<sup>36</sup> making it vitally important for pharmacists to be aware of its uses and limitations.

### Interaction

Since RYR is defined as a dietary supplement, it is regulated by Current Good Manufacturing Practices (cGMP) published by the FDA.<sup>37</sup> These regulations not only require that companies produce products that are consistent, but also that they are not adulterated and correctly labeled. A few studies validating the contents of RYR products have been performed.

The first study conducted in 2001, analyzed nine proprietary Chinese RYR dietary supplements.<sup>41</sup> The amount of total monacolin K ranged widely from 0.15 to 3.37 mg/capsule. Moreover, they found citrinin, a compound that causes kidney failure in animals and genotoxic in cultured human lymphocytes at high doses, in seven of the nine samples. In 2010, Gordon et al. examined these and other indices of product purity.<sup>36</sup> Similar to previous findings, there was a wide variability in ingredients among the different products: total monocolins ranged from 0.31 to 11.15 mg/capsule, monocolin K was 0.10 to 10.09 mg/capsule, and monocolin KA was 0.00 to 2.30 mg/capsule. Put in terms of total daily dose following serving recommendations, this would be a range of 2.71 to 24.71 total monocolins. Four products had elevated levels of citrinin. The authors of the most recent study directly contacted the FDA regarding RYR oversight.<sup>37</sup> The FDA admitted to having no information on the number of RYR manufacturers or distributors, and also reported that they are not able to ensure whether these products are consistent with cGMP regulations. These researchers did not quantify the active ingredients in the products, but rather looked at their labeling. They found that only 43 of 70 products had statin-related warnings, and none of the 101 products had been confirmed to pass a verification test (i.e. USP, Consumer Labs, NSF, or NPA). Moreover, several were combination products with other lipid-lowering agents (e.g.

coenzyme-Q10, niacin and fish oil), vitamins (e.g. folic acid, vitamin B6, and vitamin B12), and dietary supplements.

In addition to the wide variability of ingredients in RYR products, there are many safety monitoring parameters that need to be considered. Relative to lovastatin, RYR extracts were found to inhibit all six CYP450 enzymes tested (CYP2B6, 2C9, 2C19, 3A4, 1A2 and 2D6) and P-glycoprotein (P-gp) to a greater extent,<sup>39</sup> so drug-drug interactions should be assessed. Although most trials have found RYR to be well-tolerated, cases of myopathy, rhabdomyolysis, hepatotoxicity, and anaphylaxis have also been reported.<sup>38, 40</sup> Furthermore, it is considered a pregnancy category X with documented fetal abnormalities and should be taken with caution in patients with renal/hepatic impairment. Lastly, since it is a yeast product, it should not be taken if the patient is allergic to yeast products.

### Recommendations

As with all supplements, great care should be taken in helping a patient select a RYR, especially given that there are numerous discrepancies and variability in content. Despite the FDA's prohibition on lovastatin-containing RYR products, they have done little to actually regulate and enforce this. Thus, pharmacists must be able to counsel patients inquiring about RYR, especially about its safety concerns. Quantity and quality may vary not only from manufacturer to manufacturer, but from batch to batch or even bottle to bottle as well. Patients should be cautioned against its use despite its proven efficacy, due to safety concerns of consuming unknown amounts of a FDA approved drug with known drug-drug interactions and side effects. If patients have untreated dyslipidemia and are self-medicating with RYR, they may be directed to other OTC products or supplements that do not contain an active drug ingredient. They should also be advised on non-pharmacological treatment options like lifestyle changes. The best thing an individual could do is speak with their physician about a cost-effective FDA regulated pharmacological therapy option, with monitoring for safety and counseling on its use.

### St. John's Wort and Statins

St. John's wort (*Hypericum perforatum*) is an OTC herbal supplement that is widely used in the U.S., and stands as the second best-selling herbal medicine product in the nation.<sup>43</sup> Although a meta-analysis of 29 trials concluded that St. John's wort extract was superior in treating depression versus placebo<sup>44</sup>, multiple randomized controlled trials have failed to show its efficacy as a treatment for depression.<sup>45,46</sup> The current American Psychiatric Association's guidelines

## Food-Drug Interactions

for treating major depressive disorder states that St. John's wort is not recommended for use in treating depression, due to the lack of evidence and regulation.<sup>47</sup> However, St. John's wort is still commonly being used by the U.S. population as an OTC self-treatment agent for depression.

St. John's wort contains an array of compounds that may contribute to its potential pharmacological activities, including two compounds: hyperforin and hypericin.<sup>48</sup> In particular, hyperforin has been identified as an inhibitor of several neurotransmitters including serotonin, norepinephrine, and dopamine.<sup>49</sup> However, St. John's wort also presents with it an increased risk of drug-drug interactions due to the enzyme-inducing properties associated with its natural compounds.<sup>50</sup> Such activity may decrease the serum drug levels of medications, thereby jeopardizing the therapeutic efficacy of many prescription medications. One possible interaction with St. John's wort that has been identified in trials is associated with HMG-CoA reductase inhibitors, also known as statins. As statins are one of the most dispensed prescription medications in the U.S.<sup>51</sup>, the prevalence of a drug interaction with popular natural products like St. John's wort is highly likely. In order to ensure the efficacy of treatment in patients with hyperlipidemia, an assessment for possible drug interactions is warranted in individuals who are taking statin medications.

### Interaction

St. John's wort is an inducer of both CYP3A4 and P-gp, which are involved in the metabolism of many drugs in the human body.<sup>52,53</sup> This induction may be explained by St. John's wort's role as a ligand for the nuclear pregnane X receptor (PXR). Activation of the PXR increases the expression of both P-gp and CYP3A4, so increased levels of St. John's wort induces the expression of P-gp and CYP3A4 in the human body.<sup>54</sup> Another source of interaction is the natural compound hyperforin, which has been identified as an inducer of CYP3A455, an enzyme that is responsible for metabolizing about 50% of all prescription medications on the market.<sup>50</sup>

Atorvastatin, simvastatin, and lovastatin have been identified as CYP3A4 substrates<sup>56</sup>, while atorvastatin and simvastatin are also substrates of P-gp.<sup>57</sup> Therefore, the concomitant use of St. John's wort with these statin medications leads to an increase in statin metabolism, resulting in diminished efficacy. Several studies have demonstrated the effect of this drug interaction. (Table 1)

One randomized, double-blind study showed that taking St. John's wort for 2 weeks prior to taking simvastatin resulted in a statistically significant decrease in the serum concentration and the AUC of active simvastatin metabolite.<sup>58</sup> Another randomized-controlled trial tested the significance of this interaction in 16 patients with hypercholesterolemia who were being treated with a stable dose of atorvastatin. When atorvastatin was taken daily with St. John's wort, statistically significant increases were observed in both the serum LDL and total cholesterol levels, representing a decreased efficacy

of clinical importance.<sup>53</sup> Another study featured 24 patients with hypercholesterolemia who were being treated with a stable dose of simvastatin. Similar to a previous study, concomitant use resulted in significantly increased levels of serum LDL and total cholesterol.<sup>59</sup>

Table 1. St. John's wort and its effect on antihyperlipidemic therapy

	Sugimoto et al. <sup>58</sup>	Andren et al. <sup>53</sup>	Eggertsen et al. <sup>59</sup>
<b>Demographics</b>	16 healthy volunteers	16 patients with hypercholesterolemia	24 patients with hypercholesterolemia
<b>Statin</b>	Simvastatin	Atorvastatin	Simvastatin
<b>Dose/frequency</b>	10mg x1 on day 14	10mg-40mg daily	10-40mg* daily
<b>SWJ dose/frequency</b>	300mg TID	300mg BID	300mg BID
<b>Duration</b>	14 days	4 weeks	4 weeks
<b>Effect</b>	Decreased serum simvastatin active metabolite Decreased AUC (metabolite)	Increased LDL (p=0.004) Increased total cholesterol (p=0.02)	Increased LDL (p<0.0001) Increased total cholesterol (p<0.0001) Increased triglycerides in females (p=0.036)

\*Indicates the stable dose of medication each patient was originally being treated with.

The increased levels of LDL and total cholesterol demonstrated in these studies have a direct influence on the clinical outcomes of patients who are on statin medications. Excess LDL circulating in the blood can get oxidized and turn into foam cells, eventually turning into atherosclerotic plaques.<sup>60</sup> Increased plasma concentration of oxidized LDL has also been associated with increased risk of chronic heart disease.<sup>61</sup> The inadequate control of total cholesterol and LDL levels in hyperlipidemic patients using St. John's wort and statins may lead to potentially life-threatening clinical outcomes associated with the increased risk of cardiovascular disease.

### Recommendations

St. John's wort is a popular OTC supplement which is widely used as an alternative treatment option for depression. However, it poses risks of numerous drug-drug interactions as an inducer of many drug-metabolizing pathways in the human body. A pharmacist should educate patients about the lack of consistent evidence for the efficacy of St. John's wort, and APA guideline recommendations against its use as a general treatment for treating depression.

Every patient who is on simvastatin, atorvastatin, or lovastatin must be screened for the use of St. John's wort. When a concomitant use is identified, the patient must be educated about the potential drug interactions associated with this supplement, including the potential decrease in the control of hyperlipidemia. Because it is difficult to detect the diminished efficacy of statin medication in a short-term period, it is important for patients to be aware of this interaction. The patient should also be encouraged to engage in an active conversation with the physician about the efficacy of the statin treatment, with a possible in-

crease in the dose of the statin medication or the initiation of a new antidepressant.

**Grapefruit Juice and Statins**

While the concomitant use of two different drugs can result in adverse events due to drug-drug interactions, consuming certain food products while taking a medication can also influence the pharmacokinetics of drugs and ultimately affect the clinical efficacy of the medication. Grapefruit juice is a product that has numerous food-drug interactions, including calcium channel blockers, CNS modulators, and statins. Although no single constituent has been identified as the cause of these interactions, grapefruit juice contains many naturally-occurring compounds such as flavonoids and furanocoumarins which have been found to have inhibitory effects on CYP3A4 and P-gp.<sup>56</sup> The concurrent intake of statins with substances that inhibit metabolic enzymes has been shown to increase statin serum concentration levels, which may increase the risk of undesirable side effects such as rhabdomyolysis or renal failure.

According to the new 2013 ACC/AHA guidelines, statins are recommended as the primary pharmaceutical therapy for treatment of blood cholesterol to reduce the risk of ASCVD.<sup>20</sup> The Centers for Disease Control and Prevention’s report on prescription drug use revealed that the use of antihyperlipidemic medications in the U.S. doubled between 1999 and 2010.<sup>62</sup> The trend in increased use of statins is most likely to continue since the new ACC/AHA guidelines greatly expanded the criteria for statin use. As grapefruit juice and grapefruit are common foods that are widely consumed by the public, assessment for possible food-drug interactions is warranted for patients who are taking statin medications.

**Interaction**

Several statin medications such as atorvastatin, lovastatin, and simvastatin are metabolized through the CYP3A4 enzyme.<sup>56</sup> This predisposes patients that use these medications to possible drug interactions when used concomitantly with agents that inhibit or induce CYP3A4. Pravastatin, fluvastatin, pitavastatin and rosuvastatin have been shown to be metabolized by CYP3A4 at a lesser degree<sup>63</sup>, decreasing the possible risk for interactions with substances that affect CYP3A4. As demonstrated by several randomized controlled studies, grapefruit juice is one such substance that inhibits CYP3A4 in the small intestine<sup>64</sup> and increases the plasma concentration of statins with concomitant use. (Table 2)

The daily consumption of double-strength grapefruit juice prior to initiating statin medications has been shown to produce a statistically significant increase in the area under the plasma concentration-time curve (AUC) and the peak serum concentration (Cmax) of simvastatin,

atorvastatin, and their active metabolites.<sup>65,66,67</sup> Similar results occurred in studies that used regular strength grapefruit juice.<sup>68,69</sup> However, trials that demonstrated increased serum statin levels were mostly conducted with healthy, male volunteers and not patients who were already taking statin medications for hyperlipidemia. (Table 2) Therefore, the data is not representative of the actual population of patients who are at risk of potential adverse events associated with prolonged statin use.

Table 2. Effect of grapefruit juice consumption on serum statin concentration

	Kantola et al. <sup>65</sup>	Lilja et al. <sup>66</sup>	Lilja et al. <sup>67</sup>	Lilja et al. <sup>68</sup>	Fukazawa et al. <sup>69</sup>	Ando et al. <sup>70</sup>
<b>Demographics</b>	10 healthy volunteers	10 healthy volunteers	12 healthy volunteers	10 healthy volunteers	20 healthy volunteers	8 healthy volunteers
<b>Statin</b>	Lovastatin	Simvastatin	Atorvastatin	Simvastatin	Atorvastatin	Atorvastatin
<b>Dose</b>	80mg x1 on day 3	60mg x1 on day 3	40mg x1 on day 3	40mgX1 on day 3	10mg x1 on day 3	20mg daily
<b>GFJ dose/freq</b>	DS 200mL TID	DS 200mL TID	DS 200mL TID	RS 200 mL daily	RS 250mL TID	RS 250mL TID
<b>Duration</b>	3 days	3 days	3days	3 days	3 days	4 days
<b>Effect</b>	Increased Cmax, AUC	Increased Cmax, AUC	Increased AUC, Cmax(metabolite)	Increased Cmax, AUC	Increased AUC, Cmax (metabolite)	Increased AUC

While increased blood level of statins may possibly result in an increased risk of myopathy<sup>71</sup>, it is unclear whether a linear relationship exists between the changes in plasma concentration of statins and the risk of adverse events.<sup>72</sup> Multiple variables influence the risk of such adverse events, such as the rapid change in drug concentration, use of other lipid-lowering therapy, and genetic factors.<sup>73</sup> In fact, while one study utilizing daily doses of atorvastatin and grapefruit juice showed an increase in AUC of the drug, a wide variation in the AUC of atorvastatin was also present among the individuals in the control group that had consumed water instead of grapefruit juice.<sup>70</sup> The polymorphisms in CYP enzymes and transporters may produce inherent differences in each individual’s ability to metabolize statins<sup>74</sup> and may account for the varying response and efficacy of statins in different patients. Nevertheless, an analysis of FDA Adverse Event reports show that about 55% of all statin-associated rhabdomyolysis are suspected to be the result of drug-drug interactions<sup>75</sup> and multiple cases of rhabdomyolysis have been reported in patients who regularly consumed grapefruits or grapefruit juice while they were on statin medications.<sup>76,77,78</sup> Although it is not possible to know the exact clinical consequence in each patient taking statins and grapefruit juice, there is a definite risk of potentially harmful interactions with the concomitant use.

**Recommendations**

In order to ensure the safety of patients taking statin medications, each patient should be educated about the possible drug interactions of statins and the risk of potentially serious complications that could arise as a result of the interactions, such as rhabdomyolysis. Before



dispensing the medication, a pharmacist should screen the patient's profile for possible drug-drug interactions and talk to the patient about the possible risk of drug-food interactions. For patients taking simvastatin, atorvastatin, or lovastatin, the pharmacist should ask the patient about grapefruit or grapefruit juice consumption, and educate the patient about the possible adverse events associated with this interaction. In order to eliminate the risk of a possible adverse event, it may be advisable to discourage the concomitant use of these medications with grapefruit juice. Consuming large amounts of grapefruit juice (more than a quart per day) while on these medications should be discouraged in these patients.<sup>79</sup> Statin medications that do not confer the risk of this interaction and thus could be considered as alternative treatment options include pravastatin, fluvastatin, and rosuvastatin.<sup>80</sup>

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ACPE UAN#: 0100-0000-14-070-H01-P  
0100-0000-14-070-H01-T



## CONTINUING EDUCATION QUIZ QUESTIONS

### I. Anemia and the Role of the Pharmacist

ACPE UAN# 0100-0000-14-069-H01-P / 0100-0000-14-069-H01-T

- Which of the following is not typically a sign or symptom of chronic anemia?
  - Weakness
  - Tachycardia
  - Headache
  - Cold sensitivity
- Which medication does not decrease the absorption of oral iron products?
  - Levothyroxine
  - Antacids
  - Cholestyramine
  - Proton pump inhibitors
- Which of the following is true regarding vitamin B12 deficiency?
  - Oral therapy is not preferred due to only 10% absorption
  - Pernicious anemia, a form of B12 deficiency, is characterized by high values of intrinsic factor
  - Replacement therapy is rarely long term, with the issue usually resolving in 3-6 weeks
  - Though a serious outcome, neurological symptoms often resolve within a few days of treatment if treated early on
- Which oral iron product contains the highest percent of elemental iron?
  - Ferrous gluconate
  - Ferrous sulfate
  - Ferrous fumarate
  - Polysaccharide-iron complex
- Which food is/are a good source of vitamin B12?
  - Meat
  - Fish
  - Eggs
  - Dairy
  - All of the above
- What is the most common side effect of oral iron therapy?
  - Headache
  - Nausea
  - Rash
  - Joint pain
- If a patient experiences the side effect describe above (#6) what is the best way to try to prevent further complications?
  - Discontinue oral therapy
  - Instruct the patient to take the tablets in one daily dose
  - Recommend the patient takes antacids
  - Recommend the patient try taking the tablets with orange juice
- True or False: Intravenous iron sucrose is FDA approved for the treatment of iron-deficiency anemia
- Which of the following statements about folate deficiency is false?
  - Laboratory evaluations will include a low MCV
  - Alcoholism is a risk factor
  - Green leafy vegetables are a good source of folate
  - Irritability and memory impairment can be symptoms

Use the following patient case for questions 10-12:

TD is a 69 year-old female who presents with dyspnea on exertion, intermittent chest pain, cough and fatigue. Her lab values at this time are as follows:

CBC	Iron Studies	Other
Hgb 8g/dL	Serum iron 9mcg/L	MCV 72 fL/cell
Hct 26.0%	Ferritin 1 ng/mL	Reticulocyte count 3.3%
RBC 3.94 x 10 <sup>6</sup> uL	TIBC 490 mcg/dL	Vitamin B <sub>12</sub> 440 pg/mL
	TSAT 2%	Folic acid 6.4 mcg/L

- What type of anemia do these lab values indicate?
  - Iron deficiency anemia
  - Vitamin B12 deficiency anemia
  - Folate deficiency anemia
  - Pernicious anemia
- Which of the following would be an appropriate treatment for TD's condition?
  - Vitamin B12 1000mcg PO daily
  - Ferrous gluconate 300mg PO daily
  - Folic acid 0.4mg IM daily
  - Ferrous sulfate 300mg PO TID
- Which of the following statements is false regarding TD's therapy?
  - Taking her medication with orange juice will increase its absorption
  - It is expected that TD's Hgb should increase by 5g/ dL per week
  - TD may experience dark stools
  - Eating meat and beans could help aid in her treatment

### II. A Review of Common Drug-drug and Food-drug Interactions Associated with Cardiovascular Medications

ACPE UAN# 0100-0000-14-070-H01-P / 0100-0000-14-070-H01-T

- What is the concern regarding concomitant use of PPIs and clopidogrel?
  - PPIs and clopidogrel present a duplication of therapy
  - PPIs may inhibit the activation of clopidogrel causing increased CV risks
  - PPIs may cause increased hepatic elimination of clopidogrel causing increased CV risks
  - Toxic accumulation of PPIs may occur because clopidogrel are also metabolized by CYP2C19.
- Which of the following medications used for the regulation of gastric acid production presents the most concern when used with antiplatelet agents like clopidogrel?
  - Omeprazole
  - Pantoprazole
  - Ranitidine
  - Famotidine
- An elderly patient with a history of GI bleed presents to the pharmacy to refill his Plavix. He has a history of CVD and just underwent surgery for placement of a coronary stent a week ago. You notice that he is taking Plavix with aspirin, as well as pantoprazole for bleeding prophylaxis. Your response should be:
  - Consult the prescribing physician, as you should with every case taking PPIs and dual-antiplatelet therapy
  - Advise the patient to space out the dosing of his PPI, at least 4 hours apart from his antiplatelet medications
  - Call the hospital. The patient is at high risk of a sudden CV event
  - Refill the Plavix because PPIs are indicated in this patient based on his risk for GI bleed.

## CONTINUING EDUCATION QUIZ QUESTIONS CONTINUED

### A Review of Common Drug-drug and Food-drug Interactions Associated with Cardiovascular Medications

ACPE UAN# 0100-0000-14-070-H01-P / 0100-0000-14-070-H01-T

4. Which of the following contributes to the concern over fish oil supplementation in conjunction with warfarin therapy?

- a. The cost of fish oil supplementation and warfarin therapy would be excessive
- b. Fish oils would inhibit the effects of warfarin therapy
- c. Omega-3 fatty acids may decrease fibrinogen, factor VIII, and Von Willebrand factor (vWF), which may increase risk of bleeding
- d. Omega-3 fatty acids may decrease protein C, which may increase risk of bleeding

5. Fish oils show benefit in reducing atherosclerosis because of their ability to

- a. Inhibit cyclooxygenase
- b. Increase prostaglandins and thromboxane
- c. Decrease platelet aggregation
- d. Modulate nuclear transcription factors

6. Patient YL has been recently discharged from the hospital following valve reconstruction surgery. She would like to continue taking her fish oil supplements for her high triglyceride levels. How would you respond to her?

- a. She can no longer take her fish oil supplements due to its ability to increase bleeding risk
- b. She can no longer take her fish oil supplements because they will no longer be effective
- c. She no longer needs fish oil supplementation because she had major heart surgery
- d. She can restart her fish oil supplements once she is cleared by her physician

7. What is the possible explanation for the drug interaction between statin drugs and grapefruit juice?

- a. Grapefruit juice is an inducer of the enzyme that metabolizes statins
- b. Grapefruit juice worsens hyperlipidemia in patients taking statin medications
- c. Grapefruit juice is an inhibitor of the enzyme that metabolizes certain statins.
- d. Grapefruit juice is an inhibitor of the enzyme that metabolizes all statins.

8. Mrs. Jones is a 55 year-old female who was prescribed a new drug regimen for her

hyperlipidemia. (Simvastatin 20mg PO daily). However, after watching Dr. Oz talk about drug side effects on TV last night, she is hesitant to take her medication and asks for your opinion. What would you tell her?

- a. Statins are known to be safe medications with no significant drug interactions
- b. Statins are associated with side effects involving muscle pain and disorder
- c. Drinking large quantities of grapefruit juice regularly while on this medication could result in a rare but serious muscle disorder
- d. B and C

9. According to new hyperlipidemia guidelines, niacin would be recommended to treat hyperlipidemia for which of the following patient populations?

- a. First-line for a patient newly diagnosed with dyslipidemia
- b. With elevated non-HDL-C and at target LDL-C to reduce ASCVD outcomes
- c. With high-risk and intolerant to statin therapy
- d. Not recommended given the lack of support in clinical trials

10. Which statement is correct about niacin formulations?

- a. IR products are associated with hepatotoxicity
- b. Niaspan is the only FDA approved ER product and has relatively moderate risks of hepatotoxicity and flushing
- c. SR products are associated with flushing
- d. All formulations (IR, SR, and ER) are available OTC.

11. RYR is a dietary supplement that

- a. Is actively regulated by the FDA because it contains a FDA regulated drug
- b. Is considered to be illegally marketed if it contains monacolin K
- c. Has been found to have consistent levels of active ingredients
- d. Is recommended as an alternative or adjunct therapy in updated hyperlipidemia guidelines.

12. A woman approaches you stating she heard RYR is a natural product that

could help with her cholesterol. She is currently not taking anything for hyperlipidemia due to finances. What should be a justified recommendation?

- a. Yes, take RYR because it contains a FDA regulated drug used for hyperlipidemia
- b. Yes, take RYR but only purchase a product with consistent levels of monacolin K
- c. No, do not take RYR because it has not been shown to be effective
- d. No, taking RYR is not recommended due to quality concerns as well as safety concerns

13. Mrs. Young is a 50-year old female who is taking Atorvastatin 20mg PO daily for hyperlipidemia. After talking to her, you discover that she is also taking a daily dose of St. John's wort 600mg for depression. What is (are) the appropriate counseling point(s) for Mrs. Young?

- a. St. John's wort is a safe and effective, FDA-approved treatment for depressive disorders
- b. There is a risk of potentially harmful drug interaction if atorvastatin is used with St. John's wort
- c. St. John's wort may decrease the efficacy of atorvastatin
- d. B and C.

14. What is the possible explanation for the interaction between St. John's wort and Statin drugs?

- a. St. John's wort is an inducer of CYP3A4 and P-gp
- b. St. John's wort is a competitive inhibitor of statin drugs
- c. St. John's wort is an inhibitor of CYP3A4 and P-gp
- d. Statins enhance the therapeutic effect of St. John's wort

15. What is a possible adverse drug event associated with the consumption of large quantities of grapefruit juice on statin therapy?

- a. Rhabdomyolysis
- b. Stevens-Johnson Syndrome
- c. Reye Syndrome
- d. Acute pancreatitis