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### Authors

Tarn, Derjung M  
Barrientos, Maureen  
Wang, Angel Y  
[et al.](#)

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**Prevalence and Knowledge of Potential Interactions between Over-the-Counter Products  
and Apixaban**

Running Title: OTC Product-Apixaban Interactions

Derjung M. Tarn, MD, PhD<sup>1</sup>

Maureen Barrientos, BA<sup>2</sup>

Angel Y. Wang, BA<sup>3</sup>

Abhijit Ramaprasad<sup>3</sup>

Margaret C. Fang, MD, MPH<sup>4</sup>

Janice B. Schwartz, MD<sup>2,5</sup>

<sup>1</sup> Department of Family Medicine, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, USA

<sup>2</sup> Division of Geriatrics, University of California, San Francisco, San Francisco, CA, USA

<sup>3</sup> University of Chicago, Chicago, IL, USA

<sup>4</sup> Division of Hospital Medicine, University of California, San Francisco, San Francisco, CA, USA

<sup>5</sup> Division of Clinical Pharmacology, Departments of Medicine and Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA, USA

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**Corresponding author:**

Derjung Mimi Tarn, MD, PhD

David Geffen School of Medicine at UCLA, Department of Family Medicine, 10880 Wilshire Blvd., Suite 1800, Los Angeles, CA 90024

[dtarn@mednet.ucla.edu](mailto:dtarn@mednet.ucla.edu)

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## **ABSTRACT**

**Background:** Direct-acting oral anticoagulants (DOACs) such as apixaban are the most commonly prescribed anticoagulants, with advantages in that they do not require routine monitoring. However, less frequent contact with health care professionals may contribute to poor patient knowledge about potential interactions between over-the-counter (OTC) products and DOACs.

**Objective:** Determine the prevalence of OTC product (OTC medications and dietary supplements) use with potentially serious apixaban interactions and assess patient knowledge of potential interactions.

**Design:** Cross-sectional survey.

**Setting:** Academic-affiliated outpatient medical practices in Northern and Southern California.

**Participants:** 791 English- or Spanish-speaking patients prescribed apixaban.

**Measurements:** Use and knowledge of OTC medications and dietary supplements with potentially serious apixaban interactions.

**Results:** Almost all respondents (n=771; 97.5%) reported OTC product use. Thirty-three percent (n=266) took at least 1 OTC product with potentially serious apixaban interactions daily/on most days and 53 (6.7%) took multiple products (mean=2.6 [SD=2.6]). Aspirin was taken daily/most days by 119 (15%; of which 64.7% also consumed other potentially interacting OTC products); on some days by an additional 82 (10.4%). Ibuprofen and naproxen were taken daily/most days by 14 (1.8%) and some days by 225 (28.5%). Dietary supplements with potentially serious

interactions were taken daily/most days by 160 (20.2%). About 66% of respondents were either uncertain or incorrect about the potential for increased bleeding from combining NSAIDs and apixaban. Greater knowledge about OTC products with potentially serious interactions was associated with lower OTC product use (OR=0.54; 95% CI 0.35-0.85).

**Conclusion:** Significant numbers of patients take OTC products (particularly dietary supplements) with potentially serious interactions with the DOAC apixaban, and appear to lack knowledge about potentially harmful interactions. Interventions are needed to educate patients and healthcare providers about potential dangers of taking interacting OTC products in combination with apixaban and data are needed on outcomes associated with concomitant apixaban-OTC product use.

**Keywords:** anticoagulants, apixaban, over-the-counter drugs, dietary supplements, patient medication knowledge

## INTRODUCTION

Direct acting oral anticoagulants (DOACs) are now the anticoagulants of choice for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) without mechanical valves or severe mitral valve, renal, or liver disease, and are replacing warfarin for treatment of venous thromboembolic disease in patients without cancer.<sup>1,2</sup> (DOACs) have fewer food interactions, simplified dosing and monitoring regimens, and lower rates of intracranial hemorrhages compared to warfarin. DOACs also have fewer medication interactions primarily limited to potent combined P-glycoprotein (P-gp) and cytochrome p-4503A4 (CYP3A4) inhibitors (azoles, clarithromycin and selected anti-retroviral agents) or inducers (carbamazepine, phenytoin, rifabutin, rifampin, ritonavir, St Johns wort) that might alter DOAC concentrations (Table 1). Antiplatelet agents or dietary supplements with anti-platelet activity) can increase bleeding risk (Table 1).<sup>1,3-6</sup>

The vast majority of patients receiving DOACs are not followed in specialized anticoagulation clinics or at monthly intervals by health care professionals. While less frequent monitoring and fewer healthcare professional visits may benefit patients, it may also result in decreased patient education and knowledge regarding interactions between anticoagulants and over-the-counter (OTC) medications or dietary supplements.

OTC products can be bought by patients without a prescription, and consist of: 1) OTC medications and 2) dietary supplements (vitamins, minerals, herbs or other botanicals, amino acids, or other substances used to supplement the diet).<sup>7</sup> It is known that one-third of patients taking warfarin consume non-vitamin non-mineral dietary supplements with reported warfarin interactions.<sup>8</sup> As DOACs replace warfarin for anticoagulation, it is likely that a significant

fraction of DOAC patients also consume OTC products, but specific knowledge about patterns of over-the-counter (OTC) use is lacking.

Our goal was to determine the prevalence of use of OTC medications and dietary supplements with potentially serious interactions with apixaban, one of the most frequently prescribed DOACs,<sup>9, 10</sup> and to assess patient knowledge of potentially serious OTC product-apixaban interactions.

## **METHODS**

Study procedures were approved by the University of California, Los Angeles' Institutional Review Board (IRB), with the University of California, San Francisco relying on UCLA's IRB through the UC IRB Reliance Registry. Eligible patients were identified via data extractions by the UCLA and UCSF Clinical & Translational Science Institutes from the UCLA Integrated Clinical and Research Data Repository (xDR / Electronic Health Record) and UCSF electronic medical record systems. Data extractions generated lists of English and Spanish-speaking outpatients aged 18 years and older receiving at least one prescription for apixaban at UCLA (from January 1, 2017 – January 31, 2018) or UCSF (from August 2016-February, 2017 and June 1, 2017-May 30, 2018).

The survey was conducted from April to October 2018. All patients identified through database searches with an email address on file received electronic invitations to complete a one-time survey. Those without email addresses were mailed invitations via postal mail. All patients were given the opportunity to opt-out of participation. Those who did not opt-out were mailed a paper copy of the survey with a postage-paid return envelope or emailed a link to an online

REDCap survey. REDCap (Research Electronic Data Capture) is a secure, HIPAA-compliant, web-based system for building and managing web-based research projects such as surveys and databases.<sup>11</sup>

Respondents completed an eligibility screen. We surveyed patients who reported taking apixaban for more than one month, and who noted no problems in the past 12 months with “memory or thinking that interferes with your ability to do things you regularly do such as taking care of your home, managing your finances, or keeping up with TV programs.”<sup>12</sup> Participants received a \$10 gift card for completing the survey.

### **Survey instrument**

The English-language survey was translated into Spanish using forward and back translation. Cognitive testing of the survey was conducted in both English and Spanish. The survey questioned patients about how often they took a list of 3 OTC medications (aspirin, ibuprofen/naproxen (NSAIDs), acetaminophen) and 13 common dietary supplements (Gingko biloba, Chinese herbs excluding Gingko biloba, fish oil / omega-3 fatty acids / cod liver oil, flaxseed, ginger, herbal teas, melatonin, saw palmetto, St. John’s Wort, turmeric, multivitamin, vitamin D and/or calcium, and vitamin E) “while on Eliquis (apixaban)” (daily, most days, some days, as needed, never). Patients used their own discretion when selecting frequency of use; categories were not further specified. Patients also were asked to write in the names of other dietary supplements taken that were not listed. The survey queried patient knowledge about whether or not they “might bleed more easily” if they took apixaban with the following OTC products: aspirin, ibuprofen or naproxen, acetaminophen, or St. John’s Wort (5-point Likert scale responses, ranging from “strongly disagree” to “strongly agree”).

Patients were also asked if they talked to a healthcare provider about whether it was okay to take an OTC product with apixaban (yes/no), and if yes, who they spoke to (doctor, pharmacist, nurse, other healthcare provider). Other questions asked about demographics (age, sex, race/ethnicity, education level), number of prescription medications taken, self-rated health (5-point Likert scale), prior warfarin use (yes/no), and health literacy (confidence in filling out medical forms; assessed on 5-point Likert scale<sup>13-15</sup>).

The initial survey did not ask about knowledge regarding potential interactions between apixaban and Chinese herbs, ginger, ginkgo biloba, herbal tea, or turmeric, as these are not listed as interacting substances in the product label.<sup>16</sup> Since these products can have potentially serious interactions with apixaban,<sup>17, 18</sup> we subsequently surveyed respondents who reported taking at least one of these products ‘every day’ or ‘most days’ about whether they “might bleed more easily” if they took the product(s) they were on with apixaban (5-point Likert scale responses, ranging from “strongly disagree” to “strongly agree”).

#### **Classification of OTC products for potentially serious interactions with apixaban.**

OTC medications and dietary supplements with potentially serious interactions with apixaban were identified from: the approved product package insert,<sup>16</sup> the reference database Lexicomp<sup>17</sup> and the Natural Medicines database (the most authoritative resource available on dietary supplements,<sup>18</sup>) where products are classified as: avoid, consider therapy modification, monitor, or no interactions (Table 1). Concordance between two sources was used to classify agents into categories of potentially clinically relevant (serious) interactions: avoid (St. John’s wort) and consider therapy modification (changing one of the treatments) (aspirin, ibuprofen or naproxen, Chinese herbs, herbal teas, ginger, ginkgo biloba, and turmeric).<sup>17, 18</sup>



## **Knowledge Scores**

Mean knowledge scores were generated to describe patient knowledge about interactions between apixaban and aspirin, NSAIDS, acetaminophen, St. John's Wort. Knowledge scores ranged from -1 to 1, with higher scores indicating more accurate knowledge; patients received a score of : +1 if they "strongly agreed" or "agreed" that the OTC product might make them bleed more easily if taken with apixaban; 0 if they were "uncertain;" and -1 if they "strongly disagreed" or "disagreed." Scoring for knowledge about acetaminophen was reversed, with higher scores indicating that patients disagreed that potential interactions existed. Scores for the individual products were summed and divided by the number of products for which patients provided responses. Sensitivity analyses examined mean knowledge scores that included and excluded knowledge about acetaminophen, which does not interact with apixaban.

## **Data analysis.**

STATA 16.0 (StataCorp, LLC) was used for all analyses. Data are presented as means and standard deviations, frequencies, or percentages.

## **Knowledge, use of OTC products, and knowledge source.**

Unpaired t-tests were used to evaluate relationships between mean knowledge scores and regular (daily/most days) use of any OTC products with potentially serious interactions with apixaban (aspirin, NSAIDS, St. John's Wort, Chinese herbs, herbal teas, ginger, ginkgo biloba, turmeric) (yes/no). Frequencies with which patients reported seeking information from healthcare providers were tabulated. T-tests were used to examine relationships between patient knowledge about potential OTC product-apixaban interactions and: 1) discussions with

healthcare providers about whether it was okay to take an OTC product with apixaban; and 2) prior warfarin use.

### **Multivariable Analyses**

Multivariable models using multiple logistic regression evaluated regular use (daily/most days) of: 1) aspirin, ibuprofen or naproxen; 2) dietary supplements; and 3) any OTC product with potentially serious interactions with apixaban (yes/no); as primary outcome variables, with the mean knowledge score as the primary predictor. We adjusted for other predictors including: patient age; gender; race/ethnicity; health literacy; total number of prescription medications taken; and prior history of warfarin use (yes/no). Sensitivity analyses examined the mean knowledge score without acetaminophen.

## **RESULTS**

### **Patient and prescription medication use characteristics.**

Participation invitations were distributed to 4006 outpatients (UCLA n=2006; UCSF n=2000). Of 1343 respondents, 55 opted-out of participation, and 518 were excluded because they were ineligible (deceased, no longer taking apixaban, had taken it for less than 1 month, or failed the cognitive screening), giving an eligibility rate of 59.8%. Data from two additional patients were excluded due to incomplete responses to OTC product use questions. A total of 791 patients completed the survey. Applying the eligibility rate to patients for whom we were unable to assess eligibility ( $n=4006-518-793=2695$ ) the net response rate was 33% ( $793/(793+[0.598 \times 2695])$ ). Almost 60% of the respondents were male, 75.3% were white, and the mean age was 71 years (SD=11.8) (Table 2). Almost all had at least some college education. Seventy-eight

percent of the patients took apixaban for non-valvular atrial fibrillation, 22.8% for blood clots, and 10.8% for stroke (some had more than one indication). Most had been on apixaban for more than 12 months, and 34.8% had previously been on warfarin.

### **Dietary supplement use**

Daily or most days use of dietary supplements was reported by 618 patients (78.1%). The most common dietary supplements taken daily or on most days were vitamin D and/or calcium (n=421; 53.2%), followed by multivitamins (n=310; 39.2%). Other commonly used supplements were fish oil / omega-3 fatty acids / cod liver oil (n=176; 22.3%); B vitamins (n=100; 12.6%); vitamin E (n=82; 10.4%); vitamin C (n=59; 7.5%); magnesium, melatonin, and other herbal supplements (each with n=48; 6.1%); and coenzyme Q10 (n=41; 5.2%). All other dietary supplements were taken by fewer than 5% of respondents. The majority of patients n=709 (89.6%) reported at least occasional use of one or more dietary supplements; 618 (78.1%) reported daily use of at least one dietary supplement.

The most commonly taken dietary supplements with potential apixaban interactions of increased bleeding were herbal teas<sup>19, 20</sup> (n=88; 11.1%) and turmeric<sup>21-24</sup> (n=71; 9%) (Figure 1). Chinese herbs, ginger, ginkgo biloba were used in fewer than 5% of respondents. Use of St. John's Wort was rare (<1%).

### **Aspirin and NSAID use**

Aspirin was taken daily by 116 (14.7%) patients. For 41 of the 116 daily aspirin users, aspirin was the only potentially serious interacting OTC product that they consumed (5.2% of the total sample). Twenty (17.2%) of daily aspirin users took at least one other OTC product with

potentially serious interactions in combination with apixaban (either dietary supplements or NSAIDs) daily or most days. An additional 58 or 50% of daily aspirin users took apixaban in combination with another OTC product that increases bleeding risk some of the time or as needed. In total, 75 (64.7%) of daily aspirin users taking apixaban also at least occasionally consumed OTC products that are known to increase the risk of bleeding. Few took ibuprofen/naproxen daily (n=5; 0.6%) or most days (n=1.1%), but 25 (3.2%) used them on some days and 200 (25.4%) as needed. Most people took acetaminophen as needed (n=403; 51.1%) or not at all (n=268; 34%).

#### **Overall Use of OTC products (OTC medications and dietary supplements) with potentially serious interactions with apixaban.**

One-third (n=266) of the respondents reported taking at least one OTC product with potentially serious interactions with apixaban either daily or most days. Two hundred and thirteen (27%) took only one product daily or most days; of these 95 (44.6%) took only aspirin. Forty-one (5.2%) took 2 OTC products daily or most days, 11 (1.4%) took 3, and 1 (0.13%) took 4. An additional 215 (27.2%) took an OTC product with potentially serious apixaban interactions some days or as needed.

#### **Knowledge about apixaban and potential apixaban-OTC product interactions**

Patients who regularly (daily or most days) took any OTC product with potentially serious interactions with apixaban were less knowledgeable about potential OTC interactions than those not taking one regularly (p<0.01). Of all surveyed patients, 71% recognized that potential bleeding might occur with concurrent aspirin use, whereas only about half responded

correctly to questions about potential interactions between apixaban and NSAIDs or acetaminophen. Two-thirds of respondents were either uncertain or incorrect about the potential increased bleeding risk with combined NSAIDs and apixaban.

Knowledge regarding interactions of aspirin with apixaban was significantly better in non-regular aspirin users than in regular users (74% compared to 55.5% with accurate knowledge;  $p < 0.001$ ), but 22 to 29% of each group were uncertain of whether aspirin increased bleeding risk (Figure 2). Differences in knowledge between regular NSAID users and non-regular users were similar to that for aspirin with more non-regular users aware of the interaction compared to regular users (46% versus 28%, respectively;  $p = 0.01$ ) (Figure 2).

Of respondents taking St. John's Wort, 10.5% incorrectly believed there was a potential increased risk of bleeding if it was combined with apixaban (the interaction results in decreased apixaban concentrations and potentially increases stroke risk), 79.8% were uncertain if there was an interaction and 9.7% believed there was no interaction. We asked 61 of 83 participants who were regularly taking Chinese herbs, ginger, ginkgo biloba, herbal teas, or turmeric (dietary supplements with potentially serious interactions with apixaban) about whether the product(s) they were taking might lead them to bleed more easily when taken with apixaban. Only 3 participants agreed that herbal teas might interact with apixaban, and 3 agreed that turmeric might interact. All others were either unsure, disagreed, or strongly disagreed that potential interactions might occur. No significant differences in knowledge were detected in patients reporting prior warfarin use compared to those without prior warfarin use.

### **Healthcare Professional Discussions regarding Potential OTC Product-Apixaban**

#### **Interactions.**

Two-thirds of the respondents reported talking to a health care professional(s) about whether it was okay to take an OTC with apixaban; 93% spoke with physicians, 46% with pharmacists, 16.4% with nurses, and 5% with other health care professionals. Those who reported discussing OTC products with healthcare providers were significantly more knowledgeable about potential interactions with NSAIDs than those who did not ( $p < 0.001$ ), but there were no significant differences in knowledge about potential interactions with aspirin, St. John's Wort, or fish oil.

### **Relationship of Knowledge on Use of OTC Products with Potentially Serious Apixaban Interactions**

Multivariable analyses revealed that regular use of aspirin and NSAIDs occurred significantly more often when respondents were less knowledgeable about whether or not there were potential interactions between apixaban and aspirin, NSAIDs, St. John's Wort, or acetaminophen (OR 0.18; 95% CI=0.10-0.32), and when they were female (OR 0.37; 95% CI=0.23-0.60). Greater health literacy (OR 1.37; 95% CI=1.07-1.74), previous warfarin use (OR 1.61; 95% CI=1.06-2.44), and more prescription medication use (OR 1.12; 95% CI=1.05-1.20) were negatively associated with regular aspirin and NSAID use. Regular use of dietary supplements was not associated with knowledge about potential interactions. The only characteristic significantly associated with regular use of all assessed OTC products with potentially serious apixaban interactions was less knowledge about whether or not there were potential interactions between apixaban and aspirin, NSAIDs, St. John's Wort, and acetaminophen (OR=0.54; 95% CI=0.35 - 0.85). Sensitivity analyses that excluded acetaminophen from the mean knowledge score gave similar results for all outcomes assessed.

## DISCUSSION

In this cross-sectional study of apixaban patients, about one-third of respondents reported regular use of OTC products that may interact with apixaban to increase bleeding. Twenty percent of patients were regularly using OTC products with potentially serious apixaban interactions, and an additional twenty-seven percent reported that they at least occasionally took these products. Knowledge about potential OTC product-apixaban interactions was the major factor associated with lower rates of use of potentially interacting OTC products but explained only a small amount of the variation between users and non-users. Overall, knowledge regarding potential interactions was low.

The most commonly used OTC medication was aspirin. Over half of the patients taking aspirin on a regular basis accurately recognized its potential for increased bleeding when taken with apixaban, as did almost 30% of patients taking NSAIDs. We did not collect information about the reason for participants' aspirin use, but it is likely that some were taking aspirin daily for primary or secondary prevention of cardiovascular disease. Perhaps more importantly, almost two-thirds of daily aspirin users also consumed other OTC products that further increase the risk of bleeding in combination with apixaban. As emerging data on aspirin suggests that its use for primary prevention in older patients is controversial and may be associated with greater harm from bleeding than cardiovascular benefit,<sup>25-27</sup> additional considerations regarding aspirin use **is**are important.

Regular NSAID use was very low in the patients surveyed. We do not know if providers told patients to avoid regular NSAID use, nor did we ask about the reasons for patient NSAID use. However, patients who reported talking to a healthcare provider about taking an OTC

product with apixaban knew more about the potential for interactions between NSAIDs and apixaban. Knowledge about other potential interactions was unrelated to discussions with healthcare providers, suggesting that patients may not have asked about other OTC products. Potentially problematic OTC product-DOAC interactions may not be recognized by clinicians because patients typically do not tell their providers before or after they start taking OTC products,<sup>28-37</sup> either because patients take these products sporadically or because they believe that OTC products are safe.<sup>37-40</sup>

Patients who have taken OTC medications or dietary supplements without any problems prior to starting apixaban may not consider potential interactions, particularly if they ingest the supplements as part of their diet. For example, certain ethnic groups may regularly incorporate dietary supplements such as turmeric and Chinese herbs in their meals, and unless providers ask them, patients may not realize they are important to disclose. Information about potential interactions with more commonly used OTC products such as about turmeric, herbal teas, Chinese herbs, ginger, and ginkgo biloba is not on the FDA-approved prescribing information or package insert for apixaban, as opposed to St. John's Wort,<sup>16</sup> which was rarely taken by patients. As provider queries about dietary supplements have been shown to be the primary driver of patient disclosure of supplement use,<sup>28</sup> it is important for providers to ask patients about their OTC product intake and provide information about potential interactions.

This study has several limitations. The response rate of 33%, may limit the generalizability of the study. OTC product use was based on self-report and is limited by participant recall, and we asked only about use of selected dietary supplements. We also only asked about knowledge of potential interactions between selected OTC products and apixaban.



We only asked a subset of participants about knowledge of all dietary supplements with potentially serious interactions with apixaban, such as about Chinese herbs, garlic, ginger, ginkgo biloba, herbal teas, and turmeric. In addition, we did not assess the dosing of OTC products or the reasons for aspirin use. In many cases, aspirin may have been recommended by a provider, and would have been appropriate for the patient's clinical situation. Respondents were not asked what OTC products they discussed with their providers.

DOAC use is increasing, as is<sup>1</sup> OTC medication and dietary supplement use. New OTC products are constantly being adopted by patients.<sup>41</sup> This study demonstrates that patients have limited knowledge about potential serious interactions between OTC products and apixaban. Finally, as our goal was to address OTC product use, we did not address potential interactions with prescription medications. Future work should explore the adverse events that may result from these potential interactions. Healthcare providers must screen patients for OTC product use, educate patients about the potential harms of taking certain OTC products with apixaban or other anticoagulants, and report adverse events resulting from concomitant use of these products.

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- 2) ***Author Contributions.*** Study concept and design: Drs. Tarn, Fang and Schwartz; acquisition of data: Drs. Tarn and Schwartz, Ms. Barrientos and Wang, and Mr. Ramaprasad; analysis and interpretation of data: Dr. Tarn and Schwartz, Ms. Barrientos; manuscript preparation and revisions: all authors.
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## REFERENCES

- [1] January CT, Wann LS, Alpert JS, *et al.* 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*. 2014;**64**: e1-e76.
- [2] Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;**149**: 315-352.
- [3] Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National Trends in Ambulatory Oral Anticoagulant Use. *Am J Med*. 2015;**128**: 1300-1305 e1302.
- [4] Steinberg BA, Washam JB. Appropriate dosing of nonvitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation. *Trends Cardiovasc Med*. 2017;**27**: 567-572.
- [5] U.S. Food and Drug Administration. CYP3A Inducers. 2016. Available at: <https://www.fda.gov/drugs/drug-interactions-labeling/cyp3a-inducers>. Accessed on August 5, 2019.
- [6] U.S. Food and Drug Administration. Table 2-2: Examples of clinical index inhibitors for P450-mediated metabolisms (for use in index clinical DDI studies) (9/26/2016). Available at: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>. Accessed on: August 5, 2019.
- [7] Dietary Supplement Health and Education Act of 1994. Public Law 103-417. 103rd Congress. Approved October 25, 1994. Available at: [http://ods.od.nih.gov/About/DSHEA\\_Wording.aspx](http://ods.od.nih.gov/About/DSHEA_Wording.aspx). Accessed August 5, 2019.
- [8] Wittkowsky AK, Bussey HI, Walker MB, Frei CR. Dietary supplement use among anticoagulation clinic patients. *Journal of thrombosis and haemostasis : JTH*. 2007;**5**: 875-877.
- [9] O'Neal WT, Sandesara PB, Claxton JS, *et al.* Provider Specialty, Anticoagulation Prescription Patterns, and Stroke Risk in Atrial Fibrillation. *Journal of the American Heart Association*. 2018;**7**.
- [10] Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;**362**: k2505.
- [11] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;**42**: 377-381.
- [12] Holsinger T, Plassman BL, Stechuchak KM, Burke JR, Coffman CJ, Williams JW, Jr. Screening for cognitive impairment: comparing the performance of four instruments in primary care. *J Am Geriatr Soc*. 2012;**60**: 1027-1036.
- [13] Chew LD, Griffin JM, Partin MR, *et al.* Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med*. 2008;**23**: 561-566.
- [14] Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: the Diabetes Study of Northern California (DISTANCE). *J Gen Intern Med*. 2010;**25**: 962-968.
- [15] Wallace LS, Rogers ES, Roskos SE, Holiday DB, Weiss BD. Brief report: screening items to identify patients with limited health literacy skills. *J Gen Intern Med*. 2006;**21**: 874-877.

- [16] Eliquis (apixaban) Full Prescribing Contents. Revised 07/2016. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/202155s012lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202155s012lbl.pdf). Accessed on April 10, 2019.
- [17] Lexicomp Online. Available at: <https://www.wolterskluwercli.com/lexicomp-online/>. Accessed on April 10, 2019.
- [18] Natural Medicines. Available at: <https://naturalmedicines.therapeuticresearch.com/>. Accessed on April 10, 2019.
- [19] Ali M, Afzal M. A potent inhibitor of thrombin stimulated platelet thromboxane formation from unprocessed tea. *Prostaglandins, leukotrienes, and medicine*. 1987;**27**: 9-13.
- [20] Ardlie NG, Glew G, Schultz BG, Schwartz CJ. Inhibition and reversal of platelet aggregation by methyl xanthines. *Thrombosis et diathesis haemorrhagica*. 1967;**18**: 670-673.
- [21] Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice turmeric (*Curcuma longa*) inhibits aggregation and alters eicosanoid metabolism in human blood platelets. *Prostaglandins Leukot Essent Fatty Acids*. 1995;**52**: 223-227.
- [22] Shah BH, Nawaz Z, Pertani SA, *et al*. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca<sup>2+</sup> signaling. *Biochemical pharmacology*. 1999;**58**: 1167-1172.
- [23] Srivastava R, Puri V, Srimal RC, Dhawan BN. Effect of curcumin on platelet aggregation and vascular prostacyclin synthesis. *Arzneimittel-Forschung*. 1986;**36**: 715-717.
- [24] Lee CA, O'Connor MA, Ritchie TK, *et al*. Breast Cancer Resistance Protein (ABCG2) in Clinical Pharmacokinetics and Drug Interactions: Practical Recommendations for Clinical Victim and Perpetrator Drug-Drug Interaction Study Design. *Drug Metabolism and Disposition*. 2015;**43**: 490-509.
- [25] Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019.
- [26] Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019.
- [27] Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA*. 2019;**321**: 277-287.
- [28] Tarn DM, Karlamangla A, Coulter ID, *et al*. A cross-sectional study of provider and patient characteristics associated with outpatient disclosures of dietary supplement use. *Patient Educ Couns*. 2015;**98**: 830-836.
- [29] Tarn DM, Paterniti DA, Good JS, *et al*. Physician-patient communication about dietary supplements. *Patient Educ Couns*. 2013;**91**: 287-294.
- [30] Thompson JJ, Nichter M. The compliance paradox: what we need to know about "real-world" dietary supplement use in the United States. *Altern Ther Health Med*. 2007;**13**: 48-55.

- [31] Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clinical therapeutics*. 2011;**33**: 1749-1758.
- [32] Busse JW, Heaton G, Wu P, Wilson KR, Mills EJ. Disclosure of natural product use to primary care physicians: a cross-sectional survey of naturopathic clinic attendees. *Mayo Clin Proc*. 2005;**80**: 616-623.
- [33] Canter PH, Ernst E. Herbal supplement use by persons aged over 50 years in Britain: frequently used herbs, concomitant use of herbs, nutritional supplements and prescription drugs, rate of informing doctors and potential for negative interactions. *Drugs & aging*. 2004;**21**: 597-605.
- [34] Wold RS, Wayne SJ, Waters DL, Baumgartner RN. Behaviors underlying the use of nonvitamin nonmineral dietary supplements in a healthy elderly cohort. *J Nutr Health Aging*. 2007;**11**: 3-7.
- [35] Mehta DH, Gardiner PM, Phillips RS, McCarthy EP. Herbal and dietary supplement disclosure to health care providers by individuals with chronic conditions. *Journal of alternative and complementary medicine*. 2008;**14**: 1263-1269.
- [36] Kennedy J, Wang CC, Wu CH. Patient Disclosure about Herb and Supplement Use among Adults in the US. *Evid Based Complement Alternat Med*. 2008;**5**: 451-456.
- [37] Nichter M, Thompson JJ. For my wellness, not just my illness: North Americans' use of dietary supplements. *Cult Med Psychiatry*. 2006;**30**: 175-222.
- [38] Wawruch M, Kuzelova M, Foltanova T, *et al*. Characteristics of elderly patients who consider over-the-counter medications as safe. *International journal of clinical pharmacy*. 2013;**35**: 121-128.
- [39] Consumer Healthcare Products Association. Your health at hand: perceptions of over-the-counter medicine in the U.S., November 24, 2010. Available at: [http://www.yourhealthathand.org/images/uploads/CHPA\\_YHH\\_Survey\\_062011.pdf](http://www.yourhealthathand.org/images/uploads/CHPA_YHH_Survey_062011.pdf) Accessed on October 30, 2014. .
- [40] Prevention Magazine. *Consumer Use of Dietary Supplements*. Emmaus, PA: Rodale, 2001.
- [41] Mordor Intelligence. Over the Counter Drugs Market - Growth, Trends and Forecast (2019-2024). Available at: <https://www.mordorintelligence.com/industry-reports/global-over-the-counter-otc-drugs-market-industry>. Accessed on April 10, 2019. 2019.

## LEGENDS

Figure 1. Frequency of Use of OTC Products with Potentially Serious Interactions with Apixaban.

Percentage of respondents (n=791) who used dietary supplements or OTC medications with potentially serious interactions with apixaban are shown with red indicating everyday use, orange indicating use on most days, and yellow representing use on some days or as needed.

Figure 2. Knowledge about Potentially Serious Aspirin-Apixaban and NSAIDS-Apixaban Interactions in Relation to Respondent Use of Aspirin and NSAIDS.

The left panel presents respondent knowledge about aspirin-apixaban interactions and the right panel presents respondent knowledge about NSAID-apixaban interactions. Blue bars represent respondents who reported taking the OTC product with apixaban daily or on most days (n=119 for aspirin; n=14 for NSAIDs); orange bars represent respondents who reported they did not take the OTC product with apixaban (n=664 for aspirin; n=767 for NSAIDs).

Table 1. Major potential over-the-counter product and apixaban interactions<sup>17, 18</sup>

	Potentially increases bleeding risk	Increases bleeding risk	Decreases Effect	Recommendation Interaction Databases <sup>x,y,z</sup>	FDA approved Package Insert*
<b>OTC Products</b>					
Chinese Herbs <sup>a</sup>	x			Consider therapy modification	----
Ginger	x			Consider therapy modification	---
Gingko biloba	x			Consider therapy modification	---
Herbal Teas <sup>b</sup>	x			Consider therapy modification	---
St Johns wort			x	Avoid Combination	Avoid combination
Turmeric	x			Consider therapy modification	----
Aspirin		x		Consider therapy modification	Increases bleeding risk
NSAIDs		x		Monitor closely	Increases bleeding risk
<b>Prescription Medications</b>					
Clopidogrel		x		Consider therapy modification	Increases bleeding risk
Hemin		x		Avoid Combination	-----
Mifepristone		x		Avoid Combination	-----
Prasugrel, ticagralor		x		US: consider therapy modification: Canada: Avoid combination	Increases bleeding risk
Progestins, higher dose estrogens			x	Consider therapy modification	-----
SSRI, SNRI		x		Monitor	Increases bleeding risk
Vorapaxar		x		Avoid Combination	-----
Other DOACs, heparins, warfarin, thrombolytics		x		Avoid Combination	Increases bleeding risk
Strong CYP3A4-Pgp			x	Avoid Combination	Avoid Combination



Inducers <sup>c</sup>					
Strong CYP3A4-PgP inhibitors <sup>d</sup>	x			Consider therapy modification	Reduce dose (NVAf)

SSRI=selective serotonin reuptake inhibitor, SNRI= selective serotonin and norepinephrine reuptake inhibitor.

<sup>a</sup> Chinese herbs include products such as danshen, dong quai and ginseng

<sup>b</sup> Herbal teas include green and chamomile tea

<sup>c</sup> Rifampin, rifabutin, phenytoin, carbamazepine.

<sup>d</sup> Azoles, numerous retroviral agents (indinavir and ritonavir, lopinavir and ritonavir, paritaprevir and ritonavir, ombitasvir and/or dasabuvir, ritonavir, saquinavir and ritonavir, telaprevir danoprevir and ritonavir, elvitegravir and ritonavir, boceprevir), conivaptan, grapefruit juice, troleandomycin, cobicistat). FDA also lists: clarithromycin, diltiazem, nefazodone, nelfinavir, idelalisib not listed as strong inhibitors requiring dosage adjustments on approved prescribing information for apixaban.

\*[https://packageinserts.bms.com/pi/pi\\_eliquis.pdf](https://packageinserts.bms.com/pi/pi_eliquis.pdf), accessed 8/01/2019.

<sup>x</sup> Up to Date, Lexicomp

<sup>y</sup> Natural medicines database

<sup>z</sup>Herbs and supplements variably reported to increase bleeding risk: fish oil, vitamin E, flaxseed, melatonin, saw palmetto, Alfalfa, Anise, Bilberry, Bladderwrack, Bromelain, Cat's Claw, Celery, Coleus, Cordyceps, Dong Quai, Evening Primrose, Fenugreek, Feverfew, Garlic, Grape Seed, Guggul, Horse Chestnuts, Horseradish, Licorice, Prickly Ash, Red Clover, Reishi, S-adenosylmethionine, Sweet Clover, Taurine, White Willow. No interactions identified: vitamin D or calcium, acetaminophen, multivitamins.

Table 2. Patient and prescription medication use characteristics, n=791

<b>Characteristic</b>	
Age, mean (SD); range	71 (11.8); 25-99
Gender, n (%)	
Female sex	315 (39.8)
Male sex	472 (59.6)
Other or unknown	4 (0.6)
Race, n (%)	
American Indian/Alaskan Native	2 (0.3)
Asian	80 (10.1)
Black or African-American	38 (4.8)
Multiple races	14 (1.8)
Native Hawaiian/Other Pacific Islander	8 (1.0)
White	596 (75.3)
Unknown	53 (6.7)
Hispanic/Latino, n (%)	62 (7.8)
Education, n (%)	
High school graduate or less	52 (6.6)
Some college or 2-yr college	167 (21.1)
College graduate or above	566 (71.6)
Unknown	6 (0.7)
Self-reported health, mean (SD)*	3.05 (0.88)
Number of prescription medications, mean (SD), range	5.4 (2.9); 1-15
Health literacy, mean (SD)*	4.3 (0.94)
Apixaban indication, n (%)	
Atrial fibrillation	621 (78.5)
Blood clot	180 (22.8)
Stroke	85 (10.8)
After hip/knee surgery	3 (0.4)
Uncertain	5 (0.6)
Other	18 (2.3)
Duration of apixaban use	
1-6 months	36 (4.5)
7-12 months	113 (14.3)
More than 12 months	642 (81.2)

Prior warfarin use	
Yes	275 (34.8)
No	502 (63.5)
Unsure	13 (1.6)

\* Self-reported health and health literacy range from 1-5, with greater numbers indicating better health and greater health literacy

Figure 1

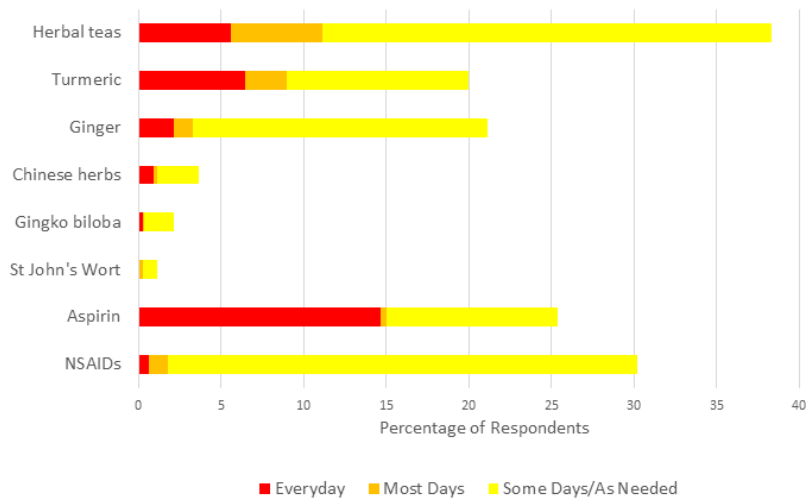


Figure 2

