Cleveland Clinic Clinical Rx Forum

From the Department of Pharmacy Drug Information Service
(216) 444-6456, option #1

Comprehensive information about medications, biologics, nutrients, and drug therapy

Formulary Information

Medication Inservices

Cleveland Clinic Clinical Rx Forum

From the Department of Pharmacy

May/June Issue **2013, Volume 1, Issue 3**

Buying Medicine Online: What Patients Should Know

By: Riane J. Ghamrawi, Pharm.D.

Introduction: For the majority of people, the Internet has become the mainstay of communication and marketing. It has offered consumers the opportunity to purchase and sell products and communicate with family and friends in the comfort of their homes. Consequently, the Internet has become a popular venue to purchase prescription medications. Increases in medication costs, pushback from drug companies, and a suffering economy, have been cited as reasons patients have favored the Internet when making medication purchases.[1,2] Additionally, the Internet comes with a multitude of references and drug specific information that enable patients to make informed and educated health-related decisions. What consumers may not be aware of is that there are fraudulent pharmacies on the Internet that may place their health at risk. This article will explain why online pharmacies have become a growing problem, where fraudulent pharmacies originate from, and what healthcare professionals can do to help protect patients from the dangers associated with fraudulent, on-line pharmacies.

Why?

An initial report by the National Association of Boards of Pharmacy (NABP) on June 29, 2012, reported that 9,734 out of 10,065 (96.7%) of online "pharmacies" were noncompliant with state and federal laws. These pharmacies have subsequently been listed as "Not Recommended" on the NABP website. In fact, only 0.73% of the surveyed websites were accredited through NABP's Verified Internet Pharmacy Practice Sites (VIPPS), Veterinary-Verified Internet Pharmacy Practice Sites (Vet-VIPPS), or approved through the NABP e-Advertiser Approval Pro-

(Continued on page 2)

Angioedema with Renin-Angiotensin-Aldosterone System Inhibitors

By: Alexander Kantorovich, Pharm.D.

Introduction: Patients with angioedema typically present with swelling of the tissues near the upper airway including the face, tongue, and lips; however, intestinal tissue can also be involved.[1] The pathophysiology of angioedema stems from a release of inflammatory vasoactive substances, such as bradykinin, histamine, and serotonin, which are responsible for inflammation, arterial vasodilation, capillary leakage, and tissue swelling.[1,2] Usually, angioedema is self-limiting, but in severe cases it can result in asphyxiation and death due to swelling around the airway. Up to 20% of all angioedema cases are life-threatening, and of those cases, 20% are fatal if a patient is not intubated.[3] Angioedema has been reported with different classes of medications, including beta blockers, statins, psychotropic agents, non-steroidal anti-inflammatory drugs (NSAIDs), and vaccines.[2] However, the family of drugs known as the renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and direct renin inhibitors (DRIs), are the most common causes of drug-induced an-

(Continued on page 4)

(Continued from page 1)

gram.[3] To be compliant with VIPPS, the accreditation process includes following the laws and restrictions of all states to which medications are dispensed, as well as the state where the dispensing site originates. Additionally, dispensing sites must be compliant with the regulations pertaining to patient privacy, authentication of prescription orders, and availability of a pharmacist to perform patient consultation as per state and federal laws and regulations.[4]

On September 28, 2012, the Food and Drug Administration (FDA) launched its national campaign, entitled BeSafeRx, to make the public aware of fraudulent Internet pharmacies and to inform consumers and healthcare providers of the dangers of these pharmacies on consumer health. The FDA reported that 25% of Internet users have utilized online pharmacies to purchase medications. The practice of purchasing medications from fraudulent pharmacies can be harmful since the potency, stability, and sterility of products may be unknown.[2] Reports have circulated linking counterfeit medication ingredients to toxic substances such as highway paint, boric acid, and floor wax. The tablets purchased may be indistinguishable from the authentic product and often can not be differentiated from the true product without the use of technology with advanced detection capabilities.[5] Ways to detect counterfeit medications are summarized in Table 1. Facts concerning counterfeit medications are included in Table 2.

Interpol, the world's largest international police organization, has worked as part of Operation Pangea, as cited in a recent FDA consumer report, to stop the sale of illegal medications online. The operation ran from September 25, 2012, until October 2, 2012. One-hundred countries participated, leading to the confiscation of 3.7 million illicit and counterfeit medications, valued at $10.5 million; subsequently, shutting down 18,000 offending websites.[6]

Where?

The NABP report listed 23% of the noncompliant sites as having non-US addresses. Of note, most fraudulent pharmacies do not even list a physical address; therefore, lack of a posted address should also serve as a warning sign.[3] These websites are operating illegally in foreign countries without strict US regulations for manufacturing, distributing, and supplying medications. Additionally, the popular and long-trusted Canadian online pharmacy websites may actually be based in other foreign countries.[5]

Table 1. How to Detect Counterfeit Medications[5]

Characteristic	Differences from Reputable Product
Packaging	Packaging looks different
Labeling	Labeling looks different than usual and necessary information required by federal law is missing (e.g., manufacturer, expiration date, lot number)
Tablet Appearance	Tablets/capsules are broken, discolored, or have different markings from previous purchases
Tablet Taste	Tablets taste different
Adverse Effects	Adverse effects that are not commonly noted in the prescribing information or that newly arise after taking the medication

Table 2. Facts Pertaining to Counterfeit Medications[7]

• Approximately 1-2% of medications in North America are fraudulent.
• The counterfeit medication industry was a $75 billion business in 2010.
• The number of fraudulent prescription drugs doubled between 2004 and 2005 and is estimated to increase at an average of 13% every year.
• Most counterfeit medications are manufactured in underdeveloped countries.
• Counterfeit medications contain little, if any, active ingredients (e.g., glue, chalk, paint, sugar)

What can be done?

Healthcare professionals are able to help through patient awareness and education. It is not only important to know how patients are taking their medications, but to also know where they are getting their medications. This is an important issue, since medications from online pharmacies intended to improve patients' health can cause harm and even result in death. Patients should be made aware of the signs of a fraudulent pharmacy which are outlined in Table 3.[8]

Conclusion: The use of the Internet to make purchases, including prescription medications, is projected to increase. It is the responsibility of healthcare professionals to not only serve as a resource guiding patients to the safest websites for purchases, but to also be on guard for fraudulent websites and know how to appropriately avoid and report offenders. Important patient and healthcare resources which provide NABP unapproved websites and access to reporting offenders include http://www.nabp.net/programs/consumer-protection/buying-medicine-online/not-recommended-sites/ and http://www.nabp.net/programs/consumer-protection/buying-medicine-online/report-a-site/, respectively. With increased community awareness of this growing problem, it is hoped that patients continue to receive the best healthcare by making medication purchases from reputable and safe sites, in order to avoid jeopardizing their health and well-being.

References:

1. Montoya ID and Jano E. Online Pharmacies: Safety and Regulatory Considerations. Int J Health Serv 2007;37(2):279-89.
2. BeSafeRx: Know Your Online Pharmacy [Internet]. U.S. Federal Drug Administration; 2012.Available from: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/BuyingMedicinesOvertheInternet/BeSafeRxKnowYourOnlinePharmacy/default.htm. Accessed: October 8, 2012.
3. Internet Drug Outlet Identification Program [Internet]: Progress Report for State and Federal Regulators: July 2012. National Association of Boards of Pharmacy; 2012. Available from http://www.nabp.net/programs/assets/NABP%20Internet%20Drug%20Outlet%20Report_July_2012_Final.pdf. Accessed: October 8, 2012.
4. Verified Internet Pharmacy Practice Sites (VIPPS) [Internet]. National Association of Boards of Pharmacy; 2012. Available from: http://vipps.nabp.net. Accessed: October 10, 2012.
5. The fight against counterfeit drugs [Internet]. CBS News; 2011. Available from: http://www.cbsnews.com/video/watch/?id=7359537n. Accessed: October 4, 2012.
6. Operation Pangea. Interpol [Internet]: Connecting Police for a Safer World; 2012. Available from: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations. Accessed: October 13, 2012.
7. Counterfeit Medications: Why should I be Concerned About Counterfeit Drugs? [Internet]. National Association of Boards of Pharmacy; 2012. Available from: http://www.nabp.net/programs/consumer protection/buying-medicine-online/counterfeit-drugs/. Accessed: October 8, 2012.
8. Is That Pharmacy Safe? Protect Yourself from Rouge Internet Sites [Internet]. National Association of Boards of Pharmacy; 2012. Available from: http://www.nabp.net/programs/CCCOCconsumer-protection/buying-medicine-online/is-that-pharmacy-safe. Accessed: October 8, 2012.

Table 3. Warnings Signs of Fraudulent Pharmacies – Information to Share with Patients[8]

• Prescriptions not required
• Prescription authorized based only on an online survey
• No contact information on website
• No pharmacist consultation offered
• Waivers requiring abstention from legal action against the website
• Only select classes of medications available for purchase
• International-based websites
• Spam solicitations

(Continued from page 1)
gioedema. Due to the widespread use of ACEIs worldwide, it is estimated that 1,000 deaths annually are a result of ACEI-induced angioedema.[3] Risk factors include history of drug rash, age >65 years, seasonal allergies, and African American race.[2,4] Also, patients with heart failure experience more angioedema than the general population when treated with ACEIs and ARBs, as heart failure increases bradykinin levels.[3] Bradykinin levels are at least twice as high in clinically stable New York Heart Association Class II heart failure. Pharmacotherapeutic agents used in the treatment of drug-induced angioedema include epinephrine at a dose of 0.3-0.5 mg administered intramuscularly, as well as steroids or antihistamines if the causative agent for angioedema is unknown.[2,5]

Mechanism of RAAS-Induced Angioedema:
Angiotensin-converting enzyme inhibitors are postulated to cause angioedema by inhibiting the degradation of bradykinin, which is metabolized by angiotensin-converting enzyme (ACE) to inactive metabolites.[2,4] This prolongs the half-life of bradykinin and allows it to exert its vasodilatory effects. The exact mechanism behind ARB-induced angioedema has not been fully elucidated, but it has been shown that increased levels of bradykinin are seen after ARB initiation due to decreased ACE activity and neutral endopeptidase metabolism.[3,6] In addition, the inhibition of the angiotensin II receptor leads to arterial vasodilatation further contributing to angioedema.[7,8] Aliskiren (Tekturna®) is currently the only DRI approved in the United States by the Food and Drug Administration; the mechanism of angioedema associated with this medication class is unknown.[3]

Comparative Incidence of Angioedema Among RAAS Inhibitors:
Angiotensin-converting enzyme inhibitor-induced angioedema has an incidence of 0.1-0.5%; however, the rate may be as high as 5.5% in the African American population.[2,3] Angioedema occurs in more patients at the initiation of therapy; over 50-60% of all cases are reported within 90 days of initiation of an ACEI. However, it can happen at anytime during therapy. One case report of angioedema occurring 8 years after initiating ACEI therapy has been published.[2-4] Soon after the introduction of ARBs, case reports began to emerge of patients experiencing angioedema whether or not they had angioedema on an ACEI previously or were naïve to any RAAS inhibitor.[1] The incidence of ARB-induced angioedema is 2.2 times less than that of ACEIs.[3] Recently, a meta-analysis compiled the incidence of ARB-induced angioedema from trials between 2001 and 2010.[4] The results were described as cumulative incidence of angioedema or severe angioedema per 1,000 persons. The incidence of ACEI-induced angioedema was 1.79 [95% confidence interval (CI), 1.73-1.85] compared to 0.62 (95% CI, 0.55-0.69) for ARBs. Of all the patients exposed to ARBs in these studies, severe angioedema was reported to be 0.02 (95% CI, 0.01-0.04) compared to 0.18 (95% CI, 0.16-0.20) for ACEIs. The incidence of angioedema with aliskiren were comparable to those of ACEIs at 1.44 (95% CI, 0.58-2.96). Unlike ACEIs, only one case of severe angioedema was reported with aliskiren, but the incidence was comparable to ACEIs at 0.21 (95% CI, 0.01-1.14). It is important to note that there were far fewer patients on aliskiren in the meta-analysis than either ACEIs or ARBs. The incidence of both RAAS inhibitor-induced angioedema as well as severe angioedema was similar with ACEIs and DRIs and less with ARBs.

Angioedema and Cross-Reactivity Among RAAS Inhibitors:
Both ACEIs and ARBs are commonly used in disease states such as heart failure, diabetes, acute coronary syndromes, and hypertension.[1,8] In all these disease states, a significant mortality benefit is seen with the use of ACEIs and ARBs. Therefore, not being able to use these agents in situations such as angioedema is problematic due to their inclusion in core measures and other guidelines which advocate for their use. The question about the use of ARBs after ACEI-induced angioedema has been debated for over a decade and the cross-reactivity between ACEI and ARB-induced angioedema was evaluated in multiple analyses.[9-14] Earlier studies garnered a cross-reactivity rate under 10%; however, the first meta-analysis had a 95% CI which spanned a range of 1.6-17% for possible cases of angioedema. As more literature emerged on the subject and more patients were included in the updated meta-analysis, cross-reactivity rates were reduced to 2.5% (95% CI, 0-6.6%) and 1.5% (95%, CI, 0-5.1%) for possible and confirmed cases of angioedema, respectively.[14] In patients with ACEI-induced angioedema, if angioedema occurs after switching to an ARB its degree of severity may be less than that of an ACEI or self-limiting; patients should be monitored closely for any symptoms of angioedema, especially during the first 90 days after initiation of therapy.[4] Currently, there are no data regarding the safety of DRI use in patients who developed angioedema with other RAAS inhibitors.[3]

Summary: Angioedema is a concerning adverse effect

of ACEIs and accounts for a significant number of deaths worldwide. The use of ARBs in patients who experienced ACEI-induced angioedema is a controversial clinical practice. From the current literature, it is evident that the rates of cross-reactivity between ACEI and ARBs for angioedema are relatively low. Hence, the clinician must assess the risk of severe life-threatening angioedema with the cardiovascular benefits seen with ARBs. In general, switching patients with ACEI-induced angioedema to an ARB is practical and seems safe especially as angioedema occurring after switching to an ARB is usually less severe than ACEI-induced angioedema or is self-limiting. After an episode of ACEI-induced angioedema, symptoms should be allowed to pass before initiation of an ARB, which should be done in a monitored setting to observe any angioedema-like symptoms. Patients should be educated regarding the possibility of ARB-induced angioedema if they previously experienced ACEI-induced angioedema.

References:

1. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. Ann Pharmacother 2011;45(4): 520-4.
2. Salih IS, Thomas SH. Causes and management of drug-induced angioedema. Prescriber 2006;17(7):14-8.
3. Makani H, Messerli FH, Romero J, Wever-Pinzon O, Korniyenko A, Berrios RS, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol 2012;110(3):383-91.
4. Toh S, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, et al. Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System. Arch Intern Med 2012;15:1-8.
5. Sica DA, Black HR. Angioedema in heart failure: occurrence with ACE inhibitors and safety of angiotensin receptor blocker therapy. Congest Heart Fail 2002;8(6):334-41.
6. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels inhypertensive humans. Circulation 2005;111(3):315-20.
7. Chiu AG, Krowiak EJ, Deeb ZE. Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology. Laryngoscope 2001;111(10): 1729-31.
8. van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J 2012;33(16):2088-97.
9. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003 Sep 6;362(9386):772-6.
10. Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med 2004;164(8):910-3.
11. Malde B, Regalado J, Greenberger PA. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Ann Allergy Asthma Immunol 2007;98(1):57-63.
12. Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol 2008;101(5):495-9.
13. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet 2008;372(9644):1174-83.
14. Haymore BR, DeZee KJ. Use of angiotensin receptor blockers after angioedema with an angiotensin-converting enzyme inhibitor. Ann Allergy Asthma Immunol 2009;103(1):83-4.

Safety Updates on Dabigatran Etexilate Mesylate(Pradaxa®): the Good and the Bad

By: Keith Anderson, Pharm.D.

Introduction: Dabigatran etexilate mesylate (Pradaxa®) is an oral, direct thrombin inhibitor approved in October 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[1] Dabigatran provides a stable hematologic response; therefore, it does not require laboratory monitoring of clotting factors. However, this has also lead to some concern given the limited experience with dabigatran-induced bleeding and lack of a reliable reversal agent. Since its approval, the Food and Drug Administration (FDA) has issued the following safety communications regarding its use:

- November 2, 2012: Update on the risk for serious bleeding events with the anticoagulant Pradaxa® (dabigatran etexilate mesylate) "Results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa® do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa® (the RE-LY trial)."[2]

- December 19, 2012: Pradaxa® (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. "Pradaxa® (dabigatran etexilate mesylate) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves…FDA is requiring a contraindication (a warning against use of Pradaxa in patients with mechanical heart valves)."[3]

(Continued on page 6)

The Good:
Dabigatran has not been shown to be associated with higher rates of bleeding than warfarin.[2]

The drug was approved by the FDA following the publication of the results from the **R**andomized **E**valuation of **L**ong-Term Anticoagulation Therap**Y** (RE-LY) trial.[4] The RE-LY trial was a multi-center, Phase III, prospective, randomized, non-inferiority, open-label study with a blinded endpoint evaluation. It included 18,113 patients with non-valvular atrial fibrillation and risk factors for stroke. Results from the study demonstrated dabigatran, at a dose of 150 mg twice daily, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared to warfarin. It should be noted that patients receiving dabigatran 150 mg twice daily experienced a significantly higher rate of gastrointestinal bleeding. On the other hand, patients who received warfarin experienced a significantly higher risk for intracranial hemorrhage and life threatening major bleeding. Select safety outcomes from the RE-LY trial comparing the dabigatran 150-mg group with warfarin are reported in Table 1.

Despite the similar rate of major bleeding with dabigatran found in the RE-LY trial, there were a large number of post-marketing reports of bleeding episodes. In response to these reports, the FDA launched an investigation into the actual rates of intracranial hemorrhage (ICH) and gastrointestinal bleeding with dabigatran compared to warfarin using insurance claims and administrative data from the Mini-Sentinel pilot of the Sentinel Initiative.[2] The Mini-Sentinel pilot is an active surveillance system created to monitor the safety of FDA-regulated medical products using pre-existing electronic healthcare data from multiple sources.[5]

The FDA investigation utilized the Mini-Sentinel database to identify inpatient diagnosis codes for ICH and gastrointestinal hemorrhage (GIH) events associated with new use of dabigatran or warfarin from October 10, 2010, through December 13, 2011. Inclusion and exclusion criteria are listed in Table 2.

Results from this analysis indicated that the observed bleeding rates associated with new use of dabigatran did not appear to be higher than those with warfarin. In particular, the incidence rate per 100,000 days at risk of ICH and GIH combined, rate of GIH events only, and rate of ICH events only were 1.8 to 2.6, 1.6 to 2.2, and 2.1 to 3.0 times higher with warfarin than with dabigatran, respectively. The FDA did note, however, that the estimates did not account for possible differences in the patient populations for the two drugs that could have affected bleeding rates, including age and the presence of other medical conditions. In addition, the diagnoses of ICH and GIH were not confirmed through medical record reviews. The FDA stated that a simple comparison using post-marketing reports of bleeding is misleading because bleeding events with warfarin are likely to be underreported compared to dabigatran. As such, the FDA has not changed its recommendations regarding dabigatran and instructs providers to continue following the dosing recommendations in the package insert. The package insert currently recommends 150 mg twice daily in patients with a creatinine clearance >30 mL/min, and to reduce the dose to 75 mg twice daily in patients with a creatinine clearance of 15-30 mL/min based on pharmacokinetic modeling.[1] The FDA is continuing an on-

Table 1. RE-LY Safety Outcomes According to Treatment Group[4]

Event	Dabigatran 150 mg twice daily (% per year)	Warfarin once daily (% per year)	Relative Risk (95% CI)	p-value
Major bleeding	3.11	3.36	0.93 (0.81–1.07)	0.31
• Life threatening	1.45	1.80	0.81 (0.66-0.99)	0.04
• Non-life threatening	1.88	1.76	1.07 (0.89-1.29)	0.47
• Gastrointestional*	1.51	1.02	1.50 (1.19-1.89)	<0.001
Intracranial hemorrhage	0.30	0.74	0.40 (0.27–0.60)	<0.001

*Includes life threatening and non-life threatening

Table 2. Inclusion and Exclusion Criteria[2]

Inclusion Criteria*	Exclusion Criteria*
Enrollment in a participating health plan with both drug and medical coverage	Administration of either anticoagulant
Diagnosis code for atrial fibrillation during this 6-month period	Diagnosis code for GIH or ICH

* During the period of 6 months prior to dispensing either drug GIH=gastrointestional hemorrhage ICH=intracranial hemorrhage

going safety review of dabigatran by conducting two additional protocol-based observational assessments using Mini-Sentinel data and monitoring post-marketing reports for evidence of factors that might lead to a bleeding event.

The Bad:
Dabigatran has been associated with an increase in bleeding and thromboembolic events in patients with mechanical prosthetic heart valves.[3]

Heart valve surgery is performed in approximately 300,000 patients per year worldwide, a number that is expected to increase due to the aging population and incidence of rheumatic heart disease in developing countries.[7,8] Mechanical valves are associated with a persistent risk of thrombosis and require life-long anti-coagulation. The **R**andomized, phase II study to **E**valuate the s**A**fety and pharmacokinetics of oral dab**IG**atran etexilate in patients after heart valve replaceme**N**t (RE-ALIGN) trial was a prospective, randomized, open-label, blinded end-point study comparing dabigatran with warfarin for 12 weeks in patients with bileaflet, mechanical heart valves.[7] The objective of the study was to identify doses of dabigatran that would be safe and effective for the prevention of thromboembolic complications in patients with mechanical heart valves. Patients aged ≥18 years and ≤75 years who underwent implantation of a bileaflet, mechanical valve (aortic, mitral, or both) during the hospital stay or a mitral bileaflet valve >3 months prior to enrollment were included. Patients were randomized to dose-adjusted warfarin (target INR was based on risk factors and position of mechanical valve) or dabigatran (see Table 3).

The RE-ALIGN trial was terminated early due to a significantly higher number of thromboembolic events (valve thrombosis, stroke, and myocardial infarction) and major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) occurring in the dabigatran arm compared to the warfarin treatment arm (Table 4). Bleeding and thromboembolic events occurred in patients who were initiated on dabigatran within 3 days after mechanical valve implantation and in patients

Table 3. RE-ALIGN Starting Dose and Dose Adjustment of Dabigatran[8]

CrCl at screening (mL/min)	Initial dose twice daily	Dabigatran plasma level*	Recommendation
<70	150 mg	<50 ng/mL	Increase to 220 mg twice daily
≥70 but <110	220 mg	<50 ng/mL	Increase to 300 mg twice daily
≥110	300 mg	<50 ng/mL	Repeat measurement within 10 days and if level <50 ng/mL switch to study warfarin or discontinue study treatment

* Taken at trough (12 hours after dose, range 10-16 hours) the morning of day 4 (window = +3 days)

Table 4. Thromboembolic and Bleeding Events from RE-ALIGN as of 12/10/12[6]

Event	Dabigatran (n=160)*	Warfarin (n=89)*
Death	1 (0.6%)	2 (2.2%)
Stroke	8 (5.0%)	0
TIA	2 (1.3%)	2 (2.2%)
VT	4 (2.5%)	0
MI	3 (1.9%)	0
Composite of events: death, stroke, SEE, TIA, VT, MI	16 (10.0%)	4 (4.5%)
Major Bleeding	6 (3.8%)	1 (1.1%)
Major bleeding in pericardial location	5 (3.1%)	0
Any bleeding	36 (22.5%)	12 (13.5%)

* Due to switches from dabigatran to warfarin, patients could contribute to both columns MI=myocardial infarction SEE=systemic embolism event TIA=transient ischemic attack VT=valve thrombosis

with valves implanted >3 months previously.[6]

Based on the results from the RE-ALIGN trial, the FDA has issued a contraindication for the use of dabigatran in patients with mechanical heart valves. The use of dabigatran in bioprosthetic valves has not been evaluated; therefore, the FDA cannot its recommend use.[6]

Conclusion: Bleeding rates associated with dabigatran do not appear to be higher than with warfarin, which are consistent with the results observed in the RE-LY trial. The FDA has not changed its recommendations regarding the use of dabigatran based on post-marketing reports of bleeding. The results from the Mini-Sentinel pilot alleviated some concerns about these risks. Additional information regarding dabigatran-associated bleeding risks will become available as the FDA conducts two additional protocol-based, observational assessments as part of its ongoing safety review of this agent. The RE-ALIGN study, which compared dabigatran to warfarin in patients with mechanical heart valve replacement, was terminated early due to increased thromboembolic events and major bleeding. In response, the FDA has required a contraindication for the use of dabigatran in patients with mechanical heart valves, which is reflected in the package insert. In addition to this contraindication, concerns with increased bleeding, absence of monitoring to determine a patient's risk of bleeding, and lack of a standardized reversal agent have limited the widespread use of dabigatran.

References:

1. Pradaxa® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; December 2012.
2. FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran). Available at http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm. Accessed: January 19, 2013.
3. FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). Available at http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm. Accessed: April 11, 2013.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
5. FDA Sentinel Initiative. Mini-Sentinel home. Available at http://mini-sentinel.org. Accessed: April 11, 2013.
6. FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. Available at http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm. Accessed: January 19, 2013.
7. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet 2009;374:565-76.
8. Van de Werf F, Brueckmann M, Connolly SJ, Friedman J, Granger CB, Härtter S, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: The randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). Am Heart J 2012;163:931-7.