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NYS-ACCP Insider

University at Buffalo School of Pharmacy and Pharmaceutical Sciences

Special points of Interest:

UBSPPS-ACCP Student Chapter Updates

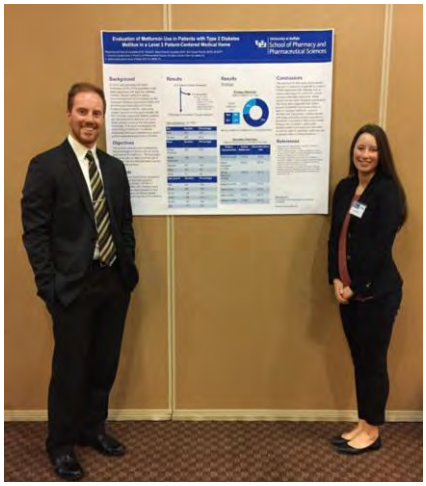
If you were to read the personal statement on your average pharmacy school application you might find the phrase, "I want to be a pharmacist to help people." The truth is, pharmacists are at the core of a patient care and can play a vital role in molding the way in which therapy is planned. Clinical pharmacists work in tandem with other health care professionals in order to optimize the outcome of a patient's care. With their exceptional knowledge of medication therapy and background as a clinician, they play a vital role within that team. SCCP's core values are centered around promoting excellence in patient care, research, and education. Each year, the University at Buffalo's SCCP chapter has been able to successfully incorporate these values into event planning for students.

In the Fall 2017 semester, the SCCP chapter set up two "Dinner and Discussion" events which enabled students to get a personalized insight into the typical day of two clinical professors. Our first event hosted Dr. Robert Wahler Jr., PharmD, CPE, who discussed varying careers in Hospice. Through his insightful dialog, Dr. Wahler was able to give students a glimpse of the palliative end-of-life care that he provides to his patients, all while being able to enjoy some Wegman's subs. It was a win-win. Additionally, our second event hosted Dr. Edward Bednarczyk, PharmD, FCCP, FAPhA, who spoke about his research in medical marijuana. With its evolutionary growth in healthcare, this currently growing topic caught the interest of many students. One of the hardest aspects to grapple with in pharmacy school is choosing which part of pharmacy appeals to you most. These Dinner and Discussion events are a

great way for students to get a more "behind the scenes" look at the profession from faculty members. The high success rate of these events will make them a postage stamp for future semesters.

In Spring of 2018, we had over fifteen students enter into the Clinical Research Challenge. From these fifteen students, a team of 4 students were chosen to represent UBSPPS in the second round of the challenge. The challenge included analyzing current research developing in the pharmaceutical field. To test students understanding of the research, a brief written assessment was given. As a pharmacist, being able to analyze medical literature is crucial in order to staying up to date on the newest findings in the profession. The Clinical Research Challenge goes hand-in-hand with the Journal Club that the organization runs every semester. This year's journal club analyzed the LEADER Trial. Students were able to get together and discuss various components of the trial as they taught one another the best ways to evaluate a primary document. The Journal Club prepares our members for the Research Challenge that proceeds it in the following months. The evaluation skills learned from both the Research Challenge and Journal Club are major skillsets that pharmacists will need to draw upon as future clinicians.

Networking also plays a dynamic role in navigating the field of pharmacy. While the pharmacy field may seem like a small profession, it is still important to create relationships with as many people as possible. Two of the best events to grow your network in SCCP are the NYS ACCP conference and the ACCP Annual conference. Held in Syracuse, NY, the NYS ACCP conference discussed current events as well as developing research in the field. It is mostly aimed towards current pharmacists. However, students who attended expressed that they greatly benefited from the knowledge that they accumulated throughout the day. Like the NYS conference, the ACCP Annual conference was a major success. The UBSPPS chapter was lucky enough to have several students present their research poster boards at the conference. This was not only a good experience for students, but proved that UB is a top school in the realm of pharmacy.



Robert Bennett (left) and Rachel E. Meyer (right) present their research at the 2017 NYS ACCP Conference

One word that describes pharmacy school would be overwhelming. There is always work to be done with what seems like no end in sight. It is important to find a portion of pharmacy that interests you or else you may struggle to find it exciting. SCCP is an organization that helps students find their way into the exciting clinical side of pharmacy. The SCCP chapter at UBSPPS is extending itself even further into the student body. The membership drive was one of the most successful in the organization's history at Buffalo, allowing fifty new members to join. The club aims to get students involved in hands on learning experiences outside of the classroom. While it is important to do well in the didactic side of pharmacy, it is just as important to get involved in the real life aspects of pharmacy. SCCP is an active part of the UBSPPS and will continue to give students the ability to grow in their education.

-Christopher Brighton, PharmD Candidate, UBSPPS Class of 2021

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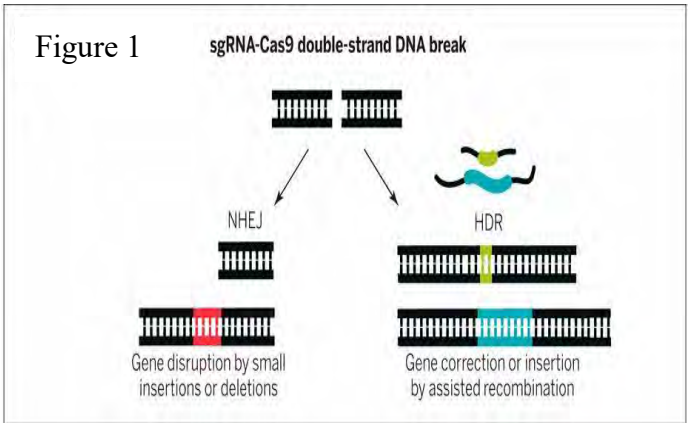
Dinner & Discussion with Dr. Robert Wahler Jr., PharmD, CPE (left) on providing palliative end-of-life care to hospice patients

CRISPR/Cas9 and its Clinical Applications

The recently discovered CRISPR (clustered regularly interspaced palindromic repeats)/Cas9 (CRISPR-associated protein) system exists in nature as an adaptive bacterial defense mechanism that serves to recognize and silence incoming foreign genetic elements such as plasmids and bacterial viruses.[1] CRISPR stores the DNA sequences of invading foreign genetic material and upon reinvasion of the same element, the system recognizes it and directs the Cas nuclease to induce a double-stranded DNA cleavage.[2] Upon excision, the DNA repair mechanism is used to induce either non-homologous end joining (NHEJ) or homologous directed repair (HDR) by inserting a specific DNA sequence as seen in Figure 1.[3, 4]



Doudna JA, Charpentier E (2014) Genome editing. The new frontier of genome engineering with CRISPR-Cas9. Science 346: 1258096

This innovative gene editing system has been widely used as a research tool, but its therapeutic application for treating genetic disorders has a particularly exciting future direction.

For instance, CRISPR/Cas9 can be used to treat monogenic recessive disorders due to loss-of-function mutations such as cystic fibrosis, sickle-cell anemia, or Duchenne muscular dystrophy by correcting the causative mutation. In dominant-negative disorders such as familial amyloid polyneuropathy and retinitis pigmentosa, NHEJ repair mechanism can be utilized to inactivate the mutated allele to achieve therapeutic benefits.[5]

It is to note that its therapeutic application is not limited to solely repairing mutations in inherited disorders. Lombardo et al. inactivated CCR5 receptor in lymphocytes through the NHEJ-mediated method which may be a viable strategy for fighting HIV infections.6 This technology can also bring curative effects against statin-resistant hyperlipidemia or hypercholesterolemia through deletion of orangiopoietin and PCSK9.[7, 8] Additionally, it can be used to engineer therapeutic cells. For instance, Couzin-Frankel modified the chimeric antigen receptor T cells ex vivo and reinfused the cells into a patient for specific cancers cell targeting.[9]

As seen above, there are variety of clinical applications to the new genome editing technology. Nevertheless, there are still challenges that must be overcome. Even though, permanent genome modification has advantages over repeated administrations like siRNA treatments, which requires continuing therapy, the long-term physiological effect is yet unclear. Additionally, it is imperative to have safe and efficacious delivery systems to the specific disease sites for genome editing therapy. One of the biggest concerns of the application of CRISPR/Cas9 is the production of off target mutations, resulting in detrimental effects to the patient. In fact, a higher frequency of off target effects has been found in human cells in comparison to mice cells; thus, researchers must find ways to minimize such adverse effects before this application can be fully utilized in clinical settings. Once such safety has been proven, it is clear that this technology will go beyond simply reducing the symptoms of disease, but cure it.

- Se Jin Kim, PharmD Candidate, UBSPPS Class of 2021

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New Drug Review: Symdeko™ (Tezacaftor-Ivacaftor)

What Is It:
Tezacaftor/ivacaftor (Symdeko™) is a novel combination drug developed by Vertex Pharmaceuticals recently approved with orphan drug status in February 2018 by the FDA for the treatment of cystic fibrosis (CF).

What Does it Treat:
CF is an autosomal recessive genetic disease that is caused by mutations in the CFTR gene, which codes for the CFTR transport protein. This chloride transporter is commonly found on epithelial cells and allows for the passage of chloride ions. This in turn, regulates the movement of sodium ions and water.

The mutations in CFTR seen with CF patients are divided into 5 classes based on resulting type of defect and the degree of function. Class I disrupts the translation of the CFTR mRNA which results in no CFTR protein present. Class II mutations result in decreased production and misfolding of CFTR protein. The most common mutation, termed F508del, which accounts for 86.2% of all CF mutations, falls into this class. Class III, known as gating mutations, result in normal protein production however they are not functional due to an inability to open. The most common mutation in this class is G551D. Class IV also results in normal protein production; however, only some allow for chloride transport due to narrower channels. Class V mutations, the least common, result in decreased but fully functional CFTR protein.

Common manifestations of CF include pulmonary infections, exocrine dysfunction, digestive problems, thick mucus build up in the lungs, and severe breathing difficulties. These can be chronically debilitating, resulting in a life expectancy of 37 years in the United States. Symdeko™ has been approved for treatment of CF in patients age 12 years and older with two F508del mutations or any 1 of 26 single mutations approved by the FDA.

Mechanism of Action:
Ivacaftor increases channel opening for patients with Class III and Class IV mutations. Tezacaftor increases delivery of CFTR transporters to the cell surface. Hence, they work together to increase both the quantity and quality of CFTR proteins present on epithelial cells.

Dose:
Symdeko™ is taken by mouth as 1 yellow tablet of Tezacaftor 100 mg/ivacaftor 150 mg in the morning and 1 blue tablet of Ivacaftor 150 mg in the evening about 12 hours apart. No dosage adjustments are required for mild hepatic and renal impairment. The evening dose of 150 mg Ivacaftor is omitted in moderate-severe hepatic impairment. No studies have been done in severe renal impairment or ESRD; however, caution is recommended. This medication should be taken with food to improve absorption. It should not be taken with strong CYP3A inducers or inhibitors, since these will alter the metabolism and exposure of the drug. In the event of a missed dose that is 6 hours or less, the missed dose can be taken. If more than 6 hours has passed, the missed dose should be omitted and the next dose should be taken at the usual time.

Adverse Drug Events:
The most common side effects include headache, nausea, sinus congestion, cough, and dizziness. Symdeko™ may also cause elevated AST and ALT and may lead to the development of cataracts. These should be monitored before and during treatment.

Studies Involved in Approval:
Three Phase III clinical trials demonstrated benefit for CF patients taking Symdeko™. The most influential was the EVOLVE trial, sponsored by Vertex Pharmaceuticals, which examined the safety and effectiveness of Symdeko™ in 509 CF patients age 12 years and older with two copies of the F508del mutation. The study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study that lasted 24 weeks. It was conducted in 91 sites across the U.S., Canada, and Europe. Patients were randomized in a 1:1 ratio to be in the treatment group or the placebo group. The randomization was stratified by age, sex, and baseline FEV_1.

The treatment group received 100 mg tezacaftor/150 mg ivacaftor in the morning and 150 mg ivacaftor 12 hours later. The placebo group followed a regimen of visually similar tablets taken as the same regimen. Key inclusion criteria for the study included homozygous F508del mutations, diagnosis of CF defined as sweat chloride greater than 60 mmol/L, and FEV% greater than 40 and less than 90% of normal. Key exclusion criteria included comorbidities that could act as confounders, any respiratory infection, exacerbation, or change in therapy within 28 days, and pregnant and nursing women.

The primary outcome examined was the absolute change in percent predicted forced expiratory volume in one second (FEV_1) from baseline through week 24 as well as numerous secondary outcome measures including change in BMI, CFQ-R domain score, change in sweat chloride, and number of pulmonary exacerbations. Of the 475 CF patients who completed the study, the mean FEV_1 at baseline was 60.0% of the predicted value. The mean absolute change from baseline through week 24 was 3.4% points in the treatment group compared to 0.6% points in the placebo group. Moreover, there was a 35% reduction in pulmonary exacerbations in the treatment group compared to the placebo group.

Overall, the study found CF patients 12 years and older with two F508del mutations or any mutation in chromosome 26 benefited from taking Symdeko™.

- Jessica Greger, PharmD Candidate, UBSPPS Class of 2019, UB SCCP P3 Student Liaison and Melissa Dhanraj, PharmD Candidate, UBSPPS Class of 2020

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On The Rise: Pharmacy-Run Anticoagulation Services in the Outpatient Setting Improves Patient Outcomes

Warfarin is often referred to as the "gold-standard" of anticoagulation therapy even though newer standards and medications have been developed. Over 30 million prescriptions are written for warfarin annually.[1] As a Vitamin K antagonist, it reduces the body's ability to clot; and thus, it's indicated for patients presenting with atrial fibrillation (AF) or with venous thromboembolism (VTE)—all of which put a patient at a higher risk for thromboembolic stroke. Recently, a new study emerged that surveyed over 2,000 patients, showing a positive correlation between community pharmacy-run anticoagulation services and therapeutic outcomes for patients. Not only can these pharmacy-run clinics deliver convenience and improve access to care, they have been shown to overall improve the welfare and therapeutic outcomes for patients.

First and foremost, due to an extremely narrow therapeutic index, warfarin is closely monitored in the inpatient setting via a blood test in which the INR is measured. It is also the most frequently used oral anticoagulant in the community.[2] This lends to a dismal statistic: according to national public health surveillance data, warfarin led to 17% of emergency department visits, and two-thirds of warfarin-related hospitalizations stemmed from toxic levels of warfarin in the blood linked to prolonged INR.[3] Treatment choices for patients, however, continue to expand as newer medications such as dabigatran and rivaroxaban offer the convenience of not requiring routine monitoring. While these novel anticoagulants may provide convenience and reduce visits to the doctor, a team of researchers at the Mayo Clinic have determined: "individuals over age 75 have a much higher risk of GI bleeds than younger patients, if using dabigatran or rivaroxaban instead of warfarin."[4] Therefore, uneclipsed and predominant within the outpatient setting, warfarin monitoring services remains to be an invaluable factor in optimal therapy.

A recent study uncovered how "ideally placed" community pharmacy is in delivering safe and effective anticoagulation services for patients requiring warfarin monitoring.[5] Boots UK, a chain pharmacy in the United Kingdom, and the University of Brighton teamed up to focus on the "outcomes and experiences patients attending the anticoagulation monitoring service provided by community pharmacists in Brighton and Hove."[6] In their study, Ingram, Kirkdale, and others reviewed outcome measures in over 2,000 patients where Community Pharmacy Anticoagulation Service (CPAMs) were incorporated: that is, the study considered nine Boots pharmacies and eight independently owned pharmacies. The transition from hospital associated anticoagulation clinics to pharmacy run clinics showed promising results: "community pharmacy managed anticoagulation services can achieve outcomes at a level consistently exceeding national and local targets for both percentage INR readings in therapeutic target range (65.4%) compared to the recommended minimum therapeutic target range of 60.00% and percentage time in therapeutic range (72.5%, CI 71.9%-73.1%) compared to the national target of 70.0%"[7]. In addition, patients scored the service highly and submitted positive feedback as over 98.6% of patients ranked their service either as good or excellent.[8]

Monitoring warfarin levels and not being able to act upon the results may negatively affect the value of the service. That is, pharmacists who complete Point of Care (POC) testing training, CITI training, and have established a collaborative practice agreement (CPA) with a physician "allows for the screening and treatment process to be completed during a single encounter, thereby improving access to care, counseling, and patient outcomes."[9] One example to mention is the Buford Road Pharmacy in Virginia, which provides POC testing and anticoagulation monitoring. During a visit at their anticoagulation clinic, the pharmacist gathers an INR measurement with the use of CoaguChek XS device. The device procures a result from a finger prick within two minutes. Consequently, the patient may review their results and have dosing adjustments applied if it is indicated—without prior approval from a physician as per collaborative practice agreement.

Patients coming to refill their warfarin prescriptions or even seeking an OTC, for instance, find convenience in an on-site anticoagulation clinic since they're already at the pharmacy.[10] Services are walk-in as well as by appointment. Not only convenience but affordability adds into the equation: "these services [are] at a reduced cost to the patient through the use of strategies such as limited administrative costs, use of student pharmacists, community pharmacy residents, and competitive pricing on products and services that are not covered by insurance."[11] INR readings alongside A1C tests and cholesterol screenings all fall under CLIA-waived tests; pharmacists have been performing such tests for years. It is worthwhile to note that even without a CPA, simply offering affordable, accessible low-risk testing at the pharmacy increases the likelihood a patient will see their physician.[12]

With the ever-changing scope of pharmacy practice, pharmacists further build the case to be recognized as providers. Firstly, when we consider the abundance of community pharmacies in the US, ranging from 59,000-67,000, we find 92% of Americans reside within 1.6 miles of a pharmacy.[13] The "ideally placed" community pharmacy is an accessible point for care and an affordable option for patients. Not only in regard to pharmacy-run anticoagulation clinics, but we see the pharmacist's role expanding into POC testing for other chronic disease management such as HIV and HCV, as well as acute infectious diseases: influenza and Strep A. The shift garners an open and even welcoming response from patients, as studied by Michael Klepser, PharmD, FCCP, who also is a faculty member of FSU College of Pharmacy. In Klepser's studies within community pharmacies involving POC tests for HIV, 96% of participants stated they were comfortable with a pharmacist preforming a finger-stick test.[14] Without a doubt, patient trust factors heavily into optimal healthcare. Pharmacists continue to grow their reputation by playing an active role within the community. According to the National Community Pharmacists Association (NCPA), "Point-of-care testing is predicted to exceed immunizations as a driver of revenue for community pharmacies, according to research from Deloitte."[15] Community pharmacy, especially those that establish a CPA, is in a good position to improve patient therapeutic outcomes not just with warfarin monitoring, but with other chronic disease management, and even acute infections—improving access to care and affordability.

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Outcomes of Dabigatran vs. Warfarin for Atrial Fibrillation in Contemporary Practice: A Summary

Introduction

Using the FDA's national electronic system, the Mini-Pilot Sentinel System, orally-dosed dabigatran was compared to adjusted dose warfarin for both thromboembolic and safety risk parameters. While previous studies (RE-LY trial) stated dabigatran (150 mg twice daily) being superior to warfarin in reducing both stroke and systemic embolism rates, additional data from RE-LY and meta-analyses suggested dabigatran having increased rates of myocardial infarction/acute coronary syndromes, as well as higher extracranial (specifically gastrointestinal) bleeding rates in patients ≥80 years old. As such, this study sought out to organize previous data and provide additional insight on these two anticoagulant therapies.

Pharmacology

Anticoagulants are a class of drugs that prevent formation of clots, thereby preventing stroke, pulmonary embolism, DVTs, and myocardial infarctions. Although both warfarin and dabigatran are anticoagulants, their pharmacologic mechanisms of action and targets differ. A clotting factor vital to the clotting process is thrombin, which activates fibrinogen to fibrin, forming the platelet plug. Warfarin is an *indirect thrombin inhibitor*, acting through depletion of active vitamin K reserves to inhibit synthesis of clotting factors (II, VII, IX, X) and proteins (C and S). Dabigatran, however, is a *direct thrombin inhibitor*, reversibly inhibiting both fibrin-bound and free thrombin.

Study Participants

Participants were those ≥21 years of age initiating dabigatran or warfarin therapy for nonvalvular atrial fibrillation between November 1, 2010 to May 31, 2014. The atrial fibrillation must have been diagnosed at most a year before the dabigatran or warfarin therapy was first dispensed (index date). Exclusions included those: with less than a year of continuous therapy and medical coverage from the index date; prior dispensing of oral anticoagulants throughout the year before the index date; with prior kidney transplant(s); on long-term dialysis before the index date; with known mechanical heart valve or mitral stenosis; residing in a nursing home/skilled-nursing facility during the index date.

Trial Design

By utilizing the FDA's Sentinel Distributed Database, a retrospective analysis with a "new user" parallel cohort design was implemented. The analysis focused mainly on initiation and longitudinal exposure to either dabigatran or warfarin using outpatient pharmacy dispensing data. To consider the patients as having been continuously exposed to the medication, a grace period of up to 7 days between prescriptions was allowed. Patients for each drug had been propensity score-matched and followed through until the available data had ended or been censored.

Primary outcomes of interest were occurrence of all strokes (including ischemic stroke), myocardial infarction, intracranial hemorrhage, and major episodes of extracranial hemorrhage. These outcomes were identified using primary discharge diagnoses.

Statistical Analysis

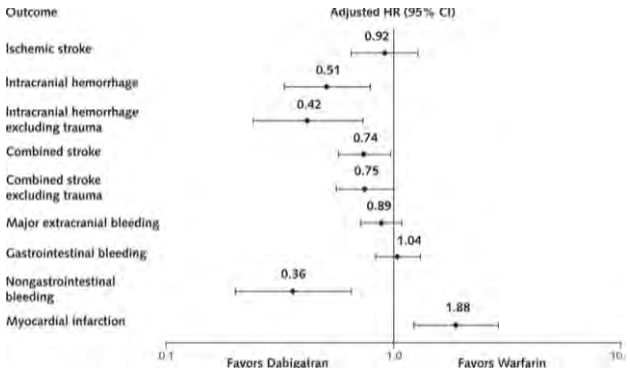
The rates of primary outcomes for dabigatran were compared against those for warfarin. Propensity scores for starting dabigatran therapy were estimated to construct a matched cohort and used to match them with those receiving warfarin in a 1:1 ratio. Cox proportional hazards regression was used to compare the incidence of stroke, bleeding events, and myocardial infarctions. In addition to sensitivity analyses, subgroup analyses were performed to find if there were any differential associations between treatment groups and outcomes in prespecified subgroups by age (<65 years, 65-74 years, 75-84 years, and ≥85 years), sex, and reduced kidney function.

Results

Ischemic stroke and intracranial hemorrhage:

The hazard ratio for ischemic stroke in the dabigatran group when compared to warfarin was 0.92 (95%CI, 0.65-1.28). The difference in the incidence of ischemic stroke between the two groups were not statistically significant. For intracranial hemorrhage, the hazard

ratio was 0.51 (95% CI, 0.33-0.79). The dabigatran group had a lower rate of intracranial hemorrhage, which was found to be statistically significant.



Major extracranial bleeding:

The hazard ratio for major extracranial bleeding (primarily gastrointestinal) in the dabigatran group when compared to warfarin was 0.89 (95% CI, 0.72-1.09). The primary analysis and sensitivity analyses. found no difference in the rate of GI bleeding. However, subgroup analyses found that rates of GI bleeding were higher with dabigatran in patients aged 75-84 and 85 or older, as well as those with reduced kidney function.

Acute myocardial infarction:

In the primary analysis, the hazard ratio for acute myocardial infarction in the dabigatran group when compared to warfarin was 1.88 (95% CI, 1.22 to 2.90). Sensitivity analyses showed a smaller and not statistically significant difference in the occurrence of this outcome. Subgroup analyses also showed a significant association between dabigatran and myocardial infarction in men (HR 2.09, 95% CI, 1.17-3.64) not women, as well as stronger associations in patients aged 75-84 (HR 4.09, 95% CI, 1.39-12.03) and 85 or older (HR 5,25, 95% CI, 1.17-23.60).

Critiques

This study had several limitations. There was no access to information on INR values, which would have helped the investigators determine longitudinal exposure more accurately and assess the quality of anticoagulation. Outcomes by dabigatran dose could not be examined, as the investigators could not achieve covariate balance between matched users by dabigatran dose.

Another limitation was the relatively short duration of the study, which had a median continuous follow-up of 123 days for patients on dabigatran and 102 days for patients on warfarin. The short follow-up period limited precision for some outcomes. Outcomes that occurred after withdrawal of dabigatran or warfarin were also not addressed.

Medication adherence also could not be assessed directly. Outpatient pharmacy dispensing data was the best alternative, but it may not be accurate in determining whether patients were truly continuously exposed to their treatment. Additionally, only commercially insured patients were studied, and it is uncertain whether the results of this study could be generalized to the uninsured or to all other patients.

Conclusion

Compared to warfarin use, dabigatran use in adults with atrial fibrillation was associated with a lower rate of intracranial hemorrhage, similar rates of ischemic stroke and extracranial hemorrhage, and possibly a higher rate of myocardial infarction. The reduced risk of intracranial hemorrhage and increased risk of GI bleeding in older patients was consistent with the results of the RE-LY trial which was referenced earlier. However, the association between dabigatran and myocardial infarction showed variability of findings in several analyses, and thus should be further investigated.

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–Jack Chen, PharmD Candidate, UBSPPS Class of 2021

Questions?

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