Impacts of Pharmaceutical Marketing on Healthcare in the District of Columbia

The Marketing and Prescribing of Anticoagulants in the District of Columbia

Government of the District of Columbia
Department of Health
Health Regulation and Licensing Administration

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Key Findings

Introduction

Stroke is a major health concern in the District of Columbia. According to the 2016 DC Community Health Needs Assessment, 3.2% of DC residents have had a stroke. Notably, the rates of stroke were highest in the 7th and 8th wards, where 5.7% and 5.5% percent of the population, respectively, had strokes (Merrill 2016). DC has an all stroke death rate of 34.0 per 100,000 overall (CDC 2016).

In 2015, the anticoagulant drugs Xarelto and Eliquis, often prescribed to prevent or treat strokes, were the drugs associated with the highest frequencies of gifts to physicians in the District of Columbia, with 691 and 639 gifts, respectively, reported to the CMS Open Payments system (Eckert 2017). While marketing payments decreased in 2016 for Xarelto and Eliquis, Medicaid and Medicare expenditures and prescription claim counts have continued to increase in the District. These highly marketed anticoagulants, along with Pradaxa, are important to continue to monitor, especially when less expensive and potentially safer alternatives are available. This report examines the promotion, use, and reimbursements of anticoagulants in the District of Columbia and follows up on the 2017 Impacts Report, *The High Cost of Highly Promoted Drugs in the District of Columbia*.

Anticoagulant Costs to Medicare and Medicaid

This report compares reimbursements by Medicare and Medicaid and marketing expenditures for three direct-acting oral anticoagulants (DOACs), Xarelto, Eliquis, and Pradaxa; a vitamin K antagonist, warfarin; and a platelet inhibitor, Plavix.

Among anticoagulants, Medicaid reimbursements have increased the most for Xarelto, a factor Xa inhibitor that accounted for $1.5 million in Medicaid reimbursement in the District of Columbia in 2016. This amount was more than seven times higher than the total Medicaid reimbursement for Eliquis, which had the second highest Medicaid reimbursement for anticoagulants ($202,896). In 2016, Xarelto had a higher total Medicaid prescription count than warfarin (4,174 vs. 3,402), an effective, established generic drug that had the second highest number of Medicaid prescriptions. This is an important point in DC Medicaid drug utilization, because prescriptions for an expensive branded drug have overtaken an inexpensive, generically available medication. In terms of prescription count in 2016, the generic form of Plavix, clopidogrel, had the largest number of total Medicaid prescriptions.

Medicare claims costs for Eliquis were the highest among all anticoagulants at $3.3 million. Xarelto had the next highest total Medicare claims cost with $3.0 million, followed by Pradaxa with $1.1 million. Clopidogrel had the highest number of Medicare claims among anticoagulants in 2016, with 17,318 claims; warfarin had 10,893 claims.

Drug Promotion in DC

In 2016, pharmaceutical and device manufacturers reported spending a total of $99.2 million in gift, advertising, and aggregate (detailing) expenses in the District of Columbia. Of the total amount reported, $81.2 million was reported to the DC AccessRx program, compared to the $18 million reported to the Federal Open Payments program. The following are the totals for marketing expenditures in DC in 2016.

- ***Aggregate (Detailing) Expenses*** accounted for $62.8 million (63.4%)
- ***Gift Expenses*** accounted for $24.7 million (24.9%)
- ***Advertising Expenses*** accounted for $11.7 million (11.8%)

Manufacturers spent more than $750,000 in gifts to physicians and teaching hospitals, marketing Xarelto, Eliquis, and Pradaxa in DC between 2014 and 2016. Among anticoagulants that were associated with marketing payments in DC, Eliquis has the highest total value of reported marketing payments since Open Payments began publishing data in August 2013. There was a decrease from 2014 to 2016 in marketing payments for both Eliquis and Pradaxa between 2013 and 2014. Gifts for Xarelto increased between 2013 and 2015, then decreased slightly in total value from 2015 to 2016.

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Methods and Data Sources

Medicare and Medicaid Prescriptions and Expenditures

Data for Medicaid expenditures for the years 2010 to 2016 were obtained from the Centers for Medicare and Medicaid Services (CMS) website.[*] Data from each year since a drug was approval, whenever available, were included in analysis including partial years after approval. In accordance with Federal guidelines, certain prescription information has been suppressed to protect private individual information, when less than eleven prescriptions were recorded for a drug in the District.[†] Medicare claims data were obtained from the CMS website.[‡] Data about Medicare claim counts and costs were available from 2013 to 2016 at the time of this report. It is important to note that data for Medicare and Medicaid costs and reimbursements do not take into account any rebates.

AccessRx Data and Open Payments Data

The District of Columbia's AccessRx Act of 2004 requires pharmaceutical companies to report marketing expenditures to the District of Columbia Department of Health (DC DOH). The DC DOH has been collecting information on pharmaceutical marketing since 2007, and researchers at the George Washington University Milken Institute School of Public Health analyze this information for DC DOH annually.

AccessRx data provide a wealth of information that no other jurisdiction in the US can match. The Physician Payments Sunshine Act of 2010 established the national Open Payments system that requires all pharmaceutical and medical device manufacturers to report payments to physicians and teaching hospitals to the Centers for Medicare and Medicaid Services (CMS). Marketing data from Open Payments contained data from 2013 through 2016. Data from 2013 were omitted from analysis because marketing information was only available for the second half of the year.

AccessRx and Open Payments serve similar purposes but capture different sets of data. Open Payments only requires companies to report on gifts given to physicians and teaching hospitals. The DC DOH AccessRx program is more comprehensive, requiring reporting for all other licensed healthcare providers (e.g. nurses, nurse practitioners, physician assistants, and pharmacists), non-teaching hospitals, healthcare staff, and organizations. Only AccessRx picks up gifts received by nurse-practitioners (NPs), nurse midwives, nurse anesthetists, physician assistants (PAs), podiatrists, and optometrists.

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[*] Medicaid data were obtained from this website: https://www.medicaid.gov/medicaid/prescription-drugs/drug-utilization-review/annual-reports/index.html

[†] A full explanation of which data are not publicly available can be found here: https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html

[‡] Medicare data were obtained from this website: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html

Furthermore, only AccessRx collects information on salaries and other payments for detailers and other personnel (employees and contractors) involved in marketing pharmaceuticals in the District. This "*Aggregate (detailing) Expenses"* category, was the largest share of marketing expenditures in DC in 2015, with more than $66 million reported. AccessRx also tracks expenditures on local advertising, including District-specific print, television and other advertisements. Another advantage AccessRx has over Open Payments is that AccessRx data go back to 2007, enabling analysis of changes over time. The first full year of Open Payments data is from 2014.

The AccessRx program releases two reports annually. The *Expenditures Report* documents annual pharmaceutical marketing expenditures for gifts (to physicians, other healthcare professionals, hospitals, and other organizations), advertising, and the salaries of detailers. The second report, *Impacts of Pharmaceutical Marketing on Healthcare in the District of Columbia*, considers how pharmaceutical marketing may affect health and healthcare in the District.

Previous *Impacts* reports include:

- *The High Cost of Highly Promoted Drugs in the District of Columbia* (2017)
- *Diabetes in the District* (2016)
- *Reporting Changes and the Effect of Gifts on Prescribing Behavior* (2015)
- *Focus on Gifts to Organizations and Influential Physicians* (2014)
- *Focus on Use of Antipsychotics in Seniors* (2013)
- *Report on the Use of Antipsychotics in Children* (2012)

Open Payments data, including physician names, are publicly available.[§] Payments to physicians and teaching hospitals are searchable online through Open Payments, allowing researchers to track patterns in gifts. Individual patients can see whether their physicians have accepted gifts from pharmaceutical companies. Although AccessRx reports are publicly available, the names of prescribers, nurses, office staff, technicians, and other people or organizations that receive payments and other gifts are confidential. Company-level expenses on advertising, drugs reps, and other marketing personnel are also confidential. Details are available only to DC DOH.

[§] Open Payments data were obtained from this website: https://openpaymentsdata.cms.gov/

I. Background on Strokes in the US and in DC

Each year, more than 795,000 people have strokes in the United States; 185,000 are recurrent strokes (Benjamin 2017). The overall rate of stroke mortality has been decreasing in the US since the early 1900s (Lackland 2014). Some potential reasons for decreased stroke mortality are increased knowledge on risk factor management, as well as major pharmacological advances in the treatment of cardiovascular disease and stroke (Mensah 2017).

Although stroke mortality has decreased overall, since 2011 there has been a deceleration in the decrease of cardiovascular disease, heart disease, and stroke mortality (Sidney 2016). From 2013 to 2015, there was a non-significant increase of 2.5% (95% CI: -1.6 to 6.9) in stroke mortality rates in the United States; among Latinos, there was a significant increase of 5.8% (95% CI: 2.1 to 9.6) (Yang 2017).

There are three main types of stroke: ischemic, hemorrhagic, and transient ischemic attack. Ischemic strokes occur when blood flow in an artery that supplies oxygen to the brain becomes blocked. They are often caused by blood clots. Hemorrhagic strokes occur when an artery in the brain leaks blood or ruptures leading to too much pressures on brain cells and causes damage. They are often caused by high blood pressure and aneurysms. Transient ischemic attacks ("mini-strokes") occur when blood flow to the brain is blocked only for a short time (CDC 2018).

About 87% of strokes that occur in the United States are ischemic strokes, caused by blood clots; the remainder are hemorrhagic, or bleeding strokes. It is estimated that strokes cost the United States up to $34 billion each year, including the cost of medications, other health care services, and missed days of work (Benjamin 2017). Nationally, stroke is responsible for about 140,000 American deaths each year, nearly 1 out of every 20 deaths (Yang 2017).

According to the 2016 DC Community Health Needs Assessment, 3.2% of DC residents have had a stroke. The rates of stroke were highest in Wards 7 and 8, where 5.7% and 5.5% percent of the population, respectively, had strokes (Merrill 2016). DC has a stroke death rate of 34.0 per 100,000 residents overall (CDC 2016).

Table 1: Stroke Death Rate per 100,000 in DC, 2013-2015[**]

Race or Ethnicity	DC Value	National Value
All Race	34.0	36.8
Black (Non-Hispanic)	42.0	51.3
White (Non-Hispanic)	21.9	35.7
Hispanic	25.0	30.9
American Indian and Alaskan Native	Insufficient Data	31.9
Asian and Pacific Islander	Insufficient Data	29.7

[**] **Source:** Interactive Atlas of Heart Disease and Stroke: U.S. Department of Health & Human Services 2016. https://nccd.cdc.gov/DHDSPAtlas/Reports.aspx

Risk Factors for Stroke

Patients with atrial fibrillation, a quivering or irregular heartbeat, are at higher risk of thrombotic (clot) strokes. Atrial fibrillation increases with age; approximately 9% of people age 65 or older have atrial fibrillation (CDC 2017).

Contributing factors to stroke include smoking, poor diet, overweight, physical inactivity, and excessive alcohol consumption. The Centers for Disease Control and Prevention (CDC) recommends managing these lifestyle factors by not smoking; maintaining a healthy diet consisting of plenty of fresh fruits and vegetables and choosing foods low in saturated fats, trans fat, and cholesterol and high in fiber; maintaining a body mass index (BMI) of less than 25, exercising at a moderate intensity for at least 150 minutes per week, and limiting alcohol consumption to no more than two drinks per day for men and one drink per day for women (CDC Healthy Lifestyles 2018).

The overall obesity rate in the District of Columbia is 22.8%. Ward 8 has the highest rate of obesity at 42.8%. One out of six (16.4%) adults in the District smokes; Wards 7 and 8 have the highest rates of smoking with 30.7% and 33.1%, respectively. The rate of physical inactivity in the District of Columbia is 20.8%. Wards 7 and 8 have the highest rates of physical inactivity with 32.3% and 41.6% respectively (Garner 2016).

II. Background on Anticoagulants

Overview

Anticoagulants are used to reduce the risk of or treat thromboembolic events, including stroke, heart attack, and pulmonary embolism. This section reviews the range of anticoagulant medications currently marketed in the United States.

There are three categories of anticoagulants: vitamin K antagonists, platelet inhibitors, and direct-acting anticoagulants (DOACs), which are also called new or novel oral anticoagulants (NOACs). Warfarin (Coumadin) is the only vitamin K antagonist used in the US. Platelet inhibitors include aspirin, clopidogrel (Plavix), ticragelor (Brilinta), and prasugrel (Effient). Direct-acting oral anticoagulants (DOACs) include dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa) (Hinojar 2015). A serious risk of anticoagulants is risk of major bleeding and there is need for an effective and timely reversal agent for these medications, as discussed below.

Warfarin is superior to antiplatelet agents for reducing stroke/systemic embolism and ischemic stroke. Some systematic reviews found an increased risk of major bleeding with warfarin, compared to antiplatelet agents; others found no difference (Sommerauer 2017).

Sixteen systematic reviews compared DOACs to warfarin with participants 65 years or older with atrial fibrillation treated with oral anticoagulation. DOACs collectively were superior to warfarin for reducing stroke, systemic embolism, and major and intracranial bleeds; however, DOACs caused more gastrointestinal bleeds than warfarin. DOACs had no advantage over warfarin for preventing myocardial infarctions, but were superior to warfarin for reducing mortality (Sommerauer 2017).

Warfarin (Coumadin)

Warfarin, a vitamin K antagonist, has been the standard of care for stroke prevention in patients with non-valvular atrial fibrillation since its approval in 1954. A generic version of warfarin has been available since 1997. Warfarin is an inexpensive, effective, and proven anticoagulant. A systematic review of systematic reviews and meta-analyses found that in seven systematic reviews, warfarin was effective for reducing stroke/systemic embolism, ischemic stroke, and mortality. Some but not all of the included systematic reviews and meta-analyses found an increased risk of major bleeding (Sommerauer 2017).

Warfarin's effects can be quickly and effectively reversed with vitamin K, (Hanslik 2004) prothrombin complex concentrate (PCCs), (Wozniak 2012) or fresh frozen plasma (Hall 2012). Warfarin requires blood monitoring and interacts with many drugs and food. Patients discontinuing warfarin may be at risk for a thromboembolic complication; in a clinical trial, 19% of patients treated with warfarin as prophylaxis after myocardial infarction experienced hypercoagulability after discontinuation (Grip 1991).

The international normalized ratio (INR) is a measure of anticoagulation used to determine warfarin doses and, once a dose is established, should be checked every few months or after a patient starts or stops a drug, dietary supplement, or new diet. As long as patients' blood tests are stable within a safe range, warfarin is a reasonable choice as an anticoagulant (The Medical Letter 2013).

Many drugs and herbs also interact with warfarin, which may cause a change in the INR (Beikang 2014). Warfarin binds to albumin, and medications that displace warfarin binding (including ibuprofen, losartan, valsartan, amlodipine and quinidine) can increase warfarin's anticoagulant effects (Vranckx 2018). Warfarin is metabolized by cytochrome P450 2C9 and 3A4, so medications affecting theses isozymes can also affect warfarin levels. Warfarin also interacts with nonsteroidal anti-inflammatory drugs, acetaminophen, and many antibiotics (Ament 2000).

Leafy greens and other foods high in vitamin K can reverse warfarin's effect. Although patients are often misinformed that they must not consume leafy greens and other vegetables high in vitamin K, this is not sound advice. Not only are these highly nutritious foods, but INR levels are easier to stabilize against a background of consistent intake of vitamin K-containing foods (Vranckx 2018). The amount of vitamin K-containing food does not matter as long as a patient's intake is relatively consistent.

Platelet inhibitors

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits platelet aggregation and has been used to lower the risk of heart attack and stroke. It is inexpensive, effective, and available over the counter. Aspirin has been shown to reduce the risk of a second heart attack or stroke; it may also prevent a first heart attack or stroke (NIH 2018).

Clopidogrel (Plavix) is an additional platelet inhibitor that can be effectively used for prevention of recurrent stroke in conjunction with, or as an alternative to, aspirin. It is indicated for acute coronary syndrome, recent myocardial infarction, recent stroke, or established peripheral arterial disease. Clopidogrel has a black box warning indicating elevated risk of cardiovascular events for patients with poor CYP2C19 metabolism (Plavix 2018).

Although the combination of Plavix with aspirin is associated with higher rates of bleeding than aspirin alone, it is an effective shorter-term stroke prevention treatment (≥90 days) (Tan 2015) and is superior to aspirin alone for patients with peripheral arterial disease; for other conditions, however, aspirin is still the recommended course of treatment in the majority of patients (Prescrire 2009).

Brilinta (ticragelor) and Effient (prasugrel) are also platelet-aggregation inhibitors. Ticragelor is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction. Effient (prasugrel) is indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis)

in a subset of patients with acute coronary syndrome. Both carry warnings about bleeding risks. Ticragelor also carries a warning about combining with aspirin; doses of aspirin more than 100 mg/day decrease the effectiveness of ticragelor (Brilinta 2018, Effient 2018).

Direct Oral Anticoagulants (DOACs)

Direct oral anticoagulants (DOACs) are being prescribed at similar rates as warfarin for anticoagulation therapy for patients with atrial fibrillation in the United States (Barnes 2015). DOACs include dabigatran (Pradaxa), a thrombin inhibitor, and all of the drugs that inhibit factor Xa, including rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa) (Hinojar 2015). DOACs target a specific enzyme involved in coagulation; by preventing platelet activation, clot formation is inhibited. DOACs are expensive medications, and no DOAC is available as a generic. Drugs.com, a source of drug pricing information, reports that rivaroxaban (Xarelto) costs up to $1,446 for 100 10mg tablets. In contrast, Drugs.com reports that warfarin is much less expensive, costing up to $52 for 100 10mg tablets.

In contrast with warfarin, DOACs do not require blood monitoring (Massachusetts Department of Health and Human Services 2018) or dietary restrictions (The Medical Letter 2013). However, risks of severe bleeding and the lack of timely reversal agents for many of these remain. Harms associated with DOACs include bleeding, rebound ischemic events, and drug interactions.

Bleeding

Although all anticoagulants can precipitate bleeding events, Xarelto use precipitates a disproportionate number of adverse events. A 2016 analysis of FDA data by the Institute for Safe Medication Practices showed that anticoagulant drugs caused 21,996 serious adverse events (primarily hemorrhages) in the U.S., including 3,018 deaths (QuarterWatch 2017). The largest number of serious adverse events in the United States were related to rivaroxaban (Xarelto).

DOAC drugs carry a black box warning regarding the risk of epidural or spinal hematomas, possibly leading to paralysis, occurring in patients who receive neuraxial anesthesia, or undergo spinal punctures. This warning appears on rivaroxaban, edoxaban, dabigatran, apixaban, and betrixaban.

When bleeding occurs, edoxaban and betrixaban lack timely and effective reversal agents. Warfarin's effects can be reversed within 10-15 minutes by a combination of prothrombin complex concentrate (PCC) and intravenous vitamin K (Hanley 2004). Dabigatran, apixaban, and rivaroxaban also have FDA-approved reversal agents. Although andexanet alfa (Andexxa), the reversal agent for rivaroxaban and apixaban, can reverse anticoagulant effects within minutes, reversal of some DOACs can take many hours. For example, the reversal agent for dabigatran (Pradaxa) is idarucizumab (Praxbind), which is very slow-acting (Prescrire 2016); in a clinical trial, patients treated with idarucizumab had a median time to bleeding cessation of 11.4 hours (Hutcherson 2017).

Rebound Ischemic Events

DOACs are short-acting and require strict adherence to mitigate risk of thrombosis (The Medical Letter 2013). Discontinuation of DOACs presents a "bounceback" or rebound risk of hypercoagulation and subsequent thromboembolism (Cundiff 2008). According to a recent observational study, patients prescribed DOACs had lower adherence rates to their medication regimens than those who took warfarin. Low adherence rates increase the risk of thrombosis (Lakkireddy 2018).

The labels for dabigatran, rivaroxaban, and apixaban carry black box warnings of thrombotic events upon premature discontinuation. Edoxaban carries a black box warning indicating that premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events.

There is no reliable measure for monitoring and evaluating coagulation in patients on DOACs. In contrast, the INR tests required for warfarin can be used to precisely target specific levels of anticoagulation effects (Prescrire 2013). INR levels can also provide an indirect measure of adherence to therapy in warfarin users. No such test is available for DOACs.

Drug interactions

DOACs do not have as many drug interactions as warfarin, but many drug interactions exist. Most DOACs are substrates for p-glycoprotein. Drugs that inhibit p-glycoprotein, including ketoconazole, cyclosporine, itraconazole, verapamil, amiodarone, clarithromycin, nelfinavir, quinidine, ritonavir and tacrolimus, can increase DOAC levels and the risk of bleeding events. Antiplatelet agents should not be added to anticoagulation therapies; the combination increases bleeding risks and results in no benefit on stroke prevention (Vranckx 2018). Combining DOACs with non-steroidal anti-inflammatory drugs can also increase the risk of bleeding.

Drug interactions are particularly common in patients with renal impairment. There are no data available on potential interactions with many medications used by people with multiple comorbidities (Vranckx 2018).

Thrombin Inhibitors

Dabigatran (Pradaxa), approved by the FDA in 2010, was the first DOAC to reach the U.S. market. Dabigatran is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin. It is indicated to reduce risk of embolism in patients with non-valvular atrial fibrillation (Pradaxa 2018). There is no generic currently available for dabigatran; however, there are tentative approvals for generics unable to be granted final approval as a result of patent protections for Pradaxa (FDA 2018). Dabigatran is not metabolized by CYP450 enzymes but is primarily metabolized by the ATP transporter p-glycoprotein, so it should not be used with

ketoconazole, cyclosporine, itraconazole, or other strong p-glycoprotein inhibitors, which can increase dabigatran levels. Verapamil may also increase levels of dabigatran, and *in vitro* studies indicate that other p-glycoprotein inhibitors, including amiodarone, clarithromycin, nelfinavir, quinidine, ritonavir, and tacrolimus may also increase dabigatran levels. Digoxin and dabigatran do not interact with each other (Vranckx 2018).

Dabigatran has an FDA-approved reversal agent, idarucizumab (Praxbind 2018). However, most data available on idarucizumab comes from a trial of 123 patients treated with dabigatran experiencing serious bleeding. Twenty-six of the patients died, eight from bleeding. Idarucizumab's risks are difficult to delineate due to a lack of comprehensive clinical trials, but a review by *Prescrire*, a drug therapeutics newsletter, states that evidence supporting its use is based on a flawed non-comparative study and its adverse effects are understudied (Prescrire 2016). Nonetheless, the existence of a reversal agent has been touted as an advantage in dabigatran promotion.

Factor Xa inhibitors

Rivaroxaban (Xarelto) became the first FDA-approved factor Xa inhibitor in 2011 (Xarelto 2017). Factor Xa inhibitors impede both the intrinsic and extrinsic pathways of the blood coagulation cascade that produces thrombin. Rivaroxaban is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; to treat deep vein thrombosis (DVT) and pulmonary embolism (PE); and to prevent the risk of recurrence of DVT and/or PE after initial treatment or hip or knee surgery (Xarelto 2017). It has been shown to be at least as effective as warfarin in patients for whom anticoagulation is indicated. However, it may cause more bleeding than other DOAC competitors (The Medical Letter 2011). Rivaroxaban is metabolized by CYP3A4 and subtypes of p-glycoprotein; levels increase when co-administered with ketoconazole, ritonavir, erythromycin, clarithromycin and fluconazole (Vranckx 2018). This interaction may increase bleeding risk.

Rivaroxaban does not have a generic option. Andexanet alfa (Andexxa) was recently approved as a reversal agent for rivaroxaban and apixaban (Andexxa 2018). Andexanet alfa effectively reverses anticoagulant effects within minutes, with the effect lasting 1 to 3 hours after administration (Connolly 2016).

Apixaban (Eliquis), another factor Xa inhibitor, was approved in 2012. Apixaban is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; to treat DVT and PE; and to prevent the risk of recurrence of DVT and/or PE after initial treatment or hip or knee surgery (Eliquis 2018). Apixaban is the only DOAC to show benefit over warfarin (Ball 2017, Innasumuthu 2013). Apixaban is metabolized by CYP3A4 and subtypes of p-glycoprotein; levels increase when co-administered with ketoconazole, ritonavir, erythromycin, clarithromycin, and fluconazole (Vranckx 2018). Andexanet alfa (Andexxa), described under rivaroxaban, is effective for apixaban reversal (Andexxa 2018).

Edoxaban (Savaysa), also a factor Xa inhibitor, was approved in 2015 and is indicated for reducing risk of stroke and systemic embolism in non-valvular atrial fibrillation, and to treat DVT and PE after initial therapy with a parenteral anticoagulant. Edoxaban has carried a black box warning since its approval in 2015 because it is less effective in renal patients. Its black box warning is for a decrease in overall efficacy and increased risk of strokes in patients with non-valvular atrial fibrillation and a creatinine clearance > 95 mL/min (Savaysa 2017).

Co-administration of amiodarone, quinidine, ketoconazole, erythromycin, dronedarone, verapamil, and cyclosporine increase edoxaban levels (Vranckx 2018). Edoxaban is not available generically, does not have a reliable measure for its anticoagulation effect, and has no reversal agent (Prescrire 2013). Because it has a similar risk of major bleeding and no reversal agent, edoxaban has no demonstrable advantage over warfarin (Prescrire 2017).

Betrixaban (Bevyxxa), approved in 2017, is the newest DOAC. It is the only DOAC indicated specifically for adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility (Skelley 2018, Bevyxxa 2017). Betrixaban levels increase when co-administered with ketoconazole, verapamil, amiodarone and would be expected to increase with other p-glycoprotein inhibitors such as itraconazole, cyclosporine, posaconazole, and telaprevir. Bextrixiban does not affect digoxin levels (Horn 2017).

III. Medicaid Expenditures in the District of Columbia

This section reviews Medicaid expenditures on anticoagulants in DC between 2011 and 2016. Tables show the total reimbursement levels for each year, along with total prescription counts and the average prescription cost to Medicaid. It is important to note that data for Medicaid costs and reimbursements do not take into account any rebates.

Xarelto (rivaroxaban)

Approved 2011, Janssen Pharmaceuticals

Table 2: Medicaid Reimbursements for Xarelto in DC, 2011-2016

Year	Total Reimbursement	Prescription Count	Average Prescription Cost
2016	**$1,501,263**	**4,174**	**$360**
2015	$967,956	2,936	$330
2014	$637,118	2,249	$283
2013	$203,354	737	$276
2012	$24,987	101	$247
2011	$453	2	$226

The total number of Medicaid prescriptions for Xarelto, as well as total Medicaid reimbursement, has increased each year since its introduction in late 2011. From 2015 to 2016, the prescription count for Xarelto increased 42.2% from 2,936 to 4,174, and the total reimbursement increased 55.1% from $967,956 to $1.5 million (Table 2).

Pradaxa (dabigatran etexilate)

Approved 2010, Boehringer Ingelheim

Table 3: Medicaid Reimbursements for Pradaxa in DC, 2010-2016

Year	Total Reimbursement	Prescription Count	Average Prescription Cost
2016	$142,138	406	$350
2015	$94,061	288	$327
2014	$124,149	434	$286
2013	$136,373	529	$258
2012	$154,718	673	$230
2011	$57,572	267	$216
2010	$1,720	9	$191

Between 2010 and 2016, the highest total Medicaid reimbursement and total Medicaid numbers of prescriptions for Pradaxa occurred in 2012 with 673 prescriptions costing $154,718. From 2012 to 2015 the number of Medicaid prescriptions for Pradaxa decreased by 57% from 673 to 288 prescriptions, and reimbursement decreased by 39% from $154,718 to $94,061. From 2015 to 2016 the number of Medicaid prescriptions for Pradaxa increased by 41% to 406, and Medicaid reimbursement increased by 51% (Table 3).

Eliquis (apixaban)

Approved 2012, Bristol Myers Squibb and Pfizer

Table 4: Medicaid Reimbursements for Eliquis in DC, 2013-2016

Year	Total Reimbursement	Prescription Count	Average Prescription Cost
2016	**$202,896**	**618**	**$328**
2015	$83,124	265	$314
2014	$10,125	35	$289
2013	$269	1	$269

From 2013 to 2016, both Medicaid prescription count and total Medicaid reimbursement for Eliquis increased each year. From 2015 to 2016, Medicaid prescription counts for Eliquis have increased 133%, from 265 to 618 prescriptions, and total Medicaid reimbursement for Eliquis increased 144%, from $83,124 to $202,896 (Table 4).

Warfarin (generic Coumadin)

Coumadin approved 1954, generic warfarin approved 1993

Table 5: Medicaid Reimbursements for Warfarin in DC, 2010-2016

Year	Total Reimbursement	Prescription Count	Average Prescription Cost
2016	$33,839	3,402	$10
2015	$55,968	4,507	$12
2014	$58,781	6,184	$10
2013	$57,298	6,463	$9
2012	$91,723	9,584	$10
2011	$63,051	6,016	$10
2010	$58,558	4,033	$15

Total Medicaid prescription counts and reimbursement for generic warfarin peaked in 2012, with 9,584 prescriptions that accounted for $91,723. From 2012 to 2016, prescription counts and Medicaid reimbursement for warfarin have decreased each year. Overall, Medicaid prescriptions for warfarin decreased by 65%, from 9,584 to 3,402, and total Medicaid reimbursement decreased by 63% from $91,723 to $33,839 (Table 5).

For branded Coumadin (warfarin), there have been fewer than 60 prescriptions and less than $2,000 in total Medicaid reimbursement each year since 2010. In 2015 and 2016, Medicaid data regarding Coumadin prescriptions were not available due to low numbers of prescriptions (Table 6).

Table 6: Medicaid Reimbursements for Coumadin in DC, 2010-2016

Year	Total Reimbursement	Prescription Count	Average Prescription Cost
2016	n/a	n/a	n/a
2015	n/a	n/a	n/a
2014	$1,661	39	$43
2013	$1,151	26	$44
2012	$1,895	55	$34
2011	$1,476	29	$51
2010	$1,611	26	$62

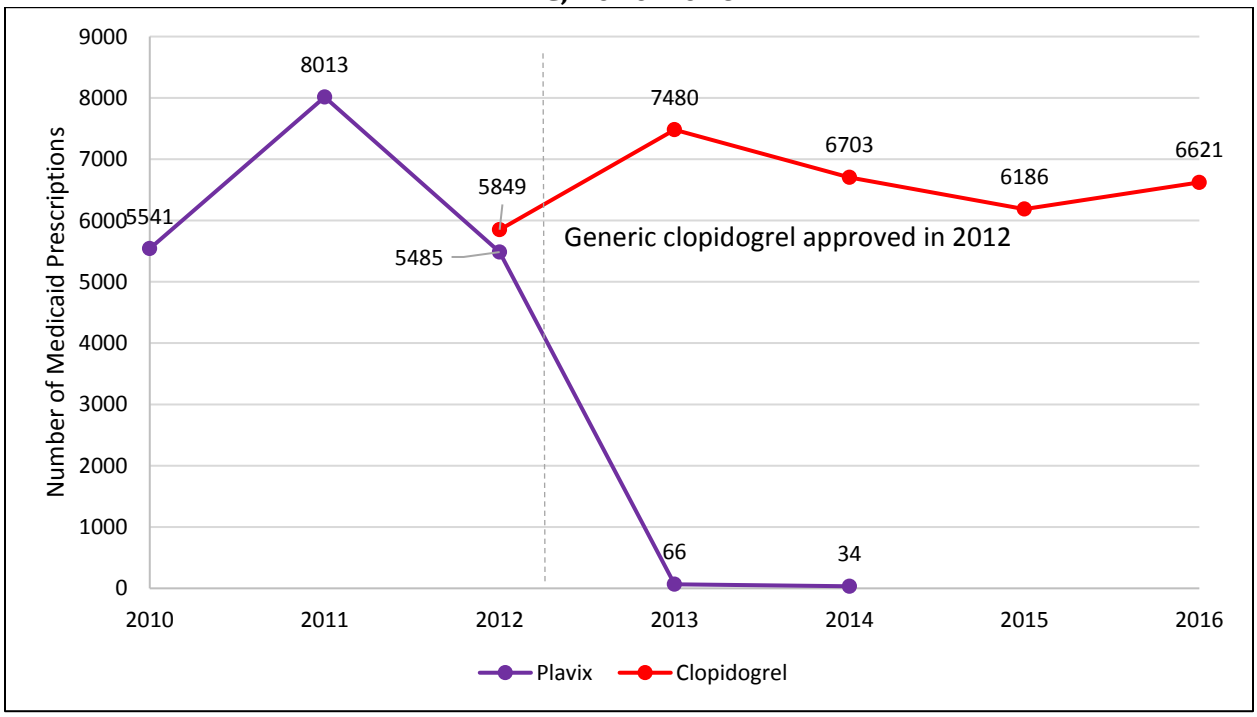
"n/a" indicates data were suppressed by CMS due to low numbers of prescriptions

Clopidogrel (generic Plavix)

Plavix approved 1997, generic clopidogrel approved 2012

Medicaid prescriptions and total Medicaid reimbursement for branded Plavix both peaked in 2011, with 8,013 prescriptions totaling $1.5 million, one year before the approval of generic clopidogrel. For generic clopidogrel, total Medicaid reimbursement and Medicaid prescription both peaked in 2013 with 7,480 prescriptions totaling $137,751 in Medicaid reimbursement. From 2013 to 2016 Medicaid prescription counts for clopidogrel decreased 11% from 7,480 to 6,621. In 2012, the year generic clopidogrel was first approved, clopidogrel had 5,849 prescriptions, compared to branded Plavix at 5,485 prescriptions (Figure 1). In 2015 and 2016 Medicaid data for Plavix were unavailable because fewer than 12 total prescriptions were filled for Medicaid beneficiaries in the District.

Figure 1: Medicaid Prescription Counts for Plavix (brand) vs. Clopidogrel (generic) in DC, 2010-2016



Comparing Medicaid Totals

Total Medicaid reimbursement of Eliquis and Xarelto increased each year following their market introductions. Xarelto, with $1.5 million, was the anticoagulant with by far the highest Medicaid reimbursement in 2016; the second highest was Eliquis with $202,896.

Table 7: Medicaid Reimbursements and (Prescription Counts) for Anticoagulants in DC, 2010-2016

Year	Xarelto	Pradaxa	Eliquis	Warfarin	Coumadin	Clopidogrel	Plavix
2016	$1,501,263 (4,174)	$142,138 (406)	$202,896 (618)	$33,839 (3,402)	n/a	$53,165 (6,621)	n/a
2015	$967,956 (2,936)	$94,061 (288)	$83,124 (265)	$55,968 (4,507)	n/a	$62,478 (6,186)	n/a
2014	$637,118 (2,249)	$124,149 (434)	$10,125 (35)	$58,781 (6,184)	$1,661 (39)	$117,788 (6,703)	$2,697 (34)
2013	$203,354 (737)	$136,373 (529)	$269 (1)	$57,298 (6,463)	$1,151 (26)	$137,751 (7,480)	$5,179 (66)
2012	$24,987 (101)	$154,718 (673)	-	$91,723 (9,584)	$1,895 (55)	$125,823 (5,849)	$1,074,967 (5,485)
2011	$453 (2)	$57,572 (267)	-	$63,051 (6,016)	$1,476 (29)	-	$1,541,108 (8,013)
2010	-	$1,720 (9)	-	$58,558 (4,033)	$1,611 (26)	-	$940,810 (5,541)

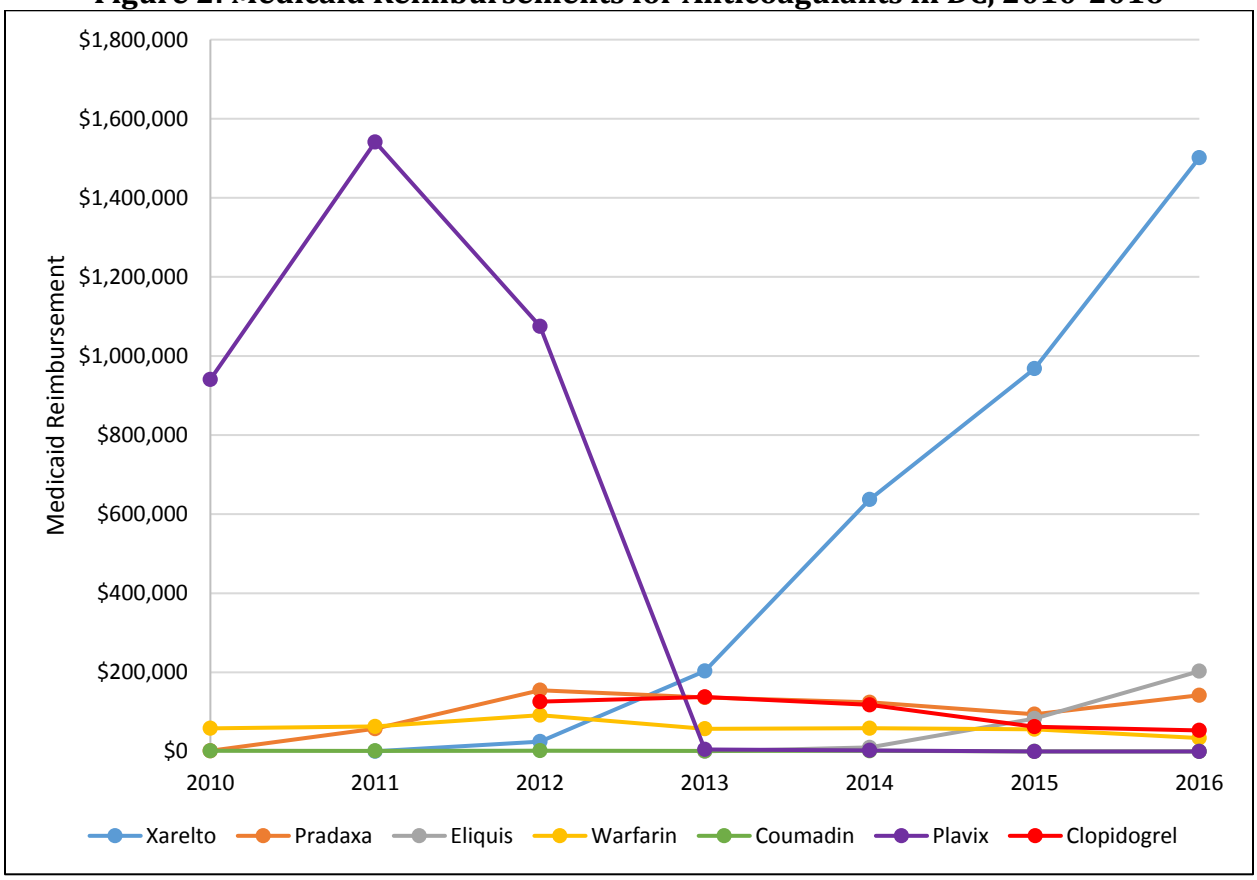
"-" indicates a drug was not yet approved by the FDA
"n/a" indicates data was suppressed by CMS due to low numbers of prescriptions

From 2012 to 2015, there was a decrease in the total Medicaid reimbursement for warfarin, Plavix, and Pradaxa. However, unlike warfarin and Plavix, which continued to decrease, the total reimbursement for Pradaxa increased between 2015 and 2016. This increase was the year after its reversing agent, Praxbind, was approved by the FDA.

In 2016, there were more Medicaid prescriptions for Xarelto than there were for warfarin, the long-established generic anticoagulant.

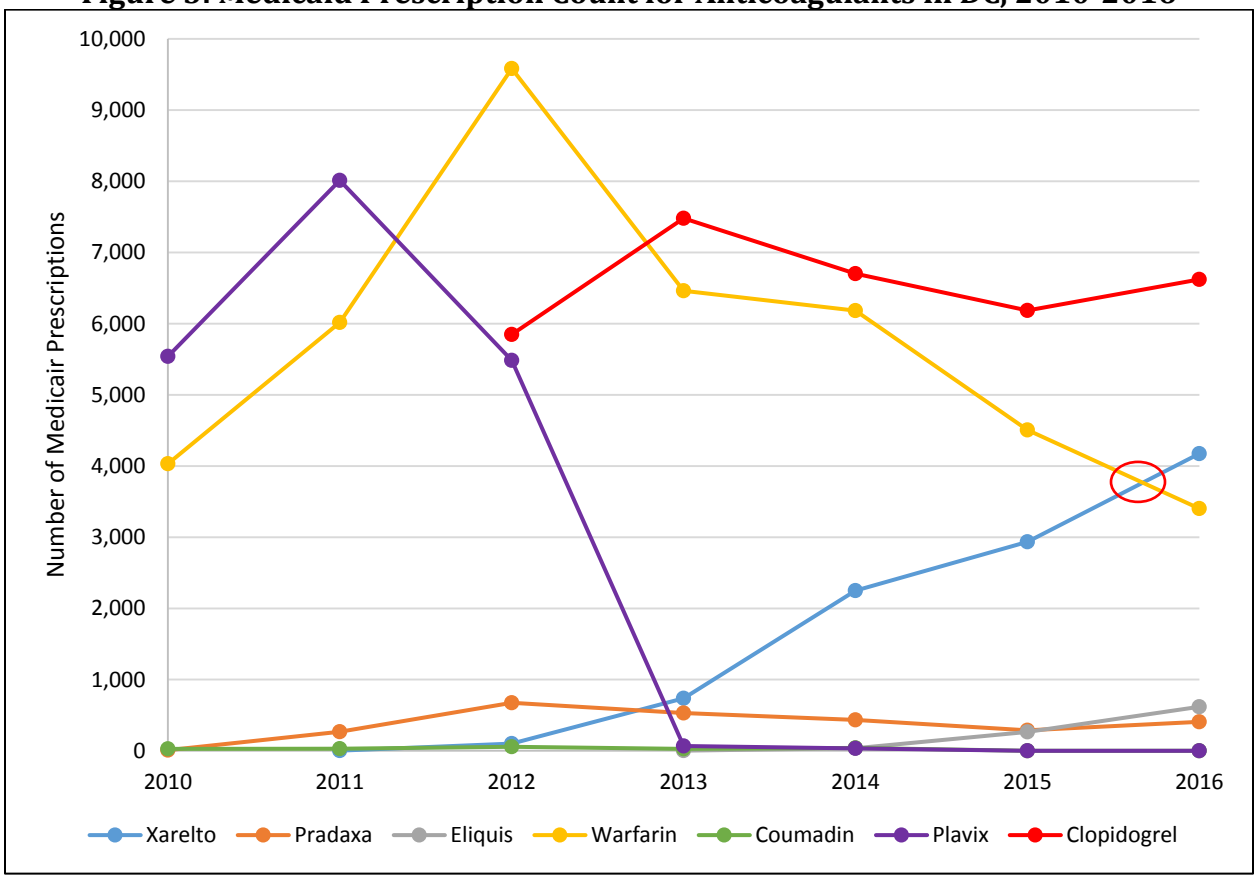
The much lower Medicaid reimbursement for warfarin compared to the other anticoagulants included in this analysis is due in part to its lower cost – warfarin is an older generic medication and is much cheaper per prescription than branded anticoagulants (Figure 2).

Figure 2: Medicaid Reimbursements for Anticoagulants in DC, 2010-2016



The number of prescriptions in DC Medicaid increased for each drug except for warfarin and Plavix from 2015 to 2016. Medicaid prescriptions for warfarin have been decreasing since 2012. Xarelto was the anticoagulant with the largest increase in number of Medicaid prescriptions from 2014 to 2016. By 2016, there were more Medicaid prescriptions for Xarelto than there were for warfarin, the long-established generic anticoagulant (Figure 3).

Figure 3: Medicaid Prescription Count for Anticoagulants in DC, 2010-2016



IV. Medicare Expenditures in the District of Columbia

This section reviews Medicare expenditures on anticoagulants in DC between 2013 and 2016 (most recent data available). The tables show total prescription claim costs for each year, as well as the prescription claim count and average prescription claim cost to Medicare. Average claim cost for Medicare prescriptions is likely higher than average prescription costs for Medicaid because Medicare beneficiaries are able to get 90-day supplies. It is important to note that data for Medicare costs and reimbursements do not take into account any rebates.

Xarelto (rivaroxaban)

Approved 2011, Janssen Pharmaceuticals

Table 8: Medicare Claims for Xarelto in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	**$2,955,210**	**6,162**	**$480**
2015	$2,315,310	5,386	$430
2014	$1,420,762	3,931	$361
2013	$612,654	1,884	$325

The claims cost to Medicare for Xarelto increased each year from 2013 to 2016. Total Medicare claims cost overall for Xarelto was nearly five times higher in 2016 than in 2013, increasing by 382% from $612,654 in 2013 to nearly $3 million in 2016. From 2013 to 2016, the total number of Medicare claims for Xarelto increased by 227%, from 1,884 to 6,162 (Table 8).

Pradaxa (dabigatran etexilate)

Approved 2010, Boehringer Ingelheim

Table 9: Medicare Claims for Pradaxa in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	**$1,087,041**	**2,256**	**$482**
2015	$939,078	2,014	$466
2014	$868,299	2,079	$418
2013	$771,349	2,173	$355

The total Medicare claim cost for Pradaxa has increased each year between 2013 and 2016. The total number of Medicare claims decreased slightly each year from 2013 to 2015 and then increased from 2015 to 2016. From 2013 to 2015 the total number of Medicare claims for Pradaxa decreased 7% overall, from 2,173 in 2013 to 2,014 in 2015, then increased 12% from 2015 to 2016 reaching 2,256 total claims. Total Medicare claim cost increased by 41% from $771,349 in 2013 to $1.1 million in 2016 due to an increase in the average claim cost. The average cost per claim increased from $355 in 2013 to $482 in 2016 (Table 9).

Eliquis (apixaban)

Approved 2012, Bristol Myers Squibb and Pfizer

Table 10: Medicare Claims for Eliquis in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	**$3,267,966**	**6,648**	**$492**
2015	$1,712,283	3,979	$430
2014	$577,752	1,538	$376
2013	$104,596	310	$337

There have been increases in total cost per claim to Medicare for Eliquis each year from 2013 to 2016. Overall, from 2013 to 2016, total Medicare claim cost for Eliquis increased by 3024%, from $104,596 in 2013 to $3.3 million in 2016. From 2013 to 2016, overall the total number of Medicare claims for Eliquis increased from 310 in 2013 to 6,648 in 2016 (Eliquis was approved in 2012) (Table 10).

Warfarin (generic Coumadin)

Coumadin approved 1954, generic warfarin approved 1993

Table 11: Medicare Claims for Warfarin in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	$121,798	10,893	$11
2015	$148,123	11,658	$13
2014	$149,424	14,621	$10
2013	**$171,810**	**14,715**	**$12**

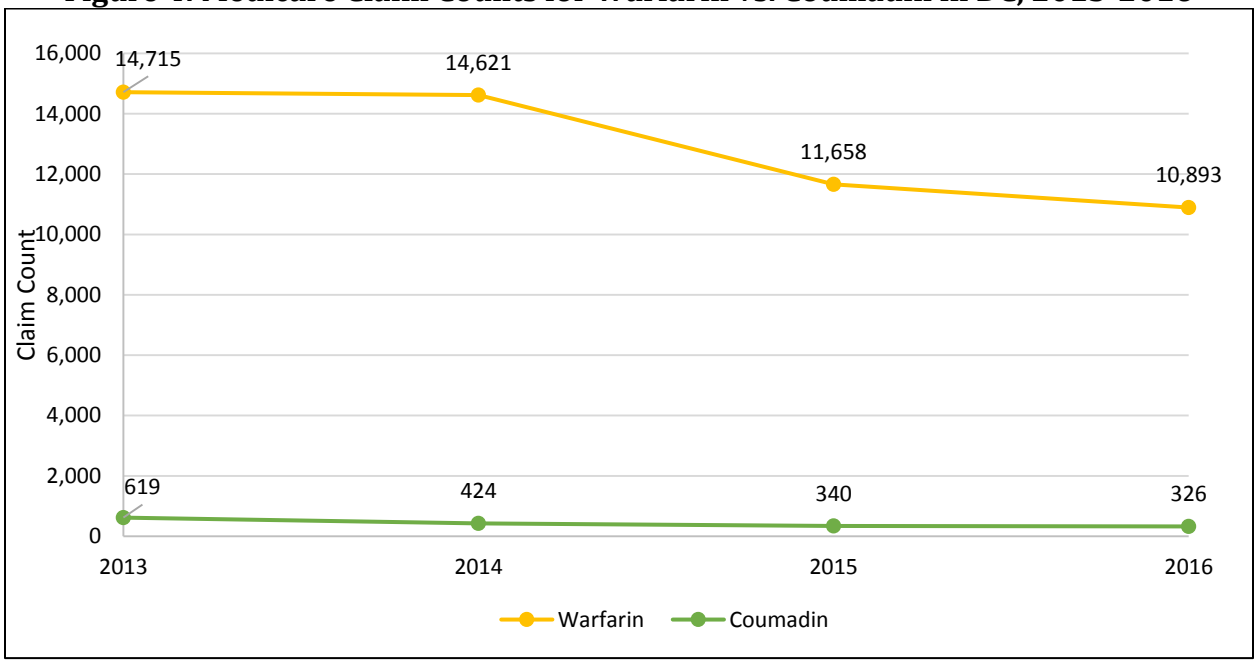
Unlike other anticoagulants, there has been a decrease in prescriptions for generic warfarin each year from 2013 to 2016 in both total Medicare claim counts and total Medicare claim cost. Total Medicare claim counts decreased 26% from 14,715 to 10,893. Total Medicare claim costs decreased by 29% from $171,810 in 2013 to $121,798 in 2016. Warfarin had the sharpest decrease in total Medicare claim counts of all of the anticoagulants examined (Table 11).

Table 12: Medicare Claims for Coumadin in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	$44,678	326	$137
2015	$43,461	340	$128
2014	$44,592	424	$105
2013	**$50,860**	**619**	**$82**

Like warfarin, branded Coumadin also saw decreases in both total Medicare claim counts and total Medicare claim cost. From 2013 to 2016 total Medicare claim counts decreased 47% from 619 in 2013 to 326 in 2016. Total Medicare claim counts decreased 12% from $50,860 in 2013 to $44,678 in 2016 (Table 12).

Figure 4: Medicare Claim Counts for Warfarin vs. Coumadin in DC, 2013-2016



Clopidogrel (generic Plavix)

Plavix approved 1997, generic clopidogrel approved 2012

For both branded Plavix and generic clopidogrel, the amount of total Medicare claims and the total Medicare claim cost peaked in 2013. In 2013, generic clopidogrel had 18,380 Medicare claims costing a total of $776,664. Clopidogrel claim counts decreased 6% from 18,380 in 2013 to 17,318 in 2016, and total claim costs decreased 66% from $776,664 in 2013 to $266,309 in 2016 (Table 13).

Table 13: Medicare Claims for Clopidogrel in DC, 2013-2016

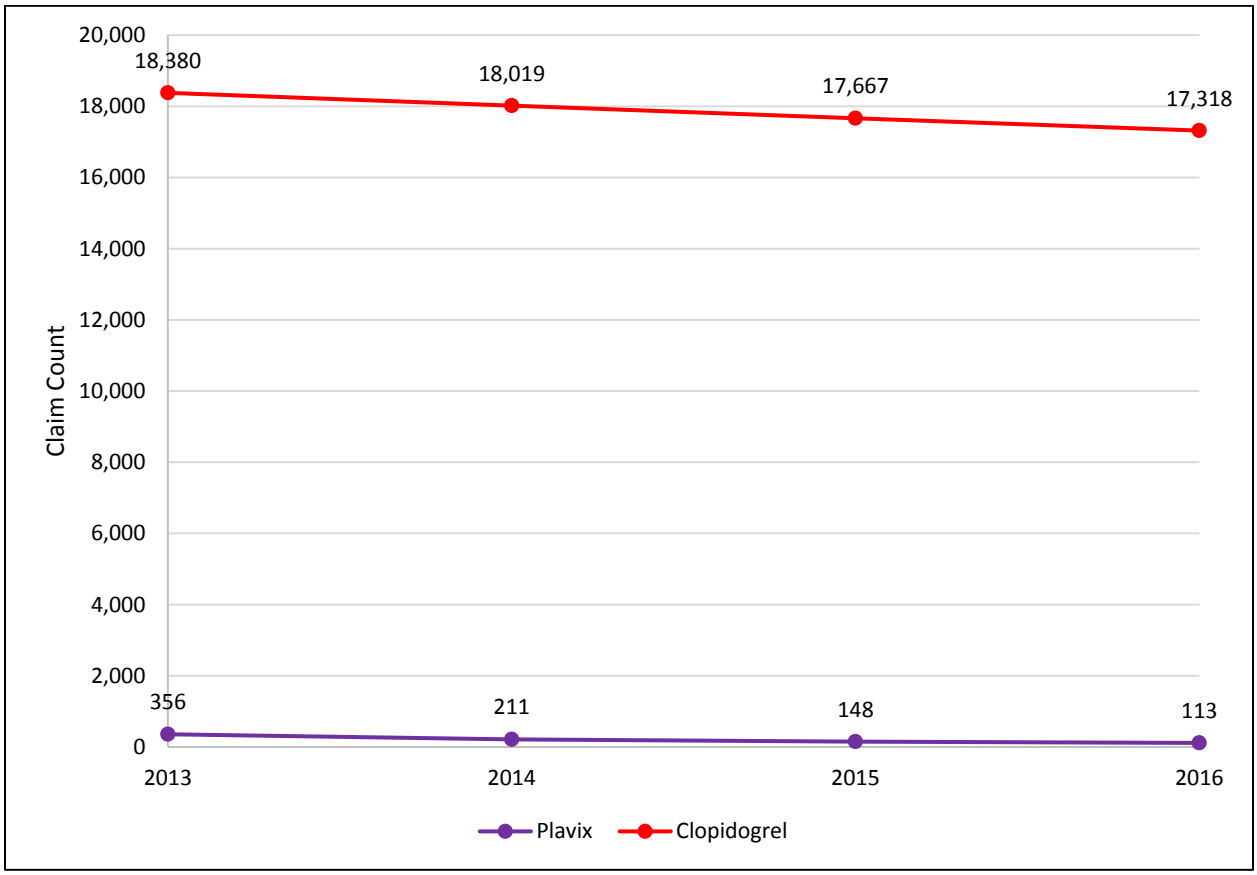
Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	$266,309	17,318	$15
2015	$270,208	17,667	$15
2014	$358,969	18,019	$20
2013	**$776,664**	**18,380**	**$42**

In 2013, branded Plavix had 356 Medicare claims, costing a total of $95,626. Plavix claim counts decreased 68% from 356 in 2013 to 113 in 2016 and total claim costs decreased 66% from $95,626 in 2013 to $32,783 in 2016 (Table 14).

Table 14: Medicare Claims for Plavix in DC, 2013-2016

Year	Total Claim Cost	Claim Count	Average Claim Cost
2016	$32,783	113	$290
2015	$38,048	148	$257
2014	$54,989	211	$261
2013	**$95,626**	**356**	**$269**

Figure 5: Medicare Claim Counts for Plavix (brand) vs. Clopidogrel (generic) in DC, 2013-2016



Comparing Medicare claim counts and total claim costs between branded Plavix and generic clopidogrel shows much higher total claim counts and claim costs for clopidogrel for every year from 2013 to 2016. However, as expected for a more expensive branded medication, the average claim cost is higher for Plavix, ranging from $257 to $290 per claim, compared to generic clopidogrel, ranging from $15 to $42 per claim.

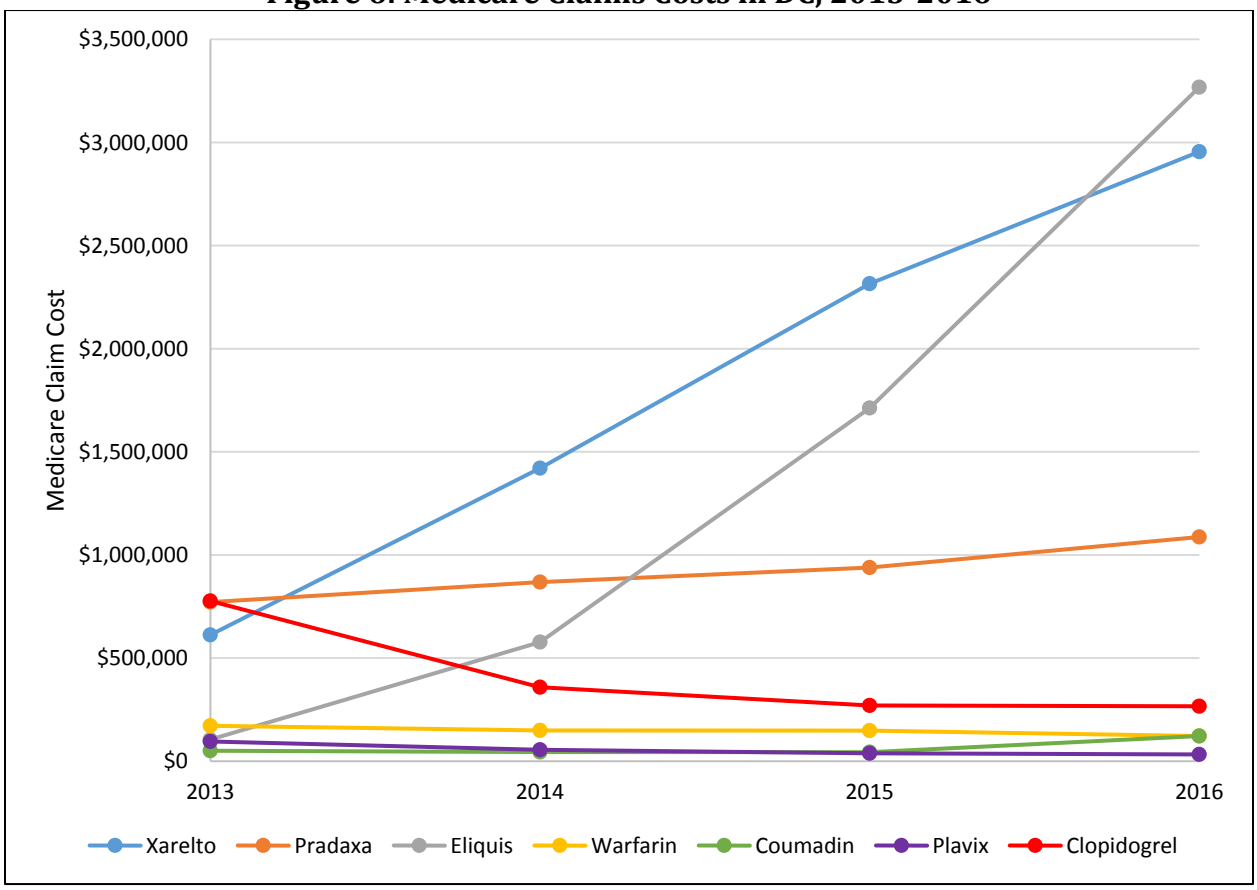
Comparing Medicare Totals

Table 15: Medicare Claim Costs (Claim Counts) in DC, 2013-2016

Year	Xarelto	Pradaxa	Eliquis	Warfarin	Coumadin	Plavix	Clopidogrel
2016	$2,955210 (6,162)	$1,087,041 (2,256)	$3,267,966 (6,648)	$121,798 (10,893)	$44,678 (326)	$32,783 (113)	$266,309 (17,318)
2015	$2,315,310 (5,386)	$939,078 (2,014)	$1,712,283 (3,979)	$148,123 (11,658)	$43,461 (340)	$38,048 (148)	$270,208 (17,667)
2014	$1,420,762 (3,931)	$868,299 (2,079)	$577,752 (1,538)	$149,424 (14,621)	$44,592 (424)	$54,989 (211)	$358,969 (18,019)
2013	$612,654 (1,884)	$771,349 (2,173)	$104,596 (310)	$171,810 (14,715)	$50,860 (619)	$95,626 (356)	$776,664 (18,380)

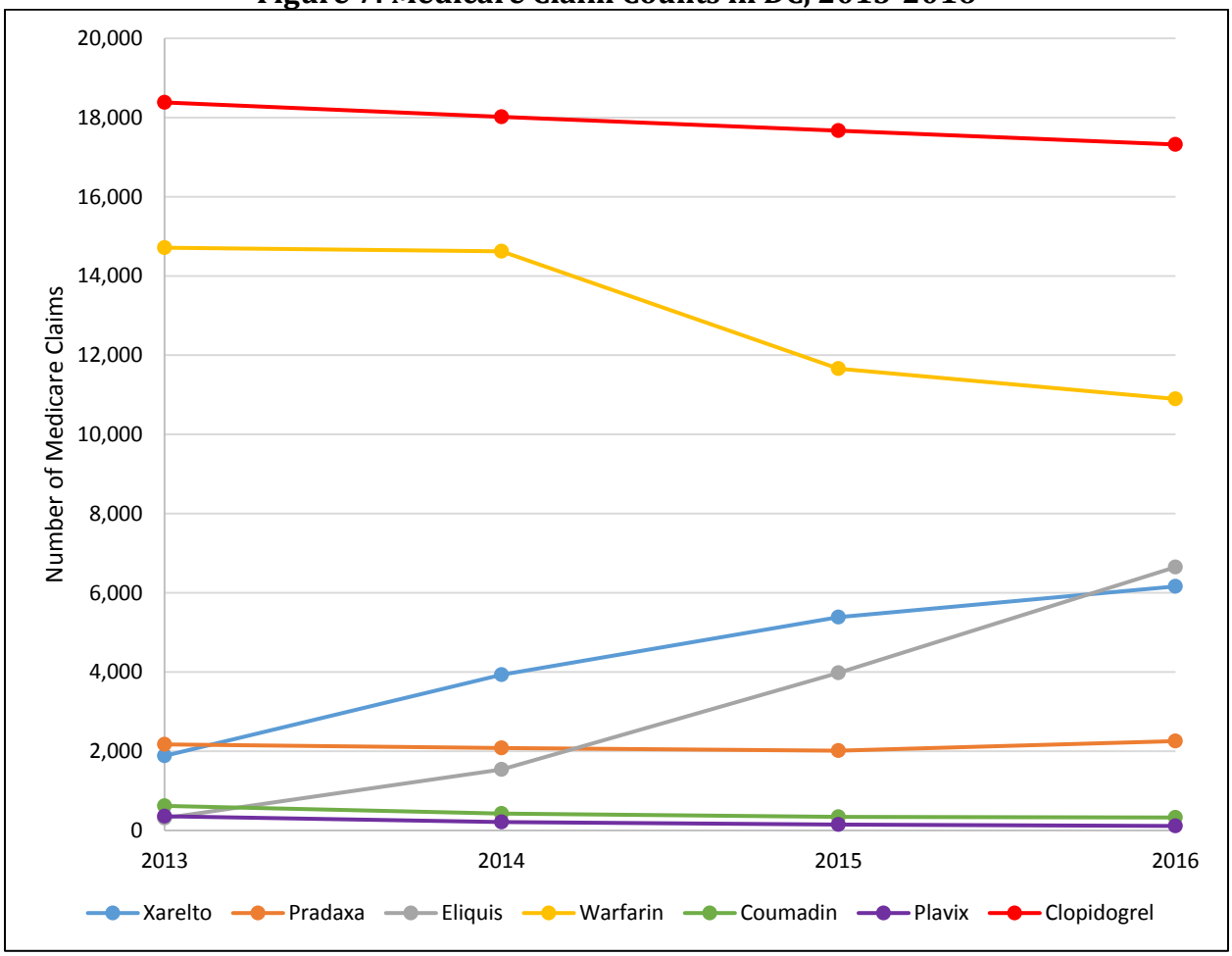
Examining the total cost of Medicare claims among various anticoagulants shows shrinking costs and use for warfarin and Coumadin. There was an increase in Medicare expenditures for Xarelto, Pradaxa, and Eliquis from 2013 to 2016. Pradaxa was the anticoagulant with the highest total cost of Medicare claims in 2013. Xarelto had the highest total cost of Medicare claims in 2014 and 2015. Eliquis had the highest total cost of Medicare in 2016. This was the first time that Eliquis surpassed Xarelto in Medicare claim cost (Figure 6).

Figure 6: Medicare Claims Costs in DC, 2013-2016



Clopidogrel (generic Plavix) was the drug with the highest number of claims from 2013 to 2016. The number of claims for warfarin has decreased since 2013, similar to the decrease in the count of Medicaid prescriptions. The number of Medicare claims for Xarelto and Eliquis increased from 2013 to 2016. Eliquis had the largest increases in number of claims among the branded anticoagulants, and had the third highest number of total Medicare claims, surpassing Xarelto, behind only clopidogrel and warfarin (Figure 7).

Figure 7: Medicare Claim Counts in DC, 2013-2016



Pradaxa has maintained similar amounts of total Medicare claims from 2013 to 2016. There was a large increase for claims for Eliquis from 2014 to 2016, surpassing Pradaxa and Xarelto in total number of total Medicare claims.

V. Pharmaceutical Marketing in the District of Columbia

This section reviews pharmaceutical marketing expenditures and reported gifts to physicians and teaching hospitals associated with the marketing of particular anticoagulant medications. Data include the total value of gifts, the frequency of gifts and evaluation of the nature of the payments or gifts. Open Payments requires indicating which drug is being marketed in associated with a gift or payment, and the system allows manufacturers to list multiple targeted products for each marketing payment.

National Direct-to-Consumer Advertising

The United States and New Zealand are the only two countries where pharmaceutical companies are allowed to market drugs directly to consumers. Between 2011 and 2015, spending by drug companies on direct-to-consumer advertising (DTCA) in the United States increased more than 60%, from $3.8 billion to $5.2 billion. Eliquis (apixaban) was among the drugs with the highest DTCA spending, with $249 million nationally. Janssen spent $106 million on DTCA for Xarelto (rivaroxaban) in 2015 (Robbins 2016).

Much of the advertising for Eliquis was targeted at men. Bristol-Myers Squibb and Pfizer, the co-marketers of Eliquis, spent $16 million for ads in male-targeted media including *Golf*, *Sports Illustrated*, and *Family Handyman* (Robbins 2016).

Promotion to Health Care Professionals

While companies spent more than $4 billion on DTCA in 2014, DTCA only represented 6.5% of companies' promotional spending. The majority of spending for promotion was dedicated to pharmaceutical detailing, which cost $44.2 billion (62.5 % of promotions) in 2014. There were more than 70,000 drug sales representatives in the US in 2014 (IMS Health 2015).

In 2016, pharmaceutical companies reported spending $62.8 million in DC on detailing expenses such as salaries and bonuses for sales representatives. Companies reported spending $14.5 million on gifts to health care professionals in DC AccessRx (DC DOH 2017). Companies spent more than $220,000 promoting anticoagulants to physicians and teaching hospitals in DC in 2016 (Open Payments data, see below).

Several studies have shown that gifts from pharmaceutical companies to health care providers are associated with differences in prescribing practices (DeJong 2016, Fleischman 2016, Perlis 2016, Sharma 2018, Yeh 2016). Gifts from pharmaceutical companies to prescribers, including physicians, advanced practice nurses and physician assistants, are associated with more prescriptions per patient, more costly prescriptions, and a higher proportion of branded prescriptions (Wood 2017).

Xarelto (rivaroxaban)
Approved 2011, Janssen Pharmaceuticals

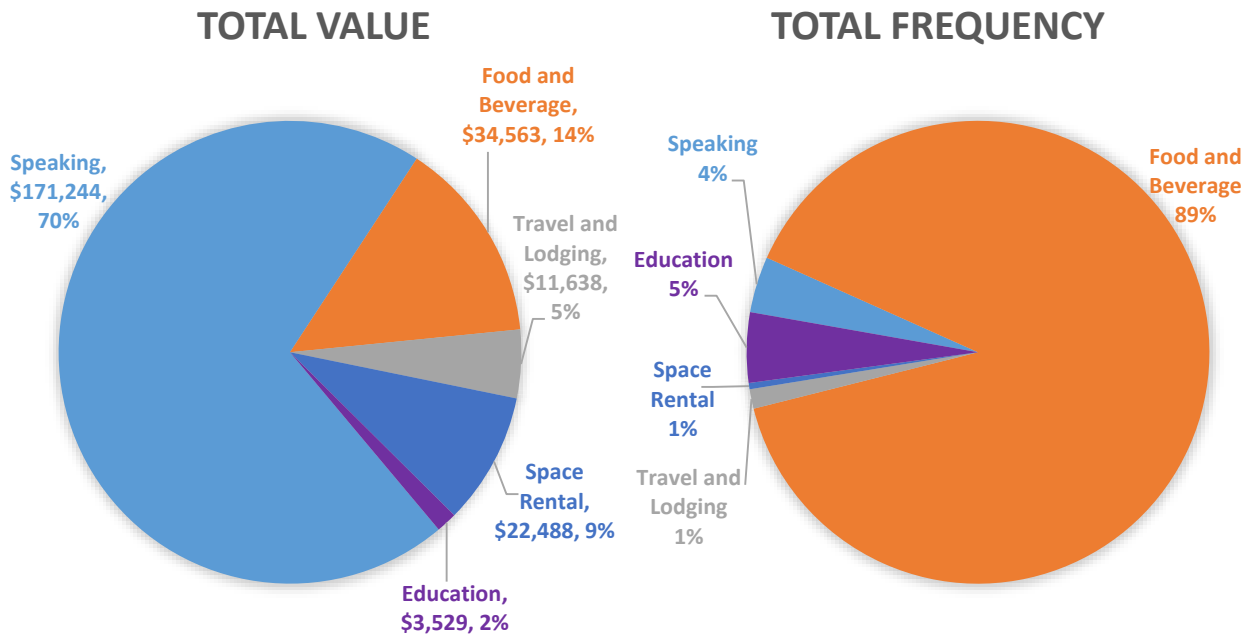
In Open Payments, for food and beverage gifts, Xarelto was often marketed along with Janssen's diabetes medications, Invokana (canagliflozin) and Invokamet (canagliflozin/metformin).

Table 16: Marketing Payments for Xarelto in DC (Open Payments)

Year	Sum of Gifts	Gift Count	Average Gift Value
2016	$90,246	599	$151
2015	**$99,133**	**691**	**$143**
2014	$54,083	546	$99

Between 2014 and 2015, the total for gifts associated with Xarelto increased by 83.3%, more than $45,000. From 2015 to 2016, there was a decrease of $9,000, roughly 9%, in the total value of gifts. There was a 13.3% decrease in the number of gifts associated with Xarelto, from 691 gifts in 2015 and 599 gifts in 2016 (Table 16).

Figure 8: Gifts Associated with Xarelto, by Nature of Payment, 2014-2016



Most of the total value of gifts associated with Xarelto was for *Speaking* fees, which accounted for 70% ($171,244) of the total amount of gifts from 2014 to 2016. *Food and Beverage* and *Space Rental* accounted for the next two largest expenses, accounting for 14% ($34,563) and 9% ($22,488) respectively. *Travel and Lodging* as well as *Education* gifts each accounted for 5% or less of the total gift value associated with Xarelto from 2014 to 2016.

Total gift frequency of Xarelto showed that the vast majority of individual gifts given were in the form of *Food and Beverage,* which accounted for 89% of gift frequency. The remaining categories each accounted for 5% or less of total gift frequency. In other words, there were small numbers of more expensive *Speaking* gifts and large numbers of cheaper *Food and Beverage* gifts associated with Xarelto (Figure 8).

Pradaxa (dabigatran etexilate)
Approved 2010, Boehringer Ingelheim

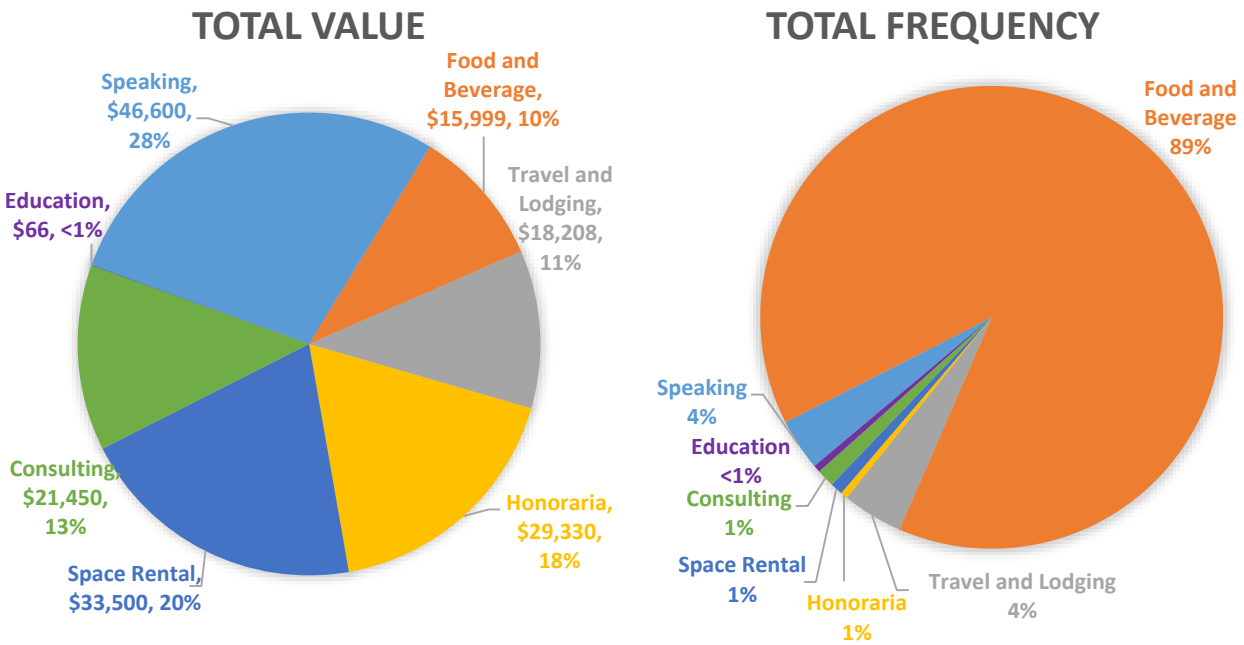
In Open Payments, Pradaxa was listed as being marketed alongside other Boehringer Ingelheim products, including its reversing agent Praxbind (idarucizumab) and its type 2 diabetes medications Jardiance (empagliflozin) and Tradjenta (linagliptin).

Table 17: Marketing Payments for Pradaxa in DC (Open Payments)

Year	Sum of Gifts	Gift Count	Average Gift Value
2016	$40,047	158	$253
2015	$54,578	185	$295
2014	**$70,528**	**458**	**$154**

The value of marketing payments related to Pradaxa has decreased since 2014, when the total value of gifts was $70,528 and the gift count was 458. In 2016, the total value of gifts was $40,047 and the gift count was 158, 43% and 66% decreases respectively. In 2014, Pradaxa had a higher total sum of gifts ($70,528; Table 17) than the sum for Xarelto ($54,083; Table 16).

Figure 9: Gifts Associated with Pradaxa, by Nature of Payment, 2014-2016



The largest portion of the total value of gifts related to Pradaxa were for *Speaking* fees, which accounted for 28% ($46,600) of the total amount of gifts between 2014 and 2016. *Space Rental* and *Honoraria* payments accounted for the next two largest sections of total value, accounting for 20% ($33,500) and 18% ($29,330) respectively. *Consulting*, *Travel and Lodging,* and *Food and Beverage* gifts accounted for 13% ($21,450), 11% ($18,208), and 10% ($15,999) of total value of gifts associated with Xarelto from 2014 to 2016 respectively. *Education* gifts accounted for less than 1% ($66) of total gift value.

Total gift frequency of Pradaxa showed the vast majority of individual gifts given were in the form of *Food and Beverage,* which accounted for 89% of gift frequency. The remaining categories each accounted for 4% or less of total gift frequency.

Similar to Xarelto, large numbers of cheaper *Food and Beverage* gifts were associated with Pradaxa (Figure 9). However, regarding total gift value, Pradaxa was associated with a more even spread of gifts over several gift categories, in contrast to Xarelto, for which *Speaking* accounted for the majority of total gift value.

Eliquis (apixaban)

Approved 2012, Bristol Myers Squibb and Pfizer

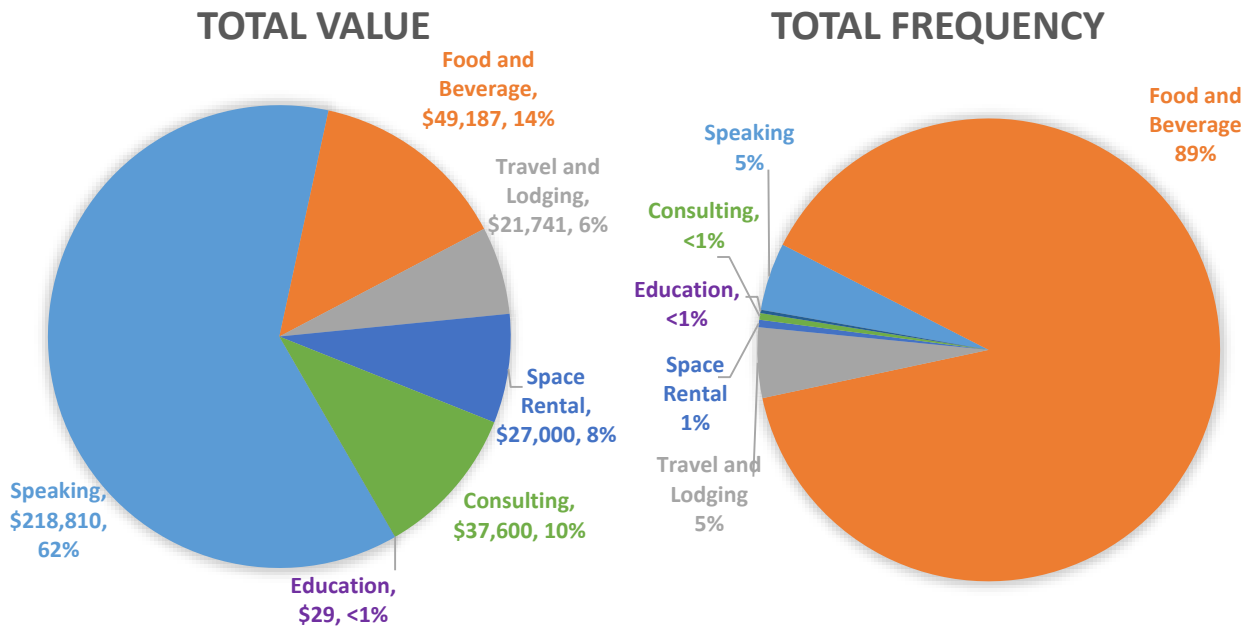
Eliquis was marketed frequently alongside other drugs co-marketed by BMS and Pfizer: Zyvox (linezolid), an antibiotic; Chantix (varenicline), a smoking cessation aid; Viagra (sildenafil), an erectile dysfunction medication; and Prevnar-13, a pneumococcal conjugate vaccine.

Table 18: Marketing Payments for Eliquis in DC (Open Payments)

Year	Sum of Gifts	Gift Count	Average Gift Value
2016	$90,554	532	$170
2015	$119,367	639	$187
2014	**$144,445**	**560**	**$258**

The total value of gifts associated with Eliquis has decreased each year since 2014, when it accounted for $144,445. The total gift value of $90,554 in 2016 was a 37% decrease from its gift value in 2014. Eliquis had a higher total value of marketing payments than both Xarelto and Pradaxa each year between 2014 and 2016.

Figure 10: Gifts Associated with Eliquis, by Nature of Payment, 2014-2016



The nature of payments for Eliquis were similar to Xarelto. Most of the total value of gifts associated with Eliquis between 2014 and 2016 was for *Speaking,* which accounted for 62% ($218,810) of the total. *Food and Beverage* and *Consulting* gifts accounted for the next two largest payments, accounting for 14% ($19,187) and 10% ($37,600) respectively. *Space Rental* and *Travel and Lodging* each accounted for less than 10% of total gift value, with $21,741 (8%) and $21,741 (6%) respectively. *Education* gifts accounted for less than 1% of the total gift value. Total gift frequency of Xarelto showed the vast majority of individual gifts given were in the form of *Food and Beverage* which, like both Xarelto and Pradaxa, accounted for 89% of gift frequency. The remaining categories each accounted for 5% or less of total gift frequency (Figure 10).

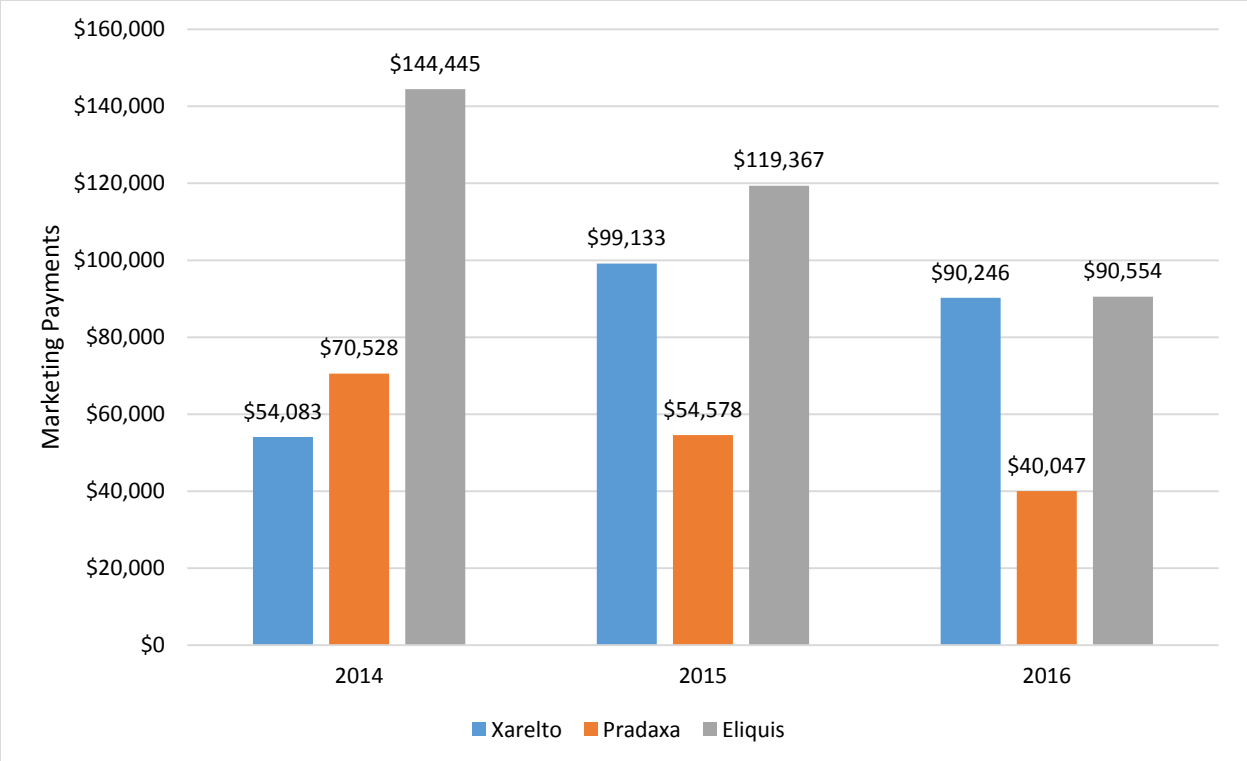
Comparing Open Payments Totals

Table 19: Gift Totals in Open Payments, 2013-2016

Year	Xarelto	Pradaxa	Eliquis
2016	$90,246	$40,047	$90,554
2015	$99,133	$54,578	$119,367
2014	$54,083	$70,528	$144,445

Manufacturers spent more than $750,000 marketing Xarelto, Eliquis, and Pradaxa between 2014 and 2016. There was a decrease from 2014 to 2016 in marketing payments for both Eliquis and Pradaxa. Eliquis has remained the anticoagulant with the highest total value of reported payments since Open Payments began publishing data. The total value of gifts for Xarelto increased between 2014 and 2015. There was a slight decrease in total gift value for Xarelto from 2015 to 2016. In 2016, total marketing payments for Eliquis and Xarelto were equivalent, with less than a $250 difference between them (Figure 11).

Figure 11: Marketing Payments for Anticoagulants in DC (Open Payments)



VI. Discussion

Conclusions from Analyses

Xarelto, Eliquis, and Pradaxa accounted for $762,981 in marketing gifts to physicians and teaching hospitals in the District of Columbia from 2014 to 2016. The vast majority of these gifts were given in the form of food and beverages, but the highest payments were made to experts for speaking engagements. This means that meals are frequently used in detailing these three drugs in the District, but the largest payments are to key opinion leaders to promote prescribing. Studies have found that acceptance of payments from industry, including industry-sponsored meals, are associated with an increased rate of prescribing the marketed drug (DeJong 2016, Yeh 2016).

Our analysis of DC marketing and prescribing for anticoagulants reflects national trends. Eliquis is being heavily marketed as a safer alternative to Xarelto, and its market share is increasing. Nationally, the manufacturers of Eliquis are outspending the manufacturers of Xarelto. BMS and Pfizer, which co-market Eliquis, spent $249 million on advertising in 2015, while J&J spent $106 million on Xarelto during this time. In the first six months of 2016, BMS spent $140 million on Eliquis, as compared to J&J's $48 million advertising spend on Xarelto. National sales of Eliquis and Xarelto were neck and neck in 2016 (McCaffrey 2016).

Increased use of DOACs has resulted in decreased use of warfarin, an older, effective drug. We observed an increase in the use of DOACs alongside a decline in the use of warfarin among the Medicaid population in the District. In 2016, for the first time, there were more prescriptions for Xarelto than for warfarin in DC Medicaid. Nationally, warfarin had more than half (55%) of market share at the end of 2016, down from 62% at the end of 2015 (McCaffrey 2016).

In terms of Medicaid spending, Xarelto accounted for over $1.5 million in reimbursements, nearly 30 times more than was reimbursed for generic clopidogrel and 50 times more than was reimbursed for warfarin. Decreasing prescriptions for warfarin, a well-established and inexpensive anticoagulant, may cost the District money and may not benefit patient health. DOACs have their place but may be overused. Rivaroxaban may be more dangerous than other DOACs. Prescribers need to be educated about the true risks and benefits of platelet inhibitors, vitamin K antagonists, and DOACs.

The American College of Cardiology and the American Heart Association guidelines consider warfarin and DOACs equivalent; for patients with severe renal impairment (a widespread problem in the District), warfarin is clearly superior. For patients with atrial fibrillation who are taking anticoagulants to prevent ischemic strokes, there is little to no advantage for DOACs (January 2014).

Patients who are doing well on warfarin should not be switched to DOACs, and warfarin should be considered for new patients as well. Warfarin is effective, inexpensive, and easily reversible, although it does require appropriate monitoring. Prescribers need education on these points and in other approaches to stroke prevention in addition to anticoagulant therapy.

Key points to emphasize in a proactive stroke prevention activities include a focus on promotion of healthy behaviors such as not smoking, maintaining a healthy weight, performing moderate physical activity, modest alcohol consumption, and maintaining a healthy diet. It has been shown that men and women who exhibited all five of these healthy lifestyle behaviors had roughly 80% lower risk of ischemic stroke compared to those who exhibited none of those behaviors (Chiuve 2008).

It is clear from this report that stakeholders and policymakers should continue to monitor the marketing and prescribing of anticoagulants in the District of Columbia.

VII. Recommendations

1. Support noncommercial education for healthcare providers on the prescription of various anticoagulants and potential dangers of certain anticoagulants.

We recommend expanding efforts to reach more prescribers in DC with unbiased educational materials and training opportunities regarding anticoagulant prescribing practices. Under the SafeRx Amendment Act of 2008, the District established the DC Center for Rational Prescribing (DCRx) program to provide DC healthcare professionals with free, noncommercial continuing education. DCRx offers more than 15 courses, and more than 3,000 people have participated in DCRx courses. This program and other noncommercial health professional training opportunities should continue to be promoted in the District of Columbia.

2. Enlist and support prescribers and pharmacists in choosing more cost-efficient anticoagulants.

We recommend prescribers and pharmacists choose generically available anticoagulants when applicable, as opposed to more expensive branded medications. There is no evidence of superiority of branded versions over generic versions of a medication in terms of effectiveness, safety, or bioequivalence. Prescribers should be informed that the efficacy and safety of warfarin has shown to be equivalent to most DOACs.

3. Monitor changes in prescribing practice related to highly marketed and newly approved anticoagulants.

Newer direct acting oral anticoagulants appear to be highly marketed through both gifts to physicians and through in-person detailing. In 2016, the more expensive brand drug, Xarelto, had a higher number of Medicaid prescriptions than the long time generic warfarin for the first time. Medicare also shows a large increase in both Eliquis and Xarelto prescriptions with a reduction in warfarin prescriptions. Changes in prescribing rates should continue to be monitored to ensure high-quality care, and to reduce unnecessary increases in Medicaid and Medicare costs.

4. Support stroke prevention and management programs focused on lifestyle interventions.

Expand activities and initiatives promoting healthy lifestyle choices, including increased access to healthy foods and opportunities for safe exercise. Diet, exercise, control of blood pressure and cholesterol levels, and diabetes control should be the foundation of both stroke prevention and treatment. A healthful diet and exercise, treatment of hypertension, hypercholesterolemia, and diabetes should be recommended as first-line strategy for stroke prevention.

5. Realign AccessRx reporting to complement and expand upon Open Payments data.

The new Open Payments data system has made payments to physicians and teaching hospitals publicly available, but unfortunately does not include information on payments to other healthcare providers (e.g. nurses and nurse practitioners) and organizations. AccessRx does collect this data in the District.

Aligning AccessRx reporting standards and requirements to the national Open Payments data would allow for more rigorous and beneficial analysis for the District's consumption. This can be accomplished in two steps:

- **Requiring pharmaceutical companies to identify a specific drug being marketed for expenditures reported to AccessRx**, as is required of the Open Payments system. This change would allow AccessRx to monitor the shift in promotions to physicians and other providers for specific drugs and report more accurately on pharmaceutical marketing trends.

- **Make AccessRx data publicly available.** AccessRx data could be extremely useful for patients and providers who want to know how their healthcare system is being influenced by pharmaceutical marketing. The data should be freely and easily accessible by the public in an online, searchable form, similar to Open Payments. Patients especially have a right to know how marketing is affecting the care being given by nursing staff, physician assistants and medical organizations.

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