National Trends in Oral Anticoagulant Use in the United States, 2007 to 2011

Kate Kirley, MD; Dima M. Qato, PharmD, MPH, PhD; Rachel Kornfield MA; Randall S. Stafford, MD, PhD; G. Caleb Alexander, MD, MS

Background—Little is known regarding the adoption of direct thrombin inhibitors in clinical practice. We examine trends in oral anticoagulation for the prevention of thromboembolism in the United States.

Methods and Results—We used the IMS Health National Disease and Therapeutic Index, a nationally representative audit of office-based providers, to quantify patterns of oral anticoagulant use among all subjects and stratified by clinical indication. We quantified oral anticoagulant expenditures using the IMS Health National Prescription Audit. Between 2007 and 2011, warfarin treatment visits declined from ≈2.1 million (M) quarterly visits to ≈1.6M visits. Dabigatran use increased from 0.062M quarterly visits (2010Q4) to 0.363M visits (2011Q4), reflecting its increasing share of oral anticoagulant visits from 3.1% to 18.9%. In contrast to warfarin, the majority of dabigatran visits have been for atrial fibrillation, though this proportion decreased from 92% (2010Q4) to 63% (2011Q4), with concomitant increases in dabigatran’s off-label use. Among atrial fibrillation visits, warfarin use decreased from 55.8% visits (2010Q4) to 44.4% (2011Q4), whereas dabigatran use increased from 4.0% to 16.9%. Of atrial fibrillation visits, the fraction not treated with any oral anticoagulants has remained unchanged at ≈40%. Expenditures related to dabigatran increased rapidly from $16M in 2010Q4 to $166M in 2011Q4, exceeding expenditures on warfarin ($144M) in 2011Q4.

Conclusions—Dabigatran has been rapidly adopted into ambulatory practice in the United States, primarily for treatment of atrial fibrillation, but increasingly for off-label indications. We did not find evidence that it has increased overall atrial fibrillation treatment rates. (*Circ Cardiovasc Qual Outcomes. 2012;5:00-00.*)

Key Words: anticoagulants ◼ coumarins ◼ other anticoagulants

Arterial and venous thromboembolic events, including stroke and myocardial infarction, are a leading cause of morbidity and mortality in the United States. Oral anticoagulants are especially critical in the prevention of thromboembolic events among high-risk patients such as many of those with atrial fibrillation. Compared with their counterparts, patients with atrial fibrillation have a 5-fold increase in stroke and oral anticoagulants reduce this risk by up to two thirds.

Warfarin, a vitamin K antagonist, has been the mainstay of oral anticoagulant treatment in the United States since 1954. Despite its effectiveness in reducing thromboembolic events, warfarin treatment has several drawbacks, including bleeding risk, potential drug interactions, and routine monitoring requirements. In addition to causing substantial morbidity and mortality, these drawbacks have contributed to undertreatment of at-risk populations and motivated the development of newer oral anticoagulant therapies.

In October 2010, the Food and Drug Administration (FDA) approved dabigatran etexilate (dabigatran), a direct thrombin inhibitor, making it the first oral anticoagulant approved since warfarin for the prevention of stroke in patients with nonvalvular atrial fibrillation. This indication is dabigatran’s only FDA-approved use. In contrast to warfarin, dabigatran does not require routine monitoring and has fewer known drug–drug interactions, and evidence suggests that it may be a cost-effective alternative to warfarin in specific subpopulations despite its 15-fold greater retail price. Dabigatran has been included in recent updates to atrial fibrillation practice guidelines, which recommend that it be considered either as an alternative treatment option to warfarin, or that it be used in preference over warfarin. However, as with any newly approved therapy, treatment with dabigatran is complicated by limited knowledge of its real-world safety and efficacy, such as its use for the prevention of thromboembolic events for nonapproved indications or patient populations.

We examined national trends in oral anticoagulant use in the United States with a focus on the impact of dabigatran on clinical practice. Although the first oral direct activated Factor X inhibitor, rivaroxaban, was approved by the FDA in
July 2011 for prophylaxis of deep venous thrombosis and in November 2011 for the prevention of stroke in patients with nonvalvular atrial fibrillation, we limited our analysis to dabigatran, given its longer availability in the market. We used data derived from a nationally representative audit of office-based providers to examine overall oral anticoagulant utilization between 2007 and 2011, with a specific focus on dabigatran and warfarin. We also examined treatment patterns by patient age, provider specialty and common indications for oral anticoagulation, with a particular emphasis on atrial fibrillation. Finally, we quantified pharmacy expenditures for warfarin and dabigatran using a nationally representative audit of retail, mail order and long-term care pharmacies.

WHAT IS KNOWN

- Arterial and venous thromboembolic events, including stroke and myocardial infarction, are a leading cause of morbidity and mortality in the United States.
- Novel orally available anticoagulants are increasingly available as alternatives to coumarins.

WHAT THIS ARTICLE ADDS

- Dabigatran has been rapidly adopted into ambulatory practice in the United States.
- Although the primary clinical use of dabigatran has been for atrial fibrillation, it is being increasingly used for off-label indications.
- This study did not provide evidence that dabigatran utilization has increased overall atrial fibrillation treatment rates.

Methods

Data

We used data from the National Disease and Therapeutic Index (NDTI), an ongoing physician survey conducted by IMS Health (Collegeville, PA). The NDTI provides diagnostic and prescribing information based upon an audit of ≈4800 physicians. Participating physicians were randomly selected from the American Medical Association and American Osteopathic Association master files, which included both members and nonmembers and provide specialty certifications based on self-report as well as secondary rosters. The NDTI sampling process selects physicians within strata defined by specialty and geographic area that are designed to capture a nationally representative sample. Sampling weights are then applied to allow extrapolation to national estimates.

Providers participating in the NDTI record information on all patient encounters during 2 consecutive workdays per quarter, generating ≈350 000 annual contact records. Although a variety of patient encounter types are reported in the NDTI (eg, phone, nursing facility), we limited our analyses to ≈85% of records from office-based encounters. For each record, physicians report all diagnosed conditions and the specific medications used or mentioned to treat each condition. Every record of a drug therapy within the NDTI is linked to a 6-digit taxonomic code capturing diagnostic information similar to the International Classification of Diseases 9th Revision (ICD-9). Several investigations have compared the NDTI with a publicly available audit of office-based medical care, the National Ambulatory Medical Care Survey (NAMCS); these evaluations suggest consistency between the NDTI and NAMCS in evaluating ambulatory patterns of care. We used the IMS Health National Prescription Audit (NPA) to derive data on prescription volume and expenditures. The NPA consists of a nationally representative sample of retail, mail order, and mass merchandise pharmacies that account for more than half of the retail pharmacies in the United States. Data reported in the NPA include estimates of the total number of new or refill prescriptions dispensed to US consumers, as well as information on estimated total direct expenditures on dispensed medications, calculated at the retail value. These data are reported as part of the pharmacies’ administrative systems used to bill consumers and health insurers for these medications.

Analyses

Our primary unit of analysis of the NDTI data was an office visit where an oral anticoagulant was used, heretofore referred to as a treatment visit. A single clinical encounter can generate multiple treatment visits if a therapy is used to treat more than 1 condition. We focused on treatment visits for warfarin and dabigatran and, in analyses investigating ambulatory care patterns for atrial fibrillation, we also examined treatment visits for oral antiplatelet agents. The antiplatelets included in our analyses were aspirin, clopidogrel, dipyridamole, prasugrel, and ticlopidine, as well as fixed dose combinations of these therapies. We excluded injectable anticoagulants from our analyses as they comprised only 3% of anticoagulants mentioned in office-based settings.

We explored common conditions for which oral anticoagulants might be prescribed, including atrial fibrillation, venous thromboembolism, coronary artery disease, heart valve disorders, hypercoagulable states and stroke, or transient ischemic attack. Although dabigatran is only FDA-approved for nonvalvular atrial fibrillation, the NDTI does not provide the ability to discern between valvular and nonvalvular disease. Therefore, we defined atrial fibrillation as the only FDA-approved indication for dabigatran use; all other conditions associated with dabigatran use were considered off-label.

We also used descriptive statistics to examine national estimates of treatment visits, dispensed medications, and costs from the first quarter of 2007 (2007Q1) through the fourth quarter of 2011 (2011Q4). We also conducted analyses of treatment visits after stratifying visits by patient age, physician specialty, and the specific diagnoses for which anticoagulation was used. In sensitivity analyses, we adjusted the treatment visit values for differences in the length of calendar quarters, however, the results were substantively unchanged and are not reported herein.

Results

Trends in Warfarin and Dabigatran Use

Between 2007Q1 and 2011Q4, warfarin treatment visits declined modestly from ≈2.1 million (M) quarterly treatment visits during 2007 to ≈1.6M visits during 2011 (Table 1, Figure 1). Dabigatran use increased from 0.062M quarterly visits (2010Q4) to 0.363M visits (2011Q4), reflecting an increase in its overall share of oral anticoagulant visits from 3.1% to 18.9% over this period. The majority of oral anticoagulant treatment visits occurred with patients aged 65–84 years, but dabigatran use was even more focused within this age group than warfarin. Approximately 6.7% of dabigatran use compared with 12.7% of warfarin use occurred among patients aged 85 years and older during 2011.

Use of Oral Anticoagulants by Clinical Indication

Between 2007Q1 and 2011Q4, the proportion of warfarin use devoted to atrial fibrillation remained constant around 41%, with the remainder associated with a variety of other clinical indications including venous thromboembolism (17%) and hypertensive heart disease (11%) (Table 2). By contrast, 92% of all dabigatran treatment visits in 2010Q4 were for atrial fibrillation, decreasing to 63% of all treatment visits by
2011Q4. The most common off-label uses of dabigatran were for coronary artery disease, hypertensive heart disease, and venous thromboembolism.

**Trends in Use of Anticoagulants and Antiplatelets for Atrial Fibrillation**

Table 3 and online-only Data Supplement Figure I depict trends in the treatment of atrial fibrillation with oral anticoagulants and antiplatelet therapies between 2007Q1 and 2011Q4. Before the introduction of dabigatran in 2010Q4, ≈60.5% of atrial fibrillation visits were treated with warfarin. This proportion decreased to 44.4% as of 2011Q4, whereas the percentage of atrial fibrillation visits treated with dabigatran increased from 4.0% (2010Q4) to 16.9% (2011Q4). Among all atrial fibrillation visits where an oral anticoagulant was used, the fraction treated with dabigatran increased from 6.7% to 27.5% over the period examined.

Antiplatelet use as monotherapy for atrial fibrillation remained fairly constant from 2007 to 2011 at roughly 4.6% of atrial fibrillation treatment visits. The percentage of visits in which neither an anticoagulant nor an antiplatelet medication was reported was approximately 35% and unchanged since dabigatran’s market debut.

**Dabigatran Use by Specialty**

Before the availability of dabigatran, the majority of visits reporting oral anticoagulant use were with physicians practicing in internal medicine (30%), cardiology (34%), and family practice (19%), with fewer visits accounted for by physicians affiliated with osteopathy (5%), oncology (3%), or other specialties (8%). By contrast, most dabigatran visits during the 5 calendar quarters of available data were accounted for by cardiologists (53%), with fewer visits associated with internal medicine (28%), family practice (10%), or other clinical fields (9%).

![National warfarin and dabigatran treatment visits, 2007 to 2011.](http://circoutcomes.ahajournals.org/)

Source: IMS Health National Disease and Therapeutic Index, 2007-2011
Prescription Sales and Costs of Warfarin and Dabigatran

Sales of warfarin remained roughly constant at ≈8.8M prescriptions per quarter from 2007 through 2010 (online-only Data Supplement Figure II). There was a slight decrease in warfarin sales in 2011, with 8.3M prescriptions in 2011Q4 being the lowest point in this 4-year period. Dabigatran sales increased from 0.073M prescriptions in 2010Q4 to 0.733M in 2011Q4, reflecting an increase in the share of sales of oral anticoagulants from 0.8% to 8.1%

Total direct expenditures on warfarin have decreased slightly from ≈$169M per quarter in 2007 to $158M in 2010; these costs further decreased since the debut of dabigatran to $144M in 2011Q4 (Figure 2). Dabigatran direct expenditures rose from $16M in 2010Q4 to $166M in 2011Q4, exceeding direct expenditures on warfarin in that quarter.

Discussion

In this national audit of ambulatory-based practice, dabigatran has been briskly adopted into clinical practice since its October 2010 FDA approval for the prevention of stroke among patients with nonvalvular atrial fibrillation. Cardiologists are responsible for much of this initial uptake. In addition to accounting for more than 18% of all oral anticoagulant visits in the most recent calendar quarter, dabigatran has also been increasingly used for off-label indications including stroke and venous thromboembolism. By the fourth quarter of 2011, dabigatran was reported in more than 1 in 4 atrial fibrillation visits where an anticoagulant was used. However, we did not find evidence thus far that the widespread undertreatment of atrial fibrillation has changed since the introduction of dabigatran.

Our findings are important considering the increasing prevalence of thromboembolic disease in the United States, as well as the costs that are incurred and the complexity of its management. The new oral anticoagulants such as direct thrombin inhibitors and activated Factor X inhibitors have the potential to substantially alter its therapeutic landscape. The extent to which these new therapies will continue to expand their market share depends upon a number of factors. Dabigatran, rivaroxaban, and other similar agents offer greater dosing convenience and fewer drug–drug interactions. These benefits must be weighed against greater costs for payers, providers, and patients, as well as uncertainties regarding their comparative safety and effectiveness, which have yet to be rigorously established beyond the clinical trials used to gain their market approval. The FDA and European Medications Agency (EMEA) recently communicated ongoing evaluations of postmarketing reports of serious bleeding events in patients taking dabigatran. Additionally, a recent meta-analysis reported a small but statistically significant increased risk of acute coronary syndrome in patients receiving dabigatran compared with warfarin. However, this same study showed a significant decrease in overall mortality for patients...
Given the narrow therapeutic window of warfarin and potential catastrophic adverse events associated with any anticoagulant use, rapid generation of evidence from postmarketing surveillance and comparative effectiveness studies are urgently needed.25

Atrial fibrillation is a particularly important area for these new therapies. Despite increases in the use of anticoagulation between 1990 and 2002,20 rates of undertreatment with antithrombotic therapies remain high. Treatment rates among high-risk patients range from 20% to 80%,26 even though only ≈15% of patients with atrial fibrillation have a contraindication to anticoagulation.27,28 A recent report suggests that the benefits of dabigatran over warfarin may increase as stroke risk increases using a common risk stratification method, the CHADS2 score.29 Despite the evidence for dabigatran’s improved efficacy in stroke prevention, and its relative ease of use, we did not observe a reduction in atrial fibrillation undertreatment since the introduction of dabigatran. Rather, ≈1 in 3 atrial fibrillation visits were not associated with any reported antithrombotic therapies. Several factors contribute to the underuse of antithrombotic therapy in atrial fibrillation, including physicians’ and patients’ perception of risks and benefits associated with these therapies.30

Our analyses of pharmacy sales indicate rapid increases in dabigatran expenditures during its first year on the US market, exceeding aggregate warfarin direct expenditures in the fourth quarter of 2011. Total direct expenditures on oral anticoagulants in 2011Q4 were nearly double compared with a year prior. Nevertheless, cost-effectiveness analyses, using estimates similar to those reported in the National Prescription Table 3.

**Table 3. Trends in use of Anticoagulants and Antiplatelets Among Patients With Atrial Fibrillation, 2007–2011**

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*Antiplaetes included anagrelide, aspirin, clopidogrel, dipyridamole, prasugrel and ticlopidine, as well as fixed-dose combinations of these therapies.

**Figure 2.** Quarterly prescription expenditures for warfarin and dabigatran (retail value), 2007 to 2011.
Audit, still indicate that dabigatran may be cost-effective relative to warfarin. The complete cost-effectiveness comparison considers direct medication costs as well as costs related to laboratory monitoring and medication-related adverse events, as well as savings due to the lower incidence of stroke in dabigatran users. Dabigatran appears particularly cost-effective among patients at high risk for stroke and among patients whose anticoagulation is difficult to maintain in the therapeutic range with warfarin. If new warfarin monitoring methods, such as less frequent laboratory assessments, are shown to be safe and effective, this cost-effectiveness comparison may shift, especially given recent evidence of significant improvement in the proportion of time spent in therapeutic anticoagulation among warfarin users and subsequent decline in the incidence of stroke.

We also found increases in dabigatran’s use for off-label indications during its short time on the market. Although stroke prevention in nonvalvular atrial fibrillation is the only FDA-approved indication for dabigatran, both treatment of acute venous thromboembolism and venous thromboembolism prevention in patients undergoing knee and hip replacements are supported with clinical trial data. The FDA-approved indications for other oral anticoagulants, such as the approval of rivaroxaban for venous thromboembolism prevention in arthroplasty, may also influence how dabigatran is used.

Despite considerable growth in dabigatran use, the fraction of use occurring among the oldest old individuals ≥85 years of age, decreased from more than 1 in 5 uses during 2010Q4 to fewer than 3% of uses in 2011Q3, though increasing again during 2011Q4. Dabigatran’s labeling urges caution in patients older than 75 years of age, recommending assessment of renal function before initiation. Whether dabigatran truly presents a higher risk to the elderly is not yet clear. The RE-LY trial reported a lower risk of major bleeding for dabigatran compared with warfarin among individuals <75 years of age, but a nonstatistically significant trend toward an increased risk of major bleeding among those ≥75 years of age. From a clinic perspective, however, dabigatran use in the most elderly may be attractive if it can be demonstrated to reduce the likelihood of under- and over-anticoagulation relative to warfarin.

Our study has several limitations. First, our primary data are based on an audit of office-based providers. Although the clinical information available is provided directly by clinicians and therefore may have more validity than information gathered through health claims or other administrative sources, we nevertheless have limited clinical details on important patient and clinical characteristics that may guide treatment decisions. For example, our data do not provide information on patient preferences, treatment failures, therapeutic switching, nor clinical information such as renal function or the nature of an individuals’ atrial fibrillation, all of which may reasonably impact clinical decision making. Second, the NDTI does not capture visits to anticoagulation clinics, and treatment patterns in nonambulatory settings may also be quite distinct from those examined herein. Third, our analyses were necessarily limited to the temporal period examined and it is likely that continued changes in the use of these therapies will occur. Fourth, physician participants in the NDTI may differ from nonparticipants, and because our data is derived from a visit-based sample, it overrepresents individuals with higher baseline levels of health care utilization. Despite this, several studies suggest substantively similar estimates of medication use when comparing the NDTI with the National Ambulatory Medical Care Survey. Finally, our study is a descriptive study of health care utilization, rather than one focused on outstanding questions of the comparative safety or effectiveness of these therapies. In addition, our study was not designed for causal inference regarding the changes in anticoagulant utilization observed.

Conclusions

New oral anticoagulants reflect the opportunities and risks that are inherent with any new therapeutic class. However, in contrast to some therapeutic areas, the potential public health impact of these medicines may be larger, given the burden of thromboembolic disease in the United States. Despite the important role of warfarin in reducing morbidity and mortality associated with atrial fibrillation and other conditions, its safety and effectiveness is closely tied to the level of anticoagulation, which is often difficult to maintain within a therapeutic window and requires ongoing monitoring. Our findings suggest that dabigatran has been rapidly adopted into ambulatory practice in the United States, primarily for treatment of atrial fibrillation but increasingly for off-label indications, and thus far without evidence of an effect on the widespread undertreatment of atrial fibrillation. Despite its limited use, the aggregate direct cost of dabigatran now exceeds that of warfarin. Significant shifts in oral anticoagulant use are likely as additional therapies become available and evidence accrues regarding their comparative safety and effectiveness relative to conventional therapies.

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Disclosures

Dr Alexander and Ms. Kornfield are consultants for IMS Health and Dr Stafford is a nonpaid member of a steering committee for IMS Health. There are no other disclosures to report.
References


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Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2012/09/05/CIRCOUTCOMES.112.967299.DC1

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL FIGURE 1: ATRIAL FIBRILLATION OFFICE VISITS TREATED WITH ANTIPLATELETS, DABIGATRAN, AND WARFARIN, 2010-2011.

Source: IMS Health National Disease and Therapeutic Index, 2010-2011

Source: IMS Health National Prescription Audit, 2007-2011