



National Trends in Ambulatory Oral Anticoagulant Use

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ABSTRACT

BACKGROUND: Four direct oral anticoagulants (DOACs) have been brought to market for the treatment of nonvalvular atrial fibrillation and venous thromboembolism. Many forces, including numerous positive trial results, emerging safety concerns, marketing, and promotion, may shape DOAC adoption by providers. However, relatively little is known regarding their ambulatory utilization compared with warfarin, as well as the degree to which they have decreased under-treatment of atrial fibrillation.

METHODS: We used the IMS Health National Disease and Therapeutic Index, a nationally representative audit of outpatient office visits, to estimate the use of warfarin and DOACs between 2009 and 2014.

RESULTS: Overall, visits with anticoagulation use increased from 2.05 (95% confidence interval [CI], 1.82-2.27) to 2.83 (95% CI, 2.49-3.17) million (M) quarterly visits ($P < .001$). Of these, DOAC use has grown to 4.21M (95% CI, 3.63M-4.79M; 38.2% of total) treatment visits in 2014 since their introduction in 2010. Use of all oral anticoagulants in treatment visits for atrial fibrillation has increased from 0.88M (95% CI, 0.74M-1.02M) to 1.72M (95% CI, 1.47M-1.97M; $P < .001$), with similar DOAC and warfarin use in 2014. Atrial fibrillation visits with anticoagulant use increased from 51.9% (95% CI, 50.4%-53.8%) to 66.9% (95% CI, 65.0%-69.3%) between 2009 and 2014 ($P < .001$). In 2014, rivaroxaban was the most commonly prescribed DOAC for atrial fibrillation (47.9% of office visits), followed by apixaban (26.5%) and dabigatran (25.5%).

CONCLUSIONS: Direct oral anticoagulants have been adopted rapidly, matching the use of warfarin, and are associated with increased use of oral anticoagulation for patients with atrial fibrillation.

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Thromboembolic events associated with atrial fibrillation and venous thromboembolism are leading causes of morbidity and mortality worldwide.¹⁻³ Prevention and treatment of thromboembolism is best achieved with oral anticoagulant

therapy. Vitamin K antagonists (primarily warfarin) have been the traditional oral anticoagulant for decades. However, 4 direct oral anticoagulants (DOACs)—dabigatran, rivaroxaban, apixaban, and edoxaban—were introduced sequentially

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into clinical practice beginning in 2010.⁴ Despite their costs, these agents have achieved popularity among both patients and providers because of their efficacy, ease of use, and favorable safety profile. As such, they are often first-line therapy for stroke prophylaxis in the context of atrial fibrillation, as well as the treatment and prevention of venous thromboembolism.

Despite the clear benefit of anticoagulation for atrial fibrillation and venous thromboembolism and the growing enthusiasm for DOACs, clinicians and public health officials remain concerned about potential underutilization of oral anticoagulants for these conditions.⁵ This has important clinical implications for the estimated 3 million patients with atrial fibrillation and approximately 75,000 patients diagnosed annually with venous thromboembolism.⁶ To date, longitudinal nationwide analyses of oral anticoagulation utilization have not demonstrated any meaningful change in the underutilization of anticoagulant therapy for atrial fibrillation patients.^{1-3,7}

To establish the utilization of anticoagulants and its impact on treatment for atrial fibrillation and venous thromboembolism, we examined a nationally representative, contemporary audit of commercially available oral anticoagulants between 2009 and 2014. In addition to extending prior work that was limited to examining the early market experience after dabigatran's US Food and Drug Administration (FDA) approval,⁷ we explored the impact of 2 additional DOACs on anticoagulant use. We also examined the change in percentage of office visits for atrial fibrillation where an anticoagulant was prescribed. We hypothesized that DOAC use would replace warfarin use for the treatment of atrial fibrillation and venous thromboembolism and that the total number of atrial fibrillation patients receiving oral anticoagulants would increase.

METHODS

Data Source

The IMS Health National Disease and Therapeutic Index (NDTI) is an ongoing survey of office-based physicians in the United States that provides nationally representative data on the patterns and treatment of disease. The database has been described in detail in previous studies.⁷⁻¹⁰ Briefly, the NDTI prospectively collects office-based clinical information from approximately 4800 physicians identified through a random audit of the American Medical Association and American Osteopathic Association databases. The NDTI data include diagnosis, physician specialty, geographic region, patient age, and gender. The NDTI survey captures

information on all clinic visits during 2 consecutive working business days per quarter, generating approximately 350,000 annual contract records. The NDTI also includes physician–patient interactions via phone call and in skilled nursing facilities (approximately 15% of all visits), which were excluded from our analysis. For each office-based encounter, all diagnosed conditions and the specific medications used or documented for each diagnosis are recorded. Each medication record within the NDTI is linked to a 6-digit taxonomic code, similar to the International Classification of Diseases, Tenth Revision, Clinical Modification, that captures diagnostic information. Using the sampling frame and weights, national estimates of office-based practice patterns can be extrapolated from NDTI data.⁷⁻¹⁰

CLINICAL SIGNIFICANCE

- The number of office visits with anticoagulant use is increasing, largely driven by new visits with direct oral anticoagulant use in atrial fibrillation patients.
- Currently, direct oral anticoagulants and warfarin are used in equal numbers of office visits for atrial fibrillation.
- Overall, oral anticoagulants are being used in an increasing percentage of office visits for atrial fibrillation.

Analyses

Our primary unit of analysis was a treatment visit, defined as an office visit in which an oral anticoagulant was used. A single medication can produce more than 1 treatment visit during a single clinical encounter if that medication is used for multiple indications. We limited our analysis to treatment visits for warfarin and the 3 DOACs available during the study period (dabigatran, rivaroxaban, and apixaban) for atrial fibrillation and venous thromboembolism in patients aged ≥ 18 years. Analysis was performed on aggregated quarterly office visit estimates, because individual patient-level data were not available. Because we are interested in outpatient treatments, we excluded injectable anticoagulants from our analyses. The institutional review board of the University of Michigan Medical School assessed this study as not regulated and waived the requirement for informed consent.

When assessing indications for oral anticoagulant use, we explored common cardiovascular conditions, specifically atrial fibrillation (including atrial flutter) and venous thromboembolism, as were coded in the visit diagnosis and linked to the use of a specific medication. Although the DOACs are FDA-approved only for nonvalvular atrial fibrillation, the NDTI does not allow for reliable distinction between valvular atrial fibrillation and nonvalvular atrial fibrillation.

We used descriptive statistics to examine national estimates of treatment visits and dispensed medications between April 2009 and December 2014. We also conducted analyses of treatment visits after stratifying visits by the indication for anticoagulation and for age ≥ 65 years. Reported data include market share analysis, defined by the proportion of observed visits associated with a specific oral anticoagulant (or class) divided by the total observed visits

associated with any oral anticoagulant. We also stratified the market share data by clinical indication. To estimate the percentage of office visits for atrial fibrillation with and without anticoagulant use, we examined all office visits with a diagnosis of atrial fibrillation (or atrial flutter) and stratified according to the use of any oral anticoagulant (warfarin, dabigatran, rivaroxaban, or apixaban) and by age ≥ 65 years between April 2009 and December 2014. Confidence intervals (CIs) for quarterly estimates were generated using a standardized 2-stage stratified cluster methodology.

We used weighted least squares linear regression with linear spline analysis to assess the quarterly trend in the estimated office visits with anticoagulant prescription use. Unlike standard linear regression, weighted least squares linear regression corrects the unequal variance in estimates by inversely weighting the estimates according to their precision. The 95% CIs for estimates of office visits, as well as the 95% CIs for the calculated rates, provided the measure of precision. Quarterly trends were statistically significant if likelihood-ratio tests yielded P values $< .05$. Statistical analysis was performed using Stata Version 13 (StataCorp, College Station, Tex).

RESULTS

Overall anticoagulation treatment visits increased from 2.05 million (M) (95% CI, 1.82M- 2.27M) in the second quarter of 2009 (2009/Q2) to 2.83M (95% CI, 2.49M-3.17M) in 2014/Q4, driven by an increase of 83,000 (83K) (95% CI, 58K-109K) visits per quarter since 2012/Q2 ($P < .001$; **Figure 1** and **Supplementary Table 1**, available online). Between 2009/Q2 and 2012/Q1, there was no significant increase in treatment visits with anticoagulant use. Although warfarin treatment visits declined between 2009 and 2014, DOAC treatment visits have risen to more than 1 million per quarter since their introduction in 2010/Q4. Among DOAC treatment visits, dabigatran accounted for

the majority of prescriptions between 2010/Q4 and 2012/Q4. However, since 2013/Q1, use of rivaroxaban is most common among the DOACs (**Figure 1**).

Warfarin and DOAC Use by Clinical Indication

Use of all oral anticoagulants in treatment visits for atrial fibrillation has increased from 0.88M (95% CI, 0.74M-1.02M) in 2009/Q2 to 1.72M (95% CI, 1.47M-1.97M) in 2014/Q4, driven by an increase of 154K (95% CI, 119K-188K) visits per quarter since 2013/Q2 ($P < .001$; **Figure 2** and **Supplementary Table 2**, available online). The increase in total anticoagulant use for atrial fibrillation visits has been largely driven by a more than 3-fold increase in DOAC use between 2013/Q2 (0.22M; 95% CI, 0.15M-0.28M) and 2014/Q4 (0.74M; 95% CI, 0.60M-0.88M). In 2014, use of DOACs was similar to warfarin use in atrial fibrillation treatment visits (**Figure 2**). As of 2014, rivaroxaban is the most commonly prescribed DOAC during atrial fibrillation office visits (48.2%), followed by apixaban (26.4%) and dabigatran (25.4%; **Supplementary Table 2**, available online). Use of dabigatran has been relatively stable since 2011/Q4, whereas use of rivaroxaban and apixaban continue to increase (**Supplementary Table 2**, available online).

Use of all oral anticoagulants in patients with venous thromboembolism has increased from 367K (95% CI, 280K-453K) visits in 2009/Q2 to 583K (95% CI, 458K-707K) in 2014/Q4, an increase of 9K (95% CI, 4K-14K) visits per quarter ($P = .001$; **Supplementary Table 2**, available online). Use of DOACs has increased since 2012 and accounts for 36% of all venous thromboembolism visits in 2014.

The majority of atrial fibrillation treatment visits with oral anticoagulant use occurred in patients aged ≥ 65 years (82.5%). Patients aged < 65 years represent a minority of treatment visits for atrial fibrillation with both DOAC use

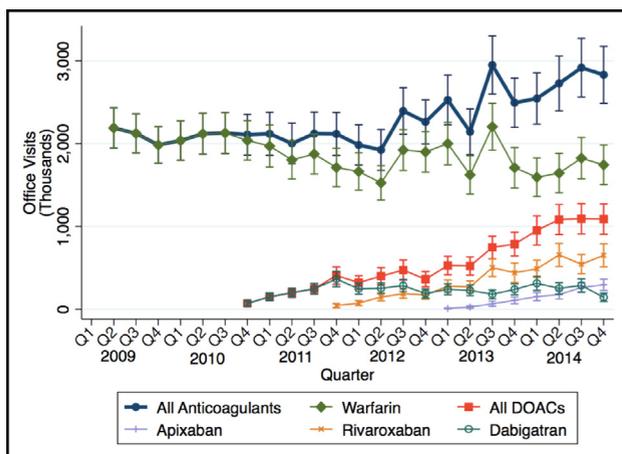


Figure 1 Quarterly use of oral anticoagulant during office visits. DOAC = direct oral anticoagulant. Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

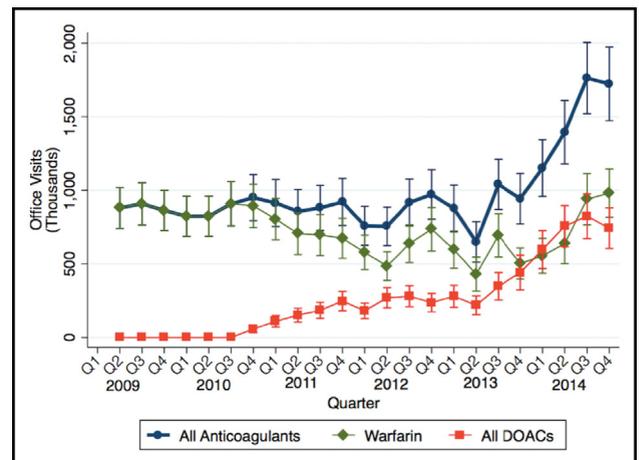


Figure 2 Quarterly visits for atrial fibrillation by anticoagulant type. DOAC = direct oral anticoagulant. Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

(23.8%) and warfarin use (15.3%). The majority of venous thromboembolism treatment visits with oral anticoagulant use occurred in patients aged <65 years (55.7%). Patients aged <65 years were common among venous thromboembolism treatment visits with DOAC use (49.3%) but represented the majority of venous thromboembolism treatment visits with warfarin use (56.5%).

Anticoagulant Use with Atrial Fibrillation Visits

Total visits for atrial fibrillation increased from 1.67M (95% CI, 1.46M-1.87M) in 2009/Q2 to 2.52M (95% CI, 2.21M-2.83M) in 2014/Q4, an increase of 170K (95% CI, 114K-225K) per quarter since 2013/Q2 ($P < .001$; [Supplementary Table 2](#), available online). The percentage of atrial fibrillation visits with anticoagulant use increased from 51.9% (95% CI, 50.4%-53.8%) in 2009/Q2 to 66.9% (95% CI, 65.0%-69.3%) in 2014/Q4, an increase of 2.3% (95% CI, 1.2%-3.4%) per quarter since 2013/Q2 ($P < .001$; [Figure 3](#)).

DISCUSSION

Using data from a large, nationally representative audit of ambulatory practice in the United States, we found continued brisk adoption of DOAC use in place of vitamin K antagonists. In particular, the use of DOACs for atrial fibrillation patients seems to be accelerating, largely driven by increasing use of rivaroxaban and apixaban alongside consistent use of dabigatran. In fact, use of DOACs is now similar to the use of warfarin for atrial fibrillation patients. Most importantly, the percentage of atrial fibrillation visits with anticoagulant use has been increasing since 2013/Q2, suggesting that more atrial fibrillation patients are receiving anticoagulation therapy.

Our findings are particularly timely given that under-treatment of atrial fibrillation patients has been a long-standing

concern.¹¹⁻¹³ This is highlighted by recent studies supporting the use of longer-term monitoring to detect occult atrial fibrillation.¹⁴⁻¹⁷ Prior studies have identified patient characteristics associated with use of warfarin vs DOACs in atrial fibrillation patients.^{18,19} However, it was not previously known whether the introduction of DOAC agents would help to increase the proportion of atrial fibrillation patients receiving anticoagulant therapy. Given the morbidity and mortality associated with the under-treatment of atrial fibrillation, our findings of increased treatment of atrial fibrillation since the advent of DOAC therapy are noteworthy.¹³ The use of the Congestive heart failure, Hypertension, Age 75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65-74, and Sex category [female] (CHA₂DS₂-VASc) score to estimate the annual risk of stroke in atrial fibrillation patients should lead to additional patients eligible for anticoagulant therapy.²⁰ However, the rise in anticoagulant therapy in our US-based cohort began before the American College of Cardiology/American Heart Association-based guidelines endorsed the use of the CHA₂DS₂-VASc score in 2014.²¹ Additionally, the national expansion of health insurance coverage associated with the Affordable Care Act did not occur until 2014, after the rise in use of anticoagulants for atrial fibrillation visits was seen in our population.²² Our population demonstrated relatively steady rates of office visits with oral anticoagulant use in the 3 years between 2009 and mid-2012. Starting in mid-2012, the number of office visits with anticoagulant use began to rise, and a similar rise in the proportion of atrial fibrillation visits with oral anticoagulant use was seen beginning in mid-2013.

Of note, rivaroxaban now accounts for half of all DOAC use in atrial fibrillation patients among this population. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)²³ and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)²⁴ trials demonstrated the superiority of dabigatran and apixaban, respectively, over warfarin. Conversely, in the The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study, rivaroxaban was not able to demonstrate superiority for either stroke prevention or major bleeding in the intention-to-treat analysis. However, once-daily dosing and its association with improved medication adherence is a potentially strong motivator for both patients and providers to adopt rivaroxaban use and may contribute to its dominant market share in our analysis.²⁵⁻²⁷

Other potential contributors to its market share include differential marketing and promotion, and early FDA approval for both venous thromboembolism and atrial fibrillation patients, as well as its formulary placement across different health plans. It remains to be seen whether the favorable trial results with apixaban will be linked to greater use over time or whether the convenience of once-daily dosing of rivaroxaban will maintain it as the most frequently used DOAC for stroke prevention in atrial

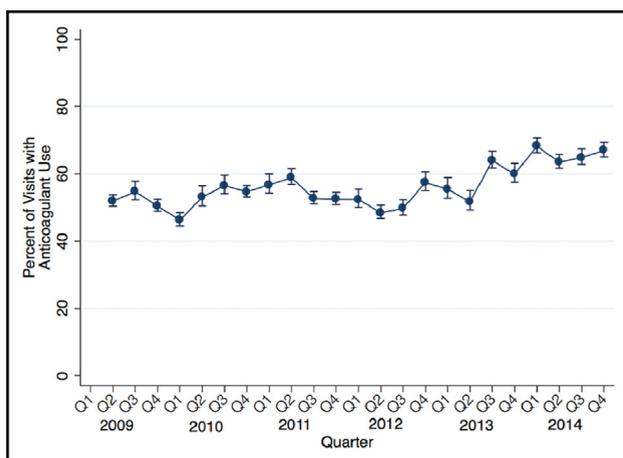


Figure 3 Percentage of quarterly office visits for atrial fibrillation with anticoagulant use. Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

fibrillation. Furthermore, despite dabigatran being the first DOAC approved for use in the United States, there have been recent concerns about myocardial infarction and bleeding risk that may impact its current and future use.²⁸⁻³¹ Apixaban was recently approved (December 2012) and has had little time to gain market share, yet its use outnumbers dabigatran for office visits in the latter half of 2014. Edoxaban was approved after the completion of data analysis and therefore is not included in this study.

Unlike visits for atrial fibrillation, we did not identify increases in anticoagulant treatment visits for venous thromboembolism after DOAC introduction. Instead, there was a small, steady increase in anticoagulant venous thromboembolism office visits throughout the study period, including before introduction of DOACs. We believe that this finding is consistent with clinical practice because nearly all patients with newly diagnosed venous thromboembolism are treated with anticoagulants. Therefore, there is not a large under-treated population of acute venous thromboembolism patients for whom the introduction of DOAC agents offers a new rationale to prescribe anticoagulation. However, use of warfarin has declined as use of DOAC agents have increased for venous thromboembolism. The DOAC use during office visits for venous thromboembolism patients is almost exclusively rivaroxaban, likely owing to the once-daily dosing and its early FDA approval for venous thromboembolism treatment.

Other recent reports have described the use of DOACs in specific patient populations.^{7,18,32-35} Initial data from a Danish national registry of atrial fibrillation patients in 2011 showed minimal use (2%-3%) of dabigatran.³⁵ Subsequent to that report, 2 studies described a rapid rise in adoption of dabigatran for atrial fibrillation patients in North America, 12%-19% of all atrial fibrillation outpatient visits in the United States and 20% of oral anticoagulant prescriptions in Canada.^{7,32-34} Most recently, Desai et al¹⁸ described higher rates of DOAC use (62%) within a single health insurer database, but without any trends over time. Additionally, none have been able to demonstrate a meaningful increase in the total atrial fibrillation population receiving anticoagulant therapy. Confirming the findings from Desai et al,¹⁸ our report finds similarly prevalent DOAC and warfarin use in atrial fibrillation patients, but in a large, nationally representative sample of patients with multiple payers, including Medicare, Medicaid, and the commercially insured.

Our results must be taken in the context of several limitations. First, although these data are derived from a nationally representative sample, they exclude care provided in emergency departments and outpatient anticoagulation clinics and may not be generalizable to all office-based practices. Despite this, a number of prior reports have demonstrated similar estimates between NDTI and the National Ambulatory Medical Care Survey.^{10,36,37} Second, estimates are based on sampling data and do not represent exact number of office visits or number of patients because a single patient may have been observed more than once. However we are unaware of any secular trends beginning in

2013 that would influence the frequency of office visits for atrial fibrillation patients. Third, use of nonprescription aspirin is not reliably captured in the NDTI dataset and therefore was not included in this analysis. Finally, although the NDTI is based on clinical information provided by clinicians or office staff, the data do not include patient-level factors and therefore limit the ability to judge the appropriateness of treatments received, such as information about individuals' renal function, history of valve replacement surgery, comorbidity burden, and decisions about switching anticoagulant therapies.

In conclusion, use of DOACs is rising rapidly and accounts for half of all anticoagulant use during atrial fibrillation office visits. Use of DOACs is rising among venous thromboembolism office visits, largely replacing the use of warfarin. Our findings suggest that DOAC adoption is associated with an increase in the number of atrial fibrillation patients treated with anticoagulant therapy. It remains to be seen whether these trends will continue or change once a DOAC reversal agent becomes available. Additionally, determining the economic impact of the shifting anticoagulant use at both a societal level and an individual level merits further investigation.³⁸

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SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.amjmed.2015.05.044>.

Supplementary Table 1 Office Visits with Oral Anticoagulant Use

Parameter	2009			2010				2011				2012				2013				2014			
	Q2	Q3	Q4	Q1	Q2	Q3	Q4																
Total visits, n (thousands)	2188	2123	1983	2036	2119	2128	2108	2119	2002	2120	2118	1983	1924	2394	2261	2526	2143	2949	2494	2544	2727	2917	2831
Warfarin visits, %	100	100	100	100	100	100	97	93	90	88	81	84	79	80	84	79	76	75	69	63	60	63	68
DOAC visits, %	0	0	0	0	0	0	3	7	10	12	19	16	21	20	16	21	24	25	31	37	40	37	38
Dabigatran visits, %	—	—	—	—	—	—	100	100	100	100	89	77	63	60	52	45	43	24	30	33	23	26	13
Rivaroxaban visits, %	—	—	—	—	—	—	0	0	0	0	11	23	37	40	48	53	52	67	56	51	61	50	60
Apixaban visits, %	—	—	—	—	—	—	0	0	0	0	0	0	0	0	0	2	5	9	14	16	16	24	27

DOAC = direct oral anticoagulant.

Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

Supplementary Table 2 Office Visits with Oral Anticoagulant Use by Diagnosis																							
Parameter	2009			2010			2011			2012			2013			2014							
	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Atrial fibrillation visits, n (thousands)	880	908	863	823	823	908	950	913	856	880	920	758	755	917	972	876	649	1041	943	1151	1394	1763	1724
Warfarin visits, %	100	100	100	100	100	100	94	88	82	79	73	76	64	70	76	68	66	67	53	48	46	53	57
DOAC visits, %	0	0	0	0	0	0	6	12	18	21	27	24	36	30	24	32	34	33	47	52	52	47	43
Dabigatran visits, %	—	—	—	—	—	—	100	100	100	100	95	84	65	67	59	49	41	20	30	32	27	25	18
Rivaroxaban visits, %	—	—	—	—	—	—	0	0	0	0	5	16	35	33	41	49	50	67	54	44	53	47	48
Apixaban visits, %	—	—	—	—	—	—	0	0	0	0	0	0	0	0	2	9	13	16	24	20	28	34	34
Venous thromboembolism visits, n (thousands)	367	387	255	321	414	442	325	423	404	456	349	422	316	452	446	653	434	552	476	505	512	368	583
Warfarin visits, %	100	100	100	100	100	100	100	99	98	99	95	100	100	97	98	90	86	83	77	62	64	72	60
DOAC visits, %	0	0	0	0	0	0	0	1	2	1	5	0	0	3	2	10	14	17	23	38	36	28	40
Dabigatran visits, %	—	—	—	—	—	—	—	100	100	100	100	—	—	0	0	0	10	0	0	0	0	6	0
Rivaroxaban visits, %	—	—	—	—	—	—	—	0	0	0	0	—	—	100	100	100	90	100	100	100	96	87	92
Apixaban visits, %	—	—	—	—	—	—	—	0	0	0	0	—	—	0	0	0	0	0	0	0	4	7	8

DOAC = direct oral anticoagulant.
Source: IMS Health National Disease and Therapeutic Index, 2009-2014.