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Web search popularity, publicity, and utilization of direct oral anticoagulants in the United States, 2008–2018

A STROBE-compliant study

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Abstract

We aimed to study the changing popularity of oral anticoagulants and the potential association between media coverage and real-world utilization practice, using time series analysis.

In this STROBE-compliant study, we used *Google Trends* data to study public interest for direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban) and warfarin in the United States (10-year coverage, beginning July 1st, 2008 ending June 30th, 2018). We validated our findings on a sample of 50 consecutive datasets (accumulated between July 6th, 2018 and October 19th, 2018), using the same search criteria. We used the *LexisNexis Academic* database to quantify monthly media coverage for DOACs and explored its association with interest by the public, using the cross-correlation coefficient function. Finally, we studied the association between public interest and real-world utilization data, including published US-wide data on ambulatory anticoagulation visits.

The approval of dabigatran in 2010 marked an increasing public interest for DOACs. Dabigatran exhibited a steep rise early after Food and Drug Administration approval that peaks in 2011, to be surpassed sequentially by rivaroxaban (2012) and apixaban (2014). Apixaban has outperformed its competitors in popularity since mid-2017, and, by the end of the observation period, was close to warfarin that is on first place. Media coverage was low before approval of the first oral DOAC (dabigatran), increased thereafter (median 13 news articles per month vs 64, $P<.001$), with peaks on the approval dates (81 vs 48, $P=.003$). Media coverage had a weak immediate impact on DOACs public interest and public interest patterns preceded changes in ambulatory anticoagulation visits by up to 5 months.

For a long-run observation period, a single *Google Trends* search will suffice to produce robust estimations of the relative popularity between treatment options, such as oral anticoagulants. Media coverage has limited immediate impact and relative public interest is a potential lead indicator of changes in actual utilization.

Abbreviations: ARIMA = autoregressive integrated moving average, DOAC = direct oral anticoagulants.

Keywords: media coverage, oral anticoagulants, popularity, publicity, trends, utilization, warfarin

1. Introduction

Internet sources have been acknowledged as valuable tools for epidemiological research and public health information.[1,2] Search engine query data may be used to monitor publication activity in relevant health topics,[3] predict disease outbreaks,[4] or monitor interest in vaccination campaigns.[5]

Google Trends, a portal provided by Google Inc. (Mountain View, CA), returns spatiotemporal data on search activity, depending on the specific keywords and time frame used by the researcher. There is no such web service to cover all queries in the United States, but the vast majority of searches use Google, rendering it a popular tool among researches to understand public behavior.[6] Notably, analyzing of search trends is not free of caveats,[7] and the reliability of digital epidemiology using *Google Trends* may vary depending on the healthcare setting.[8]

We used the *Google Trends* portal to study public interest on direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban, and edoxaban, a group of novel oral agents for nonvalvular atrial fibrillation and venous thromboembolism.[9–13] These agents emerged to complement warfarin as the standard of care, and were adopted across medical specialties,[14] as they require no monitoring, have fewer drug-drug interactions, and can provide improved safety-efficacy balance.[15]

The introduction of DOACs signifies a major public health change.[16] In the United States atrial fibrillation affects >≈2.7 million to 6.1 million individuals and the patient population is projected to rise to double by 2030,[17] while venous thromboembolism affects estimated 300,000 to 600,000 individuals per year.[18] By 2014, the use of DOACs matched

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warfarin use in the ambulatory setting,[19] and in 2015 the Medicare part D cost for DOACs reached 3 billion dollars.[14] This new category of widely used medications provided an opportunity to evaluate the association between media coverage, public interest, and changes in prescribing patterns. We used *Google Trends* to monitor changes in the public interest for oral anticoagulants in the United States and explored the impact of publicity on public interest. Finally, we associated the search query behavior with real-world prescribing practices, and more specifically, we explored whether the relative popularity of DOACs could mirror their actual utilization.

2. Methods

2.1. Public interest for DOACs

The *Google Trends* tool can provide a timeline of public interest in terms of the relative popularity of a search query. We categorized search terms in 5 distinct queries, combining generic names and U.S. brand names of Food and Drug Administration (FDA)-approved DOACs and warfarin. We set analysis timeframe at 10 years, beginning on July 1st, 2008 and ending on June 30, 2018. We set geographic region to "United States."

We exported the output graph and described the patterns of the relative popularity of the 5 competitor medications. We focused on identifiable patterns and critical time-points, including peaks/nadirs and change of rankings. We completed visual interpretation in the context of drug approval history.

2.2. Validation of web search output against sampling bias

We validated the *Google Trends* popularity patterns by repeating the search queries to obtain 50 consecutive samples (validation samples) and examined the consistency of the findings. We used the 51st sample (the most recent) as the index for our main analysis and as the reference for validation. When a researcher enters a query, the system draws a random sample from the anonymized database sample that matches geography and time, and reports the relative popularity of the search terms. The results are cached for a day, and repeating the exact query within 24 hours will return the same output. However, afterward the cache is deleted and subsequent results may differ because of sampling bias. Therefore, we collected the output of 50 queries, waiting for the cache to refresh and repeating the search process after the previous sample has expired. The collection of samples took place between July 6th, 2018 and October 20th, 2018. Google Trends data are anonymized. No information can be traced back regarding group or individual characteristics (including their demographics, level of education, skills, social media usage, etc)

2.3. Media coverage for DOACs

We used the *LexisNexis Academic* database to quantify the longitudinal variation of media coverage as a proxy for publicity, regarding the 4 new anticoagulant drugs. It provides extensive coverage of major publication resources and considered a comprehensive and credible source of information.[20–22] We pooled publicity scores by drug and month.

2.4. Association between publicity and public interest

We correlated publicity with popularity scores by drug, using the cross-correlation coefficient function).[23] The threshold for significance ($P < .05$) is $1.96/\sqrt{n}$, where n is the number of observations.[24] Up to 3-month lags (or leads) were considered relevant to the study, given that the impact of news reporting on web searching is immediate.[25,26] Cross-correlation coefficients, denoted with r, are arbitrarily classified as large effects when $|r| \geq 0.50$, medium-sized effects when $0.30 \leq |r| < 0.50$, and weak effects for $|r| < 0.30$.

As a first step, we transformed the media coverage time series, generating the residuals from an autoregressive integrated moving average process (ARIMA modeling) and adjusted for potential outliers. Adjusting for outliers in the model may reduce variability, improve model parameterization and goodness-of-fit.[27] We optimized model parameter selection using the time series regression with ARIMA noise, missing values, and outliers software by Maravall et al.[28] We ran the final model in Stata (College Station, TX) and generated the residuals.

In a following step, we filtered the web search popularity series using the media coverage model coefficients and computed the residuals. Finally, we examined the cross correlation function between the residuals of the first 2 steps. If a significant correlation between the residuals of the pre-whitened explanatory series and the dependent series is still present, we conclude that the changes observed in 1-time series (media coverage) contribute to the changes in the other time series (web search popularity). The rationale, statistical properties, and sequential steps are explicitly described in.[23,29] We used Stata for filtering, cross-correlation function analysis and the presentation of results.

2.5. Public interest patterns and real-world utilization of oral anticoagulants

We searched the published literature for articles reporting on the utilization of oral anticoagulants in the United States. We aimed for studies with nationwide coverage, recent data, usage of big databases, and extractable time trends on warfarin and DOACs utilization, covering all the approved indications and medical specialties. The 2 authors performed the search independently, and after disclosing their shortlist of eligible publications, have agreed upon the use of 2 pertinent publications to benchmark anticoagulant use in the United States.[19,30] Both cover national trends in ambulatory utilization of anticoagulants, providing quarterly data on anticoagulation treatment visits. The studies combined, included information on more than 2 million anticoagulation visits (including atrial fibrillation and venous thromboembolism) quarterly, between the 1st quarter of 2007 (2007Q1) and the last quarter of 2014 (2014Q4). We used these studies to extract the patterns of change and critical dates of oral anticoagulation utilization and compared them with the relative popularity for oral anticoagulants. For consistency of comparisons, we trimmed our *Google Trends* timeline and quarterly visit timeline, to cover from 2008 Q3 to the end of 2014, matching the last recorded visits in.[19] Studies[31–33] restricting data to specific indication and/or medical specialties were deemed as ineligible, given that the web search output cannot be analyzed on the basis of target condition or medical practice.

For simplicity, drugs are mentioned in the remaining sections with their generic names only, but refer to both their brand and generic formulas. A brief methodological framework for the study is available in Table A and detailed in the accompanying notes in the Supplementary appendix, http://links.lww.com/MD/E212. This is a STROBE (STrengthening the Reporting of OBservational studies in Epidemiology, https://www.strobe-statement.org/index.php?id=strobe-home)-compliant study. All study data are publicly available, anonymous, and institutional approval is not required.

3. Results

3.1. Outline view of public interest

Throughout the study timeline, warfarin maintained the highest relative popularity against comparators. At the end of study timeline, warfarin was in first place, but with decreasing relative popularity, followed by apixaban and rivaroxaban. Dabigatran and edoxaban ranked fourth and fifth, respectively, with the lowest relative popularity. The output of our search query is detailed in Figure 1. Since we started collecting data for our study in July 2018, the most popular and trending searches for DOACs in the United States were related to dosing, side effects and reversal agents, drug cost and package insert information. For warfarin, top searches included dosing, side effects, reversal, and diet.

3.2. Analytic view of public interest

We explored the output file to support visual findings and provide an additional analytic view of the data, working on a month-by-month basis. We recreated the *Google Trends* output graph using the monthly observations and explored timeline changes. We added reference lines to mark the specific approval dates for each DOAC, including initial and expanding indications (Table B in the Supplementary appendix, http://links.lww.com/MD/E212 depicts approval dates, drugs, and specific indications). The monthly data are graphically displayed in Figure 2, where we merged FDA critical approval dates with *Google Trends* results. The web search patterns and critical dates are summarized in Table 1.

Warfarin had the highest relative popularity (peak) in February, 2011 and the lowest in December, 2016. The relative popularity of dabigatran began to grow steeply, near its first FDA approval in October 2010, and peaked in May, 2011. The relative popularity of dabigatran had topped shortly before rivaroxaban received first FDA approvals for deep vein thrombosis prevention after hip/knee replacement (July, 2011) and atrial fibrillation (November, 2011), respectively. Dabigatran ranked second to warfarin until November 2012, when it lost second place to rivaroxaban; rivaroxaban had just received FDA approval for venous thromboembolism treatment. Thereafter, the relative popularity of dabigatran continued to decline. Beginning on October 2013, dabigatran and apixaban alternated in third and fourth place, until June 2014 where apixaban secured third place, 6 months after apixaban's first FDA approval for atrial fibrillation.

From November, 2016 to June, 2017, apixaban and rivaroxaban had a roughly equal relative popularity. From June, 2017, apixaban ranks second to warfarin only. Edoxaban, remains with minimal relative popularity in search queries since its approval in January 2015. The final rankings in search popularity of the 5 competitors were in June 2018: warfarin (1st), apixaban (2nd), rivaroxaban (3rd), dabigatran (4th), edoxaban (5th).

3.3. Validation of Google Trends output

Web search patterns and critical dates were validated against 50 Google Trends samples, consecutively drawn, using the exact criteria and timeline. There was 100% coverage regarding the timeline popularity patterns, with the exception of last observation's rankings (94%). Aside to web search patterns, Table 2 reports precision data on critical dates. Coverage exceeded 90% when 1-month deviation (plus or minus) was allowed. There were 2 exceptions to high coverage: apixaban peak (48% coverage) and warfarin nadir (72% coverage).

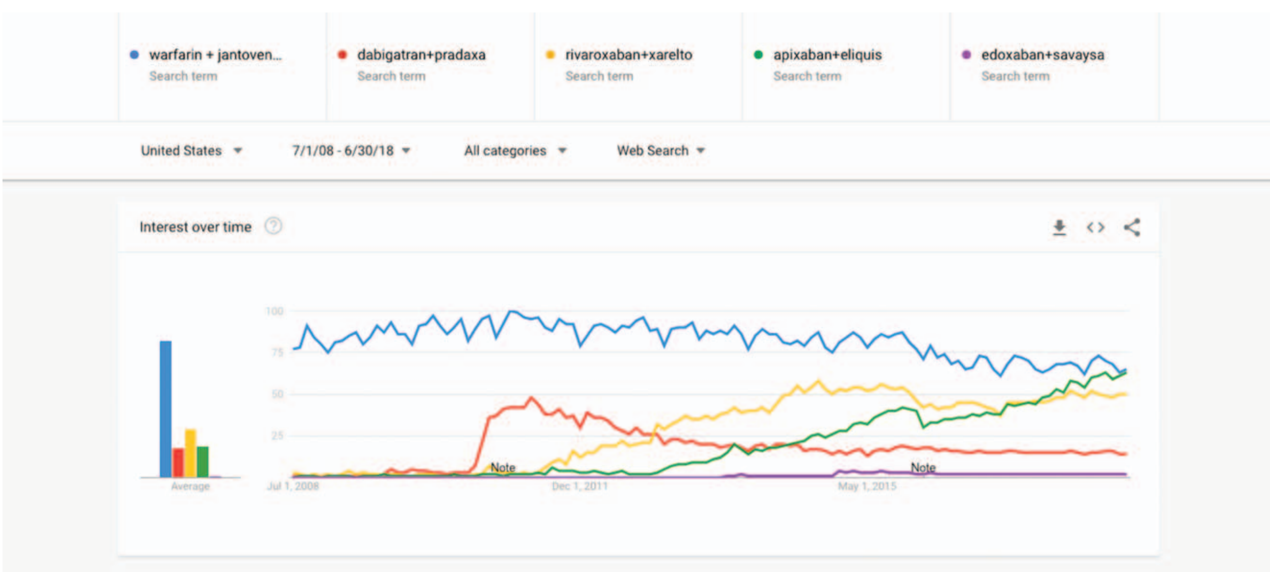

Figure 1. Google Trends output (index sample): The relative web search popularity of the 4 competitor direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) and warfarin in the United States, from July 1st, 2008 to June 30th, 2018. Initially, warfarin dominated web searches in the United States; there were no DOACs in the market. The approval of dabigatran resulted in a steep rise in relative popularity for dabigatran, followed by a sustained decline. The decrease in web search popularity for dabigatran resulted in early loss of second place to rivaroxaban, and loss of third place to apixaban later on. By the end of the observation period, apixaban and rivaroxaban compete in search popularity, and apixaban has secured second place. Thereafter, apixaban struggles with warfarin for top popularity. DOACs = dabigatran, rivaroxaban, apixaban, and edoxaban.

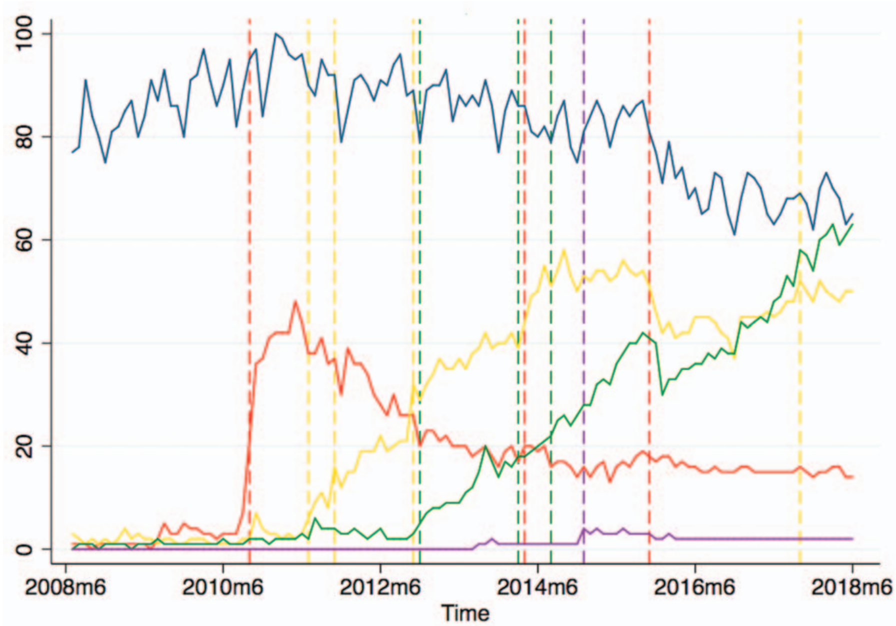

Figure 2. Monthly data on web search popularity of the 4 competitor direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) and warfarin, merged with FDA approval dates. Warfarin (blue lines); dabigatran (red lines); rivaroxaban (yellow lines); apixaban (green lines); edoxaban (purple lines). Vertical dashed lines mark FDA drug approvals (complete list in Table B, Supplementary appendix, http://links.lww.com/MD/E212). The figure highlights critical patterns of change in web search popularity for the competing drugs. Dabigatran has the peak popularity in May 2011, declining thereafter to lose 2nd place to rivaroxaban (November 2012), and 3rd place to apixaban (June 2014), respectively. Rivaroxaban and apixaban emerge consecutively after their respective FDA approvals, starting with rivaroxaban that has reached a peak on October 2014; apixaban follows in popularity but gains ground rapidly to surpass dabigatran (June 2014) and rivaroxaban (June 2017). Edoxaban has minimal activity. The study end finds apixaban with peak activity, competing with warfarin for the first place. The results were robust in validation samples. FDA = food and drug administration.

3.4. Media coverage for DOACs

DOACs attracted media coverage during the study period, with a median of 50.5 news articles (interquartile range 31.5–75) per month. Media coverage was low before October, 2010 and until the FDA approved dabigatran as the first agent for human use (median 13 news articles per month; interquartile range 9–20). It increased thereafter to a median of 64 (interquartile range 46–81; $P<.001$). The FDA approval dates were related to increased media coverage (median 81 news articles; interquartile range 61–97) compared to the remaining series dates (median 48; interquartile range 30–73, $P=.003$). The timeline for media coverage is shown in Figure 3.

Rivaroxaban ranked first in coverage, with a median of 19.9 news articles per month (interquartile range 10.2–30.4, $P<.001$ for all comparisons with competitors). Apixaban ranked second (median of 13.4 articles per month; interquartile range 7.4–22.2), outperforming dabigatran (11.2 articles per month; interquartile range 6.2–17.8, $P=.01$). Edoxaban had the fewest news articles (median 1; interquartile range 0–4.5, $P<.001$ for all comparisons). The timeline of media coverage for DOACs is shown on Figure A, B, C, D in the Supplementary appendix, http://links.lww.com/MD/E212, respectively.

Table 1

Patterns of the relative popularity for competing drugs. Critical days in chronological order. Index sample (referent) and validation samples coverage.

Index sample (referent)		Validation samples coverage (N=50)	
Patterns of web search popularity	**Dates**	**Exact month (n, %)**	**One month allowance (n, %)**
Warfarin peak	February 2011	42 (84)	43 (86)
D peak	May 2011	45 (90)	50 (100)
D loses 2nd place to R	November 2012	50 (100)	50 (100)
D loses 3rd place to A	June 2014	34 (68)	48 (96)
R peak	October 2014	49 (98)	49 (98)
E peak	January 2015	45 (90)	47 (94)
Warfarin low	December 2016	36 (72)	36 (72)
R loses 2nd place to A	June 2017	44 (88)	46 (92)
A peak	March 2018	5 (10)	24 (48)
Final rankings	W, A, R, D, E	47 (94)	Not applicable

A = apixaban, D = dabigatran, E = edoxaban, R = rivaroxaban, W = warfarin.

Table 2

Web search popularity patterns and drug utilization 2008Q3 to 2014Q4. *Google Trends* and oral anticoagulant visits time series were trimmed to match exactly.

Patterns	Web search popularity	OAC visits[19,30]	Comment
2008Q3 to 2014Q4			
D peak	May 2011	October–December 2011	5 mo lead
D loses 2nd place to R	November 2012	January–March 2013	2 mo lead
D loses 3rd place to A	June 2014	October–December 2014	4 mo lead
R peak	October 2014	April–June 2014	4 mo lag
R loses 2nd place to A	No	No	
A peak	October 2014	October–December 2014	Exact match
E peak	n/a	n/a	
Warfarin peak	February 2011	July–September 2013	>1 yr lead
Warfarin low	December 2008	April–June 2012	>1yr lead
Final rankings	W, R, A, D	W, R, A, D	exact match

A = apixaban, D = dabigatran, E = edoxaban, n/a = not applicable comparison (before edoxaban approval), OAC = oral anticoagulant visits, R = rivaroxaban, W = warfarin.

3.5. Association between media coverage and public interest

The fitted ARIMA models for media coverage by drug are presented in Table C in the Supplementary appendix, http://links.lww.com/MD/E212. Models explained the media coverage through a simple structure with low order autoregressive, differencing and moving average parts as ARIMA ($P=0$, $d=1$, $q=1$) with or without a seasonal component. Apixaban media coverage was described by a higher order autoregressive model.

A number of outliers were detected in media coverage time series. Their presence mirrored regulatory and policy changes regarding the use of DOACs, including FDA approval dates, and dates of advisory panel recommendation to support or delay of approval. These outliers mark real policy changes (intervention events) and were included in the model as intervention variables. As expected, their inclusion reduced residual model variance (white noise variance), further explaining the model. Noteworthy, adjusting for intervention events will remove common contemporary effects between the 2-time series, minimizing spurious associations (Fitted models and outliers available in Table C in the Supplementary appendix, http://links.lww.com/MD/E212).

We plotted the cross-correlation function between the model residuals of the media coverage series (pre-whitened) versus the residuals of the filtered popularity series in Figure 4. There was no evidence of a significant association between media coverage and popularity between lag −3 and lag +3. There was a weak positive association at lag 0 (synchronous) for dabigatran ($r=0.11$), rivaroxaban ($r=0.08$), apixaban ($r=0.11$), edoxaban ($r=0.05$) which failed to reach the significant cut-off, with the adjacent lags (and leads) being insignificant.

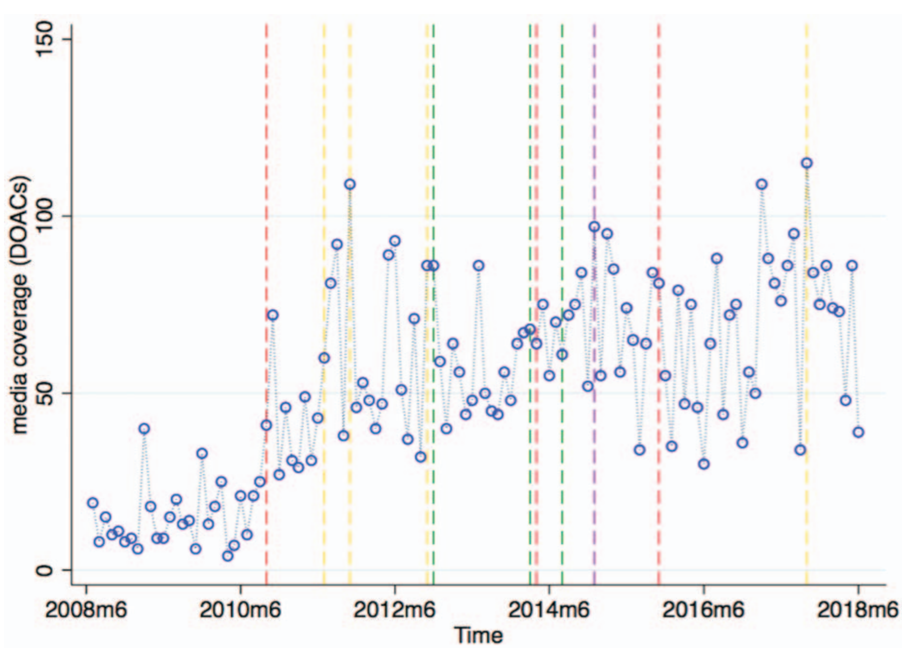

Figure 3. Monthly data on media coverage of the 4 competitor direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban), merged with FDA approval dates. Median news articles were 13 per mo before FDA approval of dabigatran in October 2010 and increased to 64 thereafter ($P<.001$). FDA approval dates attracted more media coverage (median 81 vs 48, $P=.003$). Vertical dashed lines mark FDA drug approvals. Dabigatran (red line); rivaroxaban (yellow line); apixaban (green line); edoxaban (purple line). FDA = Food and Drug Administration.

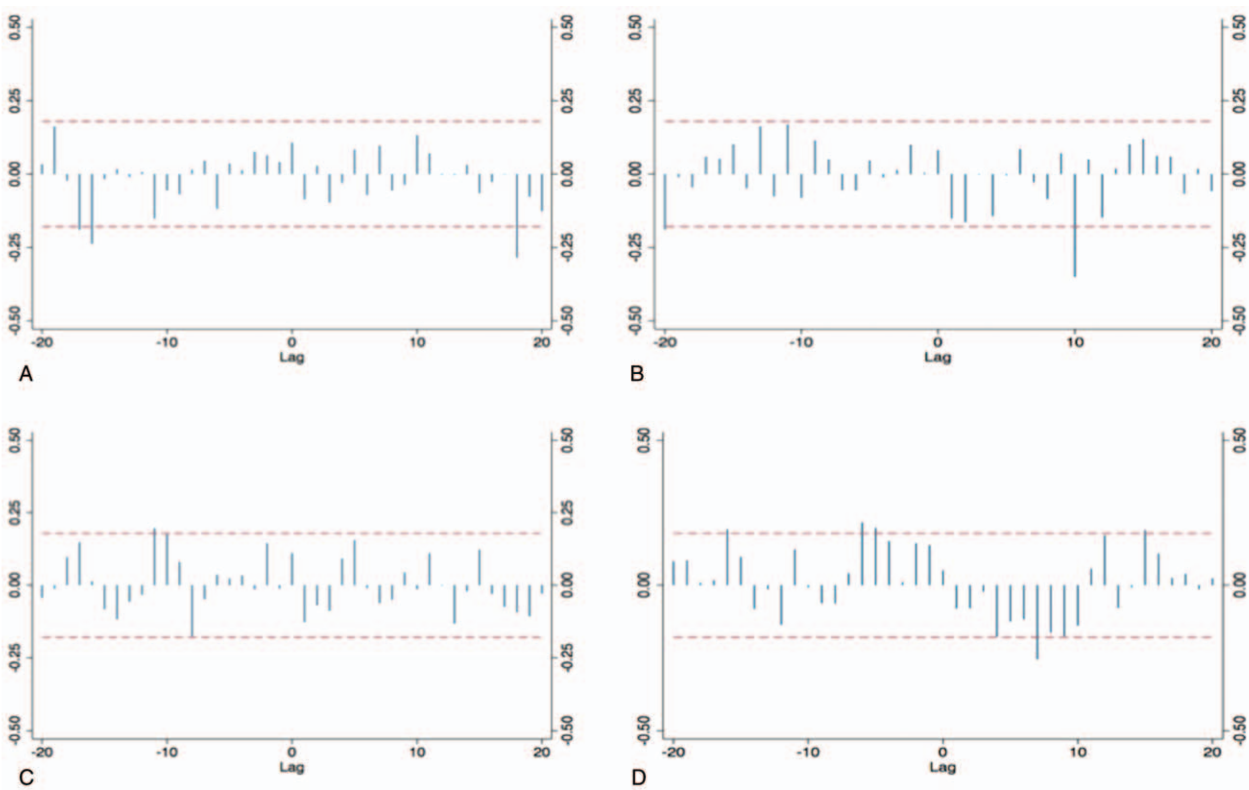

Figure 4. Cross-correlation function between the pre-whitened media coverage series (input series) and the filtered web search popularity series (output series). There was no association between publicity and web search popularity within lag-3 to lag+3 limits, where publicity effects are expected. (A) Dabigatran media coverage vs. dabigatran web search popularity (B) Rivaroxaban media coverage vs. rivaroxaban web search popularity (C) Apixaban media coverage versus edoxaban web search popularity (D) Edoxaban media coverage versus apixaban web search popularity. Vertical lines mark correlation coefficients for each lag. Dashed (red) lines mark the significant cut-off (−0.18 and +0.18, respectively).

3.6. Public interest and drug utilization

In Table 2, we compared published national trends in ambulatory visits for anticoagulants with web search popularity. For a valid comparison, we trimmed web search timeline and visit data[19,30] to overlap perfectly (2008Q3-2014Q4). The patterns of public interest perfectly mirrored the patterns of DOACs utilization. Moreover, the majority of changes in public interest preceded or matched the actual changes in ambulatory oral anticoagulation visits. Specifically, in terms of web search popularity, dabigatran and apixaban highs, and change of rankings between dabigatran, rivaroxaban, and apixaban matched perfectly or preceded the actual utilization patterns (0–5 months lead). Moreover, the final rankings in drug popularity matched the utilization rankings for the aforementioned period. An exception was the popularity of rivaroxaban that lagged 4 months the rivaroxaban peak in oral anticoagulant visits, and warfarin min/max values in the public interest, that were observed >1 year before the actual changes in warfarin visits.

4. Discussion

We studied the association between public interest, media coverage and changes in anticoagulation visits and, through a formal analysis of web search trends, showed that a researcher or clinician can have a reliable overview of the public interest regarding the use of novel anticoagulants and an indirect overview of their actual utilization. Notably, advanced statistical and analytical skills are not required, since a single search with multiple drug queries would give reproducible estimates and no further handling of data is required. The pattern of changes in relative popularity between competitors, contains all the necessary information regarding the public interest and maybe a footprint of changes in real-world utilization.

Dabigatran, the first DOAC that became commercially available in the United States, peaks in search popularity in mid-2011, ranking second to warfarin, thereafter displaying a constant decrease. The decrease in dabigatran popularity begins with the FDA approval of rivaroxaban and continues with the approval of apixaban. The decrease in search popularity results in early loss of second place to rivaroxaban, and loss of third place to apixaban later on. By the end of the observation period, apixaban, and rivaroxaban compete closely in search popularity, with apixaban having an advantage to secure second place and compete with warfarin for top popularity. Edoxaban had a minimal relative activity over its competitors. Conclusions were robust and reproducible in 50 sequential samples. For DOACs, which are a new (and relatively expensive) category of drugs, web search focused on their use through package insert information and cost, side effects and reversal (requiring specific antidotes). On the other hand, for warfarin, apart from dosing and side effects, the public interest focused on diet restrictions (which apply to warfarin but not DOACs).[13] Publicity pertinent to the competing DOACs had a weak and insignificant effect on public interest. The search trends and critical time-points, appear to substantially reflect real-world patterns and behaviors when compared to outpatient utilization of oral anticoagulants.

The *Google Trends* score reflects the relative popularity of the general public on the specified pharmacologic agents and is not expected to mirror at least directly, the prescribing behaviors and drug utilization. The interest for a specific drug exists long before FDA approval is granted, including in the earlier stages of development and through clinical studies. Physicians, and patients, policy makers, and market participants, all have all interest in new agents even before marketing authorization. Hence, media coverage and web search interest are seen long before their marketing authorization. Since the anticoagulant drugs are only prescribed by medical providers, physicians inevitably become a key determinant of web search popularity, by being web users themselves (and seeking medical information on the web) as well as by moderating the population interest for the specific drug(s). However, the association may be reciprocal, since patient awareness through web search information might influence the physician's perception of benefits and harms for a drug and thus interfere with drug selection. That is, for each given time, what we see as relative web search popularity is the output of interactions between different populations of interest. Noteworthy, only a handful of studies explored such associations. A relation between search query patterns and seasonal prescription drugs obtained from the Medical Expenditure Panel Survey was noted in a previous study.[34] Positive correlations between Google web search and antidepressant prescriptions[35] and ototopical agents prescriptions were also published,[36] using cumulative annual prescription data. A previous study on DOAC popularity was limited to web search trends, without extending to methodological aspects of data collection and validation, and lacked an association with media coverage or utilization data.[37]

Our study of DOACs web search popularity, combines several favorable characteristics that strengthen our findings. These include a real great public interest (due to the high and increasing burden of atrial fibrillation, the major indication for DOACs), a weak effect of media coverage on public interest and a straightforward selection of search terms (given that drugs are uniquely defined by their generic names and brand names). Popularity and publicity data are gathered on monthly intervals without gaps, thereby allowing for a direct association. The cross-correlation framework for analysis allows for lag effects, if present, to be identified and measured. Web trends may not mirror the true epidemiological burden when the public understands poorly or is not acquainted with the target conditions. For example, between 2009 and 2010, *Google Trends* missed the first pandemic wave of the H1N1 virus in the U.S. lagging behind the official surveillance statistics of flu, but reflected accurately the second wave.[38] Large media coverage and/or periods with spikes in disease burden may overinflate search popularity, for example, Ebola epidemic in Africa boosted media coverage and public interest in the United States,[39] while there was no epidemic in the U.S. Common diseases with minimal media coverage and information diffusion and rare diseases with a prolific audience may be poorly described.

Furthermore, research questions extending beyond a specific disease epidemiology or drug queries will be elaborate and time-consuming. Data mining, organization, and cleaning to optimize search and analysis, and the use of hundreds of terms will be required. An excellent example of such process is explained in detail by the Pew Research Center researchers for the "The Flint water crisis" in Michigan, a harmful disaster related to water contamination.[40,41] Finally, methodologies on *Google Trends* research lack standardization and publications may suffer in reproducibility.[42] Web search performance as a proxy for public interest, disease burden or drug utilization should be validated on a case-by-case scenario and indiscriminate use of such tools is not justified.

Certain limitations apply to the *Google Trends* tool. The free portal allows the direct comparison of up to 5 queries; more queries cannot be examined in a single step, unless the additional queries are examined separately and output data are handled post hoc against a common comparator. Each output is a snapshot derived from a random sample, and multiple sampling may be required to validate findings. A single *Google Trends* search may not suffice for short-run observations or closely competing drugs. The *Google Trends* interface and methodologies are periodically subject to changes and amendments that are not publicly disclosed and may interfere with findings. Increasing total searches for a specific drug over its competitors result in higher relative popularity of that drug, for the specific time division. The outputs may represent a good proxy for the relative public interests on the research topic, but do not provide qualitative information on the motive or intention, positive or negative.[41] A patient may seek for side-effects of a specific drug after being prescribed or if he experiences unwanted effects, health care personnel will search for prescribing information; investors and stock owners will seek for financial data; lawyers to file a lawsuit.

Regarding the present study, certain limitations also apply. The best available information on drug utilization did not cover the last 3½ years of the web search time series. Visits were reported on a quarterly basis and could not be decomposed into monthly estimates, precluding a direct analysis between time series. On the other hand, collapsing monthly estimates to quarterly popularity trends (by averaging or selection) would introduce bias and loss of information.

In conclusion, *Google Trends* query results were a good representation for both public interest and drug utilization for DOACs. Noteworthy, extending the DOACs paradigm, in settings of great general interest, for both patients and physicians, the patterns of web search popularity of specific drugs may serve as an early proxy to patterns of utilization. In the era of big data analysis, studying the online searching patterns provides an invaluable aid and a unique source of information to study large populations of interest. Such analyses are relevant for medical practice since they shape patient advice counseling, public health policies, and marketing strategies.

Author contributions

P.D.Z. and E.M conceived the idea, drafted the manuscript and approved the final version; P.D.Z and E.M. performed the search; P.D.Z. ran the statistical analysis.

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