Direct oral anticoagulants: analysis of worldwide use and popularity using Google Trends

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Contributions: (I) Conception and design: G Lippi, G Cervellin, EJ Favaloro; (II) Administrative support: None; (III) Provision of study materials or patients: G Lippi; (IV) Collection and assembly of data: G Lippi, C Mattiuzzi; (V) Data analysis and interpretation: G Lippi, C Mattiuzzi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
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Background: Four direct oral anticoagulants (DOACs) have been approved for clinical use by many medicines regulatory agencies around the world. Due to increasing use of these drugs in routine practice, we planned an original study to investigate their worldwide diffusion using a popular Web-search engine.
Methods: Two electronic searches were performed using Google Trends, the former using the keywords "warfarin" AND "heparin" AND "fondaparinux", and the latter using the keywords "warfarin" AND "dabigatran" AND "rivaroxaban" AND "apixaban" AND "edoxaban", both using the search criterion "prescription drug". No language restriction was applied, and the searches were carried out from the first date available in Google Trends (January 1st, 2004) to present time (June 1st, 2017).
Results: The median Google Trends score of warfarin (i.e., 86) was consistently higher than that of heparin (54; P<0.001), fondaparinux (6; P<0.001), dabigatran (11; P<0.001), rivaroxaban (5; P<0.001), apixaban (1; P<0.001) and edoxaban (1; P<0.001). Specific analysis of the trends shows that the score of warfarin exhibits a highly significant decrease over time (r=−0.40; P<0.001), whilst that of heparin has remained virtually unchanged (r=0.12; P=0.127), and that of fondaparinux has marginally increased (r=0.16; P=0.038). As regards DOACs, the scores of these drugs significantly increased during the search period (dabigatran, r=0.79; rivaroxaban, r=0.99; apixaban, r=0.98; edoxaban, r=0.78; all P<0.001). When the analysis was limited to the past five years, the dabigatran score significantly decreased (r=−0.57; P<0.001), whereas that of the other DOACs exhibited an even sharper increase. Most Google searches for DOACs were performed in North America, central-eastern Europe and Australia.
Conclusions: The results of our analysis suggest that the popularity of DOACs is constantly increasing around the world, whereas that of warfarin has exhibited a constant and inexorable decline.

Keywords: Anticoagulants; direct oral anticoagulants (DOACs); laboratory; Google Trends

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Introduction

Anticoagulant therapy is mainly used for limiting blood coagulation in patients at increased risk of thrombosis, including those with atrial fibrillation, those bearing prosthetic heart valves or severe prothrombotic conditions, as well as those with (or at risk of) venous thromboembolism and cardiovascular diseases (1,2). Due to the well-known drawbacks of traditional anticoagulant agents such as warfarin, heparin and fondaparinux, which have been thoughtfully described elsewhere (3), a new generation of anticoagulant drugs conventionally called direct oral anticoagulants (DOACs) has been designed (4), and many of these agents have already been approved for clinical use by several medicines regulatory agencies around the world (5). These agents mainly act as direct inhibitors of thrombin (i.e., dabigatran) or activated factor X (i.e., rivaroxaban, apixaban and edoxaban, so far). The increasing use of these innovative anticoagulants may soon generate a number of technical and practical problems to clinical laboratories, which will expectedly face the increasing need to measure a kaleidoscope of different drugs, so necessitating highly specific assays for the accurate assessment of their anticoagulant activity (6), occasionally even in urgent conditions (7).

Although some very recent national studies support the common perception that prescription of these cutting-edge therapeutics may be constantly increasing worldwide, mostly as suitable replacement of historical anticoagulants (8-13), no definitive statistics have been published regarding their real diffusion into different countries, nor is reliable data available on the general interest of patients and physicians about their usage.

Google Trends (Google Inc. Mountain View, CA, USA) is a free web tool based on Google Search, which displays how frequently a specific term is searched for in Google, compared to the worldwide search volume (14). The final output is a graph showing on vertical axis the relative frequency of the search term compared to the overall amount of searches over a given period of time. The numbers are placed into an arbitrary scale, comprised between 0 and 100, which reflects the search interest relative to the highest point on the chart for a given geographical location and time. Briefly, a value of 100 reflects the peak popularity for the term, a value of 50 means that the term had half the peak popularity, whereas a value of 0 means the term was less than 1% as popular as the peak. The use of Google Trends is becoming increasingly frequent in biomedical research, and this tool has already been profitably used in many scientific publications, especially for investigating epidemiological trends of specific pathological conditions (15), and also as a reliable means for reflecting real use of some types of drugs such as antibiotics (16) and antidepressants (17). Due to increasing use of DOACs in routine practice, we hence planned this original study to investigate the worldwide popularity of these agents in terms of Google Web searches of DOACs.

Methods

We carried out two electronic searches in Google Trends, the former using the keywords "warfarin" AND "heparin" AND "fondaparinux", and the latter using the keywords "warfarin" AND "dabigatran" AND "rivaroxaban" AND "apixaban" AND "edoxaban", in both cases using the search criterion "prescription drug". No language restriction was applied, and the searches were carried out from the first date available in Google Trends (i.e., January 1st, 2004) to present time (i.e., June 1st, 2017). As for the Google Trends algorithm, results were then combined and scaled according to the peak of popularity (i.e., a value of 100) recorded throughout the search period. The results were reported as cumulative Google Trends score per month and expressed as median and interquartile range (IQR). The potential significance of the trends of the scores during the search period was then assessed by performing a Spearman's correlation between time (months) and Google Trends score, whereas the Google Trends scores were compared using Mann-Whitney U test. The statistical analysis was carried out with Analyse-it (Analyse-it Software Ltd, Leeds, UK). The study was carried out in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

Results

The peak of these Google searches (i.e., a Google Trends score of 100) was recorded in February 2004 for the drug warfarin. The remaining data were then scaled according to this peak value. As shown in *Figure 1*, the Google Trends score for warfarin remained substantially higher than that of each of the other drugs throughout the search period (i.e., January 2004 and May 2017). In only one case (i.e., March 2008), did the number of searches for another drug (i.e., heparin) exceed those for warfarin. Overall, the median Google Trends score of warfarin (86; IQR, 83–89)
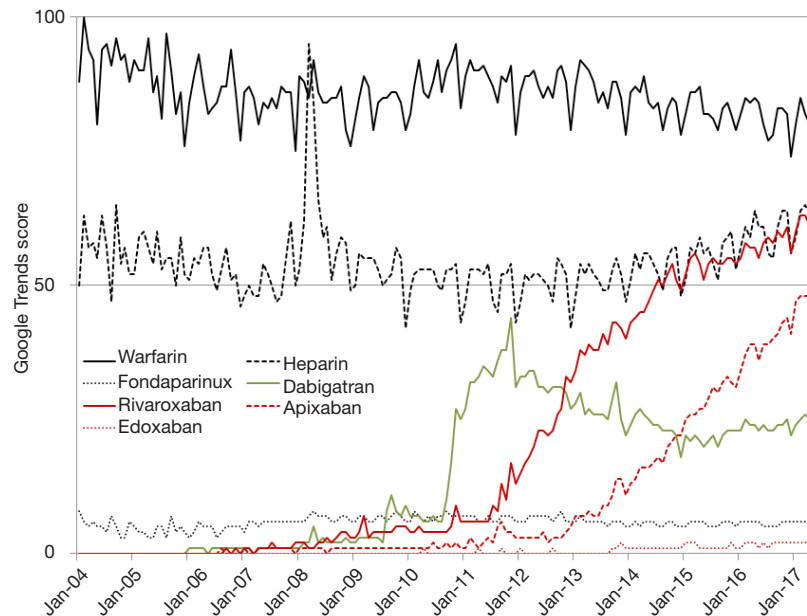
Figure 1 Evolution of the Google Trends score for warfarin, heparin, fondaparinux, dabigatran, rivaroxaban, apixaban and edoxaban between January 2004 and May 2017.

was consistently higher than that of heparin (54; IQR, 51–57; P<0.001), fondaparinux (6; IQR, 5–7; P<0.001), dabigatran (11; IQR, 1–25; P<0.001), rivaroxaban (5; IQR, 1–43; P<0.001), apixaban (1; IQR, 1–14; P<0.001) and edoxaban (1; IQR, 0–1; P<0.001). Identical results were obtained when limiting the analysis to the 5 and 2 previous years (all P<0.001). Quite interestingly, the median Google Trends scores of warfarin (3; IQR; 0–5), dabigatran (2; IQR, 0–3), rivaroxaban (0; IQR, 0–2), apixaban (0; IQR, 0–0) and edoxaban (0; IQR, 0–0) in China, the most densely populated worldwide country, were by several orders of magnitude lower compared to the rest of the world.

The specific analysis of trends shows that the Google Trends score of warfarin exhibits a highly significant decrease over time (r=−0.40; 95% CI, −0.52 to −0.26; P<0.001) (*Figure 2*), whilst that of heparin has remained virtually unchanged (r=0.12; 95% CI, −0.03 to 0.27; P=0.127), and whereas that of fondaparinux has displayed a marginally significant increase (r=0.16; 95% CI, 0.01– 0.31; P=0.038). As regards the DOACs, all the scores of these drugs exhibited a highly significant increase during the search period: dabigatran, r=0.79 (95% CI, 0.72–0.84; P<0.001); rivaroxaban, r=0.99 (95% CI, 0.99–0.99; P<0.001); apixaban, r=0.98 (95% CI, 0.97–0.98); edoxaban, r=0.78 (95% CI, 0.71–0.83; P<0.001). Nevertheless, when

the analysis was limited to the past five years, the Google Trends score of dabigatran displayed a highly significant decrease (r=−0.57; 95% CI, −72 to −37; P<0.001), whereas that of rivaroxaban (r=0.98; 95% CI, 0.97–0.99; P<0.001), apixaban (r=1.00; 95% CI, 0.99–1.00; P<0.001) and edoxaban (r=0.82; 95% CI, 0.72–0.89; P<0.001) exhibited an even sharper increase than that observed in the entire search period (*Figure 3*). Notably, the Google Trends score of warfarin seems to be collapsing sharply during the most recent 5 years (r=−0.62; 95% CI, −0.76 to −0.44; P<0.001) (*Figure 2*).

The geographical distribution of the Google searches for the DOACs over the past 5 years is shown in *Figure 4*. Most of the Google searches for dabigatran, rivaroxaban and edoxaban were performed in North America, central-eastern Europe and Australia. Notable exceptions are represented by Turkey, India, Japan, Brazil and Columbia. Interestingly, rivaroxaban, but not the other DOACs, were highly searched for in Russia, whereas New Zealand was the country with the highest peak of Google searches for dabigatran. Notably, web searches for edoxaban could only be identified in Japan, Germany and in the US so far.

Discussion

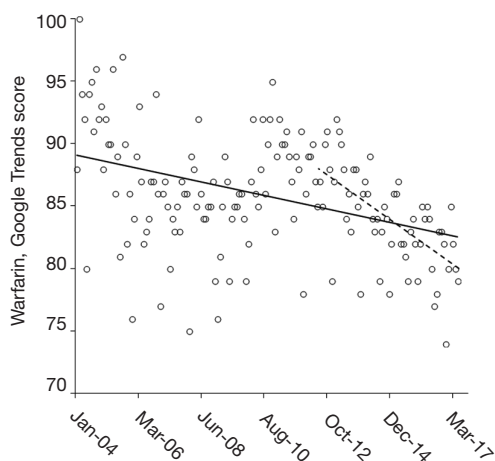An increasing number of official or evidence-based

Figure 2 Evolution of the Google Trends score for warfarin between January 2004 and May 2017. The continuous line represents the Spearman's correlation between the Google Trends score and the month of the year throughout the search period, whereas the dotted line describes the same correlation over the past 5 years.

guidelines recommend now the use of DOACs for many clinical indications, including prevention of embolism in atrial fibrillation, prevention and treatment of venous and arterial thrombosis (5). Although the mounting evidence for the equal therapeutic efficiency, the likely better safety profile, and the greater patients' acceptability may lead us to assume that a parallel increase in the number of prescriptions of these anticoagulant agents has occurred in many countries, no reliable data on their worldwide 'popularity' has been published so far to the best of our knowledge.

Google Trends is a free web tools which analyzes specific Google searches and then generates geographical and temporal information about a specific search term. Recent evidence suggests that Google Trends may be also useful in healthcare, since it provides valuable insights on population behaviors and their associations with health, disease and related treatments (15,18). The final output, the Google Trends score, is not meant to mirror, at least directly, the
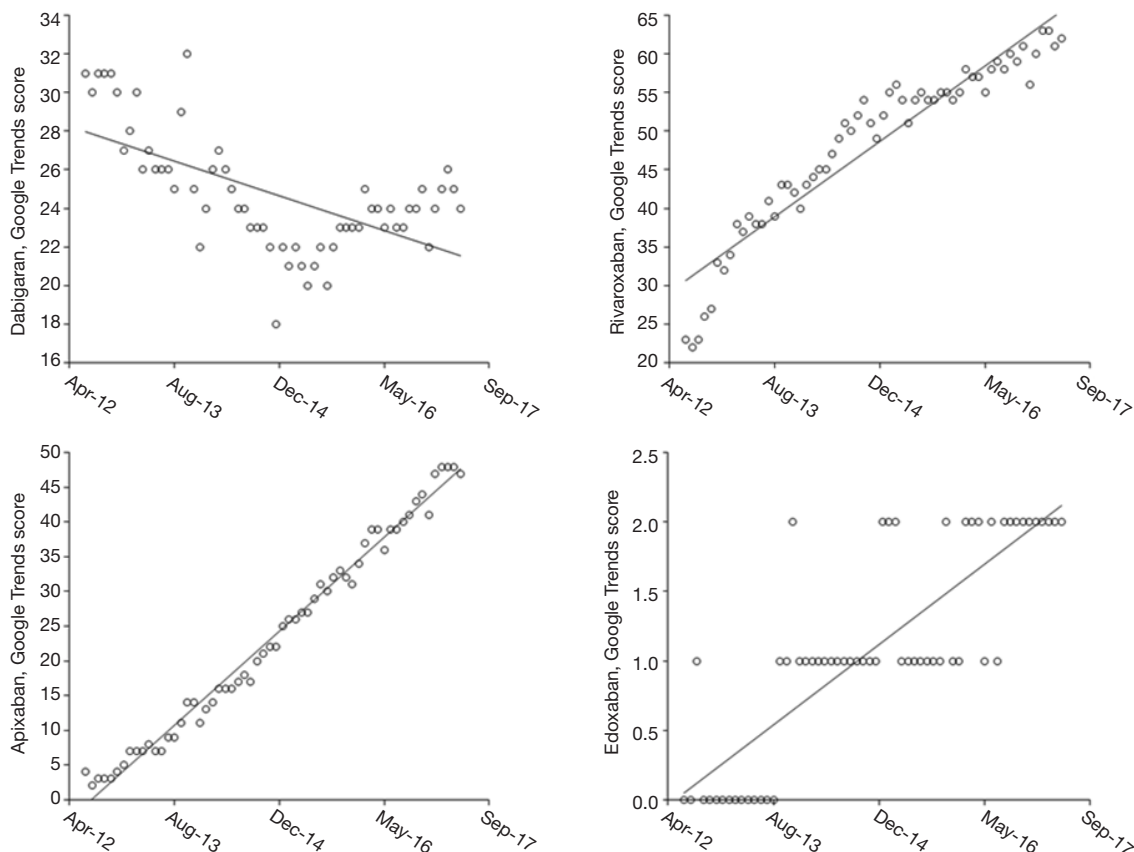

Figure 3 Evolution of the Google Trends score for dabigatran, rivaroxaban, apixaban and edoxaban over the past 5 years. The continuous line represents the Spearman's correlation between the Google Trends score and the month of the year.
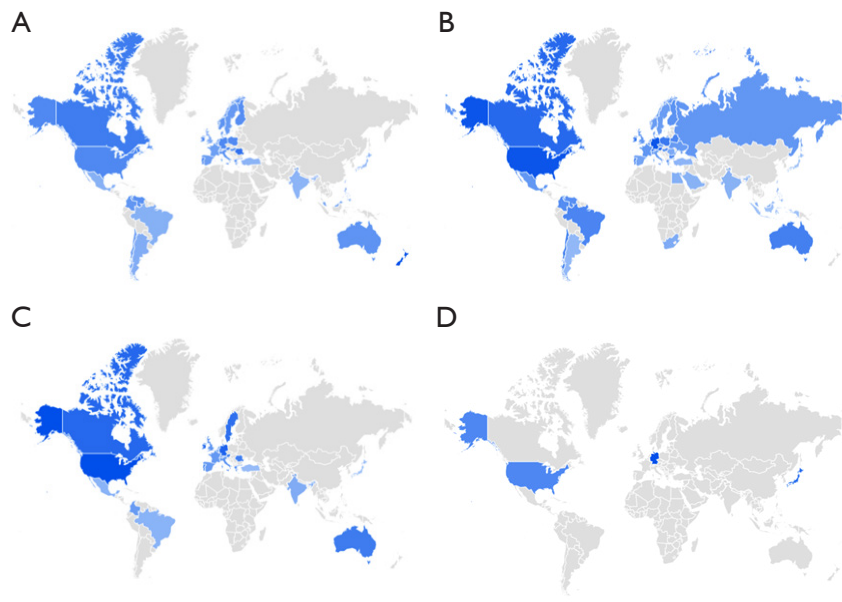
Figure 4 Geographical distribution of web searches recorded by Google Trends over the past 5 years. (A) Dabigatran; (B) Rivaroxaban; (C) Apixaban; (D) Edoxaban.

epidemiology of a given drug, but reflects the interest of the general public in that same pharmacological agent, with the final score potentially influenced also by media clamor at the time. Nevertheless, and quite understandably, the larger the use of a new therapy, the bigger the general interest of patients and physicians for that drug, as reliably proven by some earlier investigations (16,17,19).

The first interesting result emerging from our analysis is that the popularity of warfarin, the most widely used drug throughout the relative long history of anticoagulation (1), is now constantly decreasing. This has been particularly evident in the past 5 years (*Figure 2*), and is also recently evidenced in terms of prescriptions issued in Australia (20). Although the Google search popularity of heparin has remained fairly stable from 2004 to present time, the Google Trends score of the four major DOACs has instead consistently increased, with rivaroxaban reaching the same popularity as heparin, and apixaban closely approaching (*Figure 1*). This finding was also mirrored by recently published data of prescription information from Australia (20).

A subanalysis of the past 5 years reveals additional interesting aspects. The Google search popularity of dabigatran, the first DOACs to be approved and commercialized in US and Europe, has also displayed a constant decrease since the 2012, perhaps due to competition from the DOACs as they became available. This decreasing trend that was only partially reversed during the past 12 months, perhaps reflecting renewed interest post release of a commercial antidote (21). These trends also coincide with the respective time line of approvals of the three direct FXa inhibitors by many national medicines regulatory agencies (*Table 1*). Unlike dabigatran, the Google Trends score of rivaroxaban and apixaban has instead exhibited a very sharp increase, a progress that appears somewhat relentless. As regards edoxaban, the recent introduction of this drug and the still limited approval by medicines regulatory agencies around the world (22) reflects the fact that the only relevant web searches were recorded from Japan (date of approval, April 2011), Germany (date of approval, January 2016) and US (date of approval, January 2015) (*Figure 4*), so actually confirming that the use of Google Trends may be useful for investigating health care epidemiology and drugs prescription habits. Interestingly, these figures also reliably mirror those reported in real world studies in some countries (8,10,23-25), which also showed a constant decline of warfarin ordering attitude, paralleled by a substantial increase of anti-FXa inhibitors prescription and a recent decrease of dabigatran usage. This trend is also strongly supported by a sensitivity analysis, showing that DOACs are more cost-effective than warfarin for stroke prevention in patients with atrial fibrillation (26). As regards fondaparinux, the number of Web searches has remained quite constant throughout the search period, with

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Table 1 Date of official approval by the national medicines agencies of US, Europe and China and worldwide sales

Drug	FDA	EMA	CFDA	TGA	Worldwide sales (year 2015)
Dabigatran	October, 2010	March, 2008	February, 2013	April, 2011	1,430 million US$
Rivaroxaban	July, 2011	September, 2008	February, 2014	April, 2012	4,370 million US$
Apixaban	December, 2012	May, 2011	January, 2013	July, 2011	1,860 million US$
Edoxaban	January, 2015	June, 2015	Not yet approved	Not yet approved	125 million US$

FDA, US Food and Drug Administration; EMA, European Medicines Agency; CFDA, China Food and Drug Administration; TGA, Australian Therapeutic Goods Administration.
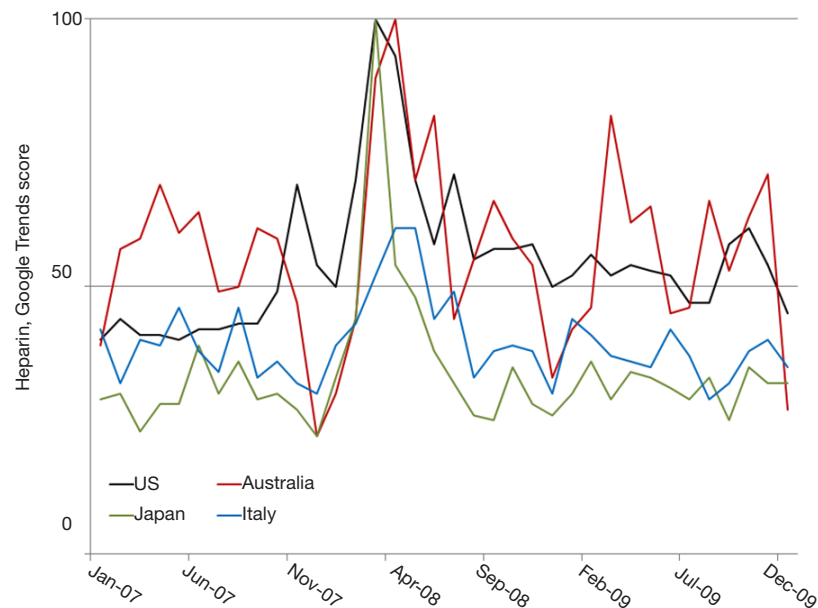
Figure 5 Evolution of the Google Trends score for heparin between January 2007 and December 2009 in US, Australia, Japan and Italy.

an overall volume nearly 10- to 15-fold lower than that of heparin and warfarin, only recently exhibiting a slightly significant increase (*Figure 1*).

A special mention here regards the analysis of the peak of Google searches for heparin, which has been observed in March, 2008. That peak was quite constant across the world, as shown in *Figure 5*, which reproduces the Google Trends score between January 2007 and December 2009 of four different countries belonging to four different continents (i.e., US, Australia, Japan and Italy). The peak can be clearly attributed to the well-known episode of major recalls of heparin by the US Food and Drug Administration (FDA) in March 2008 after discovering that some stocks of the drug were contaminated with an over-sulfated derivative of chondroitin sulfate, which are thought to have caused a number of anaphylactoid-type reactions, some of which

leading to severe hypotension up to death (27). Notably, the much lower number of Google searches recorded in Italy compared to the other three countries can be attributed to the fact that only one case of adverse reaction to contaminated heparin was reported in Europe by the European Medicine Agency (EMA), so justifying the lower media coverage (and thereby the lower general interest) over this case.

The geographical distribution of Google Trends score of the four DOACs which have been commercialized so far is quite interesting. In particular, the largest number of Google searches were found in central-eastern Europe, US, North America, Australia and few other countries (*Figure 4*), thus meaning that these cutting-edge drugs are still relatively under-utilized in the rest of the world (*Figure 6*). In particular, the Google Trends score in China
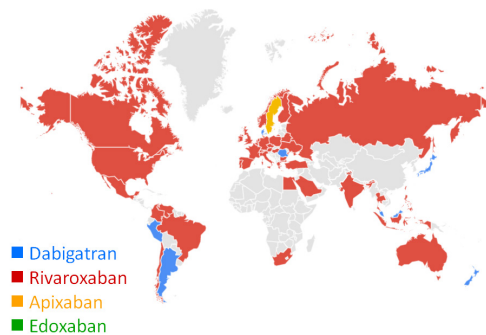
Figure 6 Evolution of the worldwide Google Trends score for dabigatran, rivaroxaban, apixaban and edoxaban in the past 5 years.
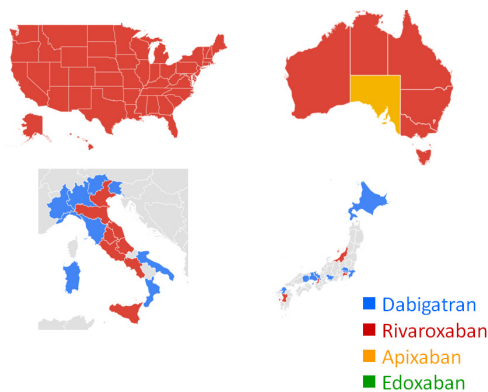

Figure 7 Evolution of the worldwide Google Trends score for dabigatran, rivaroxaban, apixaban and edoxaban in the past 5 years in US, Australia, Japan and Italy.

was close to zero, reflecting the fact that the search terms were less than 1% as popular as the worldwide peak. This is perhaps reflecting under-prescription trends, since recent data attests that oral anticoagulant therapy is still under-prescribed in over two third of patients who may actually need antithrombotic drugs (13), that only recently were three of these drugs officially approved by the China Food and Drug Administration (CFDA) (*Table 1*) (22), their cost in China is relatively high because they are mostly imported, and furthermore Google is probably less accessed in this country compared to others. Interestingly, the geographical distribution of Google Trends score of the four DOACs in US, Australia, Italy and Japan is also quite heterogeneous, as shown in *Figure 7*.

Our analysis has however some clear limitations. First, the use of Google as Web search engine is not identical

around the world, so that the data may have been influenced by geographical preference for Web-search software. Second, data generated by Google Trends may not unequivocally mirror prescription habits, but rather reflects general interest in one specific anticoagulant drug.

Conclusions

The results of our analysis suggest that the popularity of DOACs is constantly increasing around the world, whereas that of warfarin has exhibited a constant and inexorable decline. It is hence conceivable that the popularity of DOACs, and probably their usage, will eventually overcome that of traditional anticoagulants agents.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was carried out in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

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