

## Investigation of antithrombotic drug use in terms of medicine abuse during the COVID-19 pandemic period

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**Abstract** – Google Trends immediately reflect society's changing interest in a variety of topics. This study aimed to examine the use of antithrombotic drugs in terms of medicine abuse during the COVID-19 pandemic using Google Trends data. The words 'Antithrombotic drugs', 'COVID-19', and 'Blood Thinner' were searched for three periods; the COVID-19 pre-pandemic period, the COVID-19 pandemic period, and the COVID-19 vaccination period. The words 'Antithrombotic drugs', 'Aspirin', 'Coraspin', and 'Plavix' as antiaggregant, 'Coumadin', 'Eliquis', 'Pradaxa', 'Xarelto' as anticoagulants were searched comparatively for Turkey and the worldwide. Relative search volumes were evaluated using the GraphPad statistical method. The search volume for 'Blood Thinner', 'Aspirin', and 'Coraspin' increased in other periods compared to the COVID-19 pre-pandemic period. COVID-19 has altered the popularity of antithrombotics both in Turkey and worldwide. As in our study, unconscious drug consumption can be prevented when the tendencies of society, especially on drug-related issues, are determined early with epidemiological studies.

**Keywords** – Antiaggregant; Anticoagulant; COVID-19; Blood Tinner; Google Trends

### I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). The first case of COVID-19 was detected in December 2019 in Wuhan, China. This disease, which spreads worldwide, led to a pandemic [1]. The first vaccination was administered in China on 15 December 2020 and in Turkey on 3 January 2021 [2].

Although the exact mechanism is not known, it has been reported that COVID-19 is associated with coagulation abnormalities and venous and/or arterial thrombotic events [3]. Anticoagulant therapy has taken its place as standard treatment in COVID-19 due to thrombo-inflammation, intravascular coagulation syndrome, and the risk of thrombosis associated with them [4].

Antithrombotic medicines prevent the formation of fibrin chains, blood clotting, or dissolving clots. In terms of impact profiles, they are classified into three groups; i. inhibiting coagulation mechanisms (anticoagulants), ii. inhibiting platelet adhesion and/or aggregation (antiplatelet agents, antiaggregants), iii. dissolving thrombus (fibrinolytic, thrombolytics) [5]. The anticoagulant and antiaggregant drugs in the antithrombotic pharmacological class were the focus of our current study. Since the effects of antithrombotic drugs are frequently covered in the media during the COVID-19 pandemic, people's interest in such drugs has also increased. Given the increasing interest in these drugs, as several antithrombotic drugs with serious side effects are available without a prescription, their easy availability will lead to unconscious use and also life-threatening situations [6].

Today, one of the most effective and easy ways to obtain information on any subject is through digital resources. The most preferred search engine among digital resources is Google. Google Trends is the most widely accessed tool in digital epidemiology that analyzes the popularity of top search queries on Google over time in different languages and geographic regions [7], [8]. Increasing or decreasing search volumes of a word in search engines is important in examining social behavior [9]. These platforms, which enable us to obtain epidemiological information promptly, are of critical importance in terms of early detection of situations that may put society at risk and taking prompt action.

In this study, it is aimed to predict the trends in the usage of antithrombotic drugs during the COVID-19 pandemic in Turkey and worldwide with Google Trends.

## II. MATERIALS AND METHOD

### A. Data Collection Tools

In this study, the ‘all categories’ choice was selected as the category of search. In Google Trends, the ‘subject’ field searched by typing, ‘Aspirin’, ‘Coraspin’, ‘Plavix’, ‘Coumadin’, ‘Eliquis’, ‘Pradaxa’, and ‘Xarelto’, which are commonly used antithrombotic drugs across the world. The terms ‘COVID-19’ and ‘Blood Thinner’ were also searched. A search was made for Turkey from May 2019 to February 2022, and for the world from November 2018 to February 2022. The results of this search, with comma-separated values, were exported to an Excel file and analyzed.

The primary results of monthly Google relative search volume (RSV) for Turkey since May 2019 and worldwide since November 2018 for ‘Aspirin’, ‘Coraspin’, ‘Plavix’, ‘Coumadin’, ‘Eliquis’, ‘Pradaxa’, and ‘Xarelto’ were obtained and compared within three time periods.

The periods to be compared in the study were based on the beginning date of the COVID-19 pandemic and the COVID-19 vaccination dates. For this reason, the dates vary for Turkey and the world. The periods for Turkey were determined as follows. For Turkey and the world, Period 1 (the COVID-19 pre-pandemic period) covered the dates 10 May 2019-10 March 2020 and 16 November 2019-30 November 2020, respectively, while Period 2 (the COVID-19 pandemic period) covered March 2020-January 2021 and 01 December 2020-14 December

2021. For Turkey and the world, Period 3 (the COVID-19 vaccination period) included January 2021-February 2022 and 15 December 2021-February 2022, respectively. The period intervals were kept close to each other. The search terms ‘COVID-19’ and ‘Blood Thinner’ were also searched comparatively according to determined periods.

Since the generic names of the drugs are more widely known than the active substance, searches were made with the generic name. The keyword ‘Blood Thinner’ was searched in English worldwide and in Turkish for Turkey. The translation of the keywords was confirmed with the usage of translation and back-translation on Google Translate such as English-Turkish/Turkish-English [10].

### B. Statistical analysis

GraphPad Prism 6.00 (GraphPad Software, USA) was used to analyze the data. Normality was examined by the Shapiro-Wilk normality test. Since it was determined that the data obtained from Turkey and worldwide fitted the normal distribution as a result of the test, the one-way ANOVA test was used.  $p < 0.05$  values were accepted as significant and data were expressed as mean  $\pm$  standard deviation.

## III. RESULTS

The keywords ‘Aspirin’, ‘Coraspin’, ‘Plavix’, ‘Coumadin’, ‘Eliquis’, ‘Pradaxa’, and ‘Xarelto’ were searched on Google Trends from May 2019 to February 2022 for Turkey and November 2019 to February 2022 worldwide. Besides the interest in ‘COVID-19’ and ‘Blood Thinner’ by years was also evaluated. In the results, the changes according to the years were given. Also, the related queries of COVID-19 and Blood Thinner were presented.

The RSV values of Aspirin in Turkey between three different periods (the pre-COVID-19 pandemic period, the COVID-19 pandemic period, and the COVID-19 vaccination period) were  $36.66 \pm 7.09$ ,  $46.27 \pm 13.17$ , and  $44.65 \pm 12.88$  respectively. The distribution of Aspirin interest in Turkey according to the determined periods was given in Figure 1a. In the figure, it was determined that Period 2 and Period 3 had a significant increase compared to Period 1 ( $p < 0.01$ ,  $p < 0.001$ , respectively; Figure 1a).

The RSV values of Coraspin in Turkey between Period 1, Period 2, and Period 3 were  $16.02 \pm 5.75$ ,  $31.32 \pm 20.96$ , and  $47.07 \pm 17.50$ , respectively. Interest in Coraspin in Turkey was shown in Figure 1b with the indicated specified periods. According to the figure, Period 2 and Period 3 exhibited a significant increase compared to Period 1 ( $p < 0.0001$ ). Also, Period 3 was found to have a quite significant increase compared to Period 2 ( $p < 0.0001$ ; Figure 1b)

The RSV values of Plavix in Turkey between three distinct periods (Period 1, Period 2, and Period 3) were  $46.34 \pm 19.81$ ,  $39.25 \pm 23.25$ , and  $53.84 \pm 19.30$ , respectively. The distribution of Plavix interest in Turkey according to the specified year periods was given in Figure 1c. In the figure Period 3 was found to have a significant increase compared to Period 2 ( $p < 0.01$ ; Figure 1c).

The RSV values of Coumadin in Turkey between Period 1, Period 2, and Period 3 were  $30.82 \pm 13.60$ ,  $29.42 \pm 17.17$ , and  $38.43 \pm 18.46$ , respectively. The interest in Coumadin is shown in Figure 1d. According to the figure, the third period was statistically higher than the second period ( $p < 0.05$ ; Figure 1d).

The RSV values of Eliquis in Turkey between three distinct periods were  $25.07 \pm 21.85$ ,  $18.36 \pm 15.42$ , and  $31.31 \pm 18.76$ , respectively. The distribution of Eliquis interest according to the determined periods was given in Figure 1e. The third period increased significantly compared to the second period. ( $p < 0.01$ ; Figure 1e).

The RSV values of Pradaxa between Period 1, Period 2, and Period 3 were  $19.00 \pm 18.57$ ,  $6.25 \pm 10.00$ , and  $5.81 \pm 10.09$ , respectively. The distribution of Pradaxa interest according to the determined periods was indicated in Figure 1f. Based on the figure, Period 2 and Period 3 were found to have a quite significant decrease compared to the first period ( $p < 0.0001$ ; Figure 1f).

The RSV values for Xarelto between three separate periods (Period 1, Period 2, and Period 3) were  $43.75 \pm 23.12$ ,  $32.05 \pm 18.15$ , and  $43.53 \pm 22.47$ , respectively. The distribution of Xarelto interest in Turkey according to the determined periods was shown in Figure 1g. In the figure, there was a significant decrease in the second period compared to the first and third periods ( $p < 0.05$ ; Figure 1g).

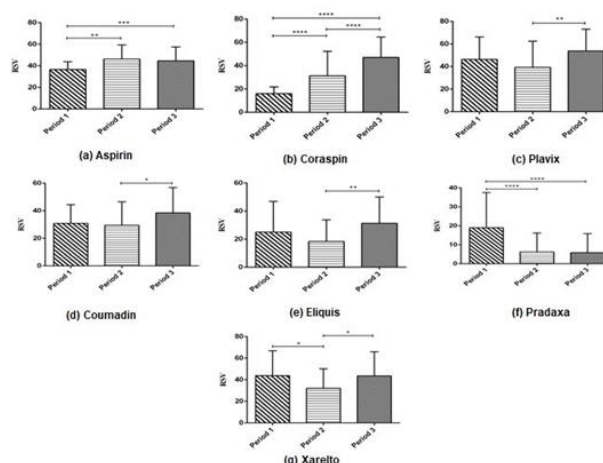


Figure 1. Comparison of the Google Trends RSV score of the selected keywords in Turkey between May 2019-February 2022 in terms of three different periods. (a) Aspirin, (b) Coraspin, (c) Plavix, (d) Coumadin, (e) Eliquis, (f) Pradaxa, and (g) Xarelto

RSV: Relative search volume scores.

RSV scores are given as the mean  $\pm$  standard deviation.

Period 1: The COVID-19 pre-pandemic period for Turkey (May 2019-March 2020)

Period 2: The COVID-19 pandemic period for Turkey (March 2020-January 2021)

Period 3: The COVID-19 vaccination period for Turkey (January 2021-February 2022)

\* $p < 0.05$

\*\* $p < 0.01$

\*\*\* $p < 0.001$

\*\*\*\* $p < 0.0001$

The RSV values of Aspirin in the world between three distinct periods (Period 1, Period 2, and Period 3) were  $64.89 \pm 5.56$ ,  $67.45 \pm 4.84$ , and  $73.46 \pm 7.59$ , respectively. The worldwide interest in Aspirin was illustrated in Figure 2a. In the figure, Period 3 was found to have a significant increase compared to Period 1 and Period 2 ( $p < 0.0001$ ; Figure 2a).

The RSV values of Coraspin in the world between Period 1, Period 2, and Period 3 were  $18.20 \pm 5.88$ ,  $23.53 \pm 16.23$ , and  $43.36 \pm 14.64$ , respectively. The worldwide interest in Coraspin was illustrated in Figure 2b. According to the figure, Period 3 exhibited a significant increase compared to Period 1 and Period 2 ( $p < 0.0001$ ; Figure 2b).

The RSV values of Plavix for the three periods from November 2018 to February 2022 were  $74.56 \pm 7.48$ ,  $70.64 \pm 11.40$ , and  $76.51 \pm 7.88$ , respectively. The distribution of interest in Plavix by year periods around the world is given in Figure 2c. In the figure, Period 3 was found to have a significant increase compared to Period 2 ( $p < 0.01$ ; Figure 2c).

The RSV values of Coumadin for the three periods from November 2018 to February 2022 were  $63.06 \pm 9.09$ ,  $53.15 \pm 9.05$ , and  $44.98 \pm 6.65$ , respectively. The distribution of Coumadin interest in the world by years was shown in Figure 2d. According to the figure, the third period was found a quite significant decrease compared to the second and first periods ( $p < 0.0001$ ). In addition, the second period displayed a significant decline compared to the first period. ( $p < 0.0001$ ; Figure 2d).

The RSV values of Eliquis for the three periods from November 2018 to February 2022 were  $55.02 \pm 5.46$ ,  $60.65 \pm 8.49$ , and  $74.19 \pm 8.33$ , respectively. Eliquis search interest was shown in Figure 2e. In the figure, there was a significant increase in Period 3 compared to Period 1 and Period 2 ( $p < 0.0001$ ). Besides, Period 2 had a significant increase compared to Period 1 ( $p < 0.001$ ; Figure 2e).

The RSV values of Pradaxa in the world between three different periods (Period 1, Period 2, and Period 3) were  $64.11 \pm 10.21$ ,  $60.29 \pm 11.26$ , and  $59.22 \pm 9.74$ , respectively. The distribution of Pradaxa interest in the world was indicated in Figure 2f. Based on the figure, Period 3 was found to have a significant decrease compared to the first period ( $p < 0.05$ ; Figure 2f).

The RSV values of Xarelto in the world between three different periods (Period 1, Period 2, and Period 3) were  $63.78 \pm 6.42$ ,  $62.69 \pm 8.74$ , and  $79.54 \pm 8.92$ , in order of the periods. The distribution of interest in Xarelto by year periods around the world is shown in Figure 2g. In the figure, there was a significant decrease in the second period compared to the first and third periods ( $p < 0.0001$ ; Figure 2g).

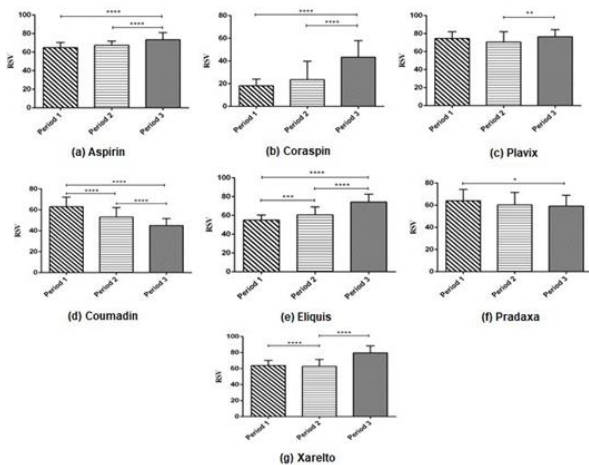


Figure 2. Comparison of the Google Trends RSV score of the selected keywords in the world between November 2019-February 2022 in terms of three different periods. (a) Aspirin, (b) Coraspin, (c) Plavix, (d) Coumadin, (e) Eliquis, (f) Pradaxa, and (g) Xarelto

RSV: Relative search volume scores.  
 RSV scores are given as the mean  $\pm$  standard deviation.  
 Period 1: The COVID-19 pre-pandemic period worldwide (November 2018-November 2019)  
 Period 2: The COVID-19 pandemic period worldwide (November 2019-December 2020)  
 Period 3: The COVID-19 vaccination period worldwide (December 2020-February 2022)  
 \* $p < 0.05$   
 \*\* $p < 0.01$   
 \*\*\* $p < 0.001$   
 \*\*\*\* $p < 0.0001$

Figure 3 exhibited the comparative search results of the search terms 'COVID-19' and 'Blood Thinner'. While the RSV value for COVID-19 reached its highest value in Period 2, its lowest value was in Period 1. The figure showed that the RSV values of the 'Blood Thinner' peaked in Period 3 (Figure 3).

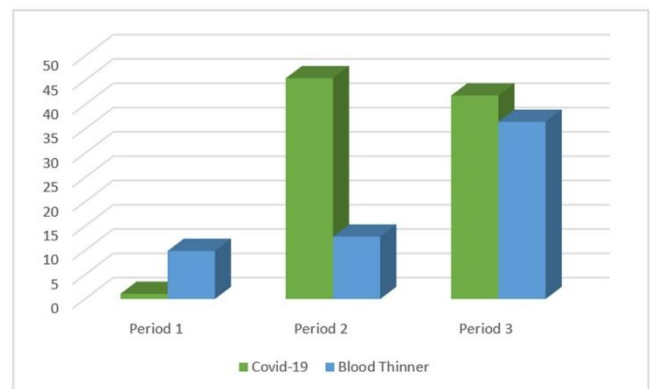


Figure 3. The mean of RSV obtained using the search words 'COVID-19' and 'Blood Thinner' in Turkey.

Period 1: The COVID-19 pre-pandemic period for Turkey (May 2019-March 2020)  
 Period 2: The COVID-19 pandemic period for Turkey (March 2020-January 2021)  
 Period 3: The COVID-19 vaccination period for Turkey (January 2021-February 2022)

Figure 4 exhibited the comparative search results of the search terms 'COVID-19' and 'Blood Thinner'. While the RSV value for COVID-19 reached its greatest value in Period 2, its lowest value was in Period 1. Moreover, the RSV values of the 'Blood Thinner' peaked in Period 3 (Figure 4).

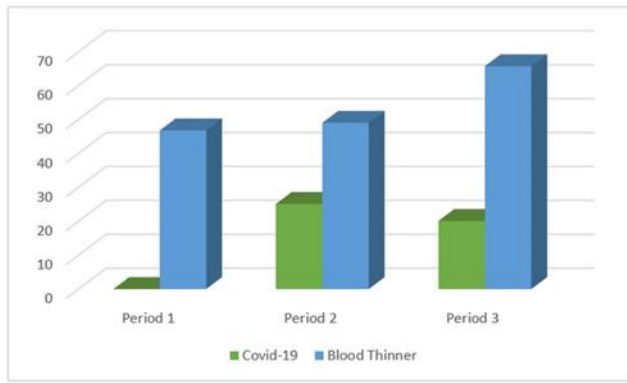


Figure 4. The mean of RSV obtained using the search words ‘COVID-19’ and ‘Blood Thinner’ in the world.

Period 1: The COVID-19 pre-pandemic period worldwide (November 2018-November 2019)

Period 2: The COVID-19 pandemic period worldwide (November 2019-December 2020)

Period 3: The COVID-19 vaccination period worldwide (December 2020-February 2022)

#### IV. DISCUSSION

Even though COVID-19 affects multiple systems in the body, the most common causes of morbidity and mortality are ARDS and thrombosis [11]. Thromboembolism has been recorded as an outcome of severe COVID-19 [12].

In our study, the search interest in Aspirin and Coraspin used in hospitalized patients during the COVID-19 period has increased compared to the pre-pandemic period. During the COVID-19 vaccination period, the search interest in Coraspin maintained the same increase. It has been reported that acetylsalicylic acid, which should be used with caution in thrombocytopenic patients with COVID-19 due to the risk of alveolar hemorrhage, reduces mortality in COVID-19 [13].

In contrast to these findings, several studies reported that Aspirin treatment increases the risk of the combined thrombotic endpoint. It has been reported that platelets clearly express the ACE2-TMPRSS2 receptor-protease axis for SARS-CoV-2 infection, while Aspirin does not inhibit thrombosis and mortality in COVID-19 [14]. For this reason, Aspirin could not be incorporated into treatment protocols for the therapy of COVID-19. Considering these health risks, public awareness should be created to prevent the increasing interest in the use of Aspirin and Coraspin, which are available without a prescription.

The interest in Plavix, which is included in the P2Y12 inhibitor antiaggregant drug group, did not significantly change during the pandemic and

vaccination periods compared to the pre-pandemic period both in Turkey and worldwide [15]. However, compared to a therapeutic dosage of Heparin alone, the use of a combination of P2Y12 inhibitor and Heparin did not enhance recovery in non-critical patients hospitalized with COVID-19 [16]. The fact that Plavix is not available without a prescription, and cannot be prescribed outside of branch physicians, can reduce the risk of the unconscious use of this drug. A similar situation applies to Coumadin, Eliquis, Pradaxa, and Xarelto.

Due to its narrow therapeutic index, Coumadin can reach a toxic dose quickly and accordingly increases the risk of hemorrhage [17]. Although it has serious side effects, there is no objection to the utilization of this drug in COVID-19 cases [12]. Contrary to these data, in our study, it was determined that the interest in Coumadin decreased during the pandemic and vaccination periods. This condition might have been caused by the fact that it is a prescribed medicine.

Long half-lives of Dabigatran (the active substance of Pradaxa), Apixaban (the active substance of Eliquis), and Rivaroxaban (the active substance of Xarelto) may increase the risk of bleeding in hepatic and renal failure, which can occur in COVID-19 with their use [18]. When these new-generation anticoagulants are examined, the search rate for Eliquis did not change during the COVID-19 pandemic period compared to the COVID-19 pre-pandemic period in Turkey, while the search rate for Pradaxa and Xarelto decreased. Although it is not easy to interpret the sudden increases in search volume worldwide, it has been seen that the search volumes of Eliquis and Xarelto increased during the COVID-19 pandemic period compared to the COVID-19 pre-pandemic period, while Pradaxa did not change. The difference in these search rates was also observed during the vaccination period. The main reason for the decrease in interest in these drugs may be their exorbitant cost. This situation makes it difficult to reach the drug along with prescription sales.

When patients who previously used antithrombotic drugs and were given low molecular weight heparin were diagnosed with COVID-19, the fact that these drugs were given cautiously in terms of bleeding or were given only for prophylactic purposes can be listed among the differences in search volumes. It was observed that the words ‘COVID-19’ and ‘Blood Thinner’ in Turkey and the

world have an increasing search volume during the pandemic and vaccination period compared to the COVID-19 pre-pandemic period. Although anticoagulant and antiaggregant therapies play a vital role in all respects in COVID-19, these drugs should not be taken unconsciously and should be used under the control of a physician due to drug-drug interaction and life-threatening hemorrhage risk.

## V. CONCLUSION

As a result, Google Trends data presented the interest in antithrombotic agents before and during the COVID-19 pandemic. This epidemiologic knowledge will provide us with ideas about the preventive and therapeutic use of antithrombotics. If clinicians and especially researchers evaluate critical knowledge gaps efficiently with such epidemiological studies, solutions can be found promptly for the benefit of society.

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