BRIEF COMMUNICATION

COVID-19 and Anticoagulation for Atrial Fibrillation: An Analysis of US Nationwide Pharmacy Claims Data

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BACKGROUND: Adherence to oral anticoagulation (OAC) is critical for stroke prevention in atrial fibrillation. However, the COVID-19 pandemic may have disrupted access to such therapy. We hypothesized that our analysis of a US nationally representative pharmacy claims database would identify increased incidence of lapses in OAC refills during the COVID-19 pandemic.

METHODS AND RESULTS: We identified individuals with atrial fibrillation prescribed OAC in 2018. We used pharmacy dispensing records to determine the incidence of 7-day OAC gaps and 15-day excess supply for each 30-day interval from January 1, 2019 to July 8, 2020. We constructed interrupted time series analyses to test changes in gaps and supply around the pandemic declaration by the World Health Organization (March 11, 2020), and whether such changes differed by medication (warfarin or direct OAC), prescription payment type, or prescriber specialty. We identified 1301,074 individuals (47.5% women; 54% age ≥75 years). Immediately following the COVID-19 pandemic declaration, we observed a 14% decrease in 7-day OAC gaps and 56% increase in 15-day excess supply (both \( P < 0.001 \)). The increase in 15-day excess supply was more marked for direct OAC (69% increase) than warfarin users (35%; \( P < 0.001 \)); Medicare beneficiaries (62%) than those with commercial insurance (43%; \( P < 0.001 \)); and those prescribed OAC by a cardiologist (64%) rather than a primary care provider (48%; \( P < 0.001 \)).

CONCLUSIONS: Our analysis of nationwide claims data demonstrated increased OAC possession after the onset of the COVID-19 pandemic. Our findings may have been driven by waivers of early refill limits and patients’ tendency to stockpile medications in the first weeks of the pandemic.

Key Words: adherence • anticoagulants • atrial fibrillation • COVID-19

Oral anticoagulation (OAC) therapy is a standard of care for thromboembolic stroke prevention in atrial fibrillation (AF).\(^1\)\(^-\)\(^3\) As AF is associated with a 5-fold increased risk of stroke,\(^4\) individuals with AF are commonly prescribed OAC with warfarin or a direct oral anticoagulant (DOAC). Long-term adherence to OAC is essential for stroke prevention,\(^5\) as is regular monitoring in those using warfarin. The SARS-COVID-19 pandemic disrupted routine health care access, but its effect on OAC access and adherence, as measured by pharmacy claims, remains unknown. We examined pharmacy fills for OAC spanning the pandemic in a US nationally representative claims database. We hypothesized that we would identify lapses in medication refills at the outset of the COVID-19 pandemic.

METHODS

Data Source and Study Population

We obtained medical and pharmacy claims in January 1, 2018 to July 31, 2020 from IQVIA. The data were
obtained under an agreement that does not allow for data sharing, thus data products will not be made publicly available. Code will be made available upon request to the corresponding author. The IQVIA Longitudinal Prescription Claims is a nationally representative database of dispensed prescriptions that captures over 89% of all outpatient prescriptions dispensed from retail, mail, and long-term care pharmacies, from all payers (commercially insured, Medicare, Medicaid, and cash). The IQVIA Medical Claims and Institutional Claims provides unadjudicated claims data for procedures and diagnoses in both office-based and institutional settings. Both data sets are linkable through an anonymous encrypted patient identifier.

We selected the cohort for study in 5 steps (Figure S1). First, we identified individuals with a pharmacy claim for OAC and a diagnosis of AF in 2018 (n=2 372 641). OAC agents included warfarin and the DOACs dabigatran, apixaban, rivaroxaban, and edoxaban.

Diagnosis of AF was defined as having a medical claim with International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes I48.0, I48.1, I48.2, and I48.91. The OAC agent filled on the first claim in 2018 was defined as the index drug. Second, we excluded individuals who switched OAC agents after January 1, 2019, as overlapping supplies of different OAC agents would have affected the calculation of outcomes. Third, we excluded those with incomplete covariate information. Fourth, we constrained for those individuals without a 120-day gap in medical or pharmacy claims during the study period (January 1, 2019–July 8, 2020). This approach facilitated exclusion of individuals with disenrollment or death, as such in- complete covariate information. Fourth, we constrained for those individuals without a 120-day gap in medical or pharmacy claims during the study period (January 1, 2019–July 8, 2020). This approach facilitated exclusion of individuals with disenrollment or death, as such in- complete covariate information. Fourth, we constrained for those individuals without a 120-day gap in medical or pharmacy claims during the study period (January 1, 2019–July 8, 2020). This approach facilitated exclusion of individuals with disenrollment or death, as such in- complete covariate information. Fourth, we constrained for those individuals without a 120-day gap in medical or pharmacy claims during the study period (January 1, 2019–July 8, 2020). This approach facilitated exclusion of individuals with disenrollment or death, as such in- complete covariate information. Fifth, we constrained for those individuals with disenrollment or death, as such incomplete covariate information.

Outcomes
The study had 2 primary outcomes: (1) 7-day gap without OAC supply, which measured lapses in medication; and (2) 15-day excess of OAC supply, which measured excess of medication supply. Both outcomes were defined on 30-day time windows for the execution of interrupted time series analyses. To define outcomes, we extracted all prescriptions for OAC in January 1, 2018 to July 31, 2020. Using the dates of fill and the days of supply, we tabulated a record of medication possession for each day of the study period for each participant. A 7-day gap without OAC was defined by ≥7 consecutive days without OAC possession and a 15-day excess supply as ≥15 excess days’ supply.

Independent Variables
The main exposure of interest was time after pandemic onset. We used the date of the World Health Organization declaration of pandemic (March 11, 2020) as start of the pandemic period. Covariates included age, sex, clinical characteristics as pertinent to the CHA2DS2- VASc score (a well-validated marker of stroke risk) and HAS-BLED score (a validated score for bleeding risk), index drug (characterized as warfarin or DOAC), prescriber specialty (primary care, cardiology, or other), payment type (cash, Medicaid, Medicare, or commercial insurance), and out- of-pocket costs spent on anticoagulation in the baseline year.

Statistical Analysis
We determined the incidence of outcomes for the overall sample and for subgroups defined by index drug (warfarin or DOAC) and by payment type for each 30-day interval during the study period. We constructed interrupted time series analyses with multivariable-adjusted logistic regression models to examine the change in 7-day gaps or 15-day OAC excess before and after the pandemic declaration. Regression models included (1) an intercept (level before pandemic); (2) continuous variable for 30-day interval (trend before pandemic); (3) an indicator variable for the post-pandemic period (change in level after pandemic declaration); and (4) the interaction between the time variable and the indicator for the postpandemic period (change in trend after pandemic declaration). Models were adjusted for the covariates listed previously. Secondary analyses evaluated effect modification by OAC agent (warfarin or DOAC), payment type, or prescriber specialty. As such, we fitted interactions between OAC agent, payment type, and prescriber specialty with changes in level and trend. Using the output of interrupted time series analyses, we predicted the observed incidence of outcomes across the study period. We then predicted the observed incidence of outcomes in the absence of pandemic, that is, as if there had been no changes in the level or trend of outcomes after March 11, 2020. Two-tailed P<0.05 was regarded as significant. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Patient Characteristics
The cohort included 1,301,074 participants with characteristics summarized in Table. The cohort was 47.5% women with nearly 30% age 65 to 74 years and 54% age ≥75 years. Apixaban was the most commonly prescribed index drug (40.6%), followed by warfarin (35.3%) and rivaroxaban (20.9%). OAC was prescribed

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primarily by cardiologists (46.0%) followed by primary care physicians (35.5%). For a large majority of the cohort (70.2%), OAC therapy was reimbursed by Medicare.

Change in Incidence of Outcomes After Pandemic Declaration by Subgroup
The increase in 15-day excess supply was more marked for DOAC (69% increase, from 20.4 to 34.6 per 1000 individuals) than warfarin users (35% increase, from 23.4 to 31.6 per 1000; P<0.001), Medicare beneficiaries (62% increase, from 21.3 to 34.4 per 1000) than those with commercial insurance (43% increase, from 22.1 to 31.6 per 1000; P<0.001), and patients prescribed OAC by a cardiologist (64% increase, from 21.5 to 35.2 per 1000) rather than a primary care provider (48% increase, from 21.9 to 32.5 per 1000; P<0.001), summarized by Figure 2 and Table S2.

The decrease in the incidence of 7-day gaps in OAC therapy was more pronounced for Medicaid beneficiaries (16% decrease, from 117.5 to 98.6 per 1000 individuals) compared with Medicare beneficiaries (13% decrease, from 73.6 to 63.8 per 1000), but the difference was at the margin of statistical nonsignificance (P=0.048). The decrease in the incidence of 7-day gaps in OAC therapy did not statistically differ between DOAC (15% decrease, from 68.8 to 58.5 per 1000 individuals) and warfarin users (11% decrease, from 82.2 to 72.8 per 1000; P=0.495), or between patients prescribed OAC by a cardiologist (13% decrease, from 73.9 to 63.2 per 1000) rather than a primary care provider (13% decrease, from 73.0 to 63.7 per 1000; P=0.956), summarized by Figure 2 and Table S2.

DISCUSSION
Our study addresses a fundamental knowledge gap in how the onset of the COVID-19 pandemic affected how patients receiving OAC maintained access to this essential therapy. Contrary to our hypothesis—the presumed expectation that fill rates would drop at the initiation of the pandemic—we observed in fact an increase in OAC possession and a subsequent decrease in the incidence of therapy gaps. These changes were more pronounced for those receiving DOAC agents, as opposed to warfarin, and for Medicare beneficiaries, as opposed to those with commercial insurance.

Our results are consistent with a prior report that possession of inhalers for pulmonary diseases increased as well.8 However, that study had limited...
generalizability as it was conducted in a single health care system. In contrast, our analysis provides the first evidence of increased possession of chronic disease medication in a nationwide sample. The observations reported here may reflect that individuals sought early refills, thereby “hoarding” medication in anticipation of constrained access because of COVID-19 and avoiding exposure to pharmacy locations. The findings may also be explained by the waiver of early refill limits on chronic therapies, mandated by multiple states and implemented by major pharmacy insurers.9

The more pronounced increase in OAC possession observed among Medicare beneficiaries compared with commercially insured enrollees may be explained by seniors’ higher risk aversion to exposure to COVID in pharmacies because of the remarkably higher COVID mortality rates in older adults. Additionally, seniors are more likely to use concurrent prescription drugs than younger patients, and with the waiving of early refill limits, they may have been more likely to refill OAC prescriptions when obtaining fills for other medications.

DOAC users showed a more pronounced increase in OAC refilling than warfarin users. This may have been a product of the more stable dosage pattern of DOACs compared with warfarin. Patients may have been less likely to refill warfarin prescriptions early owing to the likelihood of changing warfarin dosing in future international normalized ratio assessments. In contrast, DOAC users often use the same dose except for exceptional circumstances (changes in hepatic or renal function) and thus may be more likely to stockpile medication.

Patients prescribed OAC by a cardiologist rather than a primary care provider also experienced a more pronounced increase in OAC refilling than warfarin users. This may be the case because patients prescribed OAC by a cardiologist are more likely to use DOACs and are less likely to be covered by Medicaid than those prescribed OAC by a primary care provider.10,11 Payment type may be relevant because, although the pandemic-related change in incidence of therapy gaps did not differ greatly by payment type, Medicaid beneficiaries had a substantially higher incidence of therapy gaps compared with other groups consistently throughout the study period.

Our analysis has 3 principal limitations. First, IQVIA data are limited by the absence of fundamental characteristics such as race and ethnicity or the key individual- and neighborhood-level factors that exacerbated disparities during the pandemic. Hence, we are not able to analyze, for example, differences in OAC access by race/ethnicity or by socioeconomic profile. Second, IQVIA data lack information on death or disenrollment from health plans, necessitating employing claims to

**Figure 1. Observed and predicted incidence of primary outcomes.**
Trends in the incidence of 7-day gaps without OAC therapy (A) and 15-day excess of OAC supply (B) in January 2020 to June 2021. Squares represent observed incidence. Solid lines represent the incidence of outcomes predicted with interrupted time series analyses. Dashed lines represent the incidence of outcomes predicted with interrupted time series analyses in the absence of pandemic, that is, as if there had been no changes in level or trend of outcomes after March 11, 2020. The last data point in our study period was for the interval June 9, 2020 to July 8, 2020. The figures end on June 9, 2020 because this is the start of the last period we have data for. DOAC indicates direct oral anticoagulant.
ascertain continued status in the cohort. We note this is a standard practice in health services research when mortality data are not available. Our final limitation is that, as in every analysis using pharmacy claims data, we are not able to distinguish between medication possession and medication use.

CONCLUSIONS

Using nationwide claims data from IQVIA, we demonstrated an increase in possession of OAC therapy following the onset of the COVID-19 pandemic. This increase was more pronounced for DOAC users and Medicare beneficiaries.

ARTICLE INFORMATION

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Disclosures

Hernandez has received consulting fees from Pfizer and Bristol Myers Squibb, outside of the submitted work, and has served in an advisory board for Bristol Myers Squibb. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2
Figure S1
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Supplemental Material
Table S1. Results of Interrupted Time-Series Regression Analysis, Primary Analyses.

| Parameter                        | 7-Day Therapy Gap | 15-Day Excess Supply |
|----------------------------------|-------------------|----------------------|
|                                  | Coefficient       | p-Value              | Coefficient       | p-Value              |
| Baseline trend                   | -0.0234           | <.0001               | -0.0436           | <.0001               |
| Level change after 3/11/2020     | -0.9387           | <.0001               | 2.4045            | <.0001               |
| Trend change after 3/11/2020     | 0.0524            | <.0001               | -0.1247           | <.0001               |
Table S2. Results of Interrupted Time-Series Regression Analysis, Models with Subgroup Analyses.

| Interaction Variable | Parameter                                      | 7-Day Therapy Gap | 15-Day Excess Supply |
|----------------------|------------------------------------------------|-------------------|----------------------|
|                      |                                                 | Coefficient | p-Value | Coefficient | p-Value |
| DOAC use (ref=warfarin use) |                                                |               |          |             |          |
| Baseline trend       |                                                 | -0.0278      | <0.0001  | -0.0711     | <0.0001  |
| Level change after 3/11/2020 |                                             | -0.9188      | <0.0001  | 1.9243      | <0.0001  |
| Trend change after 3/11/2020 |                                            | 0.0559       | <0.0001  | -0.0946     | <0.0001  |
| Baseline level change for DOAC user |                                          | -0.1818      | <0.0001  | -0.6744     | <0.0001  |
| Baseline trend change for DOAC user |                                       | 0.0073       | <0.0001  | 0.0473      | <0.0001  |
| Level change after 3/11/2020 for DOAC user |                                   | -0.0340      | 0.4947   | 0.7938      | <0.0001  |
| Trend change after 3/11/2020 for DOAC user |                                | -0.0057      | 0.0601   | -0.0512     | <0.0001  |
| Payment type (ref=Medicare) |                                               |               |          |             |          |
| Baseline trend       |                                                 | -0.0212      | <0.0001  | -0.0451     | <0.0001  |
| Level change after 3/11/2020 |                                             | -0.9244      | <0.0001  | 2.5145      | <0.0001  |
| Trend change after 3/11/2020 |                                            | 0.0502       | <0.0001  | -0.1300     | <0.0001  |
| Baseline level change for patients paid with cash |                                    | -0.0825      | <0.0001  | 0.2885      | <0.0001  |
| Baseline level change for patients with Medicaid |                                | 0.2290       | <0.0001  | -0.2875     | <0.0001  |
| Baseline level change for patients with commercial insurance |                        | 0.0064       | 0.1167   | -0.0636     | <0.0001  |
| Baseline trend change for patients paid with cash |                                  | 0.0008       | 0.6158   | -0.0378     | <0.0001  |
| Baseline trend change for patients with Medicaid |                              | 0.0064       | 0.0052   | 0.0118      | 0.0424   |
| Baseline trend change for patients with commercial insurance |                           | -0.0082      | <0.0001  | 0.0069      | <0.0001  |
| Level change after 3/11/2020 for patients paid with cash |                          | -0.1154      | 0.5649   | 0.1176      | 0.7674   |
| Level change after 3/11/2020 for patients with Medicaid |                        | 0.5593       | 0.0482   | -0.3304     | 0.5829   |
| Level change after 3/11/2020 for patients with commercial insurance |                        | -0.0602      | 0.2721   | -0.3966     | <0.0001  |
| Trend change after 3/11/2020 for patients paid with cash |                       | 0.0112       | 0.3550   | -0.0029     | 0.9057   |
| Trend change after 3/11/2020 for patients with Medicaid |                     | -0.0342      | 0.0471   | 0.0227      | 0.5409   |
| Trend change after 3/11/2020 for patients with commercial insurance |                   | 0.0084       | 0.0115   | 0.0186      | 0.0013   |
DOAC=Direct Oral Anticoagulant.

Anticoagulant type, payment type and prescriber specialty were defined based on the last prescription for OAC filled in 2018.

| Interaction Variable | Parameter | 7-Day Therapy Gap | 15-Day Excess Supply |
|----------------------|-----------|-------------------|----------------------|
|                      |           | Coefficient | P-value | Coefficient | P-value |
| Prescriber Specialty (ref=primary care physicians) | Baseline trend | -0.0254 | <0.0001 | -0.0533 | <0.0001 |
|                      | Level change after 3/11/2020 | -0.9520 | <0.0001 | 2.1824 | <0.0001 |
|                      | Trend change after 3/11/2020 | 0.0554 | <0.0001 | -0.1109 | <0.0001 |
|                      | Baseline level change for patients prescribed by cardiologists | 0.0388 | <0.0001 | -0.2027 | <0.0001 |
|                      | Baseline level change for patients prescribed by other specialties | 0.0240 | <0.0001 | -0.1105 | <0.0001 |
|                      | Baseline trend change for patients prescribed by cardiologists | 0.0046 | <0.0001 | 0.0193 | <0.0001 |
|                      | Baseline trend change for patients prescribed by other specialties | -0.0006 | 0.2581 | 0.0062 | <0.0001 |
|                      | Level change after 3/11/2020 for patients prescribed by cardiologists | 0.0030 | 0.9556 | 0.5143 | <0.0001 |
|                      | Level change after 3/11/2020 for patients prescribed by other specialties | 0.0635 | 0.3622 | -0.0855 | 0.4842 |
|                      | Trend change after 3/11/2020 for patients prescribed by cardiologists | -0.0048 | 0.1422 | -0.0325 | <0.0001 |
|                      | Trend change after 3/11/2020 for patients prescribed by other specialties | -0.0042 | 0.3160 | 0.0057 | 0.4488 |
Figure S1. Selection of the Study Sample.

Patients who filled an OAC in 2018 (n = 6,537,295)

Excluded 1,888 with multiple OACs filled on index date (n= 6,535,407)

Selected those with a claim related to Atrial Fibrillation in 2018 (n= 2,372,641)

Selected those who did not switch OACs after 1/1/2019 (n= 2,177,001)

Excluded 3,717 with contradictory covariate information (n=2,173,284)

Selected those with no more than 120 days between each two consecutive claims (n = 1,301,074)

OAC= Oral Anticoagulant.