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Research Paper

COVID-19 pandemic and trends in clinical outcomes and medication use for patients with established atrial fibrillation: A nationwide analysis of claims data

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ABSTRACT

Study objective: The COVID-19 pandemic disrupted multiple aspects of the health care system, including the diagnosis and control of chronic conditions. This study aimed to quantify pandemic-related changes in the rates of clinical events among patients with atrial fibrillation (AF).

Design/setting/participants: In this retrospective cohort study, we identified individuals with established AF at any time before 2019 using de-identified Optum's Clinformatics® Data Mart, and followed them from 3/18/2019 to death, or disenrollment, or the end of the study (09/30/2021).

Main outcome: Rates of clinical event, including all-cause hospitalization, ischemic stroke, and bleeding. We constructed interrupted time series to test changes in outcomes after the onset of the COVID-19 pandemic (3/11/2020, date of pandemic declaration). We then identified the first month after the start of the pandemic in which outcomes returned to pre-pandemic levels.

Results: A total of 561,758 patients, with a mean age of 77 ± 9.9 years, were included in the study. The monthly incidence rate of all-cause hospitalization decreased from 2.8 % in the period immediately before the pandemic declaration to 1.7 % in the period immediately after, with p-value for level change<0.001. The rate of new ischemic stroke diagnoses decreased from 0.28 % in the period immediately before pandemic declaration to 0.20 % in the period immediately after, and the rate of major bleeding diagnoses from 0.81 % to 0.59 %, both p-values for level change<0.01. The incidence rate of ischemic stroke and bleeding events returned to pre-pandemic levels in October and November 2020, respectively.

Conclusions: The COVID-19 pandemic was associated with a decrease in health care visits for ischemic stroke and bleeding in a nationwide cohort of patients with established AF.

1. Introduction

COVID-19 had a profound impact on health care beyond COVID-19 cases and related deaths [1]. Unexpected reductions in the rates of non-COVID clinical events suggest that patients were less likely to seek care in the weeks following the declaration of the COVID-19 pandemic [2–5]. Although multiple studies have documented these reductions across disease states and countries, the impact of the pandemic on cardiovascular chronic disease management is still not fully understood. Disease-specific studies that evaluate disruptions in both treatment and

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clinical outcomes for patients with chronic disease are needed to fully understand the disruptions of care associated with the COVID-19 pandemic and to plan for future events.

Atrial fibrillation (AF) constitutes an optimal disease to evaluate the effects of the COVID-19 pandemic on outcomes because continuous adherence to treatment is crucial to reduce the risk of stroke [6]. We previously documented that in patients with established AF, the rate of all-cause hospitalization and emergency room visits decreased by 8 % and 19 % at the start of the COVID-19 pandemic [7]. However, it is unclear when rates of health care utilization among patients with established AF returned to pre-pandemic levels. Previous studies noted increased possession of oral anticoagulation (OAC) treatment in the early months of the COVID-19 pandemic, which likely represented patients' anticipation to refill prescriptions [8]. Nevertheless, to our knowledge, no studies have examined whether the COVID-19 pandemic precipitated switches from warfarin to direct oral anticoagulants (DOACs) to avoid contact with health care facilities for routine blood testing.

We used data from a cohort of patients with established AF and evaluated changes in the incidence rates of clinical outcomes (all-cause hospitalization, ischemic stroke, and major bleeding) as well as treatment disruptions. We identified the first monthly period following the onset of the pandemic in which the clinical outcome rates returned to pre-pandemic baseline levels observed prior to March 2020.

2. Materials and methods

2.1. Data source and study population

We obtained 01/01/2018–09/30/2021 de-identified claims data from Optum's de-identified Clinformatics® Data Mart Database (most recent data available at the time of analysis). This dataset is built on administrative health claims for large commercial and Medicare Advantage health plans, which includes verified, adjudicated, and de-identified medical and pharmacy claims for a geographically diverse population spanning all 50 states.

We selected the study population in three steps (Fig. 1). First, we selected 11,612,018 patients aged over 18 years before 2019 and who were continuously enrolled for the entire year of 2018. This step ensures that we had 12 months of complete data to define the baseline characteristics and to exclude patients with valvular disease. Second, we identified patients who had been diagnosed with AF at any time before 01/01/2019. AF was defined as having an inpatient or outpatient claim with an International Classification of Diseases Ninth Revision (ICD-9) code 427.31 or International Classification of Diseases Tenth Revision (ICD-10) codes 148.0, 148.1, 148.2, 148.91 in the primary or secondary position, as previously done [9–11]. The index date was 03/18/2019 for the entire cohort. This specific date was selected because the outcomes were assessed at 30-day intervals, and 03/18/2019 marks exactly 12 intervals prior to 03/11/2020 - the date when the World Health

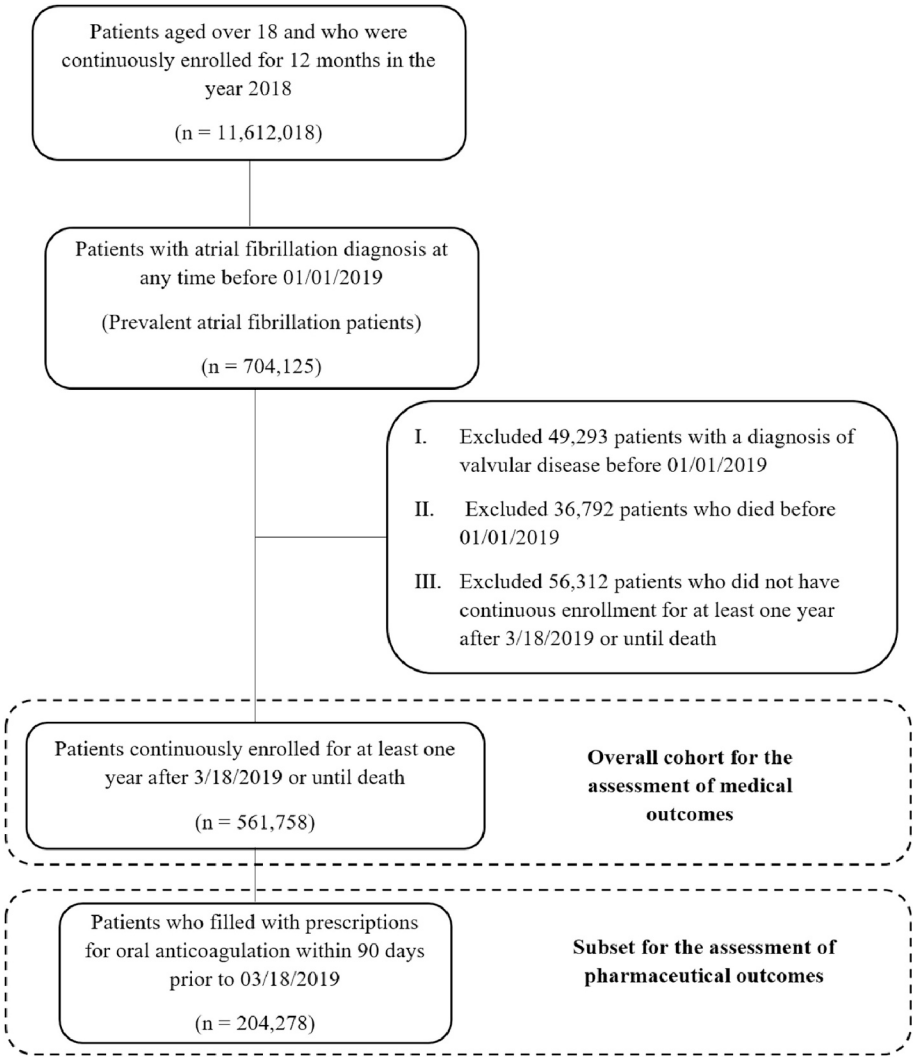

Fig. 1. Selection of the Study Sample.

Organization (WHO) declared COVID-19 a pandemic [12]. Third, we excluded patients with valvular disease or those who died before the start of the index date. Valvular disease was defined as having ICD-9 codes 394.0, V43.3 or ICD-10 codes I05.0, Z95.2 at any diagnosis field [13]. In addition, we excluded patients who did not have continuous enrollment for at least one year after the index date or until death. This ensured that we did not have missing data for the outcomes for the first year following the index date. To evaluate pharmaceutical outcomes, we further constrained the sample to individuals who were active users of OAC, defined as having a claim for any OAC including warfarin and DOACs, in the 90 days prior to the index date. The final overall sample included 561,758 patients with established AF at any time before 01/01/2019. The sub-sample used to evaluate the pharmaceutical outcomes included 204,278 patients with established AF and who were active users of OAC based on the 90-day lookback period. Patients were followed from the index date or until death, or disenrollment, or the end of the study (9/30/2021) (Supplemental Fig. 1). The Institutional Review Board at the University of California, San Diego approved this study using de-identified data as exempt.

2.2. Outcomes

Clinical outcomes included all-cause hospitalization, ischemic stroke, and major bleeding. Ischemic stroke and major bleeding events were specifically identified within the hospitalization setting. Ischemic stroke was defined as having an inpatient claim with ICD-10 code I63 [14]. Major bleeding was defined as having a claim for intracranial bleeding (ICD-10 codes I60-I62, S06.3-S06.6), or major gastrointestinal bleeding (ICD-10 codes I85.0, K25.0, K25.x, K26.x, K27.x, K28.x, K29.0, K62.5, K92.0-K92.2, where x = 0, 2, 4, 6), or other bleeding events (ICD-10 codes D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92.0, N92.1, N92.4, N93.8, N93.9, N95.0, R04) [15,16].

Pharmaceutical outcomes included OAC discontinuation, switching from warfarin to DOACs, and switching from DOACs to warfarin among individuals with AF who were active users of OAC. OAC discontinuation was defined as having 30 days or longer without possession of OAC. Switching from DOACs to warfarin was defined as having a claim for warfarin following any claim for DOACs, and vice versa for switches from warfarin to DOACs.

2.3. Independent variables

The main independent variable of interest was time after the declaration of the COVID-19 pandemic by the WHO on 03/11/2020. Demographic characteristics included age, gender, and race/ethnicity. Age was categorized into age $\geq$ 75 years and < 75 ears subgroups. Race/ethnicity was categorized into non-Hispanic White, non-Hispanic Black, Hispanic, and other. Race/ethnicity data are collected using public records and imputed with commercial algorithms with census data and first and last names [17].

2.4. Statistical analysis

We described patient characteristics in the overall cohort and subsample used to evaluate the pharmaceutical outcomes. For each 30-day interval, we calculated the incidence rate of each outcome event as the proportion of patients experiencing the corresponding outcome events divided by the population at risk in the given interval. We constructed interrupted time series analyses using linear regression model to assess changes in the incidence rates of outcomes following the onset of the COVID-19 pandemic [18,19]. The outcome variable was regressed against three key variables: 1) A continuous variable for time, which is measured in 30-day intervals; 2) an indicator variable denoting the time period after the COVID-19 pandemic declaration; 3) an interaction term between the time variable and the post-pandemic indicator. The indicator variable captures any immediate level changes in the outcome variables following the pandemic onset, represented by a change in the intercept of the regression model. The interaction term represents changes in the longitudinal trend of the outcome over the post-pandemic time period. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study sample

The overall cohort, which was used for the ascertainment of changes in medical outcomes, included 561,758 patients with established AF, of whom 47.7 % were female. The mean ± standard deviation (SD) age of the population was 77 ± 9.9, and 64.7 % of patients were aged 75 or above (Table 1). The majority of the study cohort were non-Hispanic White at 76.9 %, followed by non-Hispanic Black at 9.5 % and Hispanic at 7.6 %. In the overall cohort, 36.4 % of the patients were on OAC at baseline. Their baseline characteristics were similar to those of the overall cohort (Table 1).

3.2. Changes in clinical outcomes

The monthly incidence rate of hospitalization averaged 2.4 % in the first eight months of the study period, increased to 2.8 % in December–February 2020 and decreased to 1.7 % in the period immediately after pandemic start (3/12/2020–04/10/2020), with a significant level change of −0.86 % (*p*-value for level change<0.01), Fig. 2 and Table 2. The rates of ischemic stroke and major bleeding events also had significant decreases associated with the COVID-19 pandemic, although the magnitude was less pronounced than observed for the all-cause hospitalization outcome. Specifically, the rate of ischemic stroke decreased from 0.28 % in the period immediately before pandemic declaration (02/11/2020–03/11/2020) to 0.20 % in the period immediately after (3/12/2020–04/10/2020) with a level change of 0.05 %, and the rate of major bleeding from 0.81 % to 0.59 % with a level change of 0.11 %, both *p*-values for level change<0.01.

Seven months after the pandemic declaration, in October 2020, the incidence rate of ischemic stroke events returned to pre-pandemic levels; this is evidenced by the overlap between the confidence interval of the observed incidence rate and the counterfactual estimated absent pandemic-related changes. The incidence of major bleeding events returned to pre-pandemic levels in November 2020.

Table 1
Baseline patient characteristics.

Variable	Overall cohort (medical outcomes) (*n* = 561,758)	Subset of OAC users (pharmaceutical outcomes) (*n* = 204,278)
Female, No. (%)	267,837(47.7)	98,264(48.1)
Age, Mean (Std.)	77.0(9.9)	77.1(8.7)
Age, years		
<50, No. (%)	1333(0.65)	9713(1.7)
50–64, No. (%)	15,397 (7.5)	47,343(8.4)
65–74, No. (%)	55,470 (27.2)	139,715(24.9)
≥75, No. (%)	132,078(64.7)	364,987(65.0)
Race/ethnicity		
Non-Hispanic White, No. (%)	157,043 (76.9)	431,659(76.9)
Non-Hispanic Black, No. (%)	19,334 (9.5)	50,449(9.0)
Hispanic, No. (%)	15,466 (7.6)	43,237(7.7)
Asian, No. (%)	4202 (2.1)	12,150(2.2)
Other, No. (%)	8233 (4.0)	24,263(4.3)
Enrollment in Medicare, No. (%)	499,215(88.9)	184,357(90.25)

Abbreviation: OAC=Oral anticoagulation.

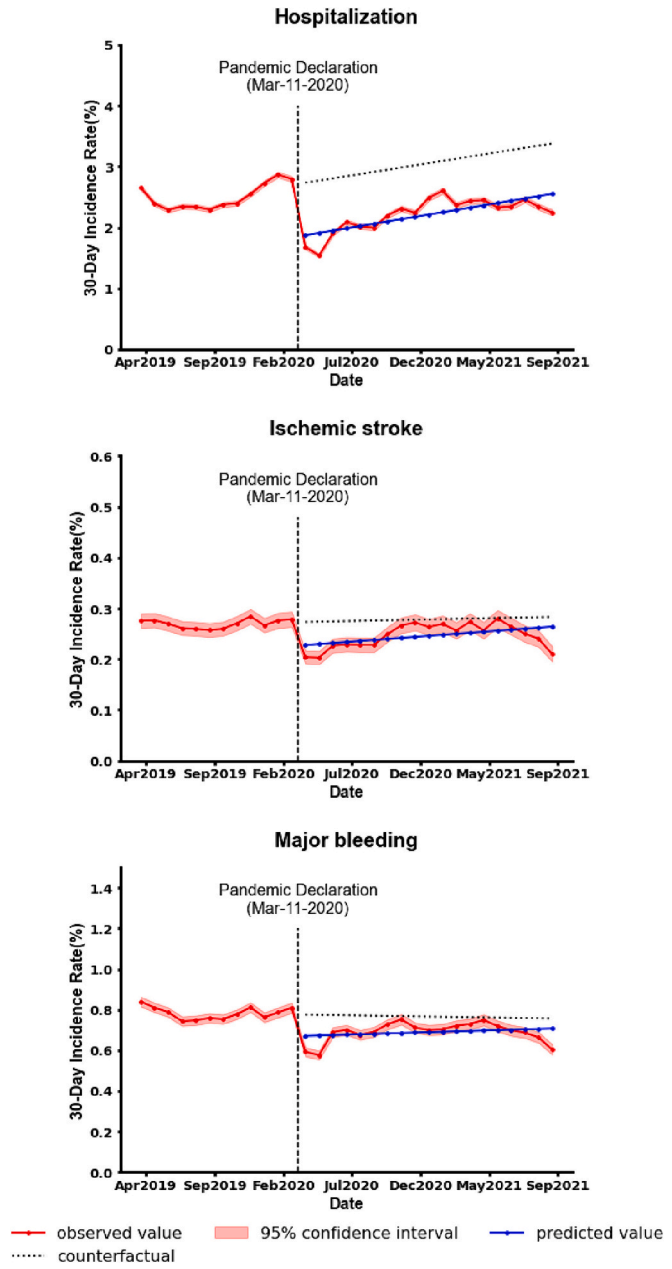

Fig. 2. Trends in clinical outcomes in patients with established atrial fibrillation associated with the Covid-19 pandemic, 03/18/2019–09/30/2021.
The figure shows trends in clinical outcomes for each 30-day interval of the study period. Solid red lines indicate the observed incidence rate; light red areas around them represent confidence intervals. Solid blue lines represent the values predicted by the regression model in the post-pandemic period. Dashed black lines represent the values that the model predicted would have been observed if there had been no change in level or trend after the onset of the COVID-19 pandemic. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Changes in OAC discontinuation and treatment switching

Before the pandemic, the OAC discontinuation incidence rate were on a downward trend, which stabilized after pandemic declaration (Table 2, Fig. 3). Throughout the study period, switches from warfarin to DOAC (1.06 %) were considerably more common than switches from DOAC to warfarin (0.12 %). Immediately after pandemic onset there was a significant decrease in the incidence rate of switches from DOACs to warfarin with a level change of 0.03 % (p-value for level change = 0.01).

Table 2
Results of Interrupted Time Series Analyses Examining Changes in the Trends of Clinical Outcomes and Pharmaceutical Outcomes Associated with the COVID-19 Pandemic.

	Level change after 03/11/2020 coefficient (p-value)	Trend change after 03/11/2020 coefficient (p-value)
Clinical outcomes		
Hospitalization	−0.86 % (<0.01)	0.00 % (0.89)
Ischemic stroke	−0.05 % (<0.01)	0.00 % (0.36)
Major bleeding	−0.11 % (<0.01)	0.00 % (0.42)
Pharmaceutical outcomes		
Switches from DOACs to Warfarin	−0.03 % (0.01)	0.00 % (0.19)
Switches from Warfarin to DOACs	−0.04 % (0.6)	0.00 % (0.96)
OAC Discontinuation	−0.82 % (<0.01)	0.10 % (<0.01)

Abbreviations: DOACs = Direct oral anticoagulants; OAC = Oral anticoagulation;
The level change represents the immediate change in the outcome following the World Health Organization declaration of pandemic on 3/11/2020. The trend change represents the change in slope.

The opposite trend was observed for switches from warfarin to DOAC, which showed an immediate but not significant increase in the first period after pandemic onset, but then returned to pre-pandemic levels.

4. Discussion

In this nationwide cohort of patients with established AF, we found a decrease in the incidence of hospitalizations for ischemic stroke and bleeding events immediately after the start of the COVID-19 pandemic. The rates of events returned to pre-pandemic levels by October – November 2020. We found no clinically significant disruptions to OAC treatment.

A previous report that examined trends in clinical events for patients with AF noted significant decreases in the rates of emergency room visits, all-cause hospitalizations, and bleeding admissions, and a marginally significant reduction in the rates of stroke admissions [7]. Consistent with these findings, our study also observed a decrease in hospitalization rates following the pandemic, as well as respective decreases in the rates of hospitalization for stroke and bleeding. There are several potential explanations for this observation. First, quarantine measures and fear of contagion may have resulted in patients delays or avoidance in seeking medical care [20]. Second, the unavailability of resources in health systems overwhelmed with COVID-19 cases may have resulted in lower likelihood of hospitalization. Patients manifesting with milder symptoms may have been managed in the outpatient setting, owing to the rapid increase in the availability and utilization of virtual visits [21]. Additionally, it has been reported that the COVID-19 pandemic caused interruptions in services, including diagnostic testing, which may have contributed to decreased diagnosis [22,23].

Our study also evaluated trends in OAC use to find a decrease in the discontinuation rate of OAC. A previous report from our research group documented increased possession of oral anticoagulation among patients with AF in the early months of the COVID-19 pandemic [24]. Increased medication possession may explain the decrease in discontinuation rates observed after the onset of the pandemic. In addition to examining discontinuation rates, our study also explored the hypothesis that patients on warfarin might switch to DOACs to avoid the need for routine blood testing at healthcare facilities, thereby minimizing their exposure risk. However, our data did not corroborate this hypothesis. It is possible that patients were not more likely to switch medications after pandemic onset due to difficulty to reach providers, or due to providers concerns to switch anticoagulants in the setting of the pandemic. Furthermore, it is important to highlight that only 36.4 % of the AF patients in our cohort were on OAC at baseline. For this reason, it is

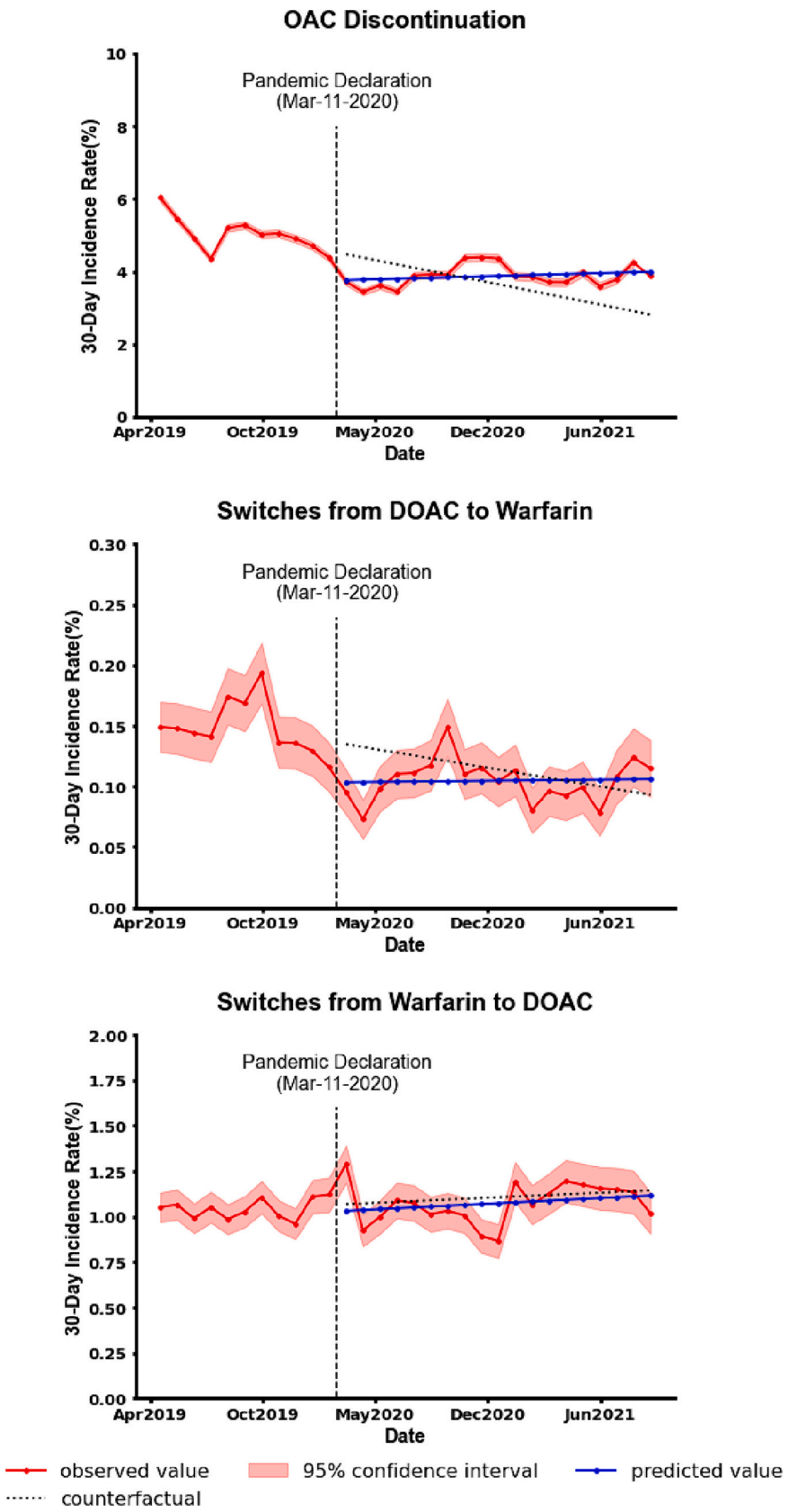

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Fig. 3. Trends in anticoagulation use in patients with established atrial fibrillation associated with the Covid-19 pandemic, 03/18/2019–09/30/2021.
Abbreviation: OAC = Oral anticoagulation;
The figure shows trends in clinical outcomes for each 30-day interval of the study period. Solid red lines indicate the observed incidence rate; light red areas around them represent confidence intervals. Solid blue lines represent the values predicted by the regression model in the post-pandemic period. Dashed black lines represent the values that the model predicted would have been observed if there had been no change in level or trend after the onset of the COVID-19 pandemic. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unlikely that the lower likelihood of OAC discontinuation during the study explains the decreased rate of ischemic strokes observed. It should be noted that the proportion of patients on OAC estimated (36.4 %) is consistent with other studies based on Optum data, which have reported approximately 40 % of AF patients on OAC treatment [25]. This consistency in the underutilization of OAC underscores the necessity of developing strategies to mitigate this underuse, even in the face of challenges posed by the pandemic.

While a previous study evaluated similar clinical outcomes, it only reported data through the summer of 2020 and was, therefore, unable to inform when rates of events returned to pre-pandemic levels [7]. While prior studies have documented disruptions in healthcare utilization associated with the COVID-19 pandemic, our analysis uniquely evaluated the extent to which these disruptions persisted over time for patients with AF. We found that for stroke and bleeding events that resulted in a hospitalization, rates did not return to pre-pandemic levels until 7–8 months after the onset of the pandemic. This evidence confirms that the decreases in healthcare utilization observed in the first weeks of the pandemic prolonged over time, underscoring their important implications for emergency preparedness in the face of future public health emergencies. These findings emphasize the critical need to develop comprehensive strategies that ensure the continuity of care or chronic cardiovascular care during public health emergencies. By prioritizing the maintenance of essential healthcare services, it is possible to mitigate the long-term effects of pandemics or other crises on healthcare outcomes.

Our study focused on evaluating changes in the incidence of clinical and pharmaceutical outcomes among patients with established AF, the potential impact of COVID-19 pandemic on AF extends beyond disruptions to chronic disease management. Emerging evidence suggests that with a diagnosis of COVID-19 is associated with increased risk of AF [26–28]. Furthermore, patients experiencing incident AF in the setting of COVID-19 infection appear to be at increased risk of worse clinical outcomes [29–31]. Previous investigations of our research team documented a decreased incidence of new onset AF in the earlier months of the COVID-19 pandemic, which is attributed to the unavailability of health care resources and the risk of contagion [9]. This initial decreased incidence of diagnosis likely resulted in delayed diagnosis, which is associated with poor prognosis. Future research should integrate the results from these investigations to paint a comprehensive picture of the impact of COVID-19 both as a diagnosis and as a health care crisis on AF and other chronic diseases. Such review efforts will be critical for the development of strategies that improve chronic disease management in public health crises.

Our study is subject to several limitations. First, our analysis relies on administrative insurance records and thus is not able to capture clinical events that did not result into an encounter with the health care system. For the same reason, it was not possible to identify the reason behind the observed decreased in the incidence rate of events - whether apparent decreases were driven by patients reluctance to seek medical care in the setting of the COVID-19 pandemic, or by a shift of management of moderate patients to the outpatient setting, or by actual decreases in the rates of patients experiencing clinical events. Second, our analysis did not evaluate the association between having a COVID-19 diagnosis and the risk of ischemic stroke or all-cause hospitalizations; this was outside of the scope of our analyses. Third, we did not evaluate trends in left atrial occlusion procedures. Nevertheless, given the relative small proportion of AF patients undergoing these procedures, it is unlikely that this limitation had a significant impact on the overall findings [32,33].

5. Conclusion

In a nationwide cohort of patients with established AF, we found a decrease in the incidence rates of ischemic stroke and bleeding events immediately after the start of the COVID-19 pandemic. The rates of events returned to pre-pandemic levels by October – November 2020.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100396.

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Ethical statement

In our study titled 'COVID-19 Pandemic and Trends in Clinical Outcomes and Medication Use for Patients with Established Atrial Fibrillation: A Nationwide Analysis of Claims Data', approved as exempt by the Institutional Review Board at the University of California, San Diego, we strictly used de-identified data, ensuring no human or animal subjects were involved in any experiments.

CRediT authorship contribution statement

Inmaculada Hernandez: Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Lanting Yang:** Writing – original draft, Methodology, Investigation, Formal analysis. **Shangbin Tang:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Teresa Cameron:** Writing – original draft, Validation, Investigation. **Jingchuan Guo:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Nico Gabriel:** Writing – review & editing, Validation, Software, Data curation. **Utibe R. Essien:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Jared W. Magnani:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Walid F. Gellad:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

Inmaculada Hernandez reports financial support was provided by National Heart Lung and Blood Institute (grants K01HL142847 and R01HL15705). Dr. Magnani is funded by R33HL144669 and R01HL143010. Dr. Guo is funded by NIDDK R01DK133465 and PhRMA Foundation Research Starter Award. The funders had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Hernandez has received consulting fees from Pfizer and Bristol Myers Squibb, outside of the submitted work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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