Prescription smoking-cessation medication pharmacy claims after stroke and transient ischemic attack

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ARTICLE INFO

Keywords: Smoke. Transient ischemic attack. Prevention. Smoking-cessation.

ABSTRACT

Smoking cessation is critical in secondary prevention after stroke and transient ischemic attack. Data regarding use of smoking-cessation interventions after stroke and transient ischemic attack are sparse. We examined the use of prescription smoking-cessation medications in these patients. This is a retrospective cohort study using 2013–2016 data from the INSIGHT Clinical Research Network, comprised of Medicare prescription claims data merged with electronic health record data for patients receiving care across five New York City health care institutions. Active smoking was ascertained based on a validated ICD-9-CM diagnosis code or the presence of an electronic health record active smoking indicator, reflecting clinician-entered data in the health record. The primary outcome was a claim for any prescription smoking-cessation medication (varenicline or bupropion) within 12 months of hospital discharge. We evaluated claims for any statin medication as a comparator because statins are a standard component of stroke secondary prevention. We identified 3,153 patients with stroke or transient ischemic attack who were active smokers at the time of their event. Among these patients, 3.1% (95% CI, 2.5–3.9) had a pharmacy claim for a prescription smoking-cessation medication at 6 months, and 4.7% (95% CI, 3.9–5.6) did at 12 months hospital discharge. In contrast, cumulative statin medication claims rates were 67.5% (95% CI, 65.5–69.5%) at 6 months and 74.6% (95% CI, 72.7–76.6%) at 12 months. Prescription smoking-cessation medications were infrequently used after stroke and transient ischemic attack.

1. Introduction

Patients who quit smoking cigarettes after stroke and transient ischemic attack (TIA) have a lower risk of recurrent stroke and cardiovascular events compared to patients who continue smoking (Epstein et al., 2017; Chen et al., 2019). For example, among 1,072 smokers with stroke or TIA in one study, 42% quit smoking soon after their event. Among the people who quit smoking, the 5-year risk of stroke, myocardial infarction, or death was 15.7% compared to 22.6% in continuing smokers (Epstein et al., 2017). Thus, smoking cessation is an integral component of secondary prevention after stroke and TIA. In addition to behavioral strategies and nicotine replacement therapy, two effective smoking-cessation prescription medications – varenicline and bupropion – were licensed for smoking cessation over the past two decades. In large meta-analyses of randomized clinical trial data, varenicline and bupropion have been found to increase the likelihood of smoking cessation compared to counseling alone, and varenicline has been found to increase cessation rates to a greater extent than nicotine replacement therapy (Cahill et al., 2015; Howes et al., 2020; Krist et al., 2021). In contrast to the general United States population, the rate of active smoking among stroke survivors has not decreased over the past 20 years (Parikh et al., 2020). The reasons for this are unclear. In this study, we examined prescription smoking-cessation medication use after stroke/TIA among New York City Medicare beneficiaries.

2. Methods

2.1. Study design

We performed a retrospective cohort study using 2013–2016 data
from the INSIGHT Clinical Research Network, which is a Patient-Centered Outcomes Research Institute-funded initiative (Zhang et al., 2020). The INSIGHT Clinical Research Network collects comprehensive electronic health record (EHR) data for over 11 million unique patients across five medical centers in New York City (NewYork-Presbyterian/Weill Cornell Medical Center, NewYork Presbyterian/Columbia University Irving Medical Center, Mount Sinai Health System, Montefiore Medical Center, and New York University Langone Medical Center). Together, these hospital care for a diverse patient population. EHR data, which include clinician-entered data such as smoking status, from the INSIGHT Clinical Research Network were merged with Medicare claims data for Medicare fee-for-service patients who had at least one encounter in these health systems. These Medicare claims data included Part D prescription drug claims data. The Weill Cornell Medicine institutional review board approved analysis of these deidentified data and did not require informed consent. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be submitted to INSIGHT Clinical Research Network (https://insight tcrn.org/).

2.2. Patient population

We included hospitalized Medicare fee-for-service beneficiaries with ischemic stroke or TIA who were active smokers at the time of the event. Patients were included if they (1) were hospitalized between January 1st, 2013 and September 30th, 2015; (2) had a diagnosis of ischemic stroke or TIA during the hospitalization; (3) were discharged to home or inpatient rehabilitation facilities; and (4) were active smokers. The study period was chosen to permit up to 1-year of follow-up after hospital discharge in the available data. Ischemic stroke and TIA were identified using standard, validated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes (Tirschwell and Longstreth, 2002; Yu et al., 2017). Active smoking was ascertained based on ICD-9-CM diagnosis code 305.1 or the presence of an EHR active smoking indicator, reflecting data entered into the EHR by clinicians. ICD-9-CM diagnosis codes have high specificity for identifying smokers but modest sensitivity (Desai et al., 2016; Wiley et al., 2013). Thus, we complemented diagnosis code data with EHR indicator data because the Centers for Medicare & Medicaid Services has incentivized EHR documentation of smoking status since 2011 as part of meaningful use policy, resulting in improved sensitivity (Huo et al., 2018). We excluded patients who died in the hospital or were discharged to long-term healthcare facilities, which are smoke-free. Additionally, patients were excluded if they were enrolled in the Medicare Advantage program during the one year follow up period because these patients’ data are not captured in the fee-for-service data we used.

2.3. Measurements

The primary outcome was a prescription drug claim for a smoking-cessation medication (varenicline or bupropion). Nicotine replacement therapy was not included in the primary outcome because these medications can be obtained without prescription. Post-hoc attempts to include nicotine replacement therapy products were unsuccessful in part because part D claims data do not include over-the-counter medications. We also evaluated prescription claims for any statin medication as a comparator. Statin medications, a standard component of stroke secondary prevention, were chosen because statin medications are not available over the counter, in contrast to other preventive medications such as aspirin. All prescription claims were identified by searching National Drug Codes in the Medicare Part D prescription claims file (United States Food and Drug Administration, 2021) The National Drug Code system, maintained by the Food and Drug Administration, provides a code for all medications (United States Food and Drug Administration, 2021) We created a list of all proprietary and nonproprietary medications names for smoking-cessation drugs and statin medications and then matched these medication names to individual drug codes. Additional covariates were demographic characteristics and comorbidities. Patients’ age, sex, race/ethnicity (as recorded in the Medicare beneficiary summary file), and Medicare and Medicaid dual eligibility status were determined from the Medicare beneficiary summary file. Dual eligibility reflects eligibility for Medicare and Medicaid, with the latter reflecting lower income and thus serving as a surrogate of socioeconomic status. The following comorbidities were tabulated using standard Medicare chronic condition codes: hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, heart failure, ischemic heart disease, chronic pulmonary disease, and asthma.

2.4. Statistical analyses

Baseline characteristics were summarized using standard descriptive statistics. We used time-to-event analysis to estimate the 6- and 12-month rates of prescription drug claims. Cumulative incidence functions were used to calculate cumulative incidence while accounting for the competing risk of death and loss of coverage of Medicare Part D (prescription drug coverage). Patients entered observation at the time of discharge from hospital admission with a stroke or TIA diagnosis and were censored at the time of death, loss of Medicare Part D enrollment, or end of one-year follow-up (last date, September 29, 2016). In subgroup analyses, we separately evaluated patients with ischemic stroke and TIA. Last, in a sensitivity analysis, we evaluated rates of smoking-cessation prescription drug claims among individuals with evidence of ongoing active secondary prevention care by limiting the cohort to only among individuals with at least one claim for a statin medication during follow-up. Alpha error was set at 0.05. Statistical analyses were performed using STATA/MP software, version 14 (StataCorp).

3. Results

We identified 34,591 hospitalizations for stroke or TIA between January 2013 and September 2015, of whom 3,153 (9.1%) were active smokers at the time of their event. The mean age of these patients was 73.6 years (standard deviation, 11.2), and 49.7% were women. These patients had a high prevalence of hypertension, hyperlipidemia, diabetes, heart disease, and pulmonary disease (Table 1). The mean follow-up duration was 0.7 years (standard deviation, 0.4).

Patients with at least one prescription drug claim for a smoking-cessation medication were younger, more often White, and had higher rates of pulmonary disease than those with no claims for these medications (Table 1). Cumulative rates of any prescription smoking-cessation medication claim among patients who were active smokers at the time of their stroke/TIA were 3.1% (95% CI, 2.5–3.9) at 6 months and 4.7% (95% CI, 3.9–5.6) at 12 months (Table 2, Fig. 1). Individually, the 12-month cumulative claims rates were 0.7% (95% CI, 0.4–1.1) for varenicline and 4.0% (95% CI, 3.3–4.9) for bupropion. In subgroup analyses, the cumulative rate of any smoking-cessation prescription medication (varenicline or bupropion) claim was 4.7% (95% CI, 3.8–5.9) at 12 months after stroke and 4.6% (95% CI, 3.4–6.3) after TIA. In contrast, cumulative statin medication claims rates were 67.5% (95% CI, 65.5–69.5%) at 6 months and 74.6% (95% CI, 72.7–76.6%) at 12 months after stroke or TIA.

In a sensitivity analysis, among patients with at least one claim for a statin medication, cumulative rates of any prescription smoking-cessation medication claim were 3.5% (95% CI, 2.7–4.4) at 6 months and 5.3% (95% CI, 4.4–6.4) at 12 months. In this sensitivity analysis, the 12-month cumulative claims rates were 0.8% (95% CI, 0.5–1.4) for varenicline and 4.5% (95% CI, 3.7–5.6) for bupropion. Additionally, the cumulative rate of any smoking-cessation medication claim was 5.4% (95% CI, 4.3–6.8) at 12 months after stroke and 5.1% (95% CI, 3.6–7.2) after TIA.
cardiovascular events, patients with stroke and TIA do not appear to be at increased risk (Tibuakuu et al., 2019). Therefore, despite their high risk for myocardial infarction, another smoking-related acute cardiovascular illness.

There are several possible explanations for our findings. First, some patients may use nicotine replacement therapy. Because nicotine replacement therapy can be obtained over the counter without a prescription, our analysis could not generate valid estimates of use of these medications. Use of nicotine replacement therapy may account for low rates of prescription medication use. Similarly, stroke survivors may increasingly be opting for non-guideline recommended smoking alternatives such as e-cigarettes (Parikh et al., 2021). Second, limited knowledge of and access to smoking-cessation therapies may contribute (Tibuakuu et al., 2019). Third, lack of experience and comfort with these medications may result in low utilization by health professionals caring for patients with stroke/TIA. Last, inadequate capture of prescription claims is possible, but we believe this is unlikely because rates of smoking-cessation claims were consistent among patients with at least one claim for a statin medication. Further, the 12-month rate of statin claims in our analysis was comparable with prior reports of statin adherence after stroke and TIA (Albright et al., 2017).

While our data suggest that statins are also underused, the key implication of our data is that effective smoking-cessation therapies appear to be utilized at low rates in secondary prevention after stroke and TIA. Some patients with stroke may be motivated to quit smoking as a reaction to having had a stroke (Sienkiewicz-Jarosz et al., 2012), and these patients may not require a smoking-cessation medication. However, multiple studies have shown that only 40-50% of patients with stroke quit smoking; there is thus room for improvement (Noubiap et al., 2021). Whether intervention to increase use of smoking-cessation interventions is needed at the patient-level or provider-level is unclear from these data, which reflect only prescription claims and not prescription issuance. Further, whether such interventions should target nicotine replacement therapy or prescription medications is also unclear on the basis of our analysis.

The key strength of this analysis is that the data are drawn from a multisite dataset that contains claims data coupled with clinician-entered EHR data. However, our results should be interpreted considering several limitations, apart from those inherent to retrospective study design. First, we were unable to account for spontaneous unaided smoking cessation and over-the-counter use of nicotine replacement therapy, which are not captured in Medicare claims data. Similarly, our data do not reflect non-pharmacological interventions, such as referral to outside counseling. Second, because our data cannot reliably capture smoking cessation, we cannot determine whether smoking-cessation medications benefited patients relative to other strategies. Third, our data may not be generalizable to other health care systems, regions of the United States, and younger patients with other forms of health insurance. Fourth, while our approach for identifying smokers is specific and we made efforts to increase sensitivity, we may not have captured all smokers. It is possible that patients who were in fact smokers but not documented as such in the EHR had even lower rates of smoking-cessation medication prescription. These limitations notwithstanding, we believe that a better understanding of prescription smoking-cessation medication use after stroke/TIA can help inform strategies to improve secondary prevention.

In conclusion, we found that less than 5% of individuals who were smokers at the time of their stroke or TIA had an insurance claim for a prescription smoking-cessation medication within 12 months. Along with behavioral interventions, optimizing use of smoking-cessation medications may be one strategy to improve secondary prevention after stroke/TIA.

5. Data access, reproducibility, and analysis

Dr. Zhang had full access to all the data in the study and takes

### Table 1
Study population characteristics, patients with stroke or transient ischemic attack and active smoking.

| Characteristic | Study Population | At least one Smoking-Cessation Medication Claim | No Smoking-Cessation Medication Claim |
|---------------|------------------|-----------------------------------------------|--------------------------------------|
| Age, mean (SD), y | 73.6 (11.2) | 68.9 (11.9) | 73.8 (11.2) |
| Female | 49.7 | 53.9 | 49.5 |
| Race | | | |
| White | 75.4 | 81.4 | 75.1 |
| Black | 14.9 | 13.0 | 15.0 |
| Other | 9.7 | 5.2 | 9.9 |
| Dual Eligible | 27.6 | 46.9 | 26.8 |
| Hypertension | 94.4 | 97.4 | 94.3 |
| Hyperlipidemia | 86.8 | 93.9 | 86.5 |
| Diabetes Mellitus | 52.6 | 51.3 | 52.6 |
| Atrial Fibrillation | 29.1 | 21.7 | 29.4 |
| Heart failure | 43.0 | 47.8 | 42.8 |
| Ischemic heart disease | 71.1 | 73.9 | 71.0 |
| Chronic pulmonary disease | 33.4 | 50.4 | 32.8 |
| Asthma | 15.2 | 30.4 | 14.6 |

Abbreviations: SD, standard deviation.

- Data are presented as number (%) unless otherwise specified.
- Baseline characteristics presented as % comparing patients with at least one drug claim for a smoking-cessation medication at 12 months to patients with zero claims. Raw numbers are not provided due to compliance with Medicare administrative claims data use agreement policies that protect privacy for cells with small absolute values.
- As reported by patients or their surrogates.
- Dual eligible indicates eligibility for both Medicare and Medicaid.
- Chronic pulmonary disease was chronic obstructive pulmonary disease and emphysema.

### Table 2
Cumulative Rates of Prescription Drug Claims at 6 and 12 months after ischemic stroke and transient ischemic attack.

| Medication | 6 Months | 12 Months |
|------------|----------|-----------|
| Any Prescription Smoking-cessation medication | 3.1% (2.5-3.9%) | 4.7% (3.9-5.6%) |
| Varenicline | 0.2% (0.1-0.6%) | 0.7% (0.4-1.1%) |
| Bupropion | 2.9% (2.3-3.6%) | 4.0% (3.3-4.9%) |
| Any statin medication (control) | 67.5% (65.5-69.5%) | 74.6% (72.7-76.6%) |

- Data are presented as cumulative rate (95% confidence interval).

4. Discussion

In this analysis of New York City Medicare beneficiaries who sought care in 5 urban health care organizations, approximately 5% of individuals with stroke or TIA who were active smokers had a claim for prescription smoking-cessation medication in the year after hospital discharge. Results were consistent among patients who had at least one claim for a statin medication during this period.

To our knowledge, these are the first data on prescription smoking-cessation medication claims rates for patients with stroke and TIA. Our findings are similar to data for Medicare beneficiaries with myocardial infarction, for whom 90-day rates for smoking-cessation medication prescription were 7.0% (Pagidipati et al., 2017). Further, in the general population, the rate of self-reported prescription smoking-cessation medication use among active smokers during our study period was 5.5% (Tibuakuu et al., 2019). Therefore, despite their high risk for cardiovascular events, patients with stroke and TIA do not appear to be using prescription smoking-cessation medications any more frequently than the general population or as compared to patients with myocardial infarction, another smoking-related acute cardiovascular illness.

Data are presented as cumulative rate (95% confidence interval).
responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

Dr. Parikh reports funding from the New York State Empire Clinical Research Investigator Program, the Florence Gould Foundation for Discovery in Stroke, and the National Institute on Aging (K23 AG073524). Additionally, this study was funded by the grant PCORI/HSD-1604-35187 from the Patient-Centered Outcomes Research Institute and the grant K99AG064030 (PI: Zhang) from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding sources have no involvement in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Author contributions

Dr. Parikh was responsible for conception and design of the work, interpretation of the data, drafting of the work, and giving final approval of the version to be published; and, he agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Zhang was responsible for design of the work, analysis and interpretation of the data, and giving final approval of the version to be published; and, he agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Mr. Restifo and Drs. Abramson, Carpenter, Navi, and Kamel were responsible for interpretation of the data, revising the work critically for important intellectual content, and providing final approval of the version to be published; and, they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CRediT authorship contribution statement

Neal S. Parikh: Conceptualization, Methodology, Investigation, Writing – original draft, Funding acquisition. Yongkang Zhang: Conceptualization, Methodology, Investigation, Data curation, Resources, Formal analysis, Visualization, Writing – review & editing, Funding acquisition. Daniel Restifo: Writing – review & editing. Erika Abramson: Writing – review & editing. Matthew J. Carpenter: Writing – review & editing. Babak B. Navi: Writing – review & editing. Hooman Kamel: Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Parikh has received medicolegal consulting compensation and prior funding from the Leon Levy Foundation unrelated to this work. Dr. Zhang: none. Mr. Restifo: none. Dr. Abramson: none. Dr. Carpenter has previously received consulting honoraria from Pfizer. Dr. Navi has received medicolegal consulting compensation. Dr. Kamel serves as a principal investigator for the NIH-funded ARCADIA trial (National Institute of Neurological Disorders and Stroke U01NS095869) which receives in-kind study drug from the BMS-Pfizer Alliance for Eliquis® and ancillary study support from Roche Diagnostics, serves as Deputy Editor for JAMA Neurology, serves as a steering committee member of Medtronic’s Stroke AF trial (uncompensated), and serves on an endpoint adjudication committee for a trial of empagliflozin for Boehringer-Ingelheim.

Acknowledgement

None.

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Fig. 1. Cumulative Rate of Prescription Drug Claims for Smoking-Cessation Medication after Ischemic Stroke and Transient Ischemic Attack. Legend: In a sample of Medicare fee-for-service beneficiaries in New York City with ischemic stroke and transient ischemic attack who were active smokers at the time of their event, the cumulative rate of smoking-cessation medication claims over one year was less than 5%.
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