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Statins are rarely prescribed for incidentally discovered covert cerebrovascular disease: a retrospective cohort in a large electronic health record (EHR) identified using natural language processing

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ABSTRACT

Introduction While incidentally discovered covert cerebrovascular diseases (id-CCD) are associated with future stroke, it is not known if patients with id-CCD are prescribed statins.

Methods Patients age ≥50 with id-CCD on neuroimaging from 2009 to 2019 with no prior ischaemic stroke, transient ischaemic attack or dementia were identified using natural language processing in a large real-world cohort. Robust Poisson multivariable regression was used to assess statin prescription among patients without prior statins.

Results Among 241 050 patients, 74 975 patients (31.1%; 4.7% with covert brain infarcts (CBI); 29.0% with white matter disease (WMD)) had id-CCD. 53.5% (95% CI 53.2 to 53.9%) were not on statins within 6 months prior to the scan. Of those, 12.0% (95% CI 11.7 to 12.3%) were prescribed statins in the next 6 months compared with 9.3% (95% CI 9.1 to 9.4%) in those without CCD, a 2.7% (95% CI 2.4 to 3.1%) absolute increase in statin prescription for those with id-CCD. In adjusted analyses, the presence of id-CCD was only associated with minor increases in statin prescription (CBI or WMD (risk ratio (RR) 1.09, 95% CI 1.05 to 1.13), CBI alone (RR 1.34, 95% CI 1.21 to 1.47), WMD alone (RR 1.05, 95% CI 1.01 to 1.09), and CBI and WMD (RR 1.23, 95% CI 1.12 to 1.35)).

Discussion Identification of id-CCD is not associated with substantial changes in statin prescription in routine clinical practice.

INTRODUCTION

Background

Preventing symptomatic stroke and dementia after detection of covert cerebrovascular diseases (CCD) such as covert brain infarcts (CBI) and white matter disease (WMD) is a priority of the American Heart Association/American Stroke Association and other organisations, but there is an absence of randomised trials to guide screening or management.[1] The European Stroke Organization's guideline on covert cerebral small vessel disease advises against antiplatelet therapy but suggests that lipid lowering with statins could be considered.[2] Notably, CCD are often discovered incidentally on neuroimaging performed for non-stroke and non-dementia indications in real-world clinical care.[3] In prior work leveraging a natural language processing (NLP) algorithm to detect CBI and WMD among people without prior symptomatic cerebrovascular disease, risk of future stroke or dementia in people with incidentally discovered (id-) CCD were elevated with adjusted hazard ratios ranging from 1.8 to 3.0 for CBI and subsequent stroke, 1.8 for WMD and subsequent stroke and ranging 1.4 to 4.1 for WMD of increasing severity and subsequent dementia.[4 5] These hazards are comparable to those demonstrated in prospective cohort studies such as the Atherosclerotic Risk in Communities Study, Cardiovascular Health Study, Framingham Offspring Cohort Study, Northern Manhattan Study and Rotterdam Scan Study.[6–8] However, qualitative studies illustrate equipoise on approaches to id-CCD: one interview study found extensive diversity with internists favouring no or minimal response and neurologists favouring secondary stroke prevention practices.[9] A recent survey of several hundred neurological specialists indicated that most would assertively address vascular risk factors, including hypercholesterolaemia.[10] In this context, it is not known how often clinicians alter clinical practices in response to id-CCD.

Objectives

We sought to assess clinical responses to id-CCD by examining the frequency of new statin prescription following id-CCD reporting on neuroimaging studies in a large health system, Kaiser Permanente Southern California (KPSC). Statins are consistently recommended for most patients with ischaemic stroke. Accordingly, new statin prescription may serve as an indicator of the degree to which clinicians manage vascular risk factors in patients with id-CCD similar to patients with prior ischaemic stroke.

METHODS

Study setting

This study was conducted at KPSC which serves approximately 4.7 million individuals with 15 hospitals and 230+ medical offices. KPSC and its electronic health record (EHR) data have been previously described.[3 4] This study was approved by the KPSC, Mayo Clinic and Tufts Medical Center (TMC) institutional review boards, with waiver for patient consent.

Design and sample

This retrospective cohort study included individuals age ≥50 enrolled from 2009 to 2019 with head neuroimaging (CT, MRI) for non-stroke and non-dementia indications and no history of ischaemic stroke, transient ischaemic attack (TIA) or dementia. The first study was considered the index scan if there were multiple studies. Frequency of scan modality and associations with id-CCD identification were described previously.[3] Brain infarction was considered covert if there was no acquired ICD code for cerebral infarction within 60 days of the scan date. Radiological definitions for brain infarcts and white matter disease were derived from STRIVE and were used to train the NLP algorithm designed at Mayo Clinic and TMC.[11–13] The NLP algorithm was further re-trained on KPSC's data. It was applied to the KPSC EHR to identify individuals with CBI or WMD.

Covariates

Data were collected on basic demographics, traditional stroke risk factors, systolic blood pressure (SBP) and statin prescription. Traditional stroke risk factors were selected based on the Framingham Stroke Risk Score and included atrial fibrillation, carotid atherosclerosis, congestive heart failure, coronary artery disease, diabetes mellitus, hypercholesterolaemia, hypertension, peripheral arterial disease and tobacco use (ever vs never).[14] Individuals were required to have at least one ICD code (or an EHR structured field indicating tobacco use) associated with a clinical encounter or in the problem list of the KPSC EHR to be considered to have a risk factor. SBP measures were averaged over 1 year and excluded extreme values less than 70 or greater than 200 to avoid measurements from periods of critical illness.

Statistical analysis

Multivariable Poisson regression with robust error variance was used to assess changes in statin prescription rates among patients without statin prescription during the 6 months prior to index scans to the 6 months following the scan. We adjusted for statin prescription indications (carotid atherosclerosis, coronary artery disease, hypercholesterolaemia, peripheral arterial disease) and traditional stroke risk factors. All analyses were performed as complete case analyses provided that there was less than 5% missing data for any one covariate. Statistical analyses were performed in R (V.3.5.1, Vienna, Austria).

Patient and public involvement

There was no patient and public involvement in this study.

RESULTS

Cohort characteristics

A total of 241 050 individuals enrolled in KPSC were included: 74 975 patients (31.1%) had id-CCD, with 11 328 (4.7%) having CBI and 69 931 (29.0%) having WMD. Of patients with id-CCD, 34 852 (46.5%) were taking statins at baseline or in the prior 6 months. This study analysed 145 811 individuals (60.5%) who were statin nonusers at baseline or in the 6 months prior, with 40 123 nonusers having id-CCD (27.5%), including with 5779 (4.0%) having CBI and 37 417 (25.7%) having WMD.

Baseline characteristics are shown in online supplemental table 1. Among statin nonusers, the cohort was predominantly middle-aged (mean 62.8, SD 10.2), female (64.2%) and non-white (57.2%). Hypercholesterolaemia (49.8%) and hypertension (48.7%) were moderately prevalent, whereas there was a low frequency of strong indications for statin prescription (carotid atherosclerosis, coronary artery disease, peripheral arterial disease).

Frequency of incident statin prescription with id-CCD

Results from adjusted analyses are in table 1. Among patients without statins in the preceding 6 months, statins were prescribed for 9780 (9.3%, 95% CI 9.1 to 9.4%) patients without id-CCD and 4820 (12.0%, 95% CI 11.7 to 12.3%) patients with id-CCD in the 6 months after the index scan. This corresponds to an absolute difference of 2.7% (2.4%–3.1%).

Statins were prescribed slightly more frequently for patients with CBI (15.7%) than for WMD (11.8%). Notably, 51.0% of patients with CBI and 53.5% with WMD were not on a statin at baseline or during the preceding 6 months. In adjusted analyses, the presence of CBI or WMD was associated with slightly increased statin prescription (risk ratio (RR) 1.09, 95% CI 1.05 to 1.13). The presence of CBI alone was associated with mildly increased prescription (RR 1.24, 95% CI 1.16 to 1.33), WMD alone was associated with slightly increased prescription (RR 1.04, 95% CI 1.002 to 1.08), and the presence of both was associated with mildly increased prescription (RR 1.23, 95% CI 1.12 to 1.35).

Table 1 Associations between demographics, risk factors and id-CCD on new statin prescription. Adjusted relative risks (aRR) and the upper and lower bounds of the confidence intervals for new statin prescription shown. All listed covariates were included in the multivariable Poisson regression analyses

Covariate	aRR	95% CI	P value
Age	0.86	0.82, 0.89	<0.0001
Female	0.91	0.88, 0.95	<0.0001
Race			
Asian and Pacific Islander	1.20	1.14, 1.27	<0.0001
African American	1.34	1.27, 1.41	<0.0001
Hispanic	1.37	1.32, 1.42	<0.0001
Multiple/other/unknown	1.01	0.88, 1.17	0.87
Stroke risk factor			
Atrial fibrillation	1.02	0.95, 1.10	0.64
Carotid atherosclerosis	1.30	1.13, 1.49	0.0003
Congestive heart failure	1.02	0.95, 1.11	0.57
Coronary artery disease	1.05	0.99, 1.11	0.08
Diabetes mellitus	1.11	1.07, 1.15	<0.0001
Hypercholesterolaemia	1.62	1.55, 1.70	<0.0001
Hypertension	0.95	0.91, 0.99	0.01
Peripheral arterial disease	0.98	0.91, 1.06	0.60
Tobacco, ever use: unknown	1.86	0.71, 4.85	0.20
Tobacco, ever use: yes	1.03	1.00, 1.07	0.05
Systolic blood pressure (mean)	1.02	1.02, 1.02	<0.0001
Covert brain infarction (present)	1.24	1.16, 1.33	<0.0001
White matter disease (present)	1.04	1.00, 1.08	0.038

In adjusted analyses, older patients and women were less likely to be started on statins, whereas people of all non-white races were more likely to be prescribed statins. Carotid atherosclerosis, diabetes mellitus, hypercholesterolaemia, hypertension and elevated mean SBP were all associated with new statin prescription.

DISCUSSION

This study demonstrates that clinicians generally do not respond to the discovery of CCD in routine care with the prescription of statins. We found a similar proportion of patients received statins in the 6 months following an index scan among those with id-CCD as those without id-CCD (12% vs 9%, respectively), suggesting that the discovery of id-CCD did not frequently influence clinical practice. This finding contrasts a recent survey of neurological specialists in which 76% indicated they would implement lipid lowering for patients with CBI.[10] These findings correspond with the perspectives of internists in the interview study, likely suggesting that id-CCD are generally encountered by non-specialists.[9] Clinical trials are warranted to determine if statins and other risk factor management may be useful for stroke prevention and dementia prevention in patients with id-CCD.

This study has several strengths and limitations. First, this study leveraged a novel NLP algorithm for cohort identification in a large EHR, allowing assessment of real-world clinical practices in a heterogeneous cohort. Second, the cohort was demographically diverse and originated in a large geographic area. Third, the focus of this analysis on statin prescription allowed for robust outcome ascertainment, as compared with challenges with assessing aspirin prescription (not recorded when obtained over-the-counter) or anti-hypertensive treatment (numerous agents).[15] Regarding limitations, this is a retrospective analysis using EHR data with possible risk of bias from systemically missing data. Fortunately, the KPSC EHR had minimal missingness for the covariates included in this study. Second, this analysis did not assess statin prescription stratified by characteristics of id-CCD such as WMD grade, so it is not known if these characteristics were associated with differences in clinician response. Nonetheless, a prior analysis in this cohort demonstrated that mild WMD detected by CT or MRI were both associated with future risk of dementia.[5]

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Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the following institutional review boards: the Kaiser Permanente Southern California Institutional Review Board (approval number 12111), the Mayo Clinic Institutional Review Board (approval number PR17-006674) and the Tufts Health Sciences Institutional Review Board (Tufts Medical Center, approval number 11953). Informed consent requirements were waived by the Institutional Review Boards.

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