Acute Vascular Ischemic Events in Patients With Central Retinal Artery Occlusion in the United States: A Nationwide Study 2003-2014

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• PURPOSE: **Central retinal artery occlusion (CRAO) confers a high risk of acute vascular ischemic events, including stroke and myocardial infarction (MI). Understanding the burden and risk factor profile of these ischemic events can serve as a valuable guide for ophthalmologists in the management and appropriate referral of these patients.**

• DESIGN: **Retrospective cross-sectional study.**

• METHODS: **The Nationwide Inpatient Sample (NIS) was queried to identify all inpatient admissions with a diagnosis of CRAO in the United States between the years 2003 and 2014. The primary outcome measure was the incidence of in-hospital acute vascular ischemic events.**

• RESULTS: **There were an estimated 17 117 CRAO inpatient admissions. The mean age was 68.4 ± 0.1 years and 53% of patients were female. The incidence of in-hospital stroke and acute MI were 12.9% and 3.7%. The incidence of stroke showed an increasing trend over the years, almost doubling in 2014 in comparison to 2003 (15.3% vs 7.7%). The combined risk of in-hospital stroke, transient ischemic attack, acute MI, or mortality was 19%. Female sex, hypertension, carotid artery stenosis, aortic valve disease, smoking, and alcohol dependence or abuse were positive predictors of in-hospital stroke.**

• CONCLUSION: **There is a significant burden of vascular risk factors, associated with an increased risk of in-hospital stroke, acute MI, and death in CRAO patients. The risk of CRAO-associated stroke is highest in women and in those with a history of hypertension, carotid artery stenosis, aortic valve disease, smoking, or alcohol abuse. (Am J Ophthalmol 2019;200: 179–186. © 2019 Elsevier Inc. All rights reserved.)**

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CENTRAL RETINAL ARTERY OCCLUSION (CRAO) IS AN ophthalmic emergency and important cause of sudden-onset vision loss.[1] The pathophysiology is predominantly embolic or thrombotic occlusion of the central retinal artery with resultant ischemia. As CRAO shares common risk factors with cerebrovascular and cardiovascular diseases,[2] it is an important clinical indicator of acute vascular ischemic events, including stroke or myocardial infarction (MI).[3]

At present, there are no effective treatment options known to significantly improve visual outcomes in CRAO patients.[4–8] Therefore, the emphasis of clinical management is on prevention of secondary vascular ischemic events. As the risk of stroke is highest in the period immediately following a CRAO,[9–12] prompt clinical evaluation to identify the underlying etiology and timely institution of stroke prevention measures is warranted.[13]

American Academy of Ophthalmology (AAO) guidelines recommend all patients with CRAO be referred to the nearest stroke center.[14] In addition, American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend all patients with suspected retinal ischemia undergo immediate brain imaging.[15] There is lack of consensus regarding the need for prompt neurologic and cardiovascular evaluation in CRAO patients; approximately 35% of ophthalmologists refer patients with acute CRAO to the emergency department (ED) for immediate evaluation.[16] Management practices differ significantly across specialties, with 75% of neurologists pursuing a hospital-based evaluation, while 82% of retina specialists opt for an outpatient evaluation.[17]

Although immediate ED referral and inpatient evaluation of all CRAO patients may be the safest, most conservative approach, such evaluations may increase the costs related to more frequent hospitalizations. Risk stratification of CRAO patients for future ischemic events and efficient triaging is imperative to ensure that those at high risk undergo emergent evaluation. Such an approach would require clinicians to better understand the risk factor profile and predictors of stroke in CRAO patients.

We conducted a nationwide study on CRAO patients spanning more than a decade (2003-2014) to investigate the following: (1) vascular risk factors and systemic conditions associated with CRAO; (2) the incidence of

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in-hospital stroke, myocardial infarction, and mortality; (3) temporal trends in the incidence of CRAO-related acute ischemic events; (4) predictors of in-hospital stroke; (5) burden and economic costs associated with inpatient CRAO admissions.

METHODS

• **DATA SOURCE AND STUDY POPULATION:** The Nationwide Inpatient Sample (NIS) was queried for the years 2003-2014, to identify all patients admitted with a diagnosis of CRAO. The NIS is the largest all-payer inpatient database in the United States and is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The sampling strategy of the NIS changed in 2012, prior to which the database comprised a 20% stratified systematic sample of all US community hospitals, with all discharges retained from those hospitals. In 2012, in an attempt to improve national estimates, the database was redesigned to include a 20% stratified sample of discharges from all hospitals in the HCUP. In 2014, the NIS contained data for approximately 8 million hospital discharges from 44 participating states, representing 98% of the US population. Sampling strata used by the NIS is based on hospital characteristics (eg, urban or rural location, teaching status, and hospital bed size). The data can be weighted according to the NIS sampling frame to generate national estimates.[18] Analyses discussed and results represent weighted national estimates. The institutional review board at West Virginia University granted this study exempt status; all data are publicly available and do not include patient identifiers. This study was conducted in adherence to the Declaration of Helsinki and US federal and state laws.

Patients with a diagnosis of CRAO, associated vascular risk factors, comorbidities, and procedures performed during hospitalization were identified using relevant International Classification of Diseases, Ninth Revision-Clinical Modification (ICD-9) codes. Charges reported in this study represent the amount that hospitals billed for services during admission. These charges do not reflect how much hospital services actually cost, the specific amounts that hospitals received in payment, or the costs incurred to the patients. Median charge per hospitalization and total charges per year were calculated and inflation-adjusted using the Consumer Price Index for Hospital Services from the US Bureau of Labor Statistics.[19]

• **STATISTICAL ANALYSIS:** Descriptive statistics were presented as frequencies with percentages for categorical variables, and mean with standard error of mean (SEM) for continuous variables. Comparisons between groups

TABLE 1. Sociodemographic and Baseline Characteristics of Study Patients

Demographic Characteristics	Results (N = 17 117 Patients)
Age, mean ± SEM, years	68.24 ± 0.12
Age, years	
<50	1950 (11.4)
50-59	2310 (13.5)
60-69	3834 (22.4)
70-79	4582 (26.8)
≥80	4441 (25.9)
Sex	
Female	9065 (53)
Male	8043 (47)
Race	
White	10 825 (63.2)
Black	2068 (12.1)
Hispanic	969 (5.7)
Others	721 (4.2)
Unknown	2535 (14.8)
Primary expected payer	
Medicare and Medicaid	11 987 (70.0)
Private insurance	3947 (23.1)
Self-pay	753 (4.4)
No charge	68 (0.4)
Others	327 (1.9)
Region	
Northwest	4173 (24.4)
Midwest	4574 (26.7)
South	5462 (31.9)
West	2908 (17.0)
Admission source	
Emergency department	7594 (44.4)
Another hospital or health care facility	1558 (9.1)
Non–health care facility	4187 (24.5)
Court or law enforcement	124 (0.7)
Others	3652 (21.3)
Disposition of patient	
Home or self-care	11 831 (69.1)
Transfer to short-term hospital	608 (3.6)
Skilled nursing or intermediate care facility	2216 (12.9)
Home health care	2293 (13.4)
Against medical advice	123 (0.7)
Bed size of hospital	
Small	1740 (10.2)
Medium	3522 (20.6)
Large	11 807 (69.0)
Location and teaching status of hospital	
Rural	1225 (7.2)
Urban nonteaching	4862 (28.4)
Urban teaching	10 983 (64.2)
Length of hospital stay, days	
Median	3.0
Mean ± SEM	4.98 ± 0.06

SEM = standard error of mean.
Data are n (%) unless otherwise indicated.

TABLE 2. Prevalence of Vascular Risk Factors and Systemic Diseases in Central Retinal Artery Occlusion

Vascular Risk Factors and Systemic Diseases	N (%) (N = 17 117 Patients)
Hypertension	12 337 (72.1)
Malignant hypertension	398 (2.3)
Diabetes mellitus	4447 (26.0)
Dyslipidemia	8712 (50.9)
Ischemic heart disease	6028 (35.2)
Angina pectoris	253 (1.5)
Congestive heart failure	2473 (14.4)
Atrial fibrillation or flutter	2689 (15.7)
Carotid artery stenosis or occlusion	3776 (22.1)
Left-sided valvular heart disease	2088 (12.2)
Mitral valve disease	829 (4.8)
Aortic valve disease	914 (5.3)
Peripheral vascular disease	1250 (7.3)
Smoking	2800 (16.4)
Alcohol dependence or abuse	531 (3.1)
Obesity	1405 (8.2)
Chronic kidney disease	2557 (14.9)
End-stage renal disease	614 (3.6)
Hypercoagulable state	323 (1.9)
Primary hypercoagulable state	289 (1.7)
Secondary hypercoagulable state	34 (0.2)
Sickle cell disease or trait	64 (0.4)
Systemic connective tissue disorders	215 (1.3)
Giant cell arteritis	676 (3.9)
Systemic vasculitis	755 (4.4)
Prior history of stroke or transient ischemic attack	1528 (8.9)

were made using the independent samples *t* test for continuous variables and the χ^2 test for categorical variables. Univariate and multiple logistic regression models were used to examine the association between vascular risk factors and stroke. The estimated odds ratio (OR) and their 95% confidence intervals (CI) from the regression models were presented. All *P* values were nominal and a value of less than .05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

• **DEMOGRAPHICS AND BASELINE CHARACTERISTICS:** The baseline and demographic characteristics are described in Table 1. From 2003 to 2014, there were an estimated 17 117 CRAO admissions. The number of admissions showed an increasing trend over the years, nearly doubling between 2003 and 2014. The mean age was 68.4 ± 0.1 years and most patients were ≥70 years old. Fifty-three percent of patients were female and the majority were white (63.2%), followed by African American (12.1%) and Hispanic (5.7%). There was disparity in the geographic distributions of CRAO admissions, being highest in the South (31.9%). Most patients were publicly insured through Medicare or Medicaid (70%), followed by private insurance (23.1%). The majority of admissions were in urban teaching hospitals (64.2%) and hospitals with a large bed size (69%). The most frequent admission source was the ED (44.4%).

TABLE 3. Incidence of In-Hospital Stroke, Acute Myocardial Infarction, or Death in Central Retinal Artery Occlusion

	N (%) (N = 17 117 Patients)
Stroke	2202 (12.9)
Ischemic stroke	2080 (12.2)
Hemorrhagic stroke	142 (0.8)
TIA	428 (2.5)
Carotid endarterectomy and carotid artery stent	1157 (6.8)
Acute MI	639 (3.7)
Cardiac intervention[a]	430 (2.5)
Systemic fibrinolytic therapy	494 (2.9)
Died during hospitalization	222 (1.3)
Combined risk of stroke, TIA, MI, or death	3248 (19.0)

MI = myocardial infarction; TIA = transient ischemic attack.
[a]Percutaneous coronary intervention; coronary artery bypass grafting.

• **VASCULAR RISK FACTORS AND ASSOCIATED SYSTEMIC DISEASES:** The most common vascular risk factor was hypertension (72.1%), followed by dyslipidemia (50.9%), ischemic heart disease (IHD; 35.2%), diabetes mellitus (DM; 26.0%), carotid artery stenosis (22.1%), smoking (16.4%), atrial fibrillation or flutter (15.7%), congestive heart failure (14.4%), chronic kidney disease (14.9%), left-sided valvular heart disease (12.2%), history of prior cerebrovascular accident or transient ischemic attack (TIA) (8.9%), obesity (8.2%), peripheral vascular disease (7.3%), and end-stage renal disease (3.6%). Malignant hypertension was present in 2.3%; 1.5% of CRAO patients had angina pectoris. Alcohol dependence or abuse was diagnosed in 3.1% of patients. Approximately 2% of patients had a diagnosis of systemic hypercoagulable state and 1.3% had connective tissue diseases. Systemic vasculitides were present in 4.4% of patients, the most common being giant cell arteritis (GCA). Vascular risk factors and associated systemic diseases are summarized in Table 2.

• **INCIDENCE OF IN-HOSPITAL STROKE, MYOCARDIAL INFARCTION, AND MORTALITY:** The risk of in-hospital stroke was 12.9%; the vast majority were ischemic in nature. The risk of developing a TIA was much lower (2.5%). During hospital admission, 3.7% of patients developed acute MI and 2.5% underwent a cardiac intervention. Carotid endarterectomy (CEA) and stenting were the most

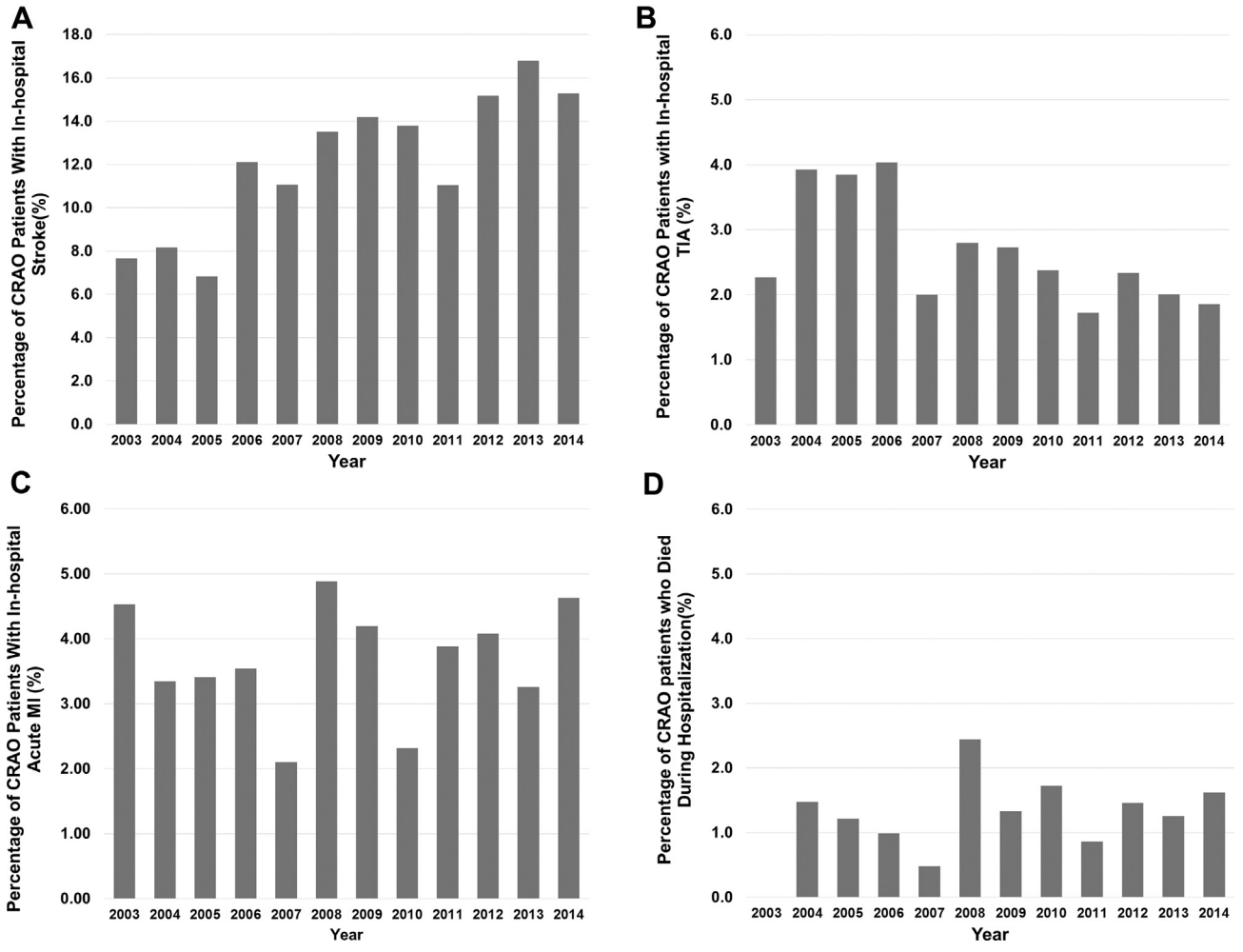

FIGURE 1. Temporal trends of in-hospital acute ischemic events in central retinal artery occlusion in the United States population: A) Acute stroke; B) Transient ischemic attack; C) Acute myocardial infarction; D) Died during hospitalization.

common procedures performed (6.8%). Systemic fibrinolytic therapy was administered in 2.9% of patients. In-hospital mortality was 1.3%. The aggregate risk of in-hospital stroke, TIA, MI, or mortality was 19% (Table 3). Temporal trends of CRAO-associated acute ischemic events are presented in Figure 1 (A-D). The incidence of stroke shows an increasing trend through the years, almost doubling in 2014 in comparison to 2003 (15.3% vs 7.7%).

• **PREDICTORS OF STROKE IN CENTRAL RETINAL ARTERY OCCLUSION:** Variable selection for the multiple logistic regression model was based on results of the univariate analysis (Table 4) and clinical judgment of the study investigators. Multiple logistic regression analysis detected female sex (OR = 1.19, 95% CI = 1.08-1.30, $P = .0003$), hypertension (OR = 1.22, 95% CI = 1.10-1.36, $P = .0003$), carotid artery stenosis (OR = 1.91, 95% CI = 1.73-2.11, $P < .0001$), aortic valve disease (OR = 1.65, 95% CI = 1.38-1.97, $P < .0001$), smoking (OR = 1.30, 95% CI = 1.16-1.47, $P < .0001$), and alcohol dependence or abuse (OR = 1.39, 95% CI = 1.09-1.75, $P = .006$) as positive predictors of stroke (Table 4).

• **RESOURCE UTILIZATION:** The median length of hospital stay was 3.0 days (mean ± SEM, 4.98 ± 0.06 days). In 2014, median inflation-adjusted charge per CRAO hospitalization was $34 668. Cumulative inflation-adjusted charges of all such hospitalizations totaled approximately $115 million. Median charge per admission and the cumulative charge per year are summarized in Figure 2.

DISCUSSION

CENTRAL RETINAL ARTERY OCCLUSION CONFERS A HIGH risk of acute vascular ischemic events, including stroke and myocardial infarction. At present, considerable variability exists among the reported rates of these ischemic

TABLE 4. Predictors of Stroke in Patients With Central Retinal Artery Occlusion Using Univariate and Multiple Logistic Regression Analysis

	Odds Ratio	95% CI (Lower-Upper)	*P* Value
Univariate Regression Analysis			
Age ≥75 years	0.91	0.83-0.99	.05
Female	1.08	0.99-1.18	.09
Prior history of stroke or TIA	0.34	0.22-0.53	<.0001
Hypertension	1.28	1.15-1.42	<.0001
Diabetes mellitus	0.89	0.80-0.99	.03
Dyslipidemia	1.11	1.02-1.22	.02
Ischemic heart disease	1.02	0.93-1.12	.65
Congestive heart failure	1.01	0.89-1.14	.92
Atrial fibrillation or flutter	1.03	0.92-1.17	.59
Carotid artery stenosis or occlusion	1.96	1.78-2.16	<.0001
Left-sided valvular heart disease	1.19	1.04-1.35	.01
Mitral valve disease	1.00	0.81-1.23	.99
Aortic valve disease	1.51	1.26-1.79	<.0001
Peripheral vascular disease	1.18	0.89-1.56	.24
Smoking	1.42	1.27-1.58	<.0001
Alcohol dependence or abuse	1.50	1.20-1.88	.0004
Obesity	1.10	0.94-1.29	.22
Chronic kidney disease	0.92	0.81-1.05	.19
End-stage renal disease	1.16	0.92-1.46	.21
Hypercoagulable state	1.26	0.93-1.71	.14
Multiple Logistic Regression Analysis			
Age ≥75 years	0.90	0.82-0.99	.04
Female	1.19	1.08-1.30	.0003
Hypertension	1.22	1.10-1.36	.0003
Dyslipidemia	0.99	0.91-1.09	.94
Carotid artery stenosis or occlusion	1.91	1.73-2.11	<.0001
Aortic valve disease	1.65	1.38-1.97	<.0001
Smoking	1.30	1.16-1.47	<.0001
Alcohol dependence or abuse	1.39	1.09-1.75	.006

CI = confidence interval; TIA = transient ischemic attack.

events. This is likely owing to differences in study methodology, with most studies either conducted at single centers or in populations that are demographically different. Therefore, they fail to provide representative data of the US population at large. This study investigates vascular risk factors and the burden of acute vascular ischemic events in the period immediately following a CRAO, while simultaneously identifying predictors of stroke in this patient population.

Consistent with prior studies, hypertension was the most common vascular risk factor associated with CRAO.[9,10] Diabetes-associated macrovascular changes, including carotid artery atherosclerosis, are important sources of emboli, whereas microvascular changes such as retinal arteriolar narrowing increase the risk of vascular occlusion.[20] In this study, 26% of CRAO patients had DM, consistent with prior reports.[2,9,21–23] The percentage of patients with dyslipidemia and IHD in our study population was, respectively, 50.9% and 35.2%, similar to studies conducted in the United States, but substantially higher than reported in a Korean population.[21]

The carotid artery and heart are the most common sources of emboli in CRAO.[2] Atherosclerotic plaques of the carotid artery can release emboli in the bloodstream that can become lodged in the central retinal artery, resulting in retinal ischemia and subsequent vision loss.[20] Ischemia is further exacerbated by poor perfusion caused by stenosis.[1] Carotid artery stenosis was present in 22.1% of patients, with most prior studies reporting rates between 25% and 40%.[2,10,20,24] Cardiac sources of emboli are commonly attributable to underlying atrial fibrillation or valvular heart disease. Atrial fibrillation increases the risk of developing retinal artery occlusion (RAO)[25]; however, the reported prevalence is variable.[10,26] This variability results from differences in detection rates, with longer monitoring strategies associated with higher detection rates.[26,27] Since all patients in this study were hospitalized and likely underwent thorough cardiac

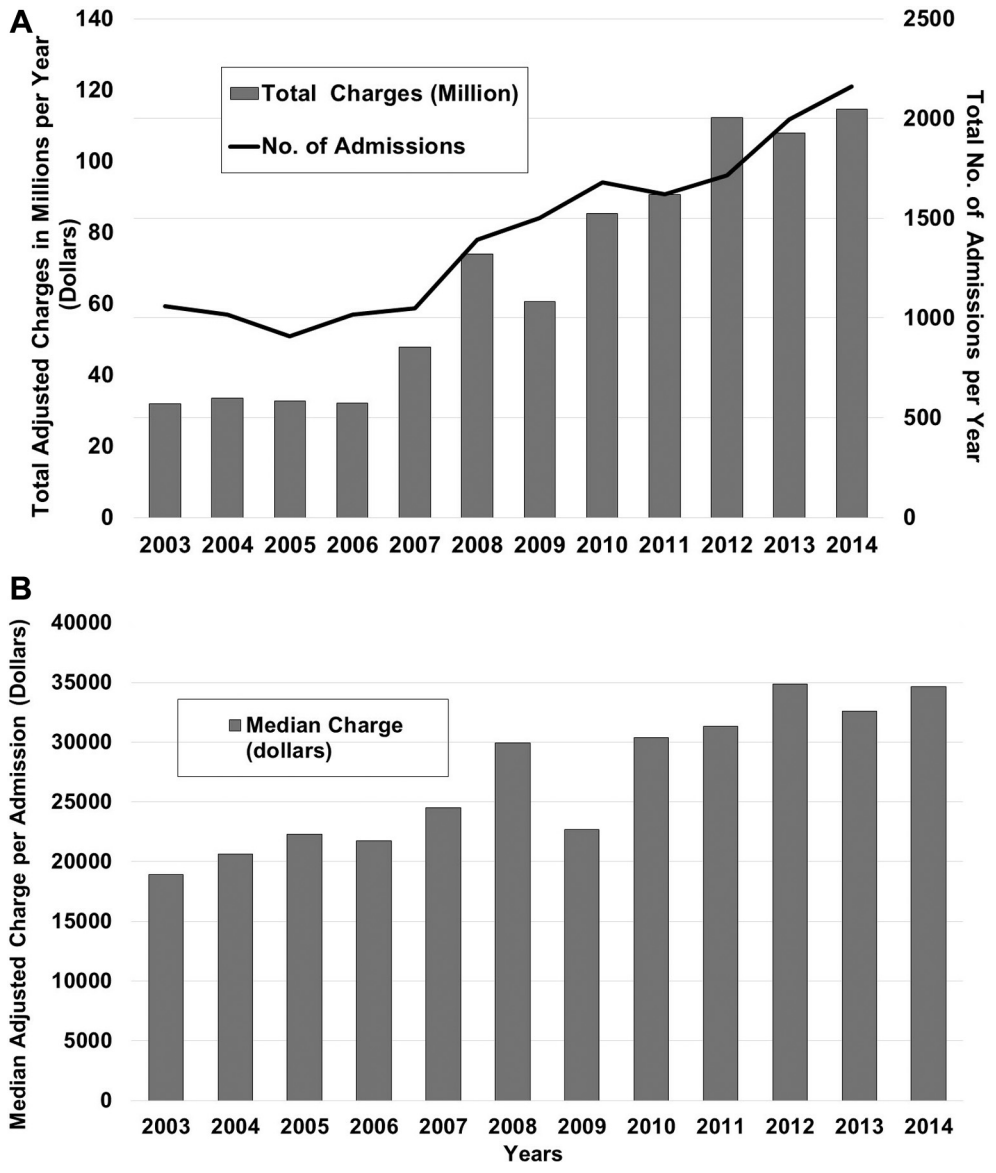

FIGURE 2. Economic burden associated with central retinal artery occlusion hospitalizations in the United States: A) Total number of admissions and inflation-adjusted charges per year; B) Mean inflation-adjusted charge per hospital admission.

evaluation, we expect a good atrial fibrillation detection rate in our study. We identified left-sided valvular heart disease in 12.2% of patients (aortic valve disease was most common), similar to previous reports.[2,10,28,29] There was a much higher prevalence of carotid artery disease than atrial fibrillation or cardiac valvular disease. This is in contrast to cerebrovascular ischemic diseases, where atrial fibrillation is more common.[10,30,31] This distinction is noteworthy from a clinical standpoint, because despite sharing a common pathophysiology, CRAO and ischemic stroke have a discordant risk factor profile.

This study found both smoking and alcohol dependence or abuse to be independent predictors of stroke. These findings emphasize the importance of lifestyle modification strategies as means of secondary stroke prevention in CRAO patients. GCA has been reported in 3.8% of CRAO patients, similar to what we observed.[32] In patients ≥65 years, GCA was present in 5.3% of patients and should be ruled out in all elderly CRAO patients.

The association between CRAO and stroke is well established.[3,10,21,33–35] Reported incidence of stroke was 27.8% in the Taiwanese population within 3 years[34] and 15% in a Korean population.[35] Risk is usually highest in the period immediately following a CRAO,[10,12,34,36,37] especially in the first 2 weeks.[36] This narrow window for stroke prevention necessitates urgent identification of risk factors so that preventive measures may be instituted in a timely manner. While there is general agreement on the increased risk of

stroke in CRAO, uncertainty remains regarding the magnitude of this risk. Some groups report this risk as 6%-7%,[10,20] while others report it as 37.3%.[24] In this study, the risk of in-hospital stroke and TIA were 12.9% and 2.5%. The discrepancy in stroke incidence may arise from variable study designs and criteria for stroke diagnosis. Some studies subjected all CRAO patients to diagnostic brain imaging, likely increasing the odds of detecting silent brain infarcts; others established diagnosis on the basis of symptoms consistent with radiographic findings.[20] In a study conducted by Helenius and associates, 24% of patients with ischemic monocular vision loss had acute brain infarcts on diffusion-weighted magnetic resonance imaging (DW-MRI); 71% of these infarcts were asymptomatic.[38] These findings were concordant with the study by Lee and associates.[39] Although silent infracts detected as incidental findings may sometimes be considered clinically insignificant, they more than double the risk of subsequent stroke.[40] All CRAO patients with silent brain lesions should undergo etiologic evaluation and management as recommended by the AHA/ASA.[41] Another interesting observation of our study is the notable increase in incidence of stroke in CRAO patients over the years. This increase can partly be explained by an aging US population, and the increasing use of DW-MRI in the recent years, which is more sensitive than computed tomography imaging, resulting in higher detection rates.

Prior history of stroke or TIA was not an independent predictor of in-hospital stroke. We postulate that patients with prior cerebral ischemic event may have likely undergone interventions to reduce the risk of future stroke, such as treatment with antiplatelet/anticoagulation therapy, lipid-lowering drugs, lifestyle changes, or CEA. The available NIS data do not permit determination of whether or not such measures were undertaken.

Prior studies demonstrate significant cardiovascular morbidity and mortality in CRAO patients. Incidence of MI in CRAO has been reported to be 21%.[20] A recent study reported the mortality risk to be 8% and the combined risk of stroke, MI, or death at 2-year follow-up to be 32%.[24] In this study, combined risk of stroke, TIA, MI, and death was 19%. The lower incidence is likely because this study only captures the risk of these events immediately following a CRAO, while others have reported these risks over a longer period of follow-up.

The strengths of this study include its large sample size and nationwide estimates, representative of the entire US population. As this study was conducted in an inpatient setting, we expect the diagnostic approach for identification of risk factors and stroke to be more thorough in comparison to outpatient settings. Limitations of the study include the lack of a control group and potential for misdiagnosis based on ICD-9 codes; however, the large sample size may mitigate or render negligible the risk of such misclassifications. This study did not capture long-term outcomes following discharge, which, although relevant, were beyond the scope of this investigation. Since this study was conducted in a hospital setting, the patient population might differ from that in an outpatient setting. Lastly, it is possible that the hospital course for a subset of patients may have been complicated by other comorbidities, resulting in inflated charges.

In summary, we report a significant burden of acute vascular ischemic events and mortality in the largest study of CRAO patients conducted to date. This study validates CRAO as an important clinical marker for future vascular ischemic events, including stroke and acute MI. The risk of CRAO-associated stroke is highest in women and in those with a history of hypertension, carotid artery stenosis, aortic valve disease, smoking, or alcohol abuse. As the incidence of CRAO associated stroke continues to rise in the United States, in the future the development of a risk prediction model can serve as a valuable and cost-effective adjunct for effective patient triaging and referral to the ED or nearest stoke center. This would ensure that high-risk CRAO patients undergo immediate evaluation within 24 hours, without incurring unnecessary costs on the healthcare system.

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