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Research Article

Risk Factors and Etiologies of Stroke in Young Adults: 6 Years Retrospective Study

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Abstract

Background: Although a large number of studies have been published on the incidence of stroke in young adults, very few have looked at etiologies in the youth of the Middle East, and none have focused on Oman.

Method: Retrospective study carried out at the Royal Hospital in Muscat. Electronic Charts were reviewed identifying all patients under 50 years of age admitted for acute stroke from 2009 to 2014. We analyzed the detailed history, past medical history, risk factors, neurologic and systemic examination, and brain imaging (CT or MRI) for each case. We identified 588 young patients163 were excluded due to other diagnosis or absence of neuroimaging (CT or MRI).

Results: Out of the 425 stroke cases. Overall, 60% of the cases were 41-50 years of age. Ischemic Stroke (IS) occurred in 69.6% compared to 30.4% for Intracranial hemorrhage (ICH). Hypertension(H) was the number one risk factor for both IS and ICH, with a prevalance 50.7% and 60.5% respectively. DM was the second leading risk factor, with a prevalence of 32.1% in IS and 27.1% in ICH. Underlying etiologies were identified in only 35.5% of cases in IS and 29.5% in ICH. Cardiac etiology and vasculopathy were most common for IS. Aneurysm was the main underlying etiology for HS.

Conclusion: In young adult Omanis, IS was more frequent than ICH. Men were more affected than women. H and DM were the leading risk factors for both stroke subtypes. Cardioembolism and vasculopathy were the main etiologies for IS. Cerebral anuerysm for HS.

Keywords: *Stroke; IS: Ischemic Stroke; ICH: Intracranial Hemorrhage; HS: Hemorrhagic Stroke: Hypertension; Cardioembolic; Vasculopathy; Dyslipidemia*

Introduction

Stroke is the second leading cause of mortality worldwide. Strokes in young adults are relatively uncommon as the disorder usually occurs in the middle-aged and elderly [1]. While a specific definition of "young stroke" is lacking, the vast majority of authors consider "young stroke" to pertain to individuals under 45 years of age [2]. Other studies extended it to 50 [3]. There are many published series concerning stroke in young patients. Comparison between studies is difficult for a number of reasons, including the methodology used, age groups, diagnostic criteria, time scale [4]. While the majority of population-based studies report rates for all stroke combined (IS , ICH, and subarachnoid hemorrhage), a few report rates for ischemic stroke alone [2]. According to available data, fewer than 5% of all strokes occur in subjects under 45 years of age, in Western countries [5]. Higher proportions, between 19 and 30%, were reported in developing countries [4,6]. The nature and etiology of stroke in young adults is different from that in older patients. Although a large number of studies have been published on the incidence of stroke in young adults, very few have looked at etiologies in the youth of the Middle East, and none have focused on Oman. In addition to the standardized stroke management used in elderly, additional investigations as well as supportive and specific therapies should be considered based on the underlying etiology. Cardio embolism, non-atherosclerotic arteriopathy -dissection of the extra cranial arteries, vasculitis, migraine , drugs, premature atherosclerosis, and hypercoagulable states are the most relevant.

Objectives and Methods

Methods

This is a 6 years retrospective single center hospital-based study performed at Royal hospital in Muscat, Oman in the first and largest stroke unit of the country from January 2009 to December 2014. Royal hospital is the reference territory hospital in Oman, with a catchment area of one million inhabitants. From January 2009 to 2012, stroke patients were admitted to General Medical Ward (GMW) whereas from 2013-2014 they were admitted to the Acute Stroke unit (ASU). The aim of this study is to identify risk factors and etiologies for stroke in the young Omani. Patient's data was retrieved from our electronic medical records system. Data was collected in data sheets, and a confidential code was assigned to each patient. No personal data was divulged in the data collection sheets except age and sex. All the data was treated with confidentiality. Stroke was defined as an acute neurologic insult due to a vascular etiology and could be either ischemic or hemorrhagic. All cases were confirmed by detailed history, examination, and brain imaging (CT or MRI). We applied consistent and rigorous definitions for risk factor identification in our chart review. Both ischemic and intracranial hemorrhage stroke subtypes were included. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Territory of stroke was classified according to imaging findings. Rare etiologies with uncertain causality, such as clotting abnormalities, were considered as a cause if diagnostic testing were exhaustive and other possible causes absent. PFO with or without atrial septal aneurysm (ASA) was considered similarly causative in the absence of other. Vasculitis screen including antinuclear Antibodies (ANA), antiphospholipid, rheumatoid screen, thrombophilia screen and in certain cases homocysteine and sickling were done in the entire patient admitted from the period 2012 - 2014 however most were missing in patients admitted at GMW.

Patient description

Patient aged 18 - 50 years with acute stroke diagnosis were included. Original sample size was 588 patients (Figure 1). There were 163 patients excluded due to other diagnosis or absence of neuroimaging (CT or MRI)). The final number of patients was 425. These patients were either admitted to GMW 2009 - 2012 or ASU 2013 - 2014. All patients had routine blood tests, chest x-ray, ECG, and brain imaging on admission. All patients had confirmed acute Stroke by neuroimaging (Head CT or MRI brain). All patients had transthoracic echocardiogram and carotid Doppler. Trans-esoph- ageal echocardiogram, cerebral CT angiogram, and other additional investigations were carried out to help further identifying unrevealed etiologies.

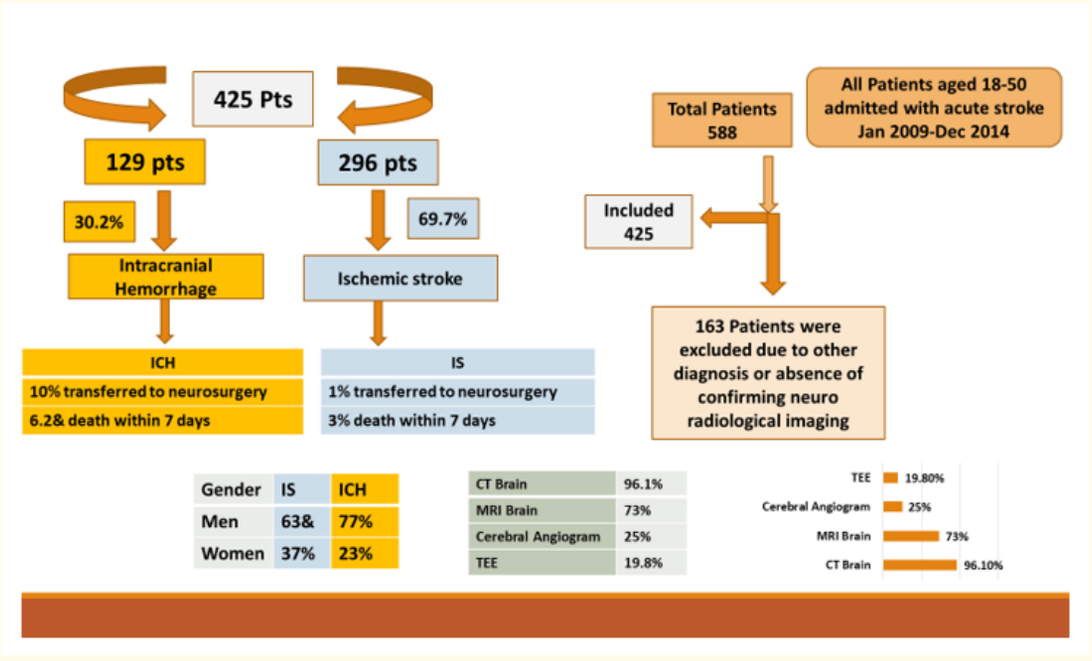

Figure 1: *Summer of the some of the study details.*

Data

The electronic medical records of all stroke patients 18 to 50 years of age, admitted between January 2009 and December 2014, were reviewed. Cases were identified through the hospital database according to the following criteria: patient admitted either through hospital ER or transferred from secondary or primary hospitals or polyclinics. Age 18 to 50 at stroke onset. Discharge diagnosis of acute stroke. Both ischemic and intracranial hemorrhagic stroke subtypes were included. Transient ischemic attack (TIA), stroke attributable to direct head trauma or strangulation, ischemic lesion attributable to immediate complications originating from subarachnoid hemorrhage, and any iatrogenic stroke as a consequence of major surgery were all excluded.

Statistical analysis

Data were described using mean and SD for continuous variables and frequency and percentage for categorical variables. Association between two categorical variables were tested using Chi-square test and Fisher's exact test. A value of $P < 0.05$ (2-sided) was considered statistically significant. Prevalence was calculated based on the total hospital admissions in the study period. All the analysis was carried out using the statistical program IBM SPSS 22 for Microsoft Windows (SPSS Inc).

Results

425 patients met the inclusion criteria, 271 (67.3%) men and 154 (32.7) women. Of these, 63.2% were 41 - 50 years of age, 25.7% were 31 - 40 years of age and only 11.1% 18 - 30 years of age. CT head and MRI brain were done in 96.10% and 73% of patients, respectively. Cardiac evaluation was done in 76% of patients, mainly by trans-thoracic echocardiography, with additional trans-esophageal echocardiography (TTE) in 19.80%. Unsurprisingly, IS was more prevalent (69.6%) than ICH (30.4%). Mean age was 40.9 years for ICH and 41.4 years for IS (Table 1).

Table 1: *Patient characteristics.*

Variable	ICH (n = 129)	IS (n = 296)
	N (%)	N (%)
Age, Mean ± SD	40.86 ± 7.09	41.43 ± 7.23
Age group		
18 - 30 years	8 (6.2)	33 (11.1)
31 - 40 years	52 (40.3)	76 (25.7)
41 - 50 years	69 (53.5)	187 (63.2)
Gender		
Men	99 (76.7)	187 (63.2)
Women	30 (23.3)	109 (36.8)
Hypertension	78 (60.5)	150 (50.7)
Diabetes Mellitus	35 (27.1)	95 (32.1)
Smoking	15 (11.6)	57 (19.3)
Alcohol	9 (7.0)	27 (9.1)
Dyslipidemia	13 (10.1)	78 (26.4)
Thyroid	0 (0)	12 (4.0)
Obesity	0 (0)	6 (2.0)
Previous stroke	11 (8.5)	41 (13.9)
Chronic Kidney Disease	9 (7.0)	26 (8.8)
Epilepsy	4 (3.1)	0 (0)
Iron Deficiency Anemia	0 (0)	5 (1.7)
Myocardial Infarction	0 (0)	27 (9.1)
Anticoagulant	4 (3.1)	32 (10.8)

Risk factors

Table 2 and 3 summarises the risk factors of IS and ICH strokes across different age groups, with the corresponding P values.

Table 2: *Risk factors of ischemic stroke by age, Statistically significant, test: chi-square test.*

	Age 18 - 30	Age 31 - 40	Age 41 - 50	
	(n = 33)	(n = 76)	(n = 187)	p value
Hypertension	2 (6.1)	35 (46.1)	113 (60.4)	0.0001*
Diabetes Mellitus	0 (0.0)	18 (23.7)	77 (41.2)	0.0001*
Smoking	5 (15.2)	13 (17.1)	39 (20.9)	0.640
Pregnancy	3 (9.1)	1 (1.3)	0 (0.0)	0.003*
Dyslipidemia	1 (3.0)	17 (22.4)	60 (32.1)	0.001*
Thyroid	0 (0.0)	3 (3.9)	9 (4.8)	0.535
Abortion	1 (3.0)	2 (2.6)	1 (0.5)	0.292
Alcohol	3 (9.1)	6 (7.9)	18 (9.6)	0.905
Morbidly Obesity	0 (0.0)	1 (1.3)	5 (2.7)	0.381
MI	0 (0.0)	6 (7.9)	21 (11.2)	0.025*
Previous stroke	2 (6.1)	5 (6.6)	34 (18.2)	0.012*
CKD	0 (0.0)	9 (11.8)	17 (9.1)	0.032*
IDA	2 (6.1)	3 (3.9)	0 (0.0)	0.006*
Anticoagulant	5 (15.2)	10 (13.2)	17 (9.1)	0.451
T1DM	0 (0.0)	4 (5.3)	0 (0.0)	0.004*
Vit.B12 Def.	1 (3.0)	1 (1.3)	2 (1.1)	0.727
Death within 7 days	1 (3.0)	1 (1.3)	7 (3.7)	0.532
HF	0 (0.0)	4 (5.3)	16 (8.6)	0.055
HIV	1 (3.0)	1 (1.3)	1 (0.5)	0.484
B. Thalassemia	1 (3.0)	0 (0.0)	0 (0.0)	0.110

Table 3: *Risk factors of ICH intracranial hemorrhagic stroke by age.*

	Age 18 - 30	Age 31 - 40	Age 41 - 50	
	(N = 8)	(N = 52)	(N = 69)	P Value
Hypertension	0 (0.0)	26 (50.0)	52 (75.4)	0.0001*
Diabetes Mellitus	0 (0.0)	6 (11.5)	29 (42.0)	0.0001*
Smoking	0 (0.0)	12 (23.1)	3 (4.3)	0.003*
Pregnancy	1 (12.5)	1 (1.9)	0 (0.0)	0.094
Dyslipidemia	0 (0.0)	9 (17.3)	4 (5.8)	0.054
Alcohol	0 (0.0)	3 (5.8)	6 (8.7)	0.455
Previous stroke	1 (12.5)	2 (3.8)	8 (11.6)	0.259
CKD	0 (0.0)	3 (5.8)	6 (8.7)	0.455
Epilepsy	3 (37.5)	1 (1.9)	0 (0.0)	0.001*
Anticoagulant	0 (0.0)	1 (1.9)	3 (4.3)	0.577

**Statistically significant, test: chi-square test.*

Hypertension was the leading risk factor for both IS and ICH across all age groups ($p < 0.000$). DM was the second most common risk factor for both stroke subtypes (27.1% for HS) and was also statistically significant ($p < 0.000$) across all age groups.

In the IS group, there were twice as many men as women (63% vs 37%). Only 0.3% of patients received thrombolysis therapy , 1% transferred to neurosurgery and 3% expired within 7 days of admission. Hypertension was number one risk factor, with a prevalence of 53.7%. Dia- betes was the second leading risk factor with a prevalence of 30.6%. The third risk factor was dyslipidemia (prevalence 21.4%) (Table 1). Dyslipidemia and history of previous stroke were the third and fourth risk factor for IS with statistically significant association with age ($p < 0.001$ and $p = 0.012$ respectively). Iron deficiency anemia, myocardial infarction and chronic kidney disease (CKD) were all had a statistically significant association with age (P values of 0.006, 0.025 and 0.032 respectively) (Table 2). Another important risk factor for IS was sub-therapeutic dosing of anticoagulation therapy, which contributed to 10.8% of the total risk factors.

In HS, there is even more male preponderance (23% female, 77% male), with 60% of patients being of Omani origin. In this group, 10% underwent surgical decompression and evacuation and 6.2% died within 7 days of admission. As in IS, hypertension and diabetes were the most common risk factors (prevalence of 60.5% and 27.1% respectively), but smoking was the third leading risk factor (prevalence 11.6%) rather than dyslipidemia (10.1%). Hypertension and diabetes had a statistically significant association with age ($p < 0.05$) (Table 3).

Etiologies

Underlying etiologies were only identified in 35.5% ($n = 105$) of cases in IS Table 3. Cardiac etiology and vasculopathy were the most common. Cardiac pathology accounted for 13.5% of the total etiology, with cardiac clot and atrial fibrillation representing 5.4% and 4.7% respectively. This was followed by mitral stenosis and prosthetic valve at 2.7% and 2% respectively. Vasculitis accounted for 8.8% of the total etiology. In this group, ANA (antinuclear antibody) was positive in 3.7% of total patients, followed by APLS (antiphospholipid antibody) with 3.4% positivity and SLE (systemic lupus erythematosis) positivity in 2.7%. A statistically significant association was there between vasculitis and age in the Ischemic group ($p = 0.0001$). Table 4 summarises the etiology of IS by gender and age.

Table 4: *Etiology of IS by gender and age.*

	Men (n = 187)	Women (n = 109)	p value	Age 18 - 30 (n = 33)	Age 31 - 40 (n = 76)	Age 41 - 50 (n = 187)	p value
	N (%)	N (%)		N (%)	N (%)	N (%)	
Unknown	128 (67.0)	63 (33.0)	0.078	14 (7.3)	43 (22.5)	134 (70.2)	0.001*
Cardiac	23 (57.5)	17 (42.5)	0.482	5 (12.5)	13 (32.5)	22 (55.0)	0.496
Vasculitis	12 (46.2)	14 (53.8)	0.087	7 (26.9)	12 (46.2)	7 (26.9)	0.0001*
Malignancy	5 (41.7)	7 (58.3)	0.133	3 (25.0)	2 (16.7)	7 (58.3)	0.273
Epilepsy	4 (36.4)	7 (63.6)	0.106	1 (9.1)	4 (36.4)	6 (54.5)	0.710
Infectious	6 (66.7)	3 (33.3)	1.000	2 (22.2)	3 (33.3)	4 (44.4)	0.417
CVT	1 (25.0)	3 (75.0)	0.143	1 (25.0)	2 (50.0)	1 (25.0)	0.277
Hematological	2 (66.7)	1 (33.3)	1.000	1 (33.3)	1 (33.3)	1 (33.3)	0.400
PE	2 (100.0)	0 (0)	0.533	1 (50.0)	0 (0)	1 (50.0)	0.192
MH	2 (100.0)	0 (0)	0.533	0 (0)	0 (0)	2 (100.0)	0.556
IV Drug	2 (100.0)	0 (0)	0.533	0 (0)	1 (50.0)	1 (50.0)	0.689
AVM	0 (0)	1 (100.0)	0.368	0 (0)	0 (0)	1 (100.0)	0.746
Hemochromatosis	1 (100.0)	0 (0)	1.000	0 (0)	1 (100.0)	0 (0)	0.234
Eclampsia	0 (0)	1 (100.0)	0.368	0 (0)	0 (0)	1 (100.0)	0.746

*Test: Chi-square test/Fisher's exact test. *: Statistically significant ($p \leq 0.05$).*

In ICH, underlying etiologies were only identified in 29.5% (n = 38) of cases Table 5. Hypertension was present in 60.5% of patients and could well be the etiology of the bleed. Specific etiology, independent of hypertension, was identified in 29.5% and included cerebral aneurysm (9.3%), cerebral venous thrombosis (6.2%), malignancy (5.4%), arteriovenous malformation (3.1%),vasculitis (3.1%), cardiac (2.3%), infectious (2.3%), protein S deficiency (0.8%), IV drug abuse (0.8%) and cavernous angioma (0.8%). Table 6 summerises the etiology of HS by gender and age.

Table 5: *Etiology of ICH by gender and age.*

	Men (n = 99)	**Women (n = 30)**	**p value**	**Age 18 - 30 (n = 8)**	**Age 31 - 40 (n = 52)**	**Age 41 - 50 (n = 69)**	**p value**
	N (%)	**N (%)**		**N (%)**	**N (%)**	**N (%)**	
Unknown	76 (83.5)	15 (16.5)	0.011*	3 (3.3)	33 (36.3)	55 (60.4)	0.016*
Aneurysm	6 (50.0)	6 (50.0)	0.032*	1 (8.3)	7 (58.3)	4 (33.3)	0.338
CVT	4 (50.0)	4 (50.0)	0.084	1 (12.5)	3 (37.5)	4 (50.0)	0.748
Malignancy	5 (71.4)	2 (28.6)	0.664	1 (14.3)	5 (71.4)	1 (14.3)	0.096
AV mal for	3 (75.0)	1 (25.0)	1.000	1 (25.0)	2 (50.0)	1 (25.0)	0.215
Vasculitis	2 (50.0)	2 (50.0)	0.231	0 (0)	1 (25.0)	3 (75.0)	0.653
Cardiac	2 (66.7)	1 (33.3)	0.551	1 (33.3)	1 (33.3)	1 (33.3)	0.141
Infectious	2 (66.7)	1 (33.3)	0.551	0 (0)	1 (33.3)	2 (66.7)	0.849
Hematology (Protein S def.)	0 (0)	1 (100.0)	0.233	0 (0)	1 (100.0)	0 (0)	0.474
IV drug	1 (100.0)	0 (0)	1.000	0 (0)	0 (0)	1 (100.0)	0.645
cavernous angioma	1 (100.0)	0 (0)	1.000	0 (0)	1 (100.0)	0 (0)	0.474

*Test: Chi-square test/Fisher's exact test. *: Statistically significant (p ≤ 0.05).*

Discussion

The recent socio-economic changes in Arab countries, including increased life expectancy and greater adoption of a westernized lifestyle, especially in the Gulf States, raise the likelihood of an increased stroke rate. To the best of our knowledge, this is the first study in Oman evaluating the risk factors and etiologies of stroke in young Omani. The exact incidence of stroke in the young in Oman is not yet known, due to lack of population-based studies and stroke registries. Globally many studies have looked at stroke risk factors in the young, but most have focused on a single stroke subtype [7-11] and none has looked at the Omani population in particular. The strength of our study is that both stroke sub types were included, and a different population is assessed. Stroke mechanisms normally more prevalent in the young are still frequently seen in the Omani population aged 45 to 49, and this is why we chose a cut-off of 50 rather than 40 years of age. Our findings suggest that the risk factor profile and etiology start to merge with those seen in patients in early midlife.

Looking at our results, our results are consistent with other similar assessments performed in Arabic and other regions. The proportion of IS compared to ICH in young Omani (69.7% IS) is similar to that found in other Asian and middle eastern countries, and lower than what is seen in the west (85% IS) [6,12-15] Of note is the incredibly significant number of strokes occurring in males, in both stroke subtypes and all age categories. This may be explained by a differing prevalence of traditional risk factors between the sexes in Oman,

especially smoking. This male preponderance was also seen in studies performed in India (76.3%) [16] but not in Qatar where men make up only 50% of IS stroke patients [13]. Indeed, the main risk factors identified, hypertension and diabetes, are consistent with findings in Arabic [6,12-15] and other developed countries [7-11].

Trying to identify the underlying etiology was extremely challenging, especially in IS, despite extensive investigation. Overall, the underlying etiology was only determined in 35% of IS, and is within the range reported in the literature which varies from 21 to 55%. The differences in the percentage of stroke of undetermined etiology likely depend on the extent and appropriateness of the diagnostic workup. The value of a very extensive diagnostic workup for strokes in the young is being questioned. French researchers reported at the American Academy of Neurology's 58th Annual Meeting in San Diego that an expensive workup is neither useful nor cost effective, and they had recommended that clinicians restrict their measurements to antiphospholipid antibodies, homocysteine level, and thrombophilia factors for young patients with stroke of unknown origin [17]. However, before calling a stroke idiopathic, prolonged holter monitoring is recommended for the young and old, as discovery of paradoxical atrial fibrillation may take up to 30 days of monitoring and sometimes even up to 2 years [18-21]. Given that AF is much more prevalent after age 60, it is hard to know how long to monitor in a young patient. The congenital cardiac anomalies are must to exclude, since it constitutes a significant cause for stroke in the young [22]. Patent foramen ovale (PFO) combined with atrial septal aneurysm is an example of an important etiology in young stroke. In our study it was quite challenging to obtain stroke patients data during their admission at GMW. This was due to the lack of dedicated stroke multidisciplinary team during that time. Some patients were discharged prematurely prior to the completion of the stroke work up in the young. This might have affected our results in identifying the underlying etiology. Therefore, a follow up study is needed.

Conclusion

Our findings contribute to the understanding of the spectrum of risk factors, and etiologies in young stroke patients. Traditional stroke risk factors were common in this patient population, but in the young a meticulous search for each patient's potential risk factors is crucial for appropriate secondary prevention. These data suggest that the risk of stroke increases with the accumulation of vascular risk factors over the years. In some young individuals, a combination of several risk factors might be sufficient to explain the stroke even if exact mechanisms remain undetermined. Moreover, these data pave the way for future studies needed on long-term outcome and how to improve it in young stroke patients. Population risk factors (undiagnosed or poorly controlled diabetes and hypertension) require attention to reduce the stroke burden. Well designed studies fulfilling published quality criteria are needed as a preparation to fighting this disabling condition in this part of the developing world.

Author Contributions

A. M. Al-Hashmi: Principle investigator, Research design, data management, report writing, interpretation of results, critical reviewing with intellectual input. S. Jose: Data Analysis (Statistical Analysist Specialist). S. Al-Mawali: R4 Internal Medicine Resident, Data collection. R. Al-Habsi: Neurology Nurse Data Collection.

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Disclosures

The authors report no disclosures.

Conflict of Interest

None.

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