DOI: http://dx.doi.org/10.48305/arya.2023.26660.2820

The Incidence of Cardiovascular Events in Small Versus Large Ischemic Stroke; A Three-Year Cohort Study

Marzieh Tajmirriahi[1], Mohammad Saadatnia[2], Hasan Shemirani[3], Masoumeh Sadeghi[4], Alireza Chamasemani[4], Ali Safaei[5]

Original Article

Abstract

INTRODUCTION: Cerebral ischemia and coronary artery disease (CAD), the major leading causes of mortality and morbidity worldwide, are pathophysiologically interrelated. Cerebral ischemic events are categorized as large or small vessels disease. The current study compares the factors related to CAD events incidence following ischemic large versus small disease CVA.

METHOD: The current cohort study was conducted on 225 patients with ischemic stroke in two groups of large (n=75) and small (n=150) vessel disease during 2018-19. The patients' demographic, medical, and clinical characteristics were recruited. They were followed for three years regarding the incidence of CAD events, including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), and sudden cardiac death (SCD). Data about the coronary angiography, computed tomography angiography (CTA), Single Photon Emission Computed Tomography (SPECT), and the therapeutic approach were gathered.

RESULTS: There were insignificant differences between the patients with small versus large vessels CVA in terms of ACS incidence (P-value=0.105), type of the events (P-value=0.836), angiographic (P-value=0.671), SPECT (P-value=0.99) and CTA findings (P-value>0.99) and approached CAD (P-value=0.728). Cox regression assessments revealed an increased risk of CAD events due to large versus small vessels disease after adjustments for hypertension, diabetes mellitus, dyslipidemia, re-stroke, and the previous history of IHD (HR=2.005, 95%CI: 1.093-2.988, P-value=0.021).

CONCLUSION: According to the findings of this study, large-vessel involvement in an ischemic stroke was associated with more than a two-fold increase in the three-year probability of ischemic heart disease incidencet.

Keywords: Coronary artery disease, Cardiovascular disease, Ischemic stroke, Cohort studies

Date of submission: *2022-May-18,* ***Date of acceptance:*** *2023-May-16*

Introduction

Cerebral ischemia and coronary artery disease (CAD) are the major leading causes of mortality and morbidity worldwide. These two conditions are epidemiologically and pathophysiologically closely related diseases and logically often coexist in the same patient

1- Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
3- Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute; Isfahan University of Medical Sciences; Isfahan; Iran

Address for correspondence: Mohammad Saadatnia. Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: mosaadatnia@yahoo.com

[1]. Besides, they share risk factors and strategies for secondary prevention, such as using antithrombotics and statin therapy [2]. CAD has been demonstrated to be the principal cause of death after a transient ischemic attack (TIA), causing even more deaths than stroke. Generally, 5-10-year follow-up studies revealed that CAD was responsible for up to 60% of deaths in patients experiencing TIA or stroke. Fatal coronary events outnumbered fatal strokes by two folds [3].

As an unpreventable systemic process, atherosclerosis plays a crucial role in the pathogenesis of CAD and ischemic cerebrovascular event (CVA). The aging of the population is another fact related to an increased risk of vascular events [4]. Besides, any acute atherosclerotic event increases the risk for another in the same or different vascular bed [5]. Further investigations have revealed diverse risk factors for the coincidence of atherosclerotic events; however, due to significant promotions in secondary prevention strategies, the risk factors may have altered trends [6].

Cerebral ischemic events are categorized as large versus small vessels disease. Large vessel disease occurs due to a sudden occlusion of main supplying brain arteries by a thrombus or an embolus [7]. In contrast, small vessel disease is a natural ongoing chronic condition caused by aging and diverse related factors [8]. Despite the efforts made to identify the factors associated with CAD events in patients with cerebral ischemic events, a paucity of knowledge is available comparing the factors related to CAD events incidence following ischemic CVA assessed in the current investigation.

Materials and Methods

Study population

The current cohort study was conducted on 225 patients admitted at the index hospital of Alzahra, affiliated with Isfahan University of Medical Sciences, due to ischemic strokes from May 2018 to March 2019. The patients were followed for over three years to assess whether any cardiovascular events occurred.

The study proposal that met the Helsinki declaration criteria was approved by the Ethics Committee of Isfahan University of Medical Sciences encoded IR.MUI.MED.REC.1398.373. The study protocol was explained to the patients or their legal guardians; they were reassured about the confidentiality of personal information and signed written consent.

Patients over 18 years old with a documented diagnosis of ischemic cerebrovascular events with large and small vessels thrombosis mechanism according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [9] were included in the study. Other diagnoses, such as transient ischemic attack, cryptogenic, or hemorrhagic cerebrovascular accidents, were defined as the unmet criteria. Reluctance to participate in the study, inability to follow up, or over 20% defect in the medical records were determined as the exclusion criteria.

The patients who met the study protocols entered the study through census sampling. They were divided into two groups of patients with large vessels (n=75) versus small vessel disease (n=150) by a panel consisting of two expert neurologists and a radiologist who interpreted the neuroimaging.

Accordingly, large vessel disease was defined as the occlusion of the main supplying arteries of the brain, including the intracranial internal carotid artery (ICA), proximal posterior, middle, and anterior cerebral arteries (PCA, MCA, and ACA, respectively), intracranial vertebral artery (VA), and/or basilar artery (BA) [10]. Small vessel disease was used to describe a series of imaging changes in the white matter and subcortical grey matter, including recent small subcortical infarct, lacunes, white matter hyperintensities (WMHs), prominent perivascular spaces (PVS), and atrophy [11].

Data collection

A checklist consisting of patients' demographic characteristics (age, gender, body mass index (BMI)), chronic medical conditions (hypertension, diabetes mellitus, and dyslipidemia), type of the ischemic stroke (small versus large vessels disease), habits (smoking and addiction), chronic medications

(use of antiplatelet agents, including aspirin or clopidogrel) and adherence to medications was designed and filled out at baseline. Moreover, the study population's adherence to anti-diabetic medications was evaluated using the validated Persian questionnaire of adherence to refills and medications scale (ARMS) [12]. The ARMS consists of 12 items divided into two subscales of adherence to refilling prescriptions and adherence to taking medications. These 12 items are assessed through 12 questions with Likert scale responses, including "none," "sometimes," "most of the times," and "all of the times". The values are given from 1 to 4. Thus the final scores range from 12 to 48 [12]. A score of 20 and less was considered adherent; otherwise, the patients were defined as non-adherent to the medications. The higher scores represented poorer adherence to the medication; therefore, the correlations have been measured inversely. The follow-up surveys were performed three years after the ischemic stroke incidence. Therefore, the patients or their first-degree family were telephoned, the study was described for them and they were requested to inform the interviewer regarding the following questions. 1) experiencing any cardiovascular events, 2) re-stroke incidence, and 3) if the response was positive, they were requested to provide their medical records, or they were gathered from the archives of the Isfahan University of Medical Sciences affiliated centers. Besides, they were requested to provide the authors with the accessible medical records of their patients or the records were recruited from the picture archiving and communication system (PACS) of the index hospitals. The records included the type of CVE and the applied imaging or medications.

The cardiovascular events were categorized as ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), and sudden cardiac death (SCD). The coronary angiography of the patients, if applicable, was interpreted as one-, two-, or three-vessel disease. Besides, the records of the patients who have performed computed tomography (CT) angiography or nuclear myocardial perfusion study using Single Photon Emission Computed Tomography (SPECT) were gathered. The CT angiographies were interpreted as moderate coronary artery disease if more than 70% of stenosis was notified. The SPECT tests were reported according to the Third Universal Myocardial Consensus guidelines [13]. All the diagnoses were made based on the existing medical records by a panel consisting of two expert cardiologists and a cardioradiologist. If the patients have undergone coronary angiography, its interpretation as one, two or three vessel disease and the applied approaches for the patients (medical follow up (NFU), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) were gathered.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 24. Continuous data were presented in mean and standard deviation, and the categorical variables were presented in percentages, and absolute numbers. Chi-square test or Fisher's exact test were administered to compare the categorical data. An Independent T-test was applied for the comparison of continuous variables. Cox regression analysis was applied to find the association between cardiac events and contributing risk factors of atherogenesis in post-stroke patients. The cardiac events were defined as STEMI, NSTEMI, UA, and SCD. The cox regressions test was performed in crude and adjusted models.

Further adjustments for the confounding impacts of the chronic medical conditions (hypertension, diabetes mellitus, dyslipidemia, re-stroke, and a previous history of IHD) were used in model 3. Full adjustments for all the mentioned factors have been considered in model 4. Hazard ratios (HRs) were reported with the corresponding 95% confidence intervals (95% CIs). A P-value of less than 0.05 was considered as the level of confidence.

Results

The current study evaluated data of 225

patients with ischemic stroke in two groups, large vessel disease (n=75) and small vessel disease (n=150). The studied population had a mean age of 71.81±8.32 years old and predominantly consisted of males (n=143, 63.5%).

The studied groups were similar in terms of age (P-value=0.071) and gender distribution (P-value=0.203), but not BMI (P-value=0.013) (Table 1).

Table 1. Demographic characteristics of the studied population

	Large vessels disease (n=75)	Small vessels disease (n=150)	P-value
Age (years), mean±standard deviation	73.15±7.20	71.14±8.88	0.071*
Gender (male), n (%)	52 (69.3)	91 (60.67)	0.203**
Body mass index (kg/m^2), mean±standard deviation	24.33±2.91	25.48±3.43	0.013*

*Independent t-test

** Chi-square test

Atherosclerosis-associated risk factors have been compared between the groups. Given that, the two groups were similar regarding chronic medical conditions, including hypertension (P-value>0.99) and diabetes mellitus (P-value=0.099), smoking (P-value=257), addiction (P-value=0.602), re-stroke incidence (P-value=0.312) and the previous history of IHD (P-value=0.359); however, dyslipidemia was statistically more among the patients suffering from small vessels disease (P-value=0.030). Detailed information is demonstrated in Table 2.

Table 2. The comparison of atherosclerosis risk factors between the groups

	Large vessels disease (n=75)	Small vessels disease (n=150)	P-value*
	N (%)		
Chronic medical conditions			
Hypertension	48 (64)	96 (64)	>0.99
Diabetes mellitus	23 (30.7)	63 (42)	0.099
Dyslipidemia	30 (40)	83 (55.3)	0.030
Habits			
Smoking	20 (26.7)	30 (20)	0.257
Addiction	7 (9.3)	11 (7.3)	0.602
Atherosclerotic events			
Re-stroke	6 (8)	7 (4.7)	0.312
History of ischemic heart disease	7 (9.3)	9 (6)	0.359
Chronic medications			
Antiplatelet agents	71 (94.7)	144 (96)	0.647
Adherence to the medications	43 (89.6)	87 (90.6)	0.842

* Chi-square test

Table 3 compares ACS incidence among patients with small versus large vessel disease. The prevalence of ACS did not differ between the groups (P-value=0.105). Furthermore, the

types of the events were not statistically different (P-value=0.836) as well. The angiographic (P-value=0.671), SPECT (P-value=0.99) and CT angiographic (P-value>0.99) findings and therapeutic approach (P-value=0.728) were similar between the groups.

Table 3. The comparison of coronary artery events between the groups

	Large vessels disease (n=75)	Small vessels disease (n=150)	P-value*
	N (%)		
The incidence of acute coronary syndrome	29 (38.7)	42 (28)	0.105*
The type of cardiac events			
STEMI	6 (20.7)	8 (19)	0.836**
NSTEMI	7 (24.1)	10 (23.8)	
UA	10 (34.5)	18 (42.9)	
SCD	6 (20.7)	6 (14.3)	
Angiographic outcome			
One vessel disease	7 (36.8)	12 (38.7)	0.671*
Two vessels disease	7 (36.8)	8 (25.8)	
Three vessels disease	5 (26.3)	11 (35.5)	
Myocardial perfusion via SPECT			
Moderate ischemia	5 (83.3)	3 (75)	0.99**
Severe ischemia	1 (16.7)	1 (25)	
Computed tomography angiography			
Moderate coronary CAD	1 (100)	2 (100)	>0.99**
Therapeutic approach			
MFU	10 (43.5)	12 (33.3)	0.728*
PCI	10 (43.5)	18 (50)	
CABG	3 (13)	6 (16.7)	

*Chi-square test
** Fisher's exact test
STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, UA: unstable angina, SCD: sudden cardiac death, SPECT: Single Photon Emission Computed Tomography, CAD: coronary artery disease, MFU: medical follow up, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting

The mean interval between the index stroke and the cardiac events was 41.96±11.40 months for those with large vessel disease versus 44.49±9.68 months for the patients admitted due to small vessel disease. Cox regression was applied in crude and adjusted models to determine the effects of risk factors on ACS incidence after an ischemic stroke. The crude model was statistically insignificant. Adjustment for the medical conditions including hypertension, diabetes mellitus, dyslipidemia, re-stroke, and the previous history of IHD was statistically significant only (HR=2.005, 95%CI: 1.093-2.988). Besides, the full-adjusted model revealed no difference between those with large vessels disease ischemic stroke compared with small vessel diseased patients (P-value=0.087) (Table 4).

Table 4. Cox regression assessment

	Hazard ratio	95% confidence interval		P-value
		Lower	Upper	
Crude model	1.621	.980	2.558	.060
Model 1	1.704	.990	2.604	.055
Model 2	1.611	.878	2.365	.148
Model 3	2.005	1.093	2.988	.021
Model 4	2.080	.936	2.642	.087

Model 1: adjusted for age and gender
Model 2: adjusted for age, gender, BMI, smoking, and addiction
Model 3: adjusted for hypertension, diabetes mellitus, dyslipidemia, re-stroke, and the previous history of IHD
Model 4: adjusted for age, gender, BMI, smoking, addiction, hypertension, diabetes mellitus, dyslipidemia, re-stroke, and the previous history of IHD

Discussion

Despite the developments in the secondary prevention strategies for cerebrovascular ischemia, CAD-related events are the most common leading long-term cause of mortality in these patients [14]. In this cohort study conducted on the patients with large versus small vessels brain ischemia who were similar in terms of demographic, habitual, and chronic medical disease characteristics, the authors found insignificant differences in regard to the incidence and type of CAD-related events, paraclinical findings, and the integral approach of management. Furthermore, cox regression assessments revealed that the patients suffering from large brain vessel disease are more than two folds at increased risk of CAD-related disease development after controlling the potential chronic medical conditions involving the vessels including hypertension, diabetes mellitus, dyslipidemia, re-stroke, and the previous history of IHD. However, controlling the other risk factors of cardiovascular diseases including advanced age, male gender, obesity and smoking revealed no association which might have occurred due to the small sample population.

Several studies in the literature have presented the incidence of CAD-related events in post-stroke patients. They have mostly presented acute myocardial infarction (AMI) as the underlying etiology of death in this group of patients. Meta-analysis studies on this issue estimated the annual AMI rate of 1.67% after an ischemic cerebrovascular event [3]. This rate has been reduced to approximately 1% by the routine use of antiplatelet and statins [15]; however, Gunnoo and colleagues presented ischemic heart disease in 3% of the assessed population with ischemic CVA [14]. The probability of events incidence decreased over time, and the cardiovascular events mainly occurred within the first five years of the ischemic stroke [16]. Further investigations showed that about half of the patients with ischemic stroke had asymptomatic coronary plaques. One-third of them had an occlusion with a clinical significance of >50% in the coronary arteries. Therefore, it is logical that many more individuals with ischemic stroke who had no history of IHD may be at risk of MI than previously appreciated [15, 17].

According to the authors' study, 38.66% of the patients suffering from large brain vessels disease experienced one of the ischemic heart diseases within three years after the index event, while this rate accounted for 28% in those with small vessels disease; however, the comparison of the groups did not statistically differ. Similarly, Lee and colleagues, in a five-year follow-up study, presented up to two folds increased risk of CAD-related events in the patients with large vessels disease compared with those suffering from small vessels disease [6]; however, Burn et al. stated no association between the vascular bed responsible for the ischemic cerebrovascular event and the probability of AMI in the future [3]. Another

meta-analysis emphasized that the association between large-artery atherosclerosis in acute ischemic stroke with the incidence of IHD was not significant [15]. Atherosclerosis is the principal underlying etiology for both ischemic cerebrovascular disease and CAD. This process involves diverse pathogeneses, including progressive plaque formation, oxidative metabolisms, and endothelial dysfunction, leading to vascular bed injuries and increased risk for arterial occlusion. The plaques may be large enough to occlude the vessels or may rupture and transport them to the small vessels [18, 19]. Given that, any impairment in the brain tissue blood supply can lead to ischemia, and it is not unexpected to have a similar phenomenon in coronary artery circulation [20].
In summary, previous studies have generally demonstrated that older age, male gender, smoking, underlying chronic medical conditions that are associated with atherogenesis such as diabetes mellitus, hypertension, and dyslipidemia, history of atrial fibrillation, and a previous history of cardiovascular heart disease were the significant predictors of heart attacks after an ischemic cerebrovascular event [21, 22]. Nevertheless, in this study, the authors detected that the size of involved vessels was independently associated with the future incidence of ischemic heart diseases regardless of the demographic characteristics and mentioned medical diseases.

Conclusion

According to the findings of this study, large-vessel involvement in an ischemic stroke was associated with a more than two-fold increase in over three years probability of ischemic heart disease incidence. Considering the significant increased risk of cardiovascular events among the CVA patients with large vessel disease, more intensive preventive care and close follow-up of the patients with large vessel disease is strongly recommended.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392(10159): 1736-1788. https://doi.org/10.1016/s0140-6736(18)32203-7
2. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45(7): 2160-236. https://doi.org/10.1161/STR.0000000000000024
3. Burns JD, Rabinstein AA, Roger VL, Stead LG, Christianson TJ, Killian JM, et al. Incidence and predictors of myocardial infarction after transient ischemic attack: a population-based study. Stroke 2011; 42(4): 935-40. https://doi.org/10.1161/STROKEAHA.110.593723
4. Sadeghi M, Heshmat-Ghahdarijani K, Talaei M, Safaei A, Sarrafzadegan N, Roohafza H. The predictive value of atherogenic index of plasma in the prediction of cardiovascular events; a fifteen-year cohort study. Adv Med Sci 2021; 66(2): 418-23. https://doi.org/10.1016/j.advms.2021.09.003
5. Calvet D, Touzé E, Varenne O, Sablayrolles J-L, Weber S, Mas J-L. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. Circulation 2010; 121(14): 1623-9. https://doi.org/10.1161/CIRCULATIONAHA.109.906958
6. Lee KJ, Kim SE, Kim JY, Kang J, Kim BJ, Han MK, et al. Five-Year Risk of Acute Myocardial Infarction After Acute Ischemic Stroke in Korea. J Am Heart Assoc 2021; 10(1): e018807. https://doi.org/10.1161/JAHA.120.018807
7. Powers WJ. Acute ischemic stroke. N Engl J Med 2020; 383(3): 252-60. https://doi.org/10.1056/NEJMcp1917030
8. Han F, Zhai F-F, Wang Q, Zhou L-X, Ni J, Yao M, et al. Prevalence and risk factors of cerebral small vessel disease in a Chinese population-based sample. J Stroke 2018; 20(2): 239. https://doi.org/10.5853/jos.2017.02110
9. Xin X-Y, Cheng L, Yang Z, Zhang Y, Zeng L-L, Liu J-R. Comparison study of ASCO and TOAST classification system in Chinese minor stroke patients. Cerebrovasc Dis 2019; 47(1-2): 95-100. https://doi.org/10.1159/000497478

10. Rennert RC, Wali AR, Steinberg JA, Santiago-Dieppa DR, Olson SE, Pannell JS, et al. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. Neurosurgery 2019; 85(suppl_1): S4-S8. https://doi.org/10.1093/neuros/nyz042
11. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke Vasc Neurol 2016; 1(3):83-92 https://doi.org/10.1136/svn-2016-000035
12. Barati M, Taheri-Kharameh Z, Bandehelahi K, Yeh VM, Kripalani S. Validation of the Short Form of the Adherence to Refills and Medications Scale (ARMS-SF) in Iranian Elders with Chronic Disease. J Clin Diagn Res 2018; 12(11):FC05-FC08. https://doi.org/10.7860/JCDR/2018/37584.12305
13. Thygesen K, Alpert J, Jaffe A, Simoons M, Chaitman B, White H, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60(16):1581-98.https://doi.org/10.1161/CIR.0b013e31826e1058
14. Gunnoo T, Hasan N, Khan MS, Slark J, Bentley P, Sharma P. Quantifying the risk of heart disease following acute ischaemic stroke: a meta-analysis of over 50000 participants. BMJ Open 2016;6(1):e009535.https://doi.org/10.1136/bmjopen-2015-009535
15. Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: systematic review and meta-analysis. J Am Heart Assoc 2018; 7(2): e007267. https://doi.org/10.1161/JAHA.117.007267
16. Touzé E, Varenne O, Chatellier G, Peyrard Sv, Rothwell PM, Mas J-L. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke 2005; 36(12): 2748-55. https://doi.org/10.1161/01.STR.0000190118.02275.33
17. Komorovsky R, Desideri A, Coscarelli S, Cortigiani L, Celegon L. Impact of carotid arterial narrowing on outcomes of patients with acute coronary syndromes. Am J Cardiol 2004; 93(12): 1552-5. https://doi.org/10.1016/j.amjcard.2004.03.012
18. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. J Am Coll Cardiol 2020; 75(3): 333-40. https://doi.org/10.1016/j.jacc.2019.11.024
19. Pierik R, Algra A, van Dijk E, Erasmus ME, Van Gelder IC, Koudstaal PJ, et al. Distribution of cardioembolic stroke: a cohort study. Cerebrovasc Dis 2020; 49(1): 97-104. https://doi.org/10.1159/000505616
20. Merkler AE, Diaz I, Wu X, Murthy SB, Gialdini G, Navi BB, et al. Duration of heightened ischemic stroke risk after acute myocardial infarction. J Am Heart Assoc 2018; 7(22): e010782. https://doi.org/10.1161/JAHA.118.010782
21. Vilanova M, Mauri-Capdevila G, Sanahuja J, Quilez A, Pinol-Ripoll G, Begue R, et al. Prediction of myocardial infarction in patients with transient ischaemic attack. Acta Neurol Scand 2015; 131(2): 111-9. https://doi.org/10.1111/ane.12291
22. Amarenco P, Lavallée PC, Labreuche J, Ducrocq G, Juliard J-M, Feldman L, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. Stroke 2011; 42(1): 22-9. https://doi.org/10.1161/STROKEAHA.110.584086

How to cite this article: Tajmirriahi M, Saadatnia M, Shemirani H, Sadeghi M, Chamasemani A, Safaei A. **The Incidence of Cardiovascular Events in Small Versus Large Ischemic Stroke; A Three-Year Cohort Study.** ARYA Atheroscler 2023; 19(5): 35-42.