Coronary Artery Disease in Patients with Ischemic Stroke and TIA

Rohit Bhatia, MD, DM,* Gautam Sharma, MD, DM,† Chetan Patel, PhD,‡ Ajay Garg, MD,§ Ambuj Roy, MD, DM,† Prerna Bali, MSc,* Nishita Singh, MD, DM,* Pranjal Sisodia, MSc,* Vishnubhatla Sreenivas, PhD,‖ M.V. Padma Srivastava, MD, DM,* and Kameshwar Prasad, MD, DM*

Background and Objectives: Ischemic stroke (IS) and coronary artery disease (CAD) share common risk factors and one may be the harbinger of the other. We aimed to study prevalence of symptomatic and asymptomatic CAD in a cohort of consecutive patients with IS and assess its relationship with intracranial and extracranial large artery cerebrovascular disease (LAD). *Methods:* All consecutive eligible IS and Transient Ischemic Attack (TIA) patients were recruited into the study. Both clinically suspected and asymptomatic patients (N = 259) underwent myocardial *Stress-rest Gated Technetium-99m (Tc99m) MIBI Myocardial Perfusion SPECT scan* performed on a dual head SPECT-CT to estimate evidence of myocardial ischemia. *Results:* Three hundred patients completed the study. Forty one patients were previously diagnosed cases of definitive CAD. Twelve patients were clinically suspected to have CAD and 247 patients were asymptomatic. Among these, 12 patients (4.81%) had a positive SPECT. The overall prevalence of CAD was 17.67% (n = 53). Presence of diabetes was an independent predictor of CAD (OR 1.98, 95% CI 1.07-3.67. *P* .02). No significant association was found between the presence of LAD and CAD in all subgroup comparisons. However, there was a suggestion of higher LAD among patients with known CAD compared with others. *Conclusions:* CAD is prevalent in patients with ischemic stroke. No definitive relationship was found between CAD and intracranial or extracranial LAD. Population based stratification tools are needed to further assess the need to detect subclinical CAD in patients with stroke.

Key Words: Coronary artery disease—ischemic heart disease—CAD—myocardial perfusion—larger artery disease—cardiac ischemia

Introduction

Ischemic stroke (IS) and coronary artery disease (CAD) share common risk factors and one may be the harbinger of the other. Long-term follow-up of stroke patients suggest that cardiac events account for a high proportionate mortality even though stroke recurrence is higher.[1-3] It is therefore imperative to study the presence of CAD among patients with IS for timely intervention and prevention of a major coronary event. Limited studies have explored this association. Although, a long-term follow-up is required to estimate the absolute risk of an acute coronary event following a stroke, published data suggests that 2%-5% of IS patients have fatal cardiac events within 90 days of stroke occurrence as the patients may harbour a clinically asymptomatic CAD.[4-6] Studies suggest a 20%-40% prevalence of silent cardiac ischemia among stroke patients detectable by

From the *Department of Neurology, All India Institute of Medical Sciences, New Delhi, India; †Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; ‡Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India; §Department of Neuroradiology, All India Institute of Medical Sciences, New Delhi, India; and ‖Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.

Grant support: The research was supported by funding from the Indian Council of Medical Research, New Delhi, India grant number DHR/GIA/33/2014.

Address correspondence to Rohit Bhatia, MD, DM, Department of Neurology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India. E-mails: rohitbhatia71@yahoo.com, rohitbhatia71@gmail.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104400

cardiac testing using thallium scintigraphy, radionuclide ventriculography or treadmill testing .

We aimed to study the prevalence of symptomatic and asymptomatic CAD in a large cohort of consecutive patients with IS and also assess its relationship with intracranial and extracranial cerebrovascular disease.

Methods

This is a prospective observational study. Following approval from the institutional ethics committee, all consecutive ischemic stroke and Transient Ischemic Attack (TIA) patients presenting to our department were screened and eligible patients were recruited into the study. The inclusion criteria included patients with ischemic strokes and TIA's, age above 18 years, premorbid or post stroke modified Rankin score upto 4 and consent to participate. Patients who were unconscious, on ventilatory support, contraindication for CTAngiogram (CTA) or MRAngiogram (MRA), contrast allergy, cardioembolic strokes due to rheumatic valvular disease, severe associated medical illnesses making long-term survival unlikely for example, advanced CRF, malignancies, severe congestive heart failure or others limiting life expectancy, lack of consent, pregnancy, involvement in a trial of another experimental intervention (drug or surgery) for acute stroke and not available for follow-up, for example, no fixed address, migrated visitor were excluded from the study.

Enrolled patients underwent a detailed history review, baseline blood investigations, electrocardiogram , transthoracic echocardiogram and transesophageal echo (in selected cases) and a 24 hours Holter recording. As a part of routine work up for stroke, each patient underwent a noncontrast CT scan of the head. CTA was done for most of the patients and MRA was done in patients where CTA was not feasible. The severity of extracranial carotid disease was estimated using North American Symptomatic Carotid Endarterectomy Study criteria. The disease was graded as mild (≤50%), moderate (50-69%) and severe (70% and above). Intracranial vascular disease was also graded as mild, moderate or severe. For the current study analysis, stenosis more than or equal to 50% was taken as suggestive of significant large artery disease.

The cardiologist reviewed the history for presence of symptoms suggestive of CAD and treatment related to any known or suspected CAD in the past. Based on the clinical evaluation and baseline investigations, patients were categorised into one of the following: those with known history of CAD supported by previous evaluation and treatment were labelled as *known CAD*, those suspected clinically as *suspected CAD* and those with no history or investigations to suggest CAD into the *asymptomatic* group. Both clinically suspected and asymptomatic patients underwent myocardial *Stress-rest Gated Technetium-99m (Tc99m) MIBI Myocardial Perfusion SPECT (MPS) scan* performed on a dual head SPECT-CT (General Electric Medical system, Infinia Hawkeye) to estimate evidence of myocardial ischemia. The myocardial perfusion scintigraphy was done under the supervision of a trained nuclear medicine expert and after clearance by the cardiologist. Patients who were not able to walk on the tread-mill due to age or physical disability underwent pharmacological stress with dobutamine infusion. For the physical exercise on the tread mill, Bruce protocol was followed. All SPECT images were analysed according to the standard criteria and agreement of 2 independent observers. The study was considered as normal (no perfusion defect on the stress and rest images) or abnormal (presence of perfusion defect on the stress). Presence of perfusion defect on the stress which normalizes on the rest images (reversible perfusion defect) was recorded as suggestive of stress induced ischemia and presence of perfusion defect on the stress which remained unchanged on the rest images (fixed perfusion defect) was recorded as suggestive of a scarred myocardium. Left ventricular ejection fraction was analysed from the gated rest images using quantitative software (Emory cardiac toolbox). Patients positive on this test were re-evaluated by the cardiologist to decide on the need for a diagnostic coronary angiography and further therapeutic decision as deemed necessary. The patients previously investigated for CAD or had been treated by either angioplasty and/or coronary artery bypass graft did not undergo any further testing. For purpose of analysis, patients with known CAD and those detected on MPS scan were grouped together in the CAD group, although separate analysis was also done for the newly detected CAD or known CAD patients.

Results

A total of 351 patients with ischemic stroke / TIA were recruited during the study period. Among these, 300 patients who completed the study are included into the final analysis (see flowchart for reasons of excluded patients Figure 1). The mean age was 54.62 +/- 11.41years (24-84 years) and 244 (81.33%) were males. Major risk factors included hypertension (75.67%), diabetes (29%), smoking (42%) dyslipidemia (21.67%), previous stroke (19.33%), atrial fibrillation (2%), family history of stroke (19.33%), alcohol consumption (9.67%) (Table 1). Holter testing could be performed on 297 patients. It was normal in 256 (86.20%) patients and showed atrial fibrillation in 12 (4.04%), frequent VPC's in 17 (5.72%) and combination of atrial premature beats and VPC's in 12 (4.04%). Echocardiography was done in all 300 patients. It was normal in 257 (85.67%) and showed presence of mild valvular disease in 1 (.33% cardiomyopathy in 17 (5.67%), hypertrophic cardiomyopathy in 1 (.33%) and concentric LVH in 24 (8%) patients.

CAD and Stroke

Forty one patients were previously diagnosed cases of definitive CAD. Among the 259 remaining patients 12

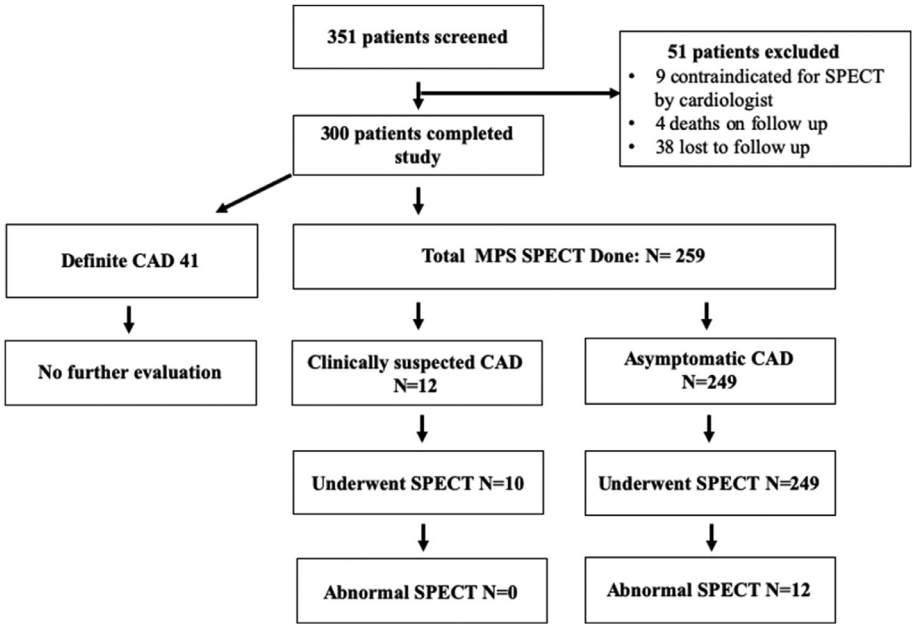

Figure 1. *Shows outline of the study. Among the 300 patients who completed the study, 41 patients were known cases of treated CAD (coronary artery disease) so did not undergo further myocardial perfusion SPECT. 259 patients underwent myocardial perfusion SPECT. 12 were detected to have features of CAD.*

patients were clinically suspected to have CAD and 247 patients were asymptomatic. Among these, 259 patients underwent a MPS (10/12 of the suspected CAD; 249 asymptomatic patients). Two patients among the suspected CAD group did not undergo the scan due to concern of the cardiologist. Among the clinically suspected patients (n = 10) who underwent the SPECT, none of the patients had a positive SPECT. Among the clinically asymptomatic patients (n = 249), 12 patients (4.81%) had a positive SPECT suggestive of CAD. Among these, 4 patients underwent coronary angiography and 2 patients underwent angioplasty and stenting. Other patients were kept on medical treatment and have been clinically stable till last follow-up. The overall prevalence of CAD was 17.67% (n = 53).

Table 1. *Demographic and risk factors among the stroke cohort*

Variable	N (%)
Age	54.62
Sex (male/female)	244/56 (81.33)
HTN[†]	227 (75.67)
DM [‡]	87 (29)
Smoking	42 (14)
Hyperlipidemia	65 (21.67)
Atrial fibrillation	6 (2)
Alcohol intake	29 (9.67)
Migraine	11 (3.67)
Previous stroke	58 (19.33)
[§] F/H stroke	58 (19.33)
[§] F/H CAD*	42 (14)
[§] F/ H DM [‡]	74 (24.67)

*Coronary artery disease.
[†]Hypertension.
[‡]Diabetes mellitus.
[§]Family history.

Comparison among patients with and without CAD is outlined in Table 2. For the purpose of analysis, patients with known CAD (n = 41) were grouped with the newly detected CAD patients (n = 12, total 53) and compared with the no CAD group (n = 247) (Table 3). Apart from high prevalence of diabetes in the CAD group, no significant differences were found among other variables. There was a trend towards higher cardioembolic stroke among patients with CAD. We also compared patients without CAD (n = 247) to the newly detected patients by the perfusion scan (n = 12). Dyslipidemia was significantly higher among the detected group. Upon comparison of the patients with known CAD (n = 41) to the ones detected newly (n = 12), it was observed that diabetes, dyslipidemia, history of previous stroke and family history of CAD were significantly higher in the known CAD group. The only independent predictor of CAD was the presence of diabetes (OR 1.98, 95% CI 1.07-3.67. *P* = .02), Table 4.

Relationship between Vascular Disease and CAD

We also analyzed the relationship of large artery atherosclerotic disease (extracranial and intracranial) to

Table 2. *Comparison of patients with and without CAD*

Characteristic	No CAD* (n = 247)	Any CAD* (n = 53)	*P* value	§OR	95%CI‖
Age	54.11 (SD 11.59)	56.98 (SD 10.30)	.098	1.02	.99-1.05
Sex (m/f) (%)	199 (80.57)/48 (19.43)	48 (84.91), 8 (15.09)	.463	.73	.32-1.66
HTN† (%)	182 (73.68)	45 (84.91)	.089	2.00	.89-4.48
DM‡(%)	65 (26.32)	22 (41.51)	.029	1.98	1.07-3.67
Smoking (%)	35 (14.17)	7 (13.21)	.855	.92	.38-2.20
Hyperlipidemia (%)	49 (19.84)	16 (30.19)	.1	1.74	.89-3.39
Atrial fibrillation (%)	4 (1.62)	2 (3.77)	.32	2.38	.42-13.35
Alcohol intake (%)	25 (10.12)	4 (7.55)	.566	.72	.24-2.17
Migraine(%)	7 (2.83)	4 (7.55)	.11	2.79	.78-9.92
Previous stroke (%)	48 (19.43)	10 (18.87)	.92	.96	.45-2.05
¶F/H stroke (%)	49 (19.84)	9 (16.98)	.633	.82	.37-1.8
¶F/H CAD (%)	31 (12.55)	11 (20.75)	.122	1.82	.85-3.91
¶F/H DM (%)	60 (24.29)	14 (26.42)	.74	1.11	.56-2.20
¶F/H hyperlipidemia (%)	1 (.40)	1 (1.89)	.27	4.73	.29-76.8

*Coronary artery disease.
†Hypertension.
‡Diabetes mellitus.
§Odds ratio.
‖Confidence interval.
¶Family history.

presence of CAD in the study. No significant association was found between the presence of significant extracranial or intracranial vascular disease and CAD (Table 5) in all subgroup comparisons. However, there was a suggestion of higher large artery disease among patients with known CAD.

Stroke Etiology Using Trial of Org 10172 in Acute Stroke Treatment (TOAST)[35] Classification among Patients With and Without CAD after Patients

Using TOAST classification, the etiology of stroke was classified as follows (n = 300): large artery atherosclerosis

Table 3. *Comparison of patients without CAD and the newly detected CAD*

Characteristic	No *CAD (n = 247)	Newly detected CAD* (n = 12)	*P* value	OR§	95% CI‖
Age	54.11 (SD 11.59)	52.91 (SD 8.96)	.0724	.99	.94-1.04
Sex (male/female) (%)	199 (80.57)/48 (19.43)	10 (83.33),2 (16.67)	.813	.829	.17-3.90
HTN† (%)	182 (73.68)	11 (91.67)	.194	3.92	.49-31.02
DM‡ (%)	65 (26.32)	2 (16.67)	.46	.56	.11-2.62
Smoking (%)	35 (14.17)	2 (16.67)	.81	1.21	.25-5.76
Hyperlipidemia (%)	49 (19.84)	7 (58.33)	.004	5.65	1.72-18.58
Atrial fibrillation (%)	4 (1.62)	(0)	.657	-	-
Alcohol intake (%)	25 (10.12)	2 (16.67)	.47	1.77	.36-8.56
Migraine (%)	7 (2.83)	1 (8.33)	.30	3.11	.35-27.5
Previous stroke (%)	48 (19.43)	0 (0)	.091	-	-
¶F/H stroke (%)	49 (19.84)	0 (0)	.087	-	-
¶F/H CAD* (%)	31 (12.55)	0 (0)	.191	-	-
¶F/H DM‡ (%)	60 (24.29)	2 (16.67)	.54	0.62	.13-2.92
¶F/HHyperlipidemia (%)	1 (0.40)	0 (0)	.825	-	-

*CAD: coronary artery disease.
†HTN: hypertension.
‡DM: diabetes mellitus.
§OR: odds ratio.
‖CI: confidence interval.
¶F/H: family history.

Table 4. *Comparison of patients with previously known CAD and newly detected asymptomatic CAD*

Characteristic	known CAD*(n = 41)	Newly detected CAD* (n = 12)	*P* value	OR§	95% CI‖
Age	58.17 (SD 10.45)	52.91 (SD 8.96)	.126	.94	.88-1.01
Sex (m/f) (%)	35 (85.37)/6 (14.63)	10 (83.33)/2 (16.67)	.863	1.16	.20-.69
HTN† (%)	34 (82.93)	11 (91.67)	.467	2.26	.25-20.49
DM‡ (%)	20 (48.78)	2 (16.67)	.062	.21	.04-1.07
Smoking (%)	5 (12.20)	2 (16.67)	.689	1.44	.24-8.56
Hyperlipidemia (%)	9 (21.95)	7 (58.33)	.021	4.97	1.27-19.49
Atrial fibrillation (%)	2 (4.88)	0 (0)	.435	-	-
Alcohol intake (%)	2 (4.88)	2 (16.67)	.20	3.9	.48-31.2
Migraine (%)	3 (7.32)	1 (8.33)	.90	1.15	.1.-12.20
Previous stroke (%)	10 (24.39)	0 (0)	.058	-	-
¶ F/H stroke (%)	9 (21.95)	0 (0)	.075	-	-
¶ F/H CAD (%)	11 (26.83)	0 (0)	.044	-	-
¶ F/H DM (%)	12 (29.27)	2 (16.67)	.391	.48	.09-2.54

*CAD: coronary artery disease.
†HTN: hypertension.
‡DM: diabetes mellitus.
§OR: odds ratio.
‖CI: confidence interval.
¶F/H: family history.

(48.34%), small vessel disease (21%), cardioembolic (9.67%), other determinate (2.42%),) and cryptogenic (16%). We also analyzed if any particular stroke etiology using TOAST classification was more predictive of presence of CAD (Table 6). Cardioembolic strokes occurred more often among patients with CAD likely due to factors related to myocardial abnormality and/or arrhythmia. A higher proportion of strokes were labeled cryptogenic among the patients with no history of CAD.

Table 5. *Association of large artery disease with CAD*

Large artery disease	No CAD*	Any CAD*	*P* value
Yes	116 (46.96)	29 (54.71)	.36
No	131 (53.04)	24 (45.28)	
Large artery disease	No CAD	Any CAD	*P* value
Intracranial	67 (57.56)	14 (44)	.35
Extracranial	49 (42.24)	15 (56)	
Large artery disease	Known CAD	No CAD	*P* value
Yes	25 (60.98)	116 (46.96)	.096
No	16 (39.02)	131 (53.04)	
Large artery disease	Known CAD	No CAD	*P* value
Intracranial	11 (44)	67 (57.76)	.209
Extracranial	14 (56)	49 (42.24)	
Large artery disease	No CAD	Newly detected CAD	*P* value
Yes	116 (46.96)	4 (33.33)	.361
No	131 (53.04)	8 (66.67)	
Large artery disease	No CAD	Newly detected CAD	*P* value
Intracranial	67 (57.56)	3 (75)	.63
Extracranial	49 (42.24)	1 (25)	
Large artery disease	Known CAD	Newly detected CAD	P value
Yes	25 (60.98)	4 (33.33)	.099
No	16 (39.02)	8 (66.67)	
Large artery disease	Known CAD	Newly detected CAD	*P* value
Intracranial	11 (44)	3 (75)	.249
Extracranial	14 (56)	1 (25)	

*Coronary artery disease.

Table 6. *Stroke etiology among patients with and without CAD*

TOAST criteria (%)	No CAD* (n = 247)	Any CAD* (n = 53)	*P* value	OR	95% CI
LAD†	116 (46.9)	29 (54.7)	.306	1.36	.75-2.40
Cardioembolism	19 (7.69)	10 (18.86)	.016	2.79	1.21-6.41
SVD ‡	55 (22.26)	8 (15.09)	.24	.62	.27-1.39
Cryptogenic	49 (19.84)	5 (9.43)	.081	.42	.15-1.11
Other	8 (3.24)	1 (1.89)	.60	.57	.07-4.69
TOAST criteria (%)	No CAD (n = 247)	Known CAD (n = 41)	*P* value	OR	95% CI
LAD	116 (46.9)	25 (60.98)	.099	1.764	.89-3.46
Cardioembolism	19 (7.69)	10 (24.39)	.002	3.87	1.65-9.08
SVD	55 (22.26)	4 (9.76)	.075	.377	.12-1.10
Cryptogenic	49 (19.84)	1 (2.44)	.025	.10	.01-0.75
Other	8 (3.24)	1 (2.44)	.786	.74	.09-6.13
TOAST criteria (%)	No CAD (n = 247)	Newly detected CAD (n = 12)	*P* value	OR	95% CI
LAD	116 (46.9)	4 (33.33)	.361	.56	.16-1.92
Cardioembolism	19 (7.69)	0 (0)	.318	–	–
SVD	55 (22.26)	4 (33.33)	.378	1.74	.50-6.01
Cryptogenic	49 (19.84)	4 (33.33)	.266	2.02	.58-6.98
Other	8 (3.24)	0 (0)	.52	–	–
TOAST criteria (%)	Known CAD(n = 41)	Newly detected CAD(n = 12)	*P* value	OR	95% CI
LAD	25 (60.98)	4 (33.33)	.091	.32	.08-1.23
Cardioembolism	10 (24.39)	0 (0)	.058	–	–
SVD	4 (9.76)	4 (33.33)	.045	4.62	.95-22.51
Cryptogenic	1 (2.44)	4 (33.33)	.011	20	1.96-203.32
Other	1 (2.44)	0 (0)	.585	–	–

*Coronary artery disease.
†Large artery disease
‡Small vessel disease.

Discussion

Population data has shown that mortality among stroke patients could be related to a major coronary event both in short- and long-term.[2,3,7,8] Coronary events in the acute phase of stroke have been estimated indirectly from acute stroke intervention trials. The TOAST trial[9] reported a .1%-1-month risk of fatal MI and the international stroke trial[10] observed a 2.9% risk. In a systematic review and meta-analysis comprising 65,996 patients of stroke and TIA, the authors found an annual risk of 2.1% (CI 95%: 1.9 -2.4) for nonstroke vascular death, 2.2% (1.7 -2.7) for total MI, .9% (.7 to 1.2) for nonfatal MI and 1.1% (.8- 1.5) for fatal MI.[11] A recent meta-analysis assessed long-term risk of MI compared to stroke after a stroke or TIA.[12] The risk of MI was 1.67%/y (95% CI 1.36-1.98) and recurrent stroke was 4.26%/y (95% CI 3.43-5.09) with a significant heterogeneity among studies. The risk however reduced with time. Appropriate determinants for future CAD risk is therefore needed for prevention of fatal coronary events.

Our study found an overall prevalence of 17.67% for CAD among patients with ischemic stroke. We could detect asymptomatic CAD among 12 (4.67%) cases of stroke. Few previous studies have assessed asymptomatic CAD among patients with stroke.[1,8,13] The prior estimates of coronary artery disease prevalence in stroke range between 20-58%. This has generally been studied using noninvasive cardiac testing. Studies have shown that rest and exercise radionuclide ventriculography (gated wall motion test), stress-rest Thallium-201 scintigraphy (Thallium treadmill test) are more sensitive than exercise treadmill test for detection of CAD.[13,14] Among 168 diabetic subjects with no symptoms of CAD who were followed up for 36+/-18 months, the authors found that stress technetium-99m sestamibi SPECT was useful in evaluating asymptomatic diabetics for the presence of CAD, and effectively risk-stratified this population.[13] Other methods like CT calcium score, CT angiography and invasive angiography are likely to be more specific. In a recent study with 99 patients, myocardial perfusion single photon emission computed tomography with Tc-99m sestamibi was compared to multi slice computed tomography (MSCT).[15] The authors concluded that either investigation provides specific information; functional information in the former and anatomical information in the latter. The MSCT has high NPV in patients with less likelihood for CAD. When compared with coronary angiography, the correlation with MSCT was good and is useful where the calcium score is low.

A recent metanalysis by Gunnoo and colleagues[16] used studies using CT, CTA, autopsy and angiography to ascertain the presence of CAD among patients with stroke. Among 17 studies with 4869 patients with ischemic stroke, a mean average of asymptomatic CAD was

observed in 52% patients with a prevalence of asymptomatic greater than or equal to 50% coronary stenosis in 32% (95% CI 19% to 47%; $P < .00001$). Eight studies with 47229 patients with ischemic stroke revealed an overall risk of MI in the year following stroke of 3% (95% CI 1% to 5%; $P < .00001$) in the absence of any suggestive history. In the recent study[6] using coronary angiography to detect occult CAD among 405 consecutive patients, any coronary plaque was present in 61.9% of patients (95% CI 56.5- 67.3) and greater than or equal to50% coronary stenosis was found in 25.7% (95% CI, 20.9 -30.5). The presence of coronary abnormalities increased as the presence of vascular disease in other vessels increased.

Historical clues are generally used to suspect CAD among patients with stroke, supplemented with electrocardiogram and echocardiography findings of low EF, and/or regional wall motion abnormality. However, this may not be sensitive enough and could over or underestimate the presence of CAD. In our study too, among the clinically suspected patients, none had an abnormal perfusion scan and among the asymptomatic patients 12 patients had features of reversible ischemia. Although angiography can give a quantitative estimation of atherosclerotic disease and may be more specific and considered a gold standard, because of its invasive nature and association with finite adverse events it is not a recommended first screening option and will have a low acceptability and cost effectiveness. A previous study observed that angiographic characterization of coronary artery obstruction may not necessarily provide information about future coronary events.[17]

It is extremely useful to have prediction models to help clinician to plan investigative and prevention strategies for asymptomatic CAD among patients with stroke. Using data from the Framingham study, authors devised a scoring system (The Framingham Coronary Heart Disease Risk Score (FCRS)) for 10 year risk prediction of primary and secondary coronary heart disease (CHD). Age, lipid profile (total cholesterol and HDL cholesterol) presence or absence of diabetes was significant for both men and women.[18] However, systolic blood pressure and cigarette smoking were significant predictors of subsequent CHD in women. A previously issued guideline also suggested the need for a validated risk stratification method for evaluation of CAD.[4] Upon application of this score to a group of stroke patients without CHD, the authors observed that a high FCRS was associated with a higher risk of MI and vascular death, but not stroke.[19]

Literature suggests a strong association of carotid stenosis with the underlying asymptomatic CAD. The association has been observed for both asymptomatic and symptomatic carotid Stenosis.[20-24] One of the studies has even shown that a subgroup of carotid Stenosis patients and no history of CAD who have coexistent intracranial occlusive disease, diabetes or peripheral vascular disease have a risk of cardiac events similar to that of patients with a history of CAD. Likewise, in the REACH registry, asymptomatic carotid stenosis ($\geq$ 70%) was also associated with cardiovascular death and the composite end-point cardiovascular death/myocardial infarction/stroke.[20]

We could not observe an association of significant stenosis of cerebrovascular vessels (extracranial or intracranial) with presence of CAD in all subgroups studied, although proportion of large artery extracranial disease was higher and there was a trend of patients with known CAD to have a higher prevalence of large artery disease, suggesting that patients who present with known CAD are more likely to have an underlying silent vascular stenosis. There could exist differences between the character of atherosclerotic process in coronary and cerebral extracranial and intracranial vessels. In a study conducted on medicolegal autopsies, the authors commented that coronary atherosclerosis sets in significantly earlier than the cerebral atherosclerosis and the "progression of the mean atherosclerotic indices" is higher in the coronary arteries compared to cerebral.[25] This might explain the trend towards presence of large artery disease among patients with known CAD. The mean age of our patients is lower than the previously published studies which may also account for the differences in the presence of significant coronary atherosclerotic disease. The relationship could become significant if multiplicity of ICAD or just presence of plaques in intracranial or extracranial circulation is considered as in some other studies.[6,24,26,27] Since we have used only significant vascular stenosis for correlation, it may have reduced the significance of the results. Also, we have not used structural imaging (CTA, Angiography), to assess extent of coronary atherosclerosis used in other studies done in the recent past which may have underestimated the presence of CAD in our study.[27]

Although a potential relationship exists between extracranial carotid stenosis and CAD in the literature there is still a lack of clear understanding about the association between intracranial atherosclerosis and coronary heart disease.[21] Two recent studies have observed a contradictory association of intracranial arterial stenosis with subclinical CAD, which may have more relevance to Asian population believed to have more intracranial than extracranial disease.[22,23] The association was stronger among patients with more than two vascular risk factors and atherosclerotic disease of both vertebrobasilar and carotid vessels.[24] Likewise, in our study too, we didn't find any relationship between intracranial stenosis and CAD. Potential differences to account for the association between extracranial and intracranial vascular disease and CAD are likely to be due to many factors observed in previous studies: differences in the composition of the arterial wall and differences in hemodynamic stress sustained by coronary and intracranial vessels, metabolic differences, lipid composition differences, vessel calibre differences and genetic differences.[28-31]

The Predicting Asymptomatic Coronary Artery Disease in Patients with Ischemic Stroke and Transient Ischemic Attack study investigators recently validated a score developed to predict greater than or equal to 50% coronary stenosis.[32] Using the FCRS (≥ 20% = 3; 10-19% = 1; <10% = 0) and severity of cervicocephalic vascular stenosis (≥ 50% = 2; <50% = 1; none = 0), the authors observed that higher score predicted severe occult coronary stenosis. Likewise, the Asymptomatic Myocardial Ischemia in Stroke and Atherosclerotic Disease AMISTAD study[6,33] set out to determine whether asymptomatic coronary atherosclerosis predicts a higher risk of major vascular event in patients with stroke and found that, from a baseline diagnosis of asymptomatic CAD, the 2-year HR of patients with stroke developing greater than or equal to 1 vessel disease (coronary stenosis >50%) was 3.43. In the recent publication from the same group, found that patients with stroke and ICAD have systemic atherosclerosis including CAD and many mechanisms that could affect stroke occurrence.[34]

Our study has limitations. All patients recruited initially did not complete the study and could have potentially affected results and significance. We included patients at different time points from onset of ischemic stroke. Although this was more realistic and pragmatic, it may have contributed to reduced detection of CAD in view of already modified risk factors and being on antiplatelets and statins. Structural coronary imaging in form of CTA to assess severity of stenosis may have led to a higher prevalence of CAD being detected. However, functional imaging may be more useful to predict dynamic and reversible ischemic perfusion deficit especially if structural imaging reveals lesser severity of stenosis.

Conclusions

CAD is prevalent in patients with ischemic stroke. Population based stratification tools are needed to further assess the need to detect subclinical CAD and aggressive risk factor control is required to prevent future risk of overt CAD and stroke recurrence. We propose that all patients should be at least screened by a cardiologist and where history or investigations are suggestive or in presence of diabetes, large artery disease, peripheral arterial disease and high Framingham risk score, may be further evaluated for presence of subclinical CAD.

Conflict of Interest

The authors report no conflict of interest.

References

1. Bhatia R, Singh A. Do all stroke patients need to be evaluated for CAD. In: Moonis M, Srivastava MVP, eds. Controversies in stroke care, Byword Publishers; 2012:95-105.
2. Dhammon MS, Sciacca RR, Rundek T, et al. Recurrent stroke and cardiac risk after first ischemic stroke: the Northern Manhattan study. Neurology. 2006;66:641-646.
3. Rokey R, Rolak LA, Harati Y, et al. Coronary artery disease in patients with cerebrovascular disease: a prospective study. Ann Neurol 1984;16:50-53.
4. Adams RJ, Chimowitz MI, Alpert JS, et al. Stroke Council and the Council on Clinical Cardiology of the American Heart Association; American Stroke Association. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. Circulation 2003;108:1278-1290.
5. Macko RF, Katzel LI, Yataco A, et al. Low-velocity graded treadmill stress testing in hemiparetic stroke patients. Stroke 1997;28:988-992.
6. Amarenco P, Lavallée PC, Labreuche J, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. Stroke 2011;42:22-29.
7. Burns JD, Rabinstein AA, Roger VL, et al. Incidence and predictors of myocardial infarction after transient ischemic attack: a population-based study. Stroke 2011;42:935-940.
8. Aggarwal Kapil, Bhatia Rohit, Sharma Gautam, et al. Prevalence of symptomatic and asymptomatic coronary artery disease in patients with stroke. Natl Med J India 2013;26.
9. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials. Stroke 2000;31:1770-1778.
10. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischemic stroke. International stroke trial collaborative group. Lancet. 1997;349:1569-1581. PubMed PMID: 9174558.
11. Touzé E, Varenne O, Chatellier G, et al. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke 2005;36:2748-2755.
12. Boulanger M, Béjot Y, Rothwell PM, et al. 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. https://doi.org/10.1161/JAHA.117.007267. pii: e007267.
13. Rokey R, Rolak LA. Coronary artery disease in patients with cerebrovascular disease: a prospective study. Ann Neurol 1984;16:50-53.
14. De Lorenzo A, Lima RS, Siqueira-Filho AG, et al. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. Am J Cardiol 2002;90:827-832.
15. Shelley S, Indirani M, Sathyamurthy I, et al. Correlation of myocardial perfusion SPECT with invasive and computed tomography coronary angiogram. Indian Heart J 2012;64:43-49. https://doi.org/10.1016/S0019-4832(12)60010-8.
16. Gunnoo T, Hasan N, Khan MS, et al. Quantifying the risk of heart disease following acute ischemic stroke: a meta-analysis of over 50,000 participants. BMJ Open 2016;6:e009535.
17. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent

myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157-1166.
18. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-1847.
19. Towfighi A, Markovic D, Ovbiagele B. Utility of Framingham coronary heart disease risk score for predicting cardiac risk after stroke. Stroke 2012;43:2942-2947.
20. Aichner FT, Topakian R, Alberts MJ, et al. REACH Registry Investigators. High cardiovascular event rates in patients with asymptomatic carotid stenosis: the REACH Registry. Eur J Neurol 2009;16:902-908.
21. Conforto AB, Leite Cda C, Nomura CH, et al. Is there a consistent association between coronary heart disease and ischemic stroke caused by intracranial atherosclerosis? Arq Neuropsiquiatr 2013;71:320-326.
22. Seo W, Yong HS, Koh S, et al. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. Eur Neurol 2008;59:292-298.
23. Yoon YE, Chang HJ, Cho I, et al. Incidence of subclinical coronary atherosclerosis in patients with suspected embolic stroke using cardiac computed tomography. Int J Cardiovasc Imaging 2011;27:1035-1044.
24. Yoo J, Yang JH, Choi BW, et al. The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography in patients with ischemic stroke. Cerebrovasc Dis 2012;33:286-294.
25. Mathur KS, Kashyap SK, Kumar V. Correlation of the extent and severity of atherosclerosis in the coronary and cerebral arteries. Circulation 1963;27:929-934.
26. Arenillas JF, Candell-Riera J, Romero-Farina G, et al. Silent myocardial ischemia in patients with symptomatic intracranial atherosclerosis: associated factors. Stroke 2005;36:1201-1206.
27. Iwasaki K, Haraoka K, Hamaguchi T, et al. Prevalence of subclinical coronary artery disease in ischemic stroke patients. J Cardiol 2015;65:71-75.
28. Uehara T, Tabuchi M, Mori E, et al. Evolving atherosclerosis at carotid and intracranial arteries in Japanese patients with ischemic heart disease: a 5-year longitudinal study with MR angiography. Eur J Neurol 2003;10:507-512.
29. Bae HJ, Yoon BW, Kang DW, et al. Correlation of coronary and cerebral atherosclerosis: difference between extracranial and intracranial arteries. Cerebrovasc Dis 2006;21:112-119.
30. Bang OY, Lee PH, Yoon SR, et al. Inflammatory markers, rather than conventional risk factors, are different between carotid and MCA atherosclerosis. J Neurol Neurosurg Psychiatry 2005;76:1128-1134.
31. Bang OY. Intracranial atherosclerotic stroke: specific focus on the metabolic syndrome and inflammation. Curr Atheroscler Rep 2006;8:330-336.
32. Calvet D, Touzé E, Varenne O, et al. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. Stroke 2010;121:1623-1629.
33. Amarenco P, Lavallée PC, Labreuche J, et al. Coronary artery disease and risk of major vascular events after cerebral infarction. Stroke 2013;44:1505-1511.
34. Hoshino T, Sissani L, Labreuche J, et al. AMISTAD investigators. Prevalence of systemic atherosclerosis burdens and overlapping stroke etiologies and their associations with long-term vascular prognosis in stroke with intracranial atherosclerotic disease. JAMA Neurol 2018;75:203-211.
35. Adams Jr HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.