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ORIGINAL RESEARCH

Burden of Coronary Artery Disease as a Predictor of New Vascular Events and Mortality in Patients With Ischemic Stroke: Insights From the Norwegian Stroke in the Young Study

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BACKGROUND: Studies in young patients with stroke identified coronary artery disease (CAD) as a main contributor to mortality. In the present NOR-SYS (Norwegian Stroke in the Young Study), we aimed to investigate the prevalence of CAD, and the impact on new vascular events and mortality.

METHODS: A total of 385 patients with ischemic stroke, aged ≤60 years, were included. CAD was defined as a history of CAD or positive coronary imaging (computed tomography or coronary angiography).

RESULTS: Mean age was 49.6 years, and 68.1% were men. The prevalence of CAD was 25.2% (n=97) (nonobstructive, 9.6% [n=37]; and obstructive, 15.6% [n=60]). In the subsample of patients without clinical CAD but with femoral plaque on ultrasound (n=58) who underwent cardiac computed tomography, 46% (n=27) had nonobstructive CAD and 28% (n=16) had obstructive CAD. During a median follow-up of 10.1 years, 36 patients (9.4%) died, 84 (21.8%) reached a composite end point of new stroke, myocardial infarction, or death, whereas 64 (16.6%) had a composite end point of new stroke or death. Event-free survival was significantly lower in patients with obstructive CAD versus no CAD or nonobstructive CAD (log-rank $P<0.001$). In the multivariable Cox regression models, CAD was a strong and independent predictor of all-cause mortality (hazard ratio [HR], 2.20 [95% CI, 1.05–4.60]; $P=0.037$) and the composite end point of death or recurrent ischemic stroke (HR, 3.24 [95% CI, 1.46–7.20]; $P=0.004$).

CONCLUSIONS: In young and middle-aged ischemic stroke survivors, a quarter of patients had CAD. CAD was an independent predictor of recurrent stroke and mortality. In patients without previous CAD, but femoral plaque on ultrasound, nearly a half had nonobstructive and one-fourth had obstructive CAD. Systematic screening with cardiac computed tomography may identify high-risk patients after ischemic stroke.

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Key Words: cardiovascular events ■ coronary artery disease ■ femoral artery plaques ■ ischemic stroke ■ long-term mortality

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CLINICAL PERSPECTIVE

What Is New?

- In the present study of young and middle-aged patients with ischemic stroke, a quarter of patients had concomitant coronary artery disease (CAD), which was a strong and independent predictor of new cardiovascular events and mortality.
- The association between CAD and cardiovascular events was independent of target organ damage (left ventricular hypertrophy, increased carotid intima-media thickness, and/or pulse wave velocity).
- In a substudy (n=58), nearly half of patients without history of CAD or symptoms, but with femoral plaques on vascular ultrasound, had nonobstructive CAD, and one-fourth had obstructive CAD on cardiac computed tomography.

What Are the Clinical Implications?

- In our study, the strategy of femoral artery screening by vascular ultrasound in patients with stroke seems to be effective and detects high-risk patients.
- This subgroup of multiple-site artery disease (cerebrovascular+peripheral artery disease+CAD) is exposed to a significantly higher risk of cardiovascular events and mortality.
- We suggest a close collaboration between stroke neurologists/specialists and cardiologists, so that young and middle-aged patients with ischemic stroke, particularly those with evidence of femoral artery plaque, are systematically screened by cardiac computed tomography.

Nonstandard Abbreviations and Acronyms

cIMT	carotid intima-media thickness
NOR-SYS	Norwegian Stroke in the Young Study

Ischemic stroke and coronary artery disease (CAD) share the same cardiovascular disease (CVD) risk factors and frequently coexist, and both are main causes of disability and mortality worldwide.[1] Although mortality rates in young adults with ischemic stroke are low compared with older patients, they are still much higher than in the general population.[2,3] Observational data from long-term follow-up studies in Western Norway showed the following: (1) a 10-fold higher mortality rate compared with age- and sex-matched controls; (2) a 5-fold higher rate of CVD in long-term stroke survivors compared with controls; and (3) nearly one-third of younger patients (aged <50 years) with ischemic stroke died after a mean follow-up of 18 years.[3] These results led us to suspect underlying subclinical CAD among patients with documented ischemic stroke.

Femoral artery plaque has been used as a screening tool for subclinical CAD, based on observations that atherosclerotic peripheral artery disease is frequently associated with coronary and cerebral atherosclerosis, and the risk of future cardiovascular events.[4] In addition, ultrasound is a cost-effective tool applicable in all patients. Early detection and timely treatment of preclinical CAD in patients with stroke may improve both short- and long-term outcomes. However, the prevalence of clinical and subclinical CAD and impact on new clinical events and mortality in young stroke survivors are not fully investigated in large-scale prospective research studies.

In the present NOR-SYS (Norwegian Stroke in the Young Study) substudy, we aimed to explore the burden of clinical and subclinical CAD, the correlation with target organ damage, and predictors of mortality in young (aged 15–44 years) and middle-aged (aged 45–60 years) ischemic stroke survivors. A secondary hypothesis was that patients with ischemic stroke with additional peripheral artery disease and CAD (multisite artery disease) represent a high-risk subgroup with increased risk of new cardiovascular events and mortality after the index ischemic stroke. Therefore, in a subsample of patients without a history of CAD with atherosclerotic plaques in femoral arteries, we aimed to investigate the presence and severity of subclinical atherosclerotic CAD, as well as their impact on long-term prognosis.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Definitions

A detailed study protocol of NOR-SYS has previously been published.[5] Briefly, a total of 385 consecutive patients, aged 15 to 60 years, with documented ischemic stroke were included in NOR-SYS, an observational, prospective research program conducted at Haukeland University Hospital, Bergen, Norway. Patients were included between September 2010 and August 2015 (Figure 1). The subtypes of ischemic stroke were classified according to the TOAST

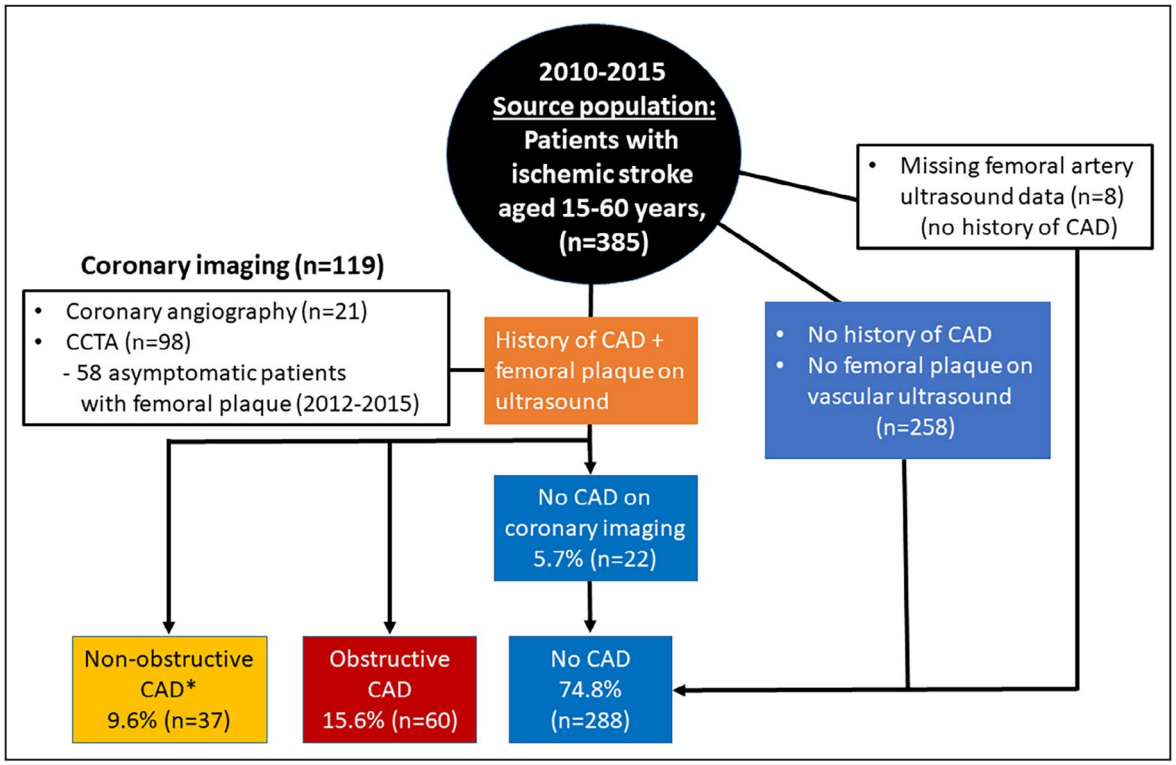

Figure 1. NOR-SYS (Norwegian Stroke in the Young Study) flowchart.
CAD indicates coronary artery disease; and CCTA, coronary computed tomography angiography.

(Trial of ORG 10172 in Acute Stroke Treatment) criteria into large-artery atherosclerosis, cardiac embolism, small-artery occlusion, stroke of other determined cause, and stroke of undetermined cause,[6] updated in 2023. This classification was based on a new assessment of the embolic subtypes compared with our previous publications.

Blood pressure (BP) was measured according to the European Society of Hypertension guidelines, as previously described.[7,8] Hypertension was defined as a history of hypertension, use of antihypertensive treatment, persistently elevated BP during hospitalization for index stroke, or elevated clinic BP (≥140/90 mmHg) and ambulatory BP (≥130/80 mmHg) at follow-up visits.[8] To avoid any influence of the recent stroke on the circadian BP rhythm,[9] ambulatory BP measurements were performed ≈3 months after the index stroke. Body mass index ≥30 kg/m^2 was considered as obesity. Diabetes was defined as previously known diabetes, use of antidiabetic treatment, or fasting blood glucose ≥7 mmol/L. Estimated glomerular filtration rate (eGFR [mL/min per 1.73 m^2]) was determined from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration equation. CAD was defined as a history of myocardial infarction, previous coronary artery bypass surgery, percutaneous coronary intervention, or significant (obstructive) atherosclerotic disease in the coronary arteries assessed by either coronary computed tomography (CT) angiography (CCTA) or conventional angiography. Target organ damage was defined as carotid-femoral pulse wave velocity of ≥10 m/s, left ventricular (LV) hypertrophy on echocardiography, or increased carotid intima-media thickness (cIMT) (>0.9 mm) on carotid ultrasound.

Assessment of Arterial Stiffness

Arterial stiffness was measured by carotid-femoral pulse wave velocity (applanation tonometry) using a Sphygmocor device (AtCor Medical, Sydney, West Ryde, Australia), as described in detail previously.[5,10]

Carotid and Femoral Artery Ultrasound

Carotid and femoral arteries were examined by a 9-3 MHz linear array transducer (iU22 Philips Medical Systems, Bothell, WA). Mean femoral IMT was obtained from predefined 4 far wall segments of both common femoral arteries and superficial femoral arteries on the right and the left side using Philips Q-Lab software (Advanced Ultrasound Quantification, Philips Ultrasound, Bothell, WA) (Figure 2).[5] In the analyses, the maximum of any mean IMT value was used, and plaques were defined as IMT ≥1.5 mm.[11] cIMT was measured by ultrasound at admission for the index stroke, as previously described.[5] Carotid artery plaque

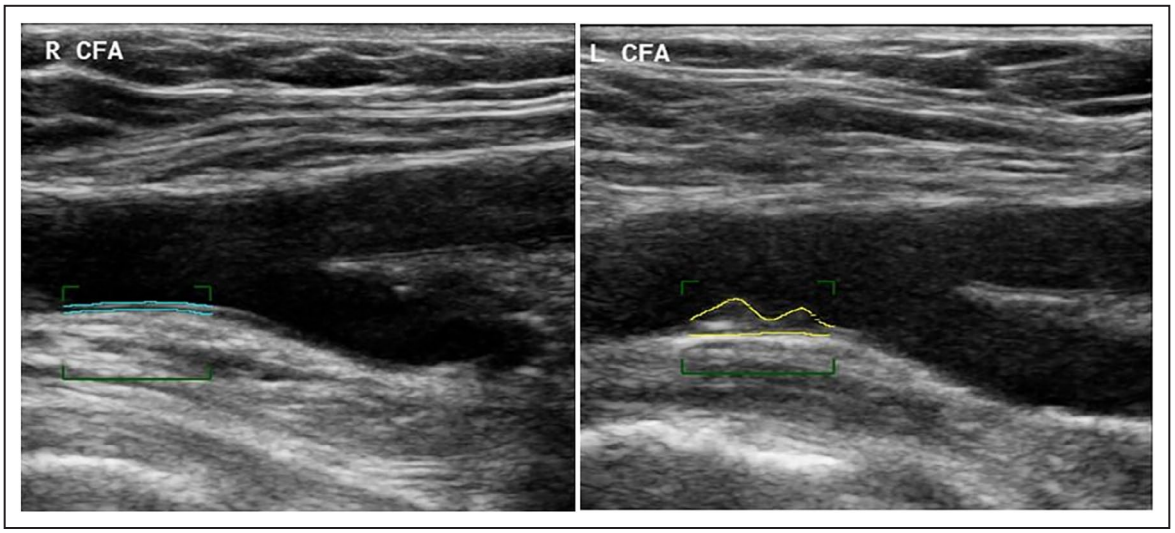

Figure 2. Measurement of normal femoral intima-media thickness in the right CFA (left panel), and plaque in the left CFA in the probe-far wall (right panel).
CFA indicates common femoral artery; L, left; and R, right.

was defined as a focal maximum IMT ≥1.5 mm according to the Mannheim consensus.[12]

Conventional Coronary Angiography and CCTA

Coronary imaging was performed in 119 patients: 98 CCTAs and 21 conventional coronary angiograms (Figure 1). Patients who had known CAD before the index stroke did not undergo new coronary angiography, but were categorized on the basis of previous angiographic findings. Among the 98 CCTAs, 58 were performed according to the substudy protocol in patients without symptoms of CAD, but presence of femoral plaque in at least 1 of the 4 femoral artery segments during index hospitalization. Asymptomatic patients with eGFR <30 mL/min per 1.73 m^2 were not referred for cardiac CT to assess subclinical CAD because of the administration of intravenous contrast agents and risk of subsequent renal function deterioration. Coronary artery calcium (CAC) scoring was assessed in all cases. Appropriate CCTA was performed in 56 of 58 patients, whereas 2 underwent conventional coronary angiography because of severely elevated CAC scores. Forty CCTAs were performed because of symptoms or acute coronary syndromes during follow-up. For ECG-triggered CT scanning, a dual-source 128-slice Siemens Somatom FLASH or the 256-slice Somatom FORCE (www.siemenshealthineers.com) was used. Noncontrast scans were obtained for CAC quantification by the Agatston method before intravenous administration of contrast agents,[13] whereas the lumen of the coronary arteries was evaluated after intravenous contrast administration. According to the Society of Cardiovascular Computed Tomography guidelines,[14] obstructive CAD was defined as ≥50% stenosis in any segments of the major epicardial arteries (Figure 3) and high-risk CAD (prognostic lesions) as obstructive lesions in the left main stem, the proximal left anterior descending artery, or affecting all 3 major arterial territories with at least 1 proximal segment involved.

Echocardiographic Evaluation

Echocardiographic examinations were performed using commercially available echocardiographic systems (276 patients by Vivid E9 system; GE Vingmed Ultrasound, Horten, Norway). Systolic and diastolic LV function, LV volumes, wall thickness, and aortic root diameter were measured according to the international guidelines.[15] The presence and severity of heart valve disease were also noted. The peak global longitudinal strain was measured by speckle-tracking analysis of the apical 4-, 2-, and 3-chamber views, using a 17-segment model. The region of interest was automatically generated and manually adjusted when necessary.

Study End Points

All-cause mortality or a composite of hospitalization for new stroke or all-cause death were the end points of interest when reviewing the electronic patient records. Follow-up was complete in all patients and calculated from the index stroke to the date of death or censoring. Patients were censored at last vital status assessment

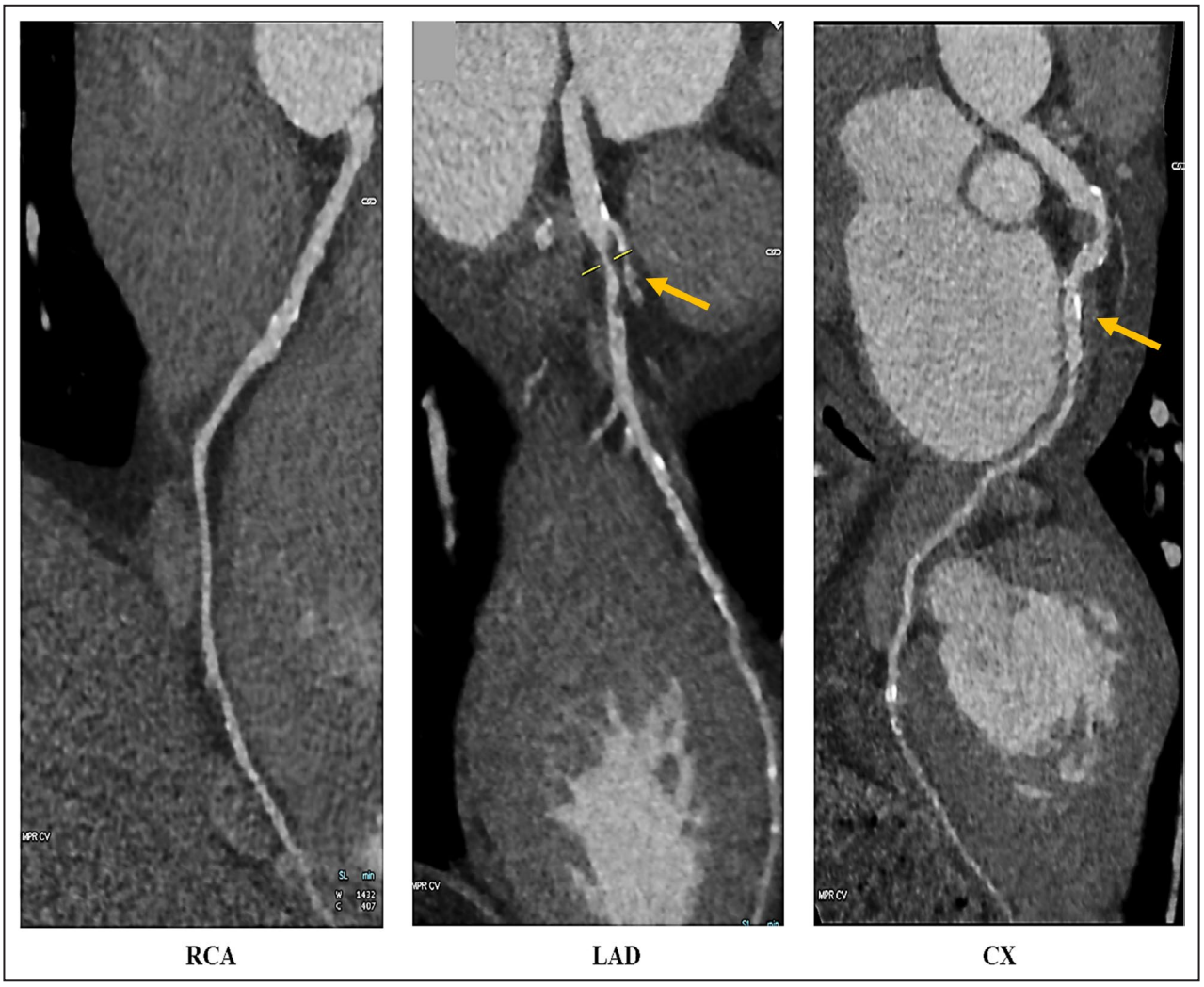

Figure 3. Coronary CT angiogram of a 44-year-old male study participant showing varying degrees of atherosclerosis in the coronary arteries.
RCA has modest, but scattered, calcification of the arterial wall, whereas the LAD has subtotal, ostial occlusion and significant lumen reduction with soft plaque (arrow). The CX displays moderate atherosclerosis in the midsection with moderate stenosis (arrow). CT indicates computed tomography; CX, left circumflex artery; LAD, left anterior descending artery; and RCA, right coronary artery.

by June 15, 2023, if they did not experience the event of interest.

Ethical Approval

The study was approved by the Regional Committee for Medical Research Ethics of Western Norway (2010/74/REK vest and 07.06.2012/74 REK vest) and conducted in accordance with the Declaration of Helsinki. All patients or their legal representatives signed a written informed consent.

Statistical Analysis

Statistical analyses were performed using the SPSS statistical program version 29 (IBM, Armonk, NY). The data were assessed for normality of distribution and transformed as appropriate. Results were expressed as proportions/percentages for categorical variables, mean±SD for normally distributed data, and median (interquartile range) for nonnormally distributed variables (CAC score). Patients were subdivided into 3 groups for comparisons: no CAD, nonobstructive CAD, and obstructive CAD. Intergroup comparison was done by independent Student *t* test (ANOVA for multiple comparison) and χ^2 test, as appropriate. Bivariate correlations were evaluated by Spearman or Pearson correlation coefficient (*R*). Event-free survival was evaluated by using the Kaplan-Meier method and Cox proportional hazard models to adjust for potential confounders. Covariate selection for the multivariable models was based on clinical considerations (sex, smoking,

Table 1. Baseline Demographics, Clinical Characteristics, and Outcomes According to the Presence (Nonobstructive Versus Obstructive) or Absence of CAD in Young and Middle-Aged Patients With Ischemic Stroke

Variable	Total study population (n=385)	No CAD (n=288)*	Nonobstructive CAD (n=37)	Obstructive CAD (n=60)	*P* value
Age, y	49.6±9.7	48.6±10.3	52.0±9.0	52.7±5.4	0.003
Men, n (%)	262 (68.1)	181 (62.8)	30 (81.1)	51 (85.0)	0.001
Current smoking, n (%)	158 (41.0)	113 (39.2)	18 (48.6)	27 (45.0)	0.436
Body mass index, kg/m^2	27.3±5.2	27.1±5.5	27.3±3.3	28.3±4.4	0.284
Obesity, n (%)	103 (26.8)	71 (24.7)	8 (22.2)	24 (39.7)	0.052
Waist circumference, cm	96.0±14.0	95±15	98±10	100±11	0.02
Atrial fibrillation, n (%)	33 (8.6)	20 (6.9)	2 (5.4)	11 (18.3)	0.013
Office systolic BP, mm Hg	133±19	131±18	138±17	142±19	<0.001
Office diastolic BP, mm Hg	81±10	81±10	83±10	86±12	0.002
Hypertension, n (%)	258 (67.0)	180 (62.5)	26 (70.3)	52 (86.6)	<0.001
Antihypertensive treatment, n (%)	230 (59.6)	155 (54.0)	24 (63.9)	51 (84.5)	<0.001
Statins, n (%)	59 (15.2)	23 (8.0)	6 (16.7)	30 (50.0)	<0.001
Diabetes, n (%)	57 (14.8)	31 (10.8)	8 (21.6)	18 (30.0)	0.001
Metabolic syndrome, n (%)†	107 (34.9)	68 (29.4)	14 (46.7)	25 (54.3)	0.002
Target organ damage, n (%)	168 (43.6)	102 (35.4)	25 (67.6)	41 (68.3)	<0.001
Hypercholesterolemia, n (%)	229 (60.1)	174 (60.8)	23 (65.7)	32 (53.3)	0.434
Total cholesterol, mmol/L	5.4±1.3	5.4±1.1	5.6±1.7	5.3±1.6	0.573
Hemoglobin, g/dL	15.0±1.4	14.9±1.4	15.2±1.1	15.1±1.5	0.328
Fasting blood glucose, mmol/L	5.9±1.9	5.6±1.6	6.0±1.4	7.1±2.7	<0.001
HbA_{1c}, %	6.0±1.9	5.7±0.8	5.9±1.2	6.6±1.6	<0.001
eGFR, mL/min per 1.73 m^2	96±17	97±17	97±14	91±17	0.057
Outcomes, n (%)					
All-cause deaths	36 (9.4)	22 (7.6)	2 (5.4)	12 (20.0)	0.008
Composite end point of stroke, AMI, and/or death	84 (21.8)	40 (13.9)	2 (5.4)	42 (70.0)	<0.001
Composite end point of stroke and/or death	64 (16.6)	40 (13.9)	2 (5.4)	22 (36.7)	<0.001

Data are given as mean±SD unless otherwise indicated. Missing cases: metabolic syndrome, 77; hypercholesterolemia, 4. AMI indicates acute myocardial infarction; BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; and HbA1c, glycosylated hemoglobin A_{1c}.

*No history of CAD, no femoral plaque on vascular ultrasound, and not screened for CAD.

†Defined according to the 2005 modified American Heart Association/National Heart, Lung, and Blood Institute criteria, as previously reported in detail.[6]

and hypertension) and significant univariate association with the end points: age, sex, smoking, hypertension, atrial fibrillation, CAD, and target organ damage in model 1 for all-cause mortality; and age, sex, smoking, hypertension, atrial fibrillation, diabetes, CAD, eGFR, cIMT, pulse wave velocity in continuous scale (m/s), and LV hypertrophy in model 2 for composite end point of death or recurrent ischemic stroke. Overall target organ damage, which incorporated increased cIMT, pulse wave velocity ≥10 m/s, and/or LV hypertrophy, was preferred over the individual components when assessing the predictors of all-cause mortality attributable to few events. Furthermore, eGFR and diabetes were not entered into model 1 because of the multicollinearity in that target organ damage; a complication of chronic kidney disease and diabetes were already present in the model. The proportional hazards assumption was systematically checked using Schoenfeld residuals, and no significant violations were found. Smoking was entered as a time-dependent covariate.

RESULTS

The study included 385 patients with a mean±SD age of 49.6±9.7 years, of whom 68.1% were men, 26.8% were obese, 53.4% were current or ex-smokers, 67.5% had hypertension, and 8.6% had atrial fibrillation. Atrial fibrillation was less common in younger patients aged 15 to 44 years, compared with middle-aged patients aged 45 to 60 years (2.2% versus 10.6%; *P*=0.011). On the basis of the screening algorithm and coronary imaging, the prevalence of CAD was 25.2% (95% CI, 20.8%–29.6%) (n=97) (nonobstructive, 9.6% [95% CI, 7.0%–12.5%] [n=37]; and obstructive, 15.6% [95% CI, 12.2%–19.5%] [n=60]). The rest, 74.8% (n=288), was classified as no CAD (Figure 1).

Table 2. Ischemic Stroke Subtypes According to the TOAST Classification in Patients With No CAD, Nonobstructive CAD, and Obstructive CAD

Subtype	Total study population (n=385)	No CAD (n=288)	Nonobstructive CAD (n=37)	Obstructive CAD (n=60)	*P* value
LAA	27 (7)	14 (5)	1 (3)	12 (20)	<0.001
CE	105 (27)	76 (26)	6 (16)	23 (38)	
SAO	74 (19)	58 (20)	7 (19)	9 (15)	
SOC	41 (11)	36 (12)	2 (5)	3 (5)	
SUC	138 (36)	104 (36)	21 (57)	13 (22)	

Data are given as number (percentage). CAD indicates coronary artery disease; CE, cardiac embolism; LAA, large-artery atherosclerosis; SAO, small-artery occlusion; SOC, stroke of other determined cause; SUC, stroke of undetermined cause; and TOAST, Trial of Org 10 172 in Acute Stroke Treatment.

Clinical Characteristics of Patients According to the Presence of CAD

Baseline demographics and clinical characteristics according to the severity of CAD are presented in Table 1, and ischemic stroke subtypes according to the TOAST classification are presented in Table 2. Patients with obstructive CAD had more often large-artery atherosclerosis and cardiac embolism TOAST subtypes, whereas patients with nonobstructive CAD were more likely to have stroke of undetermined cause (Table 2). There was a progressive increase in age, BP, proportion of men, and prevalence of hypertension, diabetes, and metabolic syndrome with increasing CAD severity (from no CAD to nonobstructive CAD and obstructive CAD). Statins were more frequently used by patients with obstructive CAD compared with those with no CAD or nonobstructive CAD. Although there was no significant difference in body mass index between groups, waist circumference differed significantly, with obstructive CAD representing the highest waist circumference. Atrial fibrillation was nearly 3-fold more common in patients with obstructive CAD compared with patients with no CAD or those having nonobstructive CAD. Mean cIMT, pulse wave velocity, LV mass, and filling pressure(measured by early diastolic mitral inflow velocity (E) divided by early diastolic mitral annular tissue velocity (e') (E/e' ratio)) were all highest in patients with obstructive CAD and lowest in patients with no CAD (Table 3). LV ejection fraction was equally represented across the groups (*P*-ANOVA=0.297), but global longitudinal strain was significantly impaired (less negative) in patients with obstructive CAD

Table 3. Arterial Stiffness Indexes and Echocardiographic Parameters According to the Presence (Nonobstructive Versus Obstructive) or Absence of CAD in Young and Middle-Aged Patients With Ischemic Stroke

Variable	Total study population (n=385)	No CAD (n=288)*	Nonobstructive CAD (n=37)	Obstructive CAD (n=60)	*P* value
Mean carotid IMT, mm	0.84±0.29	0.80±0.26	0.96±0.35	0.97±0.33	<0.001
Carotid plaque, n (%)	38 (9.9)	20 (7.0)	8 (21.6)	10 (16.9)	0.003
PWV, m/s	7.8±1.9	7.5±1.8	8.6±2.0	8.7±2.3	<0.001
PWV ≥10 m/s, n (%)	44 (12.5)	24 (9.0)	7 (21.2)	13 (24.1)	0.003
High for age PWV, n (%)†	56 (15.9)	33 (12.4)	9 (27.3)	14 (25.9)	0.008
LV mass, g	179±57	174±57	179±37	205±62	0.008
LV mass index, g/m$^{2.7}$	39.4±11.8	38±12	40±8	44±13	0.002
LV hypertrophy, %	43 (15.6)	29 (13.6)	5 (18.5)	9 (25.0)	0.199
LV ejection fraction, %	63±7	64±7	64±5	62±8	0.297
Global longitudinal strain, %	−17±3	−18±3	−18±2	−16±3	0.023
Stroke volume index, mL/m^2	50±15	50±13	52±22	50±17	0.843
E/e′ ratio	9±4	9±4	10±3	11±4	0.017
Left atrial volume index, mL/m^2	23±9	23±9	21±9	23±9	0.046

Data are given as mean±SD unless otherwise indicated. Missing values: carotid plaque, 4; PWV, 32; LV mass, 109. CAD indicates coronary artery disease; IMT, intima-media thickness; LV, left ventricular; E/e' ratio, early diastolic mitral inflow velocity (E) divided by early diastolic mitral annular tissue velocity (e'); and PWV, pulse wave velocity.

*No history of CAD, no femoral plaque on vascular ultrasound, and not screened for CAD.

†PWV higher than age-adjusted normative values, as previously reported in detail.[8]

Table 4. Cardiac CT Findings in a Subsample of Patients (n=58) With No Symptoms of CAD, But Evidence of Femoral Plaque in at Least 1 of the 4 Femoral Artery Segments Assessed by Vascular Ultrasound

Coronary artery calcium score (AU)	Median (25th–75th percentile)
	37 (0–215)

Prognostic (high-risk) lesions	Left main stem (segment 5)	Proximal and/or mid LAD (segments 6–7)
No atherosclerosis	43 (74.1)	17 (29.3)
Atherosclerosis: nonobstructive	15 (25.9)	28 (48.3)
Atherosclerosis: obstructive	0	13 (22.4)

Data are given as number (percentage). AU indicates arbitrary unit; CAD, coronary artery disease; CT, computed tomography; and LAD, left anterior descending artery.

(–16%) and preserved (more negative) in patients with no CAD (–18%; *P*=0.023). Mean cIMT and pulse wave velocity had a moderate positive correlation (*R*=0.42; *P*<0.001), whereas the correlation of CAC score with cIMT (*R*=0.048; *P*=0.651) and pulse wave velocity (*R*=0.18; *P*=0.096) was poor. The prevalence of target organ damage was comparable between patients with obstructive and nonobstructive CAD, but was nearly twice as high compared with patients with no CAD (Table 1). The laboratory findings of the study groups are presented in Table 1.

Characteristics of Patients Screened for Subclinical CAD

In the substudy of 58 patients without history of CAD, who underwent cardiac CT as part of screening for subclinical CAD following the detection of femoral plaque on vascular ultrasound, 46% (n=27) had nonobstructive CAD and 28% (n=16) had obstructive CAD (17.2% had 1-vessel disease, 3.4% had 2-vessel disease, and 6.9% had 3-vessel disease), and 26% (n=15) had normal coronary arteries. The distribution of CAC score categories and prognostic (high-risk) lesions in the coronary arteries is presented in Table 4 and Figure 4A. The percentage of nonobstructive lesions in the left main stem was 26% (n=15), with no obstructive lesions, whereas a vast majority of patients had anatomically a normal left main stem (Figure 4B). Nonobstructive lesions in the proximal or mid left anterior descending artery appeared in 48.3% (n=28), obstructive lesions in 22.4% (n=13), whereas in 29.3% (n=17) patients, the left anterior descending artery was found to be normal (Figure 4B).

Outcomes

During a median follow-up of 10.1 years (interquartile range, 8.9–11.5 years), 36 deaths (9.4%) occurred: 4 in the younger group of 15 to 44 years and 32 in the middle-aged group of 45 to 60 years (*P*=0.055). Overall 1-year mortality was 3.1%. The proportion of patients who deceased was 20.0% (n=12) in patients with obstructive CAD and 7.4% (n=24) in patients with no CAD or nonobstructive CAD (*P*=0.002) for the whole study period. A total of 84 (21.8%) patients reached the composite end point of recurrent stroke, myocardial infarction, or death, with as many as 70% (n=42/60) of those with obstructive CAD. In the study period, 64 (16.6%) patients had a composite end point of recurrent stroke or death (28 recurrent strokes and 36 deaths), of whom 12.9% (n=42) were in the no CAD or nonobstructive CAD groups, and 36.7% (n=22) in the obstructive CAD group (Table 1).

Univariate predictors of all-cause mortality and the composite events of all-cause mortality+new stroke

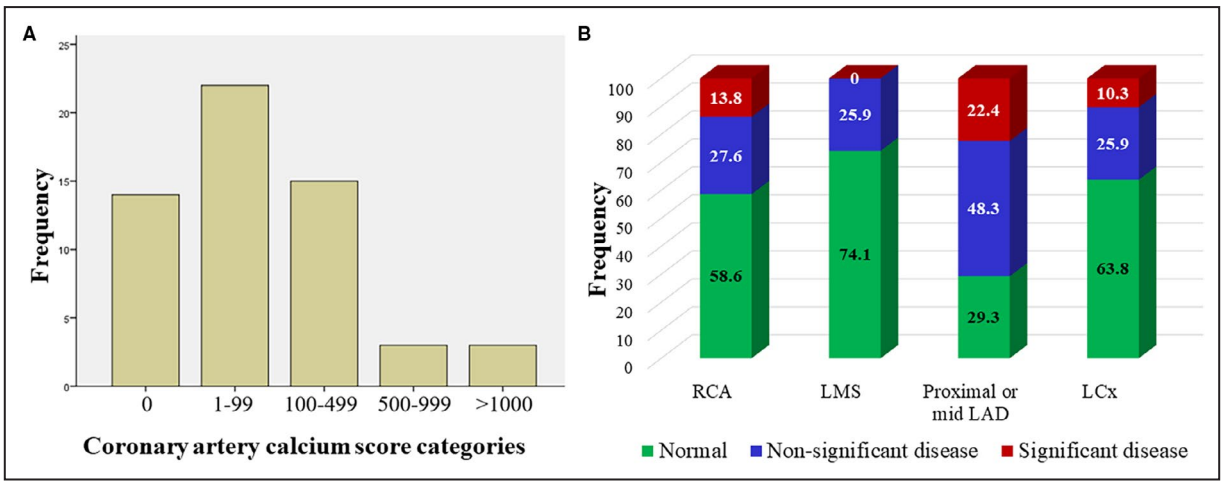

Figure 4. Findings on coronary imaging.
A, Distribution of coronary artery calcium score. **B**, Burden of significant and nonsignificant coronary artery disease in the RCA, LMS, LAD, LCx, and left main arteries with prognostic importance (LMS and proximal and mid LAD). LAD indicates left anterior descending artery; LCx, left circumflex artery; LMS, left main stem; and RCA, right coronary artery.

Table 5. Predictors of All-Cause Death and Composite Events in Univariate and Multivariable Cox Regression Analyses

	All-cause death		Composite events (death and/or stroke)	
	Univariate			
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.06 (1.01–1.11)	0.015	1.03 (1.00–1.06)	0.057
Male sex	1.04 (0.51–2.12)	0.850	1.27 (0.69–1.96)	0.562
Smoking	2.55 (1.19–5.47)	0.016	1.17 (0.71–1.93)	0.541
Body mass index, kg/m^2	0.95 (0.88–1.03)	0.220	1.02 (0.98–1.07)	0.341
Atrial fibrillation	2.76 (1.21–6.31)	0.016	2.37 (1.24–4.55)	0.009
Coronary artery disease	3.09 (1.54–6.19)	0.001	3.34 (2.00–5.61)	<0.001
Log CAC score	1.10 (0.56–2.15)	0.784	1.04 (0.67–1.60)	0.865
Hypertension	2.41 (1.00–5.82)	0.050	3.55 (1.69–7.46)	0.001
Antihypertensive treatment	1.80 (0.83–3.88)	0.135	2.48 (1.34–4.60)	0.004
Diabetes	2.39 (1.11–5.12)	0.026	2.41 (1.28–4.53)	0.006
Target organ damage	6.46 (2.68–15.57)	<0.001	2.53 (1.50–4.24)	<0.001
Total cholesterol, mmol/L	0.71 (0.53–0.96)	0.024	0.86 (0.69–1.06)	0.145
eGFR, mL/min per 1.73 m^2	0.97 (0.96–0.98)	<0.001	0.98 (0.97–0.99)	0.001
Office systolic BP, mm Hg	1.00 (0.98–1.03)	0.768	1.01 (1.00–1.03)	0.067
Office diastolic BP, mm Hg	1.01 (0.97–1.05)	0.590	1.02 (1.00–1.05)	0.044
Mean carotid IMT, mm	3.70 (1.77–7.45)	0.001	2.01 (1.02–3.98)	0.045
PWV, m/s	1.17 (0.97–1.40)	0.101	1.16 (1.02–1.31)	0.023
LV hypertrophy	4.20 (1.46–12.12)	0.008	3.33 (1.64–6.76)	0.001
LV ejection fraction, %	0.97 (0.90–1.04)	0.365	0.97 (0.93–1.01)	0.173

	Multivariable			
	Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (per year)	1.03 (0.97–1.08)	0.318	1.01 (0.95–1.07)	0.760
Male sex	1.63 (0.79–3.37)	0.189	1.64 (0.75–3.61)	0.215
Current smoking	1.23 (0.64–2.39)	0.534	0.89 (0.43–1.83)	0.749
Atrial fibrillation	1.61 (0.67–3.88)	0.284	1.99 (0.72–5.46)	0.184
Coronary artery disease	2.19 (1.03–4.67)	0.042	3.33 (1.48–7.52)	0.004
Hypertension	0.93 (0.38–2.30)	0.875	1.62 (0.57–4.59)	0.365
Diabetes			1.26 (0.51–3.12)	0.619
eGFR, mL/min per 1.73 m^2			0.98 (0.96–1.00)	0.064
Mean carotid IMT, mm			1.33 (0.38–4.62)	0.658
PWV, m/s			1.09 (0.91–1.31)	0.367
LV hypertrophy			1.95 (0.85–4.46)	0.115
Target organ damage*	4.39 (1.78–10.82)	0.001		

BP indicates blood pressure; CAC, coronary artery calcium; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IMT, intima-media thickness; LV, left ventricular; and PWV, pulse wave velocity.

*Defined as PWV ≥10 m/s, presence of left ventricular hypertrophy on echocardiography, or increased carotid IMT (>0.9 mm) on carotid ultrasound.

are presented in Table 5. The CAC score did not predict all-cause death or combined events. However, CAD (previously known clinical CAD+newly detected obstructive CAD on CCTA or coronary angiography) was associated with a nearly 3.1-fold increased risk of all-cause mortality and 3.3-fold risk of the combined event of all-cause mortality and recurrent stroke. Kaplan-Meier curves showed significantly (log-rank *P*<0.001) lower event-free survival for patients with obstructive CAD versus no CAD or nonobstructive CAD (Figure 5A and 5B). In a multivariable Cox regression model (model 1), CAD was identified as an independent predictor of all-cause mortality (hazard ratio [HR], 2.19 [95% CI, 1.03–4.67]; *P*=0.042) after adjustment for age, sex, smoking, hypertension, atrial fibrillation, and overall target organ damage (Table 5). In a different

multivariable Cox regression model (model 2) adjusted for age, sex, smoking, atrial fibrillation, hypertension, diabetes, eGFR, mean cIMT, pulse wave velocity, and LV hypertrophy, CAD was identified as a strong and independent predictor of the composite end point of all-cause mortality or recurrent ischemic stroke (HR, 3.33 [95% CI, 1.48–7.52]; *P*=0.004). In the same multivariable Cox regression model (model 2), when hypertension and the individual components of target organ damage (cIMT, pulse wave velocity, and LV hypertrophy) were replaced by overall target organ damage, CAD (HR, 2.52 [95% CI, 1.43–4.43]; *P*=0.001), overall

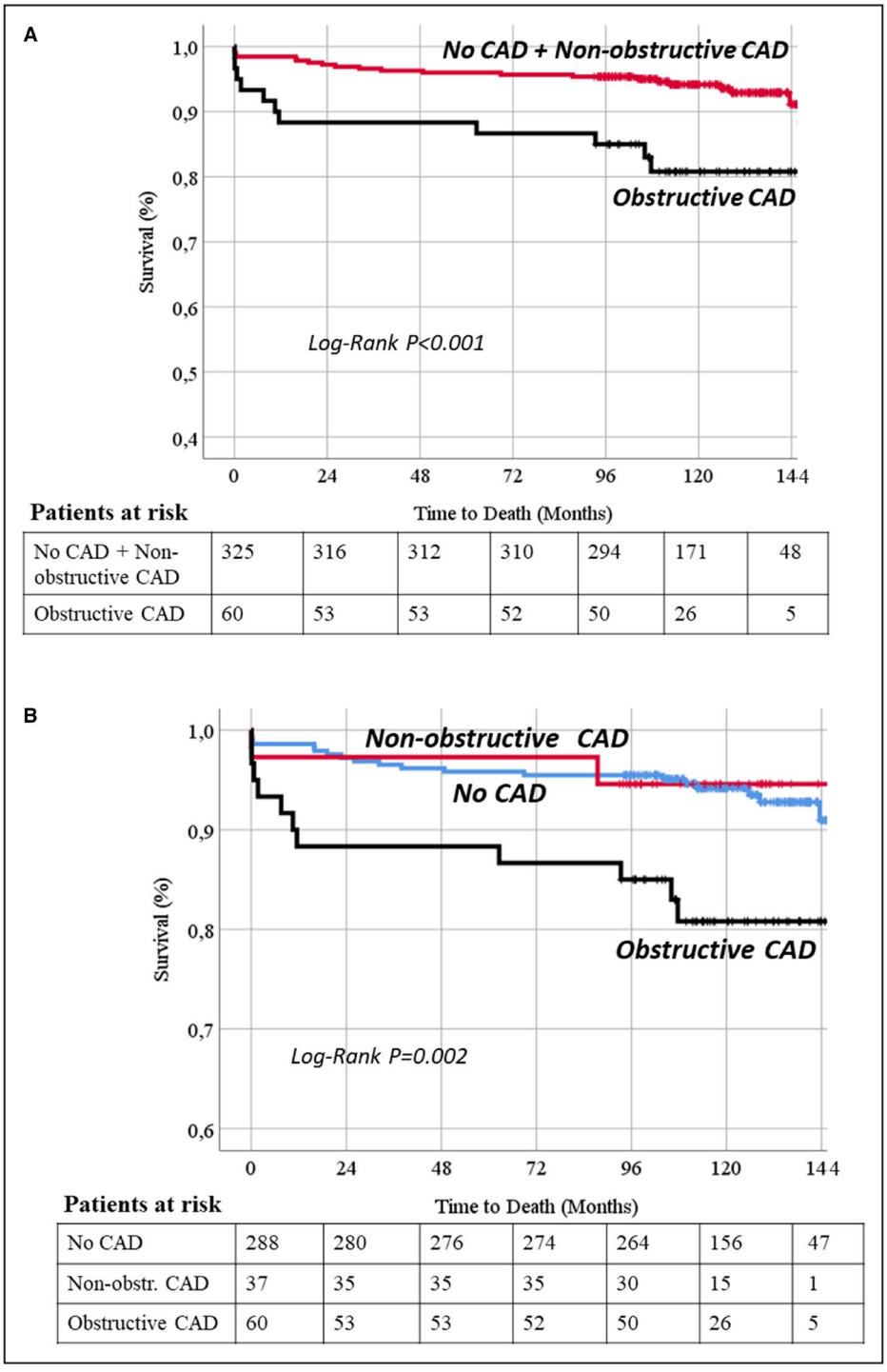

Figure 5. Kaplan-Meier curves.
A, Overall survival in patients with no CAD and nonobstructive CAD vs obstructive CAD. **B**, Overall survival in patients with normal coronary arteries (no CAD), nonobstructive CAD, and obstructive CAD. CAD indicates coronary artery disease.

target organ damage (HR, 1.87 [95% CI, 1.06–3.28]; *P*=0.001), and lower eGFR (HR, 1.01 [95% CI, 1.00–1.03]; *P*=0.032) remained significantly associated with a higher risk of the composite end point of all-cause mortality or recurrent ischemic stroke independent of the nonsignificant association of age, sex, smoking, diabetes, and atrial fibrillation.

In the substudy of 58 patients, with regard to subclinical CAD, there were 1 (6.7%) death in the no CAD group, 1 (4%) death in the nonobstructive CAD group, and 3 (16.7%) deaths in the obstructive CAD group (*P*=0.328). Median CAC score was 29 (range, 0–3443) in patients who survived versus 124 (range, 0–1347) in patients who deceased (*P*=nonsignificant). In this subgroup, CAC score did not predict all-cause mortality (HR, 1.57 [95% CI, 0.72–3.42]; *P*=0.259) or combined events (all-cause mortality+stroke) (HR, 1.02 [95% CI, 0.58–1.80]; *P*=0.950).

DISCUSSION

In the present study of young and middle-aged patients with ischemic stroke, a quarter of patients had concomitant CAD, which was a strong and independent predictor of new cardiovascular events and mortality. Patients with CAD had a significantly higher burden of traditional cardiovascular risk factors and were more likely to have increased arterial stiffness, higher LV mass, more often diastolic dysfunction, and subclinical systolic LV dysfunction. Interestingly, the association between CAD and cardiovascular events was independent of target organ damage (LV hypertrophy, increased cIMT, and/or pulse wave velocity) and lower eGFR.

CAD in Patients With Stroke

Patients with ischemic stroke or transient ischemic attack have a high risk of myocardial infarction, and myocardial infarction was identified as a major cause of death in previous long-term follow-up studies.[16–19] It has been demonstrated that patients with ischemic stroke who did not have previously known CAD had approximately a 2-fold higher risk of subsequent myocardial infarction compared with the general population.[17] Notably, the age-adjusted risk for future myocardial infarction was higher in patients aged <60 years at the time of index stroke/transient ischemic attack. These results highlight the importance of studies identifying subgroups of patients with ischemic stroke at highest risk of future myocardial infarction. However, there are still only few studies in the literature investigating the burden and prognostic impact of CAD in patients with stroke, particular in younger patients with stroke.

When myocardial infarction is associated with ischemic stroke, the risk of morbidity and mortality increases substantially.[20,21] Therefore, the detection of atherosclerotic CAD at a preclinical stage in these patients is of paramount importance to initiate preventive treatment and prevent plaque rupture and acute myocardial infarction. Given the shared risk factors for stroke and CAD, management of patients with stroke, particularly young patients, often requires a multidisciplinary approach involving stroke physicians, cardiologists, and specialists in emergency medicine.[22] Coronary CT/CCTA is now an established noninvasive imaging modality for the assessment of CAD, with high sensitivity for ruling out obstructive CAD.[23,24] In addition, CCTA has the ability to detect early subclinical CAD, quantify plaque burden, and identify vulnerable plaque features. CAC scoring is an attractive imaging modality for younger and middle-aged individuals to improve risk stratification of patients with atherosclerotic CVD.[24] The key advantages of CAC scoring are its relatively low cost, widespread availability, and no need for intravenous contrast administration. The higher the CAC score, the higher the burden of underlying atherosclerotic plaques, and thereby increased risk of plaque rupture and new vascular events, such as myocardial infarction or stroke. Calcium content is seen as an end stage of an atherosclerotic plaque, indicating that the plaque already existed for a potentially long time. CAC score is a strong predictor of obstructive CAD and future acute coronary events. Nevertheless, data on the use of CCTA for improving CVD risk stratification in patients with ischemic stroke, especially young and middle-aged patients, are sparse. Nearly a half of our patients without history of CAD or symptoms, but with femoral plaques on vascular ultrasound, had nonobstructive CAD, and one-fourth had obstructive CAD. In the vast majority of patients in this subset, left anterior descending artery (proximal and mid) was the most commonly affected coronary artery (71%). These patients would have been missed if not screened by CCTA.

Prevalence of CAD in Patients With Stroke

In previous studies, the prevalence of CAD in patients with stroke (mean age, 54.6–76 years) was reported to be between 18% and 52%.[25–28] Indeed, autopsy series have shown even higher (80%) prevalence of CAD in patients with stroke (mean age, 59.0–72.3 years),[29,30] depending on patients' age and burden of underlying CVD. Some studies by design systematically excluded younger patients (aged <40 years) and those with symptomatic myocardial infarction or previous coronary artery bypass graft surgery, underestimating the prevalence of CAD in patients with stroke.[26] Furthermore, in a prospective study of 405 patients with stroke (mean age, 62.6 years; 74% men), the prevalence of asymptomatic myocardial ischemia,

documented by angiography for research purposes, was reported to be as high as 77%.[31] The huge variation in the prevalence estimates across the studies can be explained by several factors, including age of the populations studied, symptomatic status, method for the definition of CAD, and the imaging modality used for diagnosing CAD. We found a 25% overall prevalence of CAD (including 16% angiographically obstructive CAD) in our young and middle-aged patients with ischemic stroke. However, we expect that the true prevalence of CAD in our study may be underestimated as CCTA was not performed systematically in all patients.

Predictors of Recurrent Cardiovascular Events and Mortality

We demonstrated that event-free survival was significantly lower in patients with obstructive CAD versus no CAD, as shown by Kaplan-Meier curves. This was confirmed by multivariable Cox regression models, in which CAD was an independent predictor of all-cause mortality and composite end point of death or recurrent ischemic strokes adjusted for potential confounders and prognosticators.

In a multicenter cohort study of 682 203 patients with first ischemic stroke (mean age, 63 years), stratified by sex and age categories (<75/≥75 years), a composite of newly diagnosed cardiovascular complications, including ischemic heart disease following an incident ischemic stroke, was found in 20% of the patients (comparable for both sexes), and was associated with significantly worse long-term prognosis compared with stroke survivors without recurrent vascular complications.[32] However, the composite of newly diagnosed cardiovascular complications in this study did not only include ischemic heart disease, but also heart failure, atrial fibrillation, ventricular arrhythmias, and Takotsubo syndrome. Furthermore, the same author group acknowledged that it was unclear whether the new-onset cardiovascular complications, diagnosed after ischemic stroke, were the consequences of stroke, or contributed to stroke, and therefore appealed for more prospective research studies.[33] Alqahtani et al investigated the impact of acute myocardial infarction complicating acute ischemic stroke on early mortality and showed that acute myocardial infarction complicating ischemic stroke was rare, but associated with a 3-fold increased risk of mortality and 50% increase in the length of hospital stay, and with significant financial burden.[34] Other studies have also shown that serious cardiac events were common in the acute period after stroke and associated with a dismal prognosis.[35] However, as mentioned earlier, it is not always easy to determine whether the new-onset cardiovascular complications, such as acute myocardial infarction and/or heart failure, in the context of acute ischemic stroke, are consequences of (neurogenic stunning myocardium) or contributors to stroke. Long-term follow-up data on the burden and prognostic impact of CAD in patients with ischemic stroke are scarce in the literature. Here, we present data on CAD and recurrent stroke during a 10-year follow-up of young and middle-aged patients with ischemic stroke. CAD, but not atrial fibrillation or LV ejection fraction, was an independent predictor of mortality. This suggests that CAD is a major negative determinant of early and long-term prognosis in patients with ischemic stroke. In a prospective follow-up study of 970 young patients with stroke (aged 15–49 years) from Finland,[2] a total of 15.7% patients died and 13.6% experienced a recurrent stroke during a mean±SD follow-up of 10.2±4.3 years. These estimates are higher than ours despite the fact that our study included patients up to 60 years. A possible explanation may be the use of statins on a more liberal basis, and more aggressive approach for low-density lipoprotein–lowering criteria over the past decades. In their univariate analyses,[2] CAD was associated with higher mortality. However, in the multivariable models, the focus was directed toward the prognostic value of recurrent stroke, and not CAD. Furthermore, although the reported 4.6% CAD prevalence might well be representative in their younger stroke population, this estimate again highlights the importance of a careful CAD definition and systematic screening by multimodality coronary imaging, which, per design, was not part of their study. Our strategy of femoral artery screening by vascular ultrasound and the algorithm of coronary imaging in patients with stroke seem to be effective and detect high-risk patients, in whom optimal treatment of the traditional cardiovascular risk factors is essential to reduce the risk of future vascular events.

Finally, in a most recent study of 406 patients (median age, 71.8 years; 57.9% men) with acute ischemic stroke or transient ischemic attack, Lainelehto et al explored the impact of CT angiography-defined atherosclerotic burden in the brain-supplying arteries (cervicocerebral arteries) on mortality.[36] After a median follow-up of 7.3 years, 136 patients died, including 77 from cardiovascular causes. CAD, with a prevalence of 15.7% in their study, was associated with mortality in univariate Cox regression analyses. However, after extensive adjustments of the multivariable models, it was the cervicocerebral atherosclerosis burden score, but not CAD, that was associated with mortality. The findings of the study by Lainelehto et al suggest that knowledge of the overall atherosclerosis burden is prognostically relevant information instead of a simplified approach of presenting binary data (presence of or absence of CAD, peripheral artery disease, or carotid plaque). Indeed, we showed that proportion of patients with large-artery atherosclerosis according to the TOAST classification was significantly higher in those with obstructive CAD,

whereas patients with nonobstructive CAD were more likely to have stroke of undetermined cause (cryptogenic stroke), highlighting the need for an extensive post-stroke investigation. However, regardless of the burden of cervicocerebral atherosclerosis, patients with first-ever ischemic stroke and evidence of atherosclerosis in other arterial beds, in particular CAD or peripheral artery disease, pose a higher risk of early mortality.[37] Our results indicate that patients with multiple-site artery disease (cerebrovascular+peripheral artery disease+-CAD) are at higher risk of cardiovascular events. These are in line with previous reports showing that patients with a triple territory disease (atherosclerosis in cerebrovascular, coronary, and peripheral vascular beds) had a 3.5-fold risk of death compared with patients with a single territory disease and a 1.6-fold risk of death compared with patients with a double territory disease at a 10-year follow-up.[38] However, patients in these studies were not screened for asymptomatic CAD or peripheral artery disease, probably underestimating the real burden of multiple-site artery disease.

Clinical Implications

In younger and middle-aged stroke survivors, holistic and personalized cardiovascular health improvement strategies are required to reduce the risk of new cardiovascular events and the associated risk of mortality. Identification of patients with CAD is crucial, because CAD is one of the main causes of mortality in patients with stroke independent of the presence of other target organ damage or increased arterial stiffness. Therefore, we suggest a close collaboration between stroke neurologists/other stroke specialists and cardiologists, so that young and middle-aged patients with ischemic stroke, particularly those with evidence of femoral artery plaque, are systematically screened by a cardiac CT. This approach may help to develop more robust primary and secondary prevention strategies for young ischemic stroke survivors. Maintaining ideal cardiovascular health through mitigating modifiable risk factors for stroke and CAD, such as physical inactivity, poor diet, smoking, excessive alcohol consumption, sleep disorders, hypertension, diabetes, obesity, and hyperlipidemia, is essential to prevent premature vascular events. Indeed, a comprehensive cardiovascular health approach was recently introduced by the American Heart Association, termed "Life's Essential 8" metric,[39] and this approach has been shown to be associated with a lower lifetime risk of both CAD and stroke.

Limitations

Some patients with missing femoral ultrasound data (n=8) either because of unconsciousness at presentation leading to early death, or severe obesity, poor image quality, local site infections, or postpuncture conditions after cerebral thrombectomy, or those with moderate to severe renal failure, or lack of consent for cardiac CT were not referred for cardiac CT. Similarly, patients with other obvious reasons for stroke, such as patent foramen ovale or hypercoagulable disorders without any atherosclerosis on initial assessment, were not referred for cardiac CT. Cardiac CT was introduced in 2012, 2 years after start of inclusion, and patients with femoral plaques in the initial phase were not included in the substudy. On the basis of these considerations, the true prevalence of CAD in our study may be underestimated. The result of multivariable analyses should be cautiously interpreted, particularly for the causal relationships between variables. Although multivariable models were adjusted for potential confounders and prognosticators based on univariate associations, clinical relevance, and priori knowledge, the discriminatory effects of the variables in the models on outcome were not assessed, and should be validated in other cohorts with extended follow-up. Finally, this is a single-center study, and the results may not be applicable to other centers.

CONCLUSIONS

In the present study of young and middle-aged ischemic stroke survivors, the prevalence of CAD was 25%. In the substudy of 58 patients, without history of CAD, who underwent cardiac CT as part of screening for subclinical CAD following the detection of femoral plaque on vascular ultrasound, 46% had nonobstructive CAD and 28% had obstructive CAD. This subgroup of multiple-site artery disease (cerebrovascular+peripheral artery disease+CAD) may be exposed to significantly higher risk of cardiovascular events and mortality, and deserves an extensive evaluation of overlapping risk factors and cardiovascular imaging, including a low threshold for cardiac CT with regard to better risk stratification and treatment, and thereby reducing the risk of future vascular events and premature death.

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Disclosures

None.

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