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Long-term risk of stroke after acute coronary syndrome: the ABC-10* study on heart disease

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Abstract

Background Previous studies link myocardial infarction to increased stroke risk. This long-term prospective study examines stroke incidence and stroke-related mortality in acute coronary syndrome (ACS) patients, identifying risk factors and geographic disparities.

Methods We enrolled 535 ACS patients admitted to hospitals across three provinces in the Veneto region of Italy. Patients' residences were classified into three urban and three rural areas in each province. Patients were followed prospectively for 24 years or until death. Survival analysis was conducted using uni- and Multivariable Cox regression models.

Results All patients, except for three, completed the follow-up, totaling 6.151 person-years. During follow-up, 84 patients experienced a stroke, with 85% being ischemic and 15% hemorrhagic, proving fatal in 43 cases. The stroke incidence rate was 14/1.000 person-years. Older age (HR 1.84; 95% CI 1.30–2.60), atrial fibrillation (AF) (HR 2.64; 95% CI 1.49–4.67), and a higher albumin-to-creatinine ratio (ACR) tertile (HR 1.38; 95% CI 1.04–1.83) were independent predictors of overall stroke risk, while higher estimated glomerular filtration rate tertile (eGFR) (HR 0.71; 95% CI 0.53–0.95) was independent predictor a lower risk. A sub-analysis revealed older age (HR 2.67; 95% CI 1.60–4.45) and AF (HR 2.95; 95% CI 1.38–6.32) as independent predictors of fatal stroke. Unexpectedly, we observed a higher fatal stroke risk in urban areas (HR 1.89; 95% CI 1.03–3.48) and southern provinces (HR 1.71; 95% CI 1.15–2.53).

Conclusion This long-term cohort study reinforces the role of established clinical predictors (age, AF, renal function) in post-ACS stroke risk and highlights novel geographic disparities in fatal stroke outcomes. These findings support the integration of geographic and clinical risk stratification in long-term secondary prevention strategies.

Keywords Acute coronary syndrome, Stroke, Fatal stroke, Myocardial infarction, Urban-rural, Geographic difference, Follow-up studies

*ABC is an acronym for Adria, Bassano, Conegliano, and Padova Hospitals.

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Introduction

Globally, ischemic heart disease remains the number one cause of death, responsible for 16% of the world's total deaths, while cerebral stroke is the second leading cause of death, responsible for approximately 11% of total deaths and the number one cause of disability. Both are the top two causes of death in Italy for both men and women [1].

Previous studies have documented an increased risk of stroke, mainly ischemic stroke (IS), in patients who survived myocardial infarction (MI), with a 1-year risk ranging from 2 to 4% [2–4]. Coronary heart disease and some subtypes of IS are linked by inflammation and the development of atherosclerosis, and share several risk factors including age, hypertension, dyslipidemia, smoking, and diabetes. Additionally, MI can itself be a risk factor for stroke through mechanisms such as emboli, either during revascularization or from atrial fibrillation (AF) in association with acute MI or from blood stasis in a poorly functioning left ventricle [3]. However, most of these reports were based on retrospective analysis and were limited to short follow-up duration. Moreover, relatively few studies have examined the incidence and long-term outcomes of stroke in patients with ACS without ST-segment elevation [4–6], and to our knowledge, there are no reports about the geographic differences in stroke risk in this specific population.

In this long-term prospective study, we assessed the incidence of stroke and its clinical outcome, defined as fatal stroke, in a cohort of patients discharged alive after an index hospitalization for acute coronary syndrome (ACS) and followed for 24 years. An additional objective was to identify baseline risk factors associated with stroke occurrence in this high-risk population. We also explored potential geographic disparities in stroke risk across different areas within the Veneto region of Italy.

Methods

Patients

The ABC Study on Heart Disease (https://www.abcstudy.foundation/) is an ongoing prospective study designed to represent, as closely as possible, an unbiased population of patients with ACS. It includes Caucasian patients admitted to the intensive care units of three general hospitals in Italy's Veneto region between June 1995 and January 1998 with definite diagnosis of ACS, including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina pectoris (UAP) (supplementary Figure S1). The diagnostic criteria for ACS and patient eligibility were described previously [7].

Each patient was assigned an anonymous code, and neither the baseline nor the follow-up database contained any personal identifiers or confidential data.

Urban-rural classification

As detailed previously [8], the ABC study includes patients admitted to hospitals in the following cities in Veneto region in Italy: Conegliano-Vittorio Veneto (Treviso province, northern area), Bassano (Vicenza province, central area), and Adria-Cavarzere (Rovigo province, southern area). Geographic classification into urban and rural areas was based on the *Programma di Sviluppo Rurale del Veneto 2014–2020* (PSR), using criteria defined by EU Regulation 1305/2013 and the OECD methodology, refined with 2011 census data. Municipalities were classified based on population density, economic structure, and development characteristics. Urban areas included provincial capitals (>150 inhabitants/km^2), while remaining municipalities were categorized into rural subtypes [9]. The total population within the study area is 586,976, with 24% residing in urban, and 76% in rural areas [9, 10].

Measurements and follow-up

A comprehensive medical history was obtained from each patient through a review of medical records and direct interviews conducted at the time of enrolment. The baseline clinical and laboratory data analyzed were collected within the first seven days of hospitalization in the intensive coronary care unit, as previously described in detail [11–13].

Clinical follow-up assessments were performed for each patient at 1, 3, 5, 7, 10, 12, 15, 17, 20, 22, and 24 years after enrolment (7).

For this analysis, the pre-specified primary endpoint was the occurrence of cerebral stroke, defined according to the World Health Organization (WHO) criteria as a focal neurological deficit of sudden onset, persisting for at least 24 h or resulting in death and confirmed by the presence of an infarct in brain imaging. This included both ischemic stroke (IS) and hemorrhagic stroke (HS) [14]. The secondary endpoint was fatal stroke, defined as any stroke event (ischemic or hemorrhagic) that directly resulted in death within 30 days of onset, as documented by clinical records, death certificates, or official mortality data.

Data were collected from scheduled clinical examinations, public administration databases, hospital records, family physicians, post-mortem examinations, and death certificates. Information on medications administered during the index hospitalization as well as subsequent follow-up treatments was documented. All data following enrolment were recorded prospectively in accordance with the ABC Study on Heart Disease protocol [12]. Baseline and follow-up data were initially recorded in two separate datasheets. These datasets were subsequently merged upon the completion of the 24-year follow-up period.

Statistical analysis

For the statistical analysis, unpaired Student's t-tests were applied to compare continuous variables, while Pearson's chi-square (χ^2) tests were used for categorical variables. Log transformation was applied to variables with a highly skewed distribution (as ACR, eGFR, LDH) to approximate normality and allow for parametric analyses. This approach was chosen to stabilize variance and improve the interpretability of hazard ratios in Cox regression models. In cases where patients discontinued follow-up before completing the 24-year period, their data were censored at the time of dropout. Patients with missing baseline data ($n = 23$) were excluded from analysis. No imputation was performed.

In the survival analysis, continuous variables were categorized into terciles based on increasing values. Stroke incidence rates with person-time denominators were calculated. Person-time at risk was accumulated from index admission for ACS until stroke onset, death, or end of follow-up, whichever came first. Cox proportional hazards regression analysis was conducted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of stroke. We used cause-specific Cox proportional hazards regression to estimate the association between covariables and the risk of first occurrence of stroke (ischemic or hemorrhagic) after acute myocardial infarction. Deaths from non-stroke causes were treated as censoring events. The multivariable model was built up using backward stepwise regression based on the univariable significance-based selection, however, age and sex which were kept steady in the model. Furthermore, all non-significant variable at multivariable level were forward stepwise retested, one at a time, before setting the final multivariable model. To verify the proportional hazards assumption, scaled Schoenfeld residuals were examined. No significant violations were detected, and all covariates satisfied the assumption within the 95% confidence interval. Survival curves were constructed using cumulative incidence, based on Cox regression analysis, as a function of incident stroke [15]. In addition, Kaplan–Meier survival curves were generated to visualize the unadjusted stroke-free survival over time in selected subgroups. Differences between groups were assessed using the log-rank test. These curves are presented as supplementary material to complement the adjusted risk estimates.

Results for continuous variables were presented as medians with interquartile ranges (IQRs), while categorical variables were reported as counts and percentages. Statistical significance was defined as a two-tailed P value of < 0.05 unless stated otherwise. All statistical analyses were conducted using STATA version 18 (College Station, Texas, USA).

Results

Patient characteristics

Of the 741 consecutive unselected patients deemed eligible upon admission, the study excluded 84 patients due to diagnoses other than ACS, 23 with missing baseline data and 54 patients due to residing outside the Veneto region. Forty-five of the remaining 580 patients died during the index hospitalization, leaving 535 patients enrolled in the post-discharge follow-up **(**Fig. 1**).**

Unless pre-empted by death, all enrolled patients completed the follow-up representing 6151 Person-years except for three patients for whom survival time was censored before 24 years: two withdrew consent and one moved overseas. The median age of the study population was 67 years, 70% were male, and 318 patients (59%) were residing in rural areas. ACS was distributed as follows: STEMI 62%, NSTEMI 21% and UAP 17%.

During the follow-up period, 84 patients (16%) experienced an acute stroke event, with 85% being ischemic and 15% hemorrhagic. The stroke proved fatal in 43 patients, Fig. 1. Patients who experienced a stroke and those who did not, shared most of the baseline demographic and clinical characteristics as detailed in Table 1.

Overall stroke risk during follow-up

The incidence rate (IR) of stroke during the entire span of the follow-up time was 14/1000 person-year (95%CI: 11–17). The median time from enrolment to first stroke diagnosis was 7 years (interquartile range (IQR): from 3 to 15 years). Stroke IR by different clinical variables are provided in Table 2. The urban vs. rural stroke IR/1000 person-years was: 16.7 vs. 14.8 in the northern province ($p = 0.7$), 14.5 vs. 9.7 in the middle province ($p = 0.4$), and 17.1 vs. 11.5 in the southern province ($P = 0.2$).

Univariable Cox regression analyses of predictors of stroke within 24 years after ACS are shown in Table 3. Older age (HR 2.4; 95%CI 1.8–3.2), female gender (HR 1.8; 95%CI 1.1–2.8), baseline diabetes (HR 2.0; 95%CI 1.2–3.3), heart failure (HR 2.4; 95%CI 1.6–3.8), AF (HR 3.4; 95%CI 2.1–5.6) and higher albumin-to-creatinine ratio (ACR) (HR 1.7; 95%CI 1.2–2.3) were all associated with an increased risk of stroke. while higher estimated glomerular filtration rate (eGFR), reperfusion, statin and beta-blockers treatment during follow-up were associated with a decreased risk; HR= (0.6(95%CI 0.4–0.7), 0.5(95%CI 0.3–0.8), and 0.4(95%CI 0.3–0.6), respectively). Similar results were observed in Kaplan–Meier curves showing unadjusted stroke–free survival (Supplementary Figure S2). These unadjusted results, visualized in Supplementary Figure S2, provide a useful complement to the adjusted Cox models, reinforcing the associations between stroke risk and key clinical variables such as age, AF, and renal function markers.

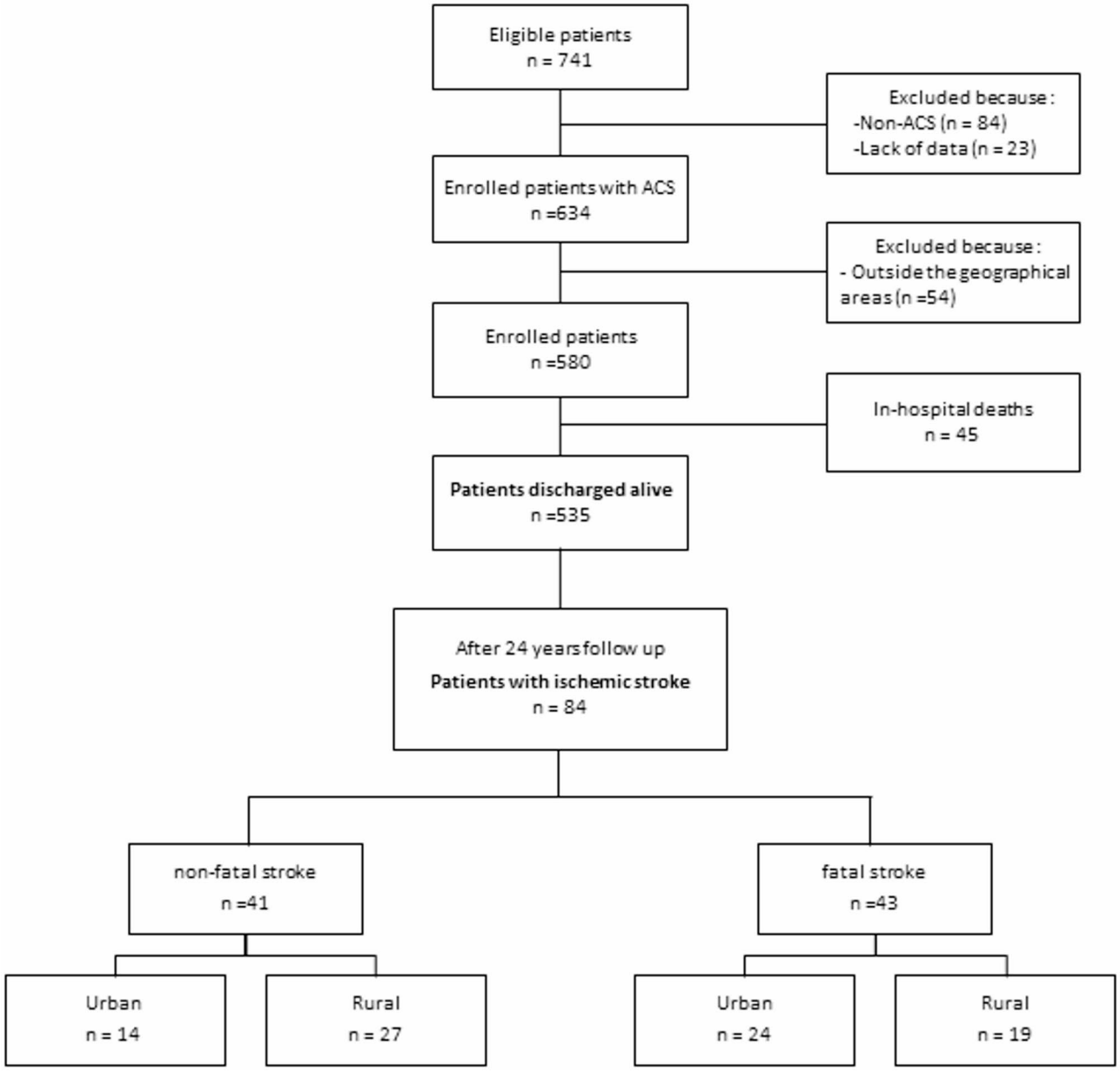

Fig. 1 Flow diagram of the study population and progress during follow-up. *ACS* acute coronary syndrome

In multivariable analysis: older age, atrial fibrillation and higher ACR were independent predictors of the stroke, while higher eGFR was independently associated with a lower risk, Table 3; Fig. 2.

Interestingly, we observed that patients who experienced a stroke during follow-up in our cohort had a lower prevalence of prior myocardial infarction (15% vs. 26%, $P = 0.03$, Table 1). To explore the possibility of survivor bias, we conducted a competing risk analysis using a Fine and Gray model, accounting for non-stroke mortality as a competing event. The analysis demonstrated that prior MI was significantly associated with a reduced subdistribution hazard of stroke (SHR 0.54; 95% CI, 0.30–0.97; $P = 0.041$), suggesting that patients with prior MI may have died earlier from other causes, thus being less likely to experience a stroke during follow-up. A supplementary Figure S3 Showing Kaplan–Meier estimates of overall survival stratified by history of prior myocardial infarction at baseline with patients with prior MI demonstrated significantly lower overall survival over the follow-up period, supporting the hypothesis of increased early mortality in this subgroup.

Risk of fatal stroke

A sub-analysis of the 43 patients who had a fatal stroke revealed an IR of 7/1000 person-years (95% CI: 5–9),

Table 1 Baseline characteristics of ACS patients with and without stroke

	Overall population	No stroke	Stroke	*P* value
	(*n* = 535)	(*n* = 451)	(*n* = 84)	
Demographics and clinical data				
Age, years.	67(59–75)	67(58–75)	70(63–75)	0,10
Females	158(30)	129(29)	29(34)	0,31
Body mass index, kg/m2*	26(24–28)	26(24–28)	25(24–28)	0,50
Current smokers	192(36)	166(37)	26(31)	0,30
Alcohol consumption	400(75)	332(74)	68(81)	0,14
Education > Elementary school	133(25)	112(25)	21(25)	0,97
Diabetes mellitus	123(23)	101(22)	22(26)	0,49
Hypertension	258(48)	217(48)	41(49)	0,81
Prior myocardial infarction	132(25)	119(26)	13(15)	0,03
Physical activity	35(7)	31(7)	4(5)	0.45
Area of residence				
Urban	217(41)	179(40)	38(45)	0.28
Rural	318(59)	272(60)	46(54)	
Provinces of residence				
north	175(33)	146(32)	29(34)	0.28
middle	137(26)	120(27)	17(20)	
south	223(42)	185(41)	38(45)	
In-hospital characteristics				
Prehospital time delay, min* (*n* = 442)	180(120–510)	180(120–525)	180(120–480)	0,70
Systolic blood pressure, mmHg	120(110–130)	120(110–130)	120(110–130)	0,45
Diastolic blood pressure, mmHg	80(70–80)	80(70–80)	75(70–80)	0,11
Heart rate, beats/min	70(60–82)	70(60–82)	72(60–82)	0,49
Killip class > 1[a]	180(34)	149(33)	31(36)	0,55
Left ventricular ejection fraction, %	52(46–60)	52(46–60)	53(49–63)	0,03
Atrial fibrillation[ab]	69(13)	48(11)	21(25)	< 0.0001
ST-elevation myocardial infarction	331(62)	271(60)	60(71)	0,07
Thrombolysis[a]	183(34)	152(34)	31(37)	0,47
Laboratory data				
Creatine kinase-MB peak, U/L*	102(43–208)	100(43–208)	116(49–194)	0,35
LDH peak, U/L*	851(512–1390)	842(512–1380)	931(500–1404)	0,69
Hemoglobin, g/L	14(13–15)	14(12–15)	14(13–15)	0,37
Blood glucose, mg/dL	120(100–159)	119(99–159)	129(104–161)	0,47
Total cholesterol, mg/dL*	207(178–243)	207(176–244)	212(184–234)	0,90
eGFR (ml/min x 1.73 m^2) *	73(61–87)	74(62–87)	73(59–83)	0,57
ACR (mg/g)	19(7–53)	18(7–56)	20(8–50)	0,82
Treatment[b]				
PTCA/CABG	35	35	36	0,78
Antiplatelet	476(89)	396(88)	80(95)	0,04
Anticoagulants	148(28)	123(27)	25(30)	0,64
Statin	247(46)	213(47)	34(41)	0,31
Beta-blockers	289(54)	245(54)	44(52)	0,74

Data are presented as median (interquartile range) or number (%)

ACR = Urinary albumin-to-creatinine excretion ratio; *eGFR* = Estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; *LDH* = lactate dehydrogenase-1 isoenzyme; *PTCA/CABG* = percutaneous transluminal coronary angioplasty/ Coronary artery bypass grafting

* P values were calculated using Log-transformed data

[a] During the first 7 days of hospital stay

[b] At any time during follow-up

Table 2. The median time from enrolment to fatal stroke was 6 years (IQR 3–13 years). The urban vs. rural stroke IR/1000 person-years was:7.3 vs. 4.4 in the northern province ($p = 0.4$), 3.8 vs. 1.8 in the middle province ($p = 0.5$), and 15.1 vs. 6.6 in the southern province ($P = 0.03$). These trends were further illustrated in Supplementary Figure S1, which displays a geographic map of fatal stroke incidence stratified by urban/rural

Table 2 Incidence rate of total and fatal stroke 24 years after acute coronary syndrome

		Total stroke		Fatal stroke	
		IR/1000 person-years	Log-rank P	IR/1000 person-years	Log-rank P
Overall		14		7	
Enrollment age terciles	1st	6	< 0,0001	2	< 0,0001
	2nd	17		9	
	3rd	29		20	
Gender	Male	12	0,01	6	0,03
	Female	21		11	
Body mass index terciles	1st	17	0,38	10	0,15
	2nd	13		7	
	3rd	12		5	
Diabetes mellitus	No	12	0,004	5	0,005
	Yes	24		14	
Hypertension	No	12	0,20	5	0,11
	Yes	16		9	
Smoking	No	17	0,01	8	0,09
	Yes	10		5	
Total cholesterol terciles	1st	14	0,33	8	0,01
	2nd	17		10	
	3rd	11		3	
Heart failure	No	11	0,0001	5	0,002
	Yes	25		14	
LVEF terciles	1st	15	0,41	8	0,40
	2nd	16		8	
	3rd	12		5	
Atrial fibrillation[a][b]	No	11	< 0,0001	5	0,0001
	Yes	37		20	
eGFR Terciles	1st	25	0,0001	16	< 0,0001
	2nd	14		5	
	3rd	8		4	
ACR terciles	1st	8	0,002	4	0,02
	2nd	13		6	
	3rd	21		12	
Area of residency	Urban	17	0,10	10	0,01
	Rural	12		5	
Province of residency	North	16	0,44	6	0,01
	Middle	11		3	
	South	14		10	

ACR Urinary albumin-to-creatinine excretion ratio; *eGFR* Estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; *IR* Incidence rate; *LVEF* Left ventricular ejection fraction

[a] During the first 7 days of hospital stay and at any time during follow-up

[b] At any time during follow-up

classification and province showing the regional variation in fatal stroke burden. While formal interaction testing was not performed, these descriptive trends suggest a possible geographic gradient in fatal stroke outcomes that may reflect differences in healthcare access or environmental exposures that warrants further investigation.

Univariable Cox regression analyses of predictors of fatal stroke within 24 years after ACS showed similar results as older age, female gender, baseline diabetes, heart failure, AF, and higher albumin-to-creatin ratio were all associated with an increased risk of fatal stroke, Table 3. Higher eGFR, reperfusion, and beta-blocker treatment during follow-up were associated with a decreased risk. Similar results were observed in Kaplan–Meier curves showing unadjusted fatal stroke–free survival (Supplementary Figure S4). Supplementary Figure S4 illustrates the cumulative incidence of fatal stroke across clinical subgroups, reinforcing the magnitude of risk associated with age, and AF, and area of residency.

Table 3 Uni- and multivariable analysis of predictors of overall stroke 24 years after ACS

Predictor of risk	Overall stroke risk		Fatal stroke	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Univariable analysis				
Enrollment age terciles	2,43 (1,81 – 3,27)	< 0,0001	3,36 (2,17 – 5,20)	< 0,0001
Female gender	1,79 (1,14 – 2,81)	0,01	1,90 (1,02–3,54)	0,04
BMI terciles	0,82 (0,63 – 1,08)	0,16	0,69 (0,47 – 1,01)	0,06
Current smoking	0,56 (0,35 – 0,89)	0,01	0,58 (0,30 – 1,11)	0,10
Alcohol consumption	1,40 (0,81 – 2,42)	0,23	1,42 (0,66 – 3,07)	0,37
Education > Elementary school	0,91 (0,68 – 1,21)	0,50	0,77 (0,49 – 1,20)	0,25
Diabetes mellitus	2,02 (1,24 – 3,30)	0,005	2,46 (1,29 – 4,68)	0,006
Hypertension	1,29 (0,84 – 1,99)	0,24	1,61 (0,88 – 2,95)	0,12
Prior myocardial infarction	0,87 (0,48 – 1,58)	0,65	1,19 (0,57 – 2,48)	0,65
Physical activity	0,51 (0,19 – 1,39)	0,19	0,52 (0,13 – 2,15)	0,37
Residency area (rural-urban)	1,39 (0,91 – 2,14)	0,13	2,08 (1,14 – 3,80)	0,02
Residency provinces (north-middle-south)	0,94 (0,73 – 1,20)	0,61	1,47 (1,00–2,15)	0,04
Systolic blood pressure terciles	1,00 (0,75 – 1,33)	0,99	0,99 (0,66 – 1,48)	0,96
Diastolic blood pressure terciles	0,88 (0,67 – 1,17)	0,40	0,80 (0,53 – 1,20)	0,28
Heart rate terciles	1,25 (0,94 – 1,67)	0,13	1,46 (0,98 – 2,17)	0,06
Left ventricular ejection fraction	0,89 (0,69 – 1,15)	0,38	0,80 (0,55 – 1,14)	0,22
ST-elevation myocardial infarction	1,38 (0,86 – 2,22)	0,18	1,14 (0,60 – 2,17)	0,68
Killip class > 1[a]	2,44 (1,55 – 3,84)	< 0,0001	2,56 (1,39 – 4,74)	0,003
Atrial fibrillation[ab]	3,40 (2,06 – 5,59)	< 0,0001	3,59 (1,84 – 7,01)	< 0,0001
Thrombolysis[a]	0,77 (0,50 – 1,21)	0,26	0,59 (0,31 – 1,13)	0,11
Total cholesterol terciles	0,89 (0,68 – 1,15)	0,37	0,65 (0,44 – 0,95)	0,03
eGFR terciles	0,55 (0,42 – 0,73)	< 0,0001	0,46 (0,31 – 0,68)	< 0,0001
ACR terciles[b]	1,68 (1,24 – 2,27)	0,001	1,72 (1,14 – 2,60)	0,01
PTCA/CABG[b]	0,50 (0,31 – 0,78)	0,002	0,25 (0,12 – 0,54)	< 0,0001
Antiplatelet[b]	0,93 (0,34 – 2,57)	0,90	1,10 (0,26 – 4,60)	0,89
Anticoagulants[b]	0,98 (0,62 – 1,57)	0,94	0,53 (0,25 – 1,15)	0,11
Beta-blockers[b]	0,40 (0,26 – 0,62)	< 0,0001	0,30 (0,16 – 0,56)	< 0,0001
Multivariable analysis				
Enrollment age terciles	1,84 (1,30 – 2,60)	0,001	2,67 (1,60 – 4,45)	< 0,0001
Female gender	1,01 (0,62 – 1,64)	0,97	0,95 (0,49 – 1,84)	0,88
Atrial fibrillation[b]	2,64 (1,49 – 4,67)	0,001	2,95 (1,38 – 6,32)	0,005
eGFR terciles	0,71 (0,53 – 0,95)	0,02	0,66 (0,43 – 1,02)	0,06
ACR terciles	1,38 (1,04 – 1,83)	0,03	1,38 (0,93 – 2,06)	0,11
Area (rural-urban)	1,25 (0,81 – 1,94)	0,31	1,89 (1,03–3,48)	0,04
Provinces (north-middle-south)	1,04 (0,80 – 1,36)	0,76	1,71 (1,15 – 2,53)	0,008

BMI Body mass index, *eGFR* Estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula, *ACR* Urinary albumin-to-creatinine excretion ratio, *PTCA/CABG* percutaneous transluminal coronary angioplasty/ Coronary artery bypass grafting

[a] During the first 7 days of hospital stay

[b] At any time during follow-up

At the multivariable analysis, older age and AF were independent predictors of fatal stroke, Table 3.

Unexpectedly, we also observed an association between geographic areas of residence and the long-term risk of fatal stroke as the risk increased going from rural to urban areas (HR 2.1; 95%CI 1.1–3.8) and from north to middle and south provinces (HR 1.5; 95%CI 1.0-2.1) with the univariable Cox regression analysis. Results remained significant using multivariable Cox regression models, Table 3; Fig. 3.

Discussion

Stroke represents a formidable challenge in healthcare irrespective of the underlying clinical condition due to its substantial impact on morbidity and mortality [16]. Previous studies have established an association between myocardial infarction and increased stroke risk.

Although our findings confirm this well-known association, they also offered important insights derived from a unique, long-term observational perspective. The 24-year follow-up period, which is seldom reported in the literature, allowed for the evaluation of stroke risk over a

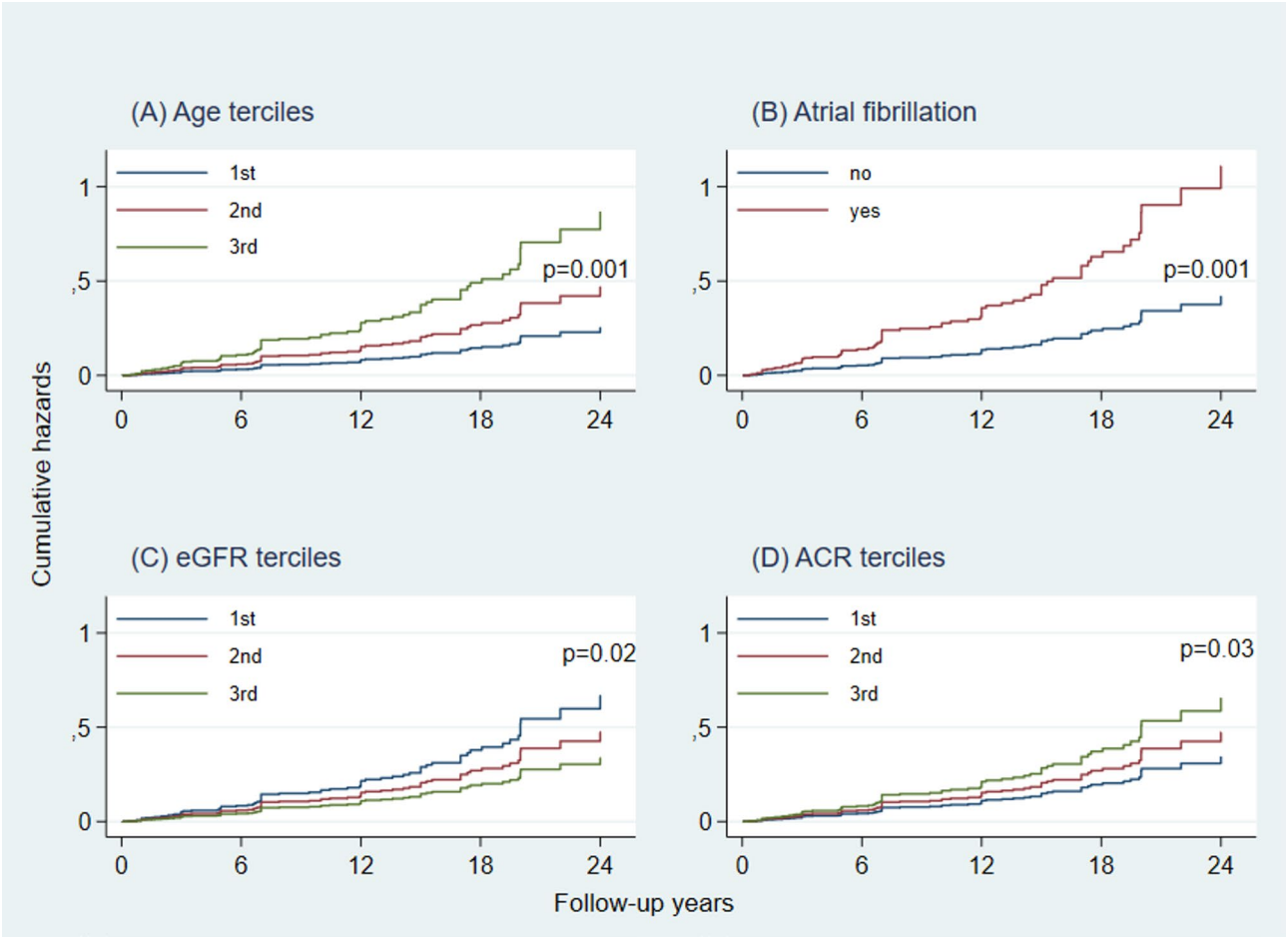

Fig. 2 Nelson-Aalen cumulative hazard estimate, based on fully adjusted Cox regression analysis, of overall stroke by different clinical variables. *eGFR* Estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula, *ACR* Urinary albumin-to-creatinine excretion ratio

full natural disease course. However, it is important to acknowledge that the cohort was enrolled between 1995 and 1998, before the introduction of troponin-based diagnostics and several modern evidence-based therapies for ACS, such as primary percutaneous coronary intervention (PCI), dual antiplatelet therapy, and high-intensity statins. As such, the diagnostic criteria, risk stratification, and treatments used reflect historical clinical standards, which limits the direct generalizability of our findings to contemporary patient populations. Nonetheless, the long-term follow-up of a well-characterized cohort offers valuable insights into the residual and evolving risk of stroke in ACS survivors, especially in the absence of routine modern interventions.

The ABC study shed light on several baseline clinical predictors correlated with an increased risk of long-term stroke, such as older age, AF, and a higher ACR. In contrast, the study found that a higher eGFR was associated with a reduced risk of stroke in this particular population. These findings provide valuable guidance for healthcare professionals in identifying and managing stroke risk factors among ACS patients, ultimately contributing to improved patient outcomes and quality of care. Moreover, the study identified a geographical association with the risk of fatal stroke, highlighting the significance of understanding regional differences in stroke risk and implementing targeted preventive strategies.

Our study revealed an overall stroke incidence rate of 14 per 1000 person-years among patients with ACS with a cumulative incidence surpassing 15%, consistent with findings from prior investigations. For instance, Hurskainen et al. retrospectively documented a cumulative stroke incidence exceeding 10% during a 14-year follow-up of 8,049 ACS patients [6]. Long-term stroke is a critical outcome among patients with ACS, given its significantly high associated mortality. Notably, approximately half of the post-discharge strokes in our cohort resulted in fatalities, a finding also in line with previous research involving ACS patients [6, 17].

The mechanisms contributing to the persistently elevated risk of stroke up to 25 years after ACS are likely multifactorial, involving chronic inflammation and

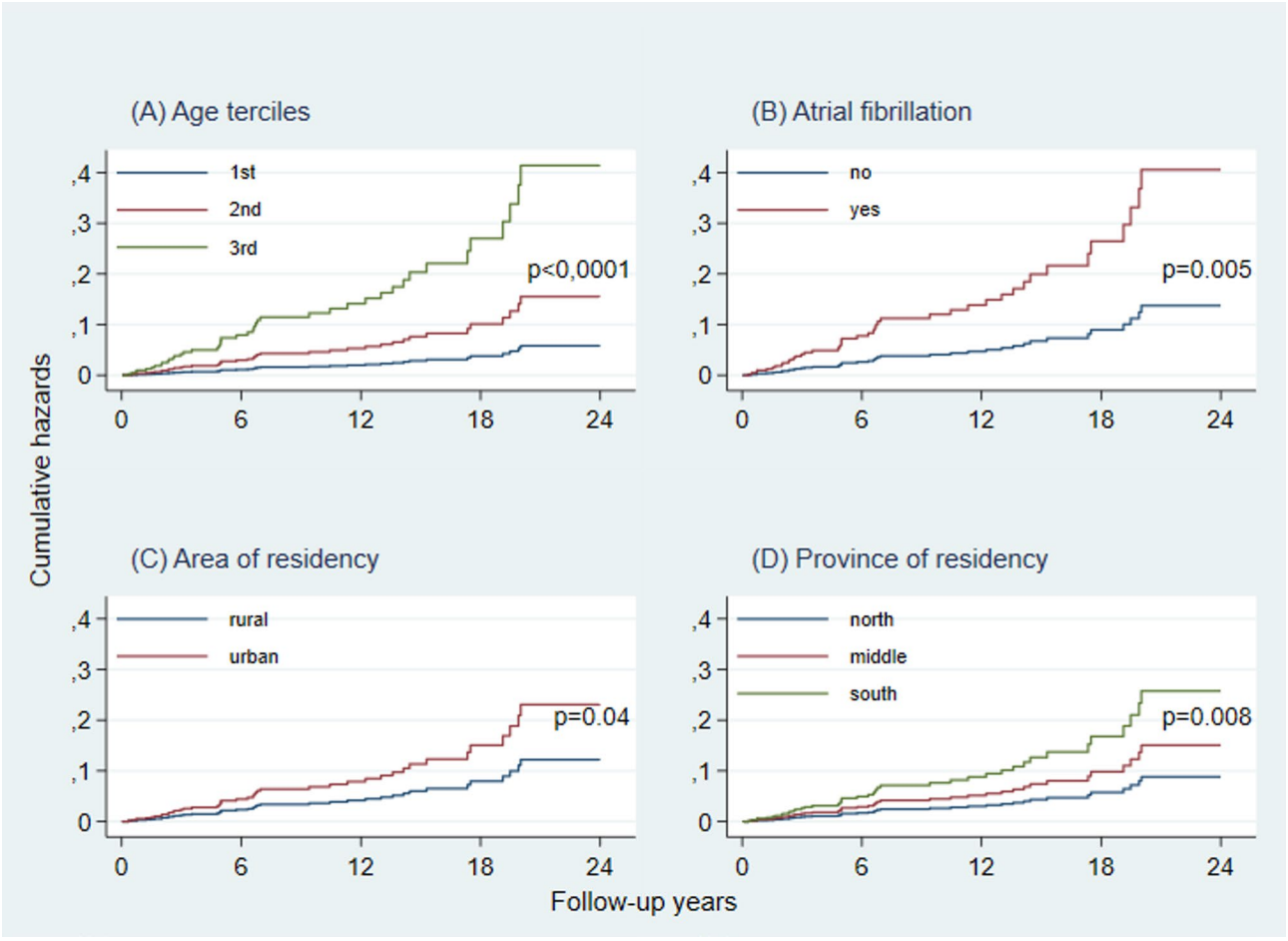

Fig. 3 Nelson-Aalen cumulative hazard estimate, based on fully adjusted Cox regression analysis, of fatal strokes by different clinical variables

shared risk factors associated with atherosclerosis. These elements may reflect overlapping pathophysiological processes that underlie both coronary and cerebrovascular disease [6, 18]. However, we our data are observational in nature and do not provide direct mechanistic evidence. The use of the albumin-to-creatinine ratio in our analysis was intended as a surrogate marker of systemic inflammation, but we recognize that this is an indirect measure. While our results suggest a link between systemic inflammation and stroke risk, they are not mechanistic. Therefore, these findings should be considered exploratory and interpreted with caution. Future prospective studies using validated inflammatory biomarkers (e.g., hs-CRP, IL-6) and mechanistic endpoints are warranted to more clearly define the role of inflammation in post-ACS stroke.

The present study has identified several important risk factors for long-term stroke in patients with ACS. In particular, older age and AF were found to be independent predictors for both total and fatal stroke which is consistent with the findings of previous studies [17]. AF is an established risk factor for stroke, primarily due to its association with the formation of cardiac emboli. In the setting of AMI, AF can manifest either as a pre-existing condition or as a complication. Previous studies indicate an incidence ranging from 2 to 21% for AF complicating AMI [19, 20]. Consistent with our results, studies also showed that patients with AF following AMI had a significantly higher long-term risk for fatal and non-fatal stroke compared to those without AF regardless of their age, gender or interventional treatment [20, 21]. However, it is important to note that all clinical predictors, including atrial fibrillation, renal function, and ACR, were assessed at baseline and were not updated during follow-up. This may have led to misclassification and residual confounding, as risk profiles likely evolved during the 24-year period.

Our study integrates and advances existing literature on the association between eGFR, ACR, and stroke risk, demonstrating that patients with lower eGFR or higher ACR levels have an increased stroke risk [22, 23]. Notably, we found that higher eGFR predicts lower hemorrhagic stroke (HS) risk, consistent with findings from the Rotterdam study by Bos et al., which followed 4937

participants for an average of 10.2 years. In that study, decreased eGFR was a strong risk factor for hemorrhagic stroke, but not for ischemic stroke [24].

Our findings also corroborate the extensive body of evidence from epidemiological studies indicating that geographic differences in stroke mortality are genuine and not merely a result of reporting biases or data collection inconsistencies. Several factors, including socioeconomic status, lifestyle and dietary habits, genetic and biological characteristics, and environmental factors influence these disparities [25–27]. In our study, geographic disparities in fatal stroke risk were observed within the Veneto region, with higher rates in urban and southern provinces. While our dataset did not include direct measures of potential explanatory variables, we could suggest that, differences in healthcare accessibility, including variable proximity to stroke units and specialized care, may contribute to outcome variation. Urban industrialized areas may also face greater exposure to environmental risk factors such as air pollution, which has been linked to increased stroke risk in northern Italian populations. Furthermore, socioeconomic gradients within the region, including differences in education level, income, and health literacy, may influence stroke awareness, prevention, and timely access to acute care. These factors, although not captured in our study, could partially explain the regional disparities we observed and warrant further investigation. However, we acknowledge that our geographic findings are hypothesis-generating, as we lacked direct data on these relevant explanatory variables. Therefore, these associations should be interpreted cautiously, and future studies incorporating such contextual data are needed to confirm and explain these disparities.

Given the potentially devastating consequences of stroke, it's crucial to identify high-risk ACS patients promptly. This facilitates the implementation of targeted management strategies, such as aggressive risk factor modification, optimized medical therapy, and vigilant monitoring. These proactive approaches not only help reduce stroke incidence but also enhance overall patient outcomes while alleviating the strain on healthcare resources.

This long-term cohort study reinforces the role of established clinical predictors (age, AF, renal function) in post-ACS stroke risk and highlights novel geographic disparities in fatal stroke outcomes. These findings support the integration of geographic and clinical risk stratification in long-term secondary prevention strategies.

Limitations

Our prospective study boasts several notable strengths. Chief among them is the exceptionally prolonged follow-up period, which spans an impressive 24 years and remarkably features minimal dropouts. To the best of our knowledge, this research is one of the first studies to examine the prognostic value of baseline clinical variables over such an extended follow-up period following acute coronary syndrome (ACS). Furthermore, the inclusion of comprehensive baseline characteristics, ongoing medical treatment records, and the employment of advanced statistical methodologies all serve as pivotal pillars reinforcing the robustness and depth of our investigation. However, our study has several limitations. A significant limitation of the ABC Study is that the diagnosis of myocardial infarction did not include troponin measurement, as this biomarker was not in use during the initial enrolment period. Instead, we relied on clinical presentation, ECG findings and the rise and gradual decline of creatine kinase (CK) and creatine kinase-MB (CK-MB) as biochemical markers of myocardial necrosis. In the absence of troponin-based diagnosis, some cases of non-ST-elevation myocardial infarction (NSTEMI) may have been misclassified as unstable angina, potentially underestimating the burden of myocardial damage in the cohort. This limitation also affects direct comparability with modern ACS populations, where high-sensitivity troponin assays allow more accurate stratification of ACS subtypes. Despite this, the long-term follow-up and consistent diagnostic approach across the cohort still allow meaningful insights into stroke risk following ACS. Additionally, it is important to acknowledge that the clinical criteria and management strategies applied at baseline reflect the standards of care in the 1990s, as the cohort was enrolled over two decades ago. Consequently, several of the cited references predate 2020 and correspond to the evidence base available at that time. While this limits the direct applicability of our findings to patients treated under current clinical guidelines, the long-term outcomes observed remain of clinical relevance. They offer valuable historical insight into the natural progression of stroke risk following ACS and underscore the necessity for long-term surveillance in this patient population. Future studies are warranted to determine whether advances in contemporary management, such as optimized antithrombotic regimens, widespread use of primary percutaneous coronary intervention (PCI), and updated risk stratification tools, translate into reduced long-term cerebrovascular risk. Nonetheless, our findings are consistent with those of a recent study by Hurskainen et al., which included 8,049 patients with ACS, over 85% of whom underwent primary PCI, yet long-term stroke risk remained substantial, suggesting that residual risk persists despite contemporary therapies (6).

A limitation of our analysis is that baseline predictors, including atrial fibrillation, renal function, and albuminuria, were assessed only at the time of the index myocardial infarction. Repeated measures were not systematically available during the long-term follow-up.

As such, we were unable to perform time-dependent Cox regression, which may more accurately account for changes in risk over time. This reliance on baseline-only measurements introduces potential misclassification bias, especially for variables known to evolve over time, such as renal function, atrial fibrillation, and albuminuria underestimating their time-varying effects. This limitation reflects the nature of our study design, which focused on baseline characteristics and long-term outcomes. Despite this limitation, the use of baseline predictors remains informative for post-MI risk stratification in clinical practice. Yet, further studies with repeated measures would better capture dynamic risk.

Furthermore, it is important to consider that variations in access to healthcare resources and the availability of advanced acute stroke treatments—such as intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT)—may have influenced stroke incidence and outcomes over the study period and across geographic areas. Although we observed significant differences in the incidence of stroke across different geographic areas of the Veneto region and between urban and rural settings, our study was not designed to explore the underlying causes of these differences. In particular, we did not have access to detailed data on socio-economic status, environmental exposures (such as air pollution), healthcare access, which may vary geographically and could contribute to the observed patterns. Therefore, while our findings highlight a potentially important geographical variation in stroke risk following acute myocardial infarction, further population-based studies are needed to investigate the role of social, economic, and environmental determinants. Nevertheless, our findings provide important preliminary evidence suggesting that geographic and urban/rural differences may influence long-term cerebrovascular outcomes after myocardial infarction, and they warrant further investigation using more comprehensive datasets.

Due to the historical design and long-term nature of the cohort, detailed clinical data regarding stroke severity, neurological deficits, or functional outcomes (e.g., disability scores, NIHSS or modified Rankin Scale) were not systematically available throughout the follow-up period. As such, our analyses focused on stroke occurrence and fatality, but could not characterize long-term stroke-related disability. This limits the interpretation of clinical impact beyond mortality.

Although stroke and fatal stroke incidence rates were quantified over 24 years, direct comparison with the general population was not feasible due to the absence of age- and comorbidity-matched longitudinal data from the Veneto region over a similar timeframe. This limits the ability to contextualize absolute risk levels; however, the observed rates remain clinically relevant, particularly given the aging nature of the cohort and the prolonged risk horizon following ACS. Future studies utilizing contemporary population registries may clarify the excess stroke burden attributable to ACS in long-term survivors. An important methodological limitation of our study is the absence of a comprehensive competing risk analysis. Given the extended duration of follow-up and the high cardiovascular mortality observed in this population, death (particularly from non-stroke cardiovascular causes) represents a significant competing event that may preclude the occurrence of stroke. We used cause-specific Cox proportional hazards regression models to estimate the association between clinical covariates and the risk of first stroke following acute myocardial infarction, as it provides valid estimates of the cause-specific hazard, which is useful for understanding the effects of risk factors. While this approach is appropriate for investigating etiological relationships and consistent with prior long-term studies, it does not account for the impact of competing events on the absolute risk of stroke and may therefore overestimate its cumulative incidence. Although our analyses offer important insights into stroke risk, future studies should employ competing risk models, such as the Fine–Gray subdistribution hazard model, to more accurately quantify stroke-specific risk in long-term follow-up settings. In our study, we performed a limited competing risk analysis for prior myocardial infarction using the Fine–Gray approach; however, broader application was not feasible due to dataset constraints. This limitation underscores the need for future research to incorporate competing risk methodologies, particularly in populations with substantial non-stroke mortality, as exclusive reliance on conventional Cox models may lead to biased risk estimates and misinform long-term prognostic evaluations.

Finally, the exclusively Caucasian composition of our cohort, while contributing to internal homogeneity, limits the external validity and generalizability of our findings to more diverse, multiethnic populations. Genetic variability, along with socioeconomic and healthcare disparities, may significantly influence both acute coronary syndrome outcomes and stroke risk profiles in different demographic groups. Validation of our findings in multiethnic and international cohorts is warranted to determine their broader applicability.

Conclusions

The ABC study provided insights into the long-term incidence and risk factors for stroke among ACS patients. Notably, it identified a number of baseline clinical predictors associated with a higher risk, including older age, AF, and a higher ACR. Conversely, a higher eGFR was correlated with a lower risk of stroke. Additionally, the study identified a geographical association with the risk of fatal

stroke. This underscores the importance of considering both individual clinical predictors and broader geographic factors in stroke prevention policies.

Given that the cohort was enrolled before the advent of modern ACS management strategies, these findings primarily reflect the natural course of disease in an earlier treatment era. Nonetheless, the prolonged follow-up highlights the enduring residual risk of stroke in ACS survivors and supports the need for ongoing risk stratification and surveillance. Future research in contemporary, multiethnic populations is essential to validate these findings, assess the impact of modern therapies, and further investigate regional disparities in stroke outcomes.

Supplementary Information

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Supplementary Material 1—Figure S1: Map of Veneto region showing, participating hospitals, patients at enrollment and IR of fatal stroke by the end of follow-up

Supplementary Material 2—Figure S2: Kaplan–Meier curve for stroke-free survival stratified by different clinical variables.

Supplementary Material 3—Figure S3: Kaplan–Meier estimates of overall survival stratified by history of prior myocardial infarction.

Supplementary Material 4—Figure S4: Kaplan–Meier curve for fatal stroke-free survival stratified by different clinical variables.

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Author contributions

Dr. G. Berton and Dr. H.T. Mahmoud researched literature and conceived the study. Dr. R. Cordiano and Dr. F. Cavuto were involved in protocol development, the original data collection, data handling, and patient follow-up. Dr. G. Berton and Dr. H.T. Mahmoud contributed to the data analysis and interpretation, figures, and manuscript preparation. Mr. D. Merotto and Mr. ML. Dario wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethical approval

The study protocol adhered to the Declaration of Helsinki and received approval from the ethics committee of Adria, Bassano, Conegliano hospitals.

Consent for publication

Not applicable.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Competing interests

The authors declare no competing interests.

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