Impact of living and socioeconomic characteristics on cardiovascular risk in ischemic stroke patients

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Objective **We aimed to stratify the risk of vascular event recurrence in patients with cerebral infarction according to living and socioeconomic characteristics and geographic region.**
Method **The Outcomes in Patients with TIA and Cerebrovascular Disease (OPTIC) study is an international prospective study of patients aged 45 years or older who required secondary prevention of stroke [following either an acute transient ischemic attack, minor ischemic strokes, or recent (less than six-months previous), stable, first-ever, nondisabling ischemic stroke]. A total 3635 patients from 245 centers in 17 countries in four regions (Latin America, Middle East, North Africa, South Africa) were enrolled between 2007 and 2008. The outcome measure was the two-year rate of a composite of major vascular events (vascular death, myocardial infarction and stroke).**
Results **During the two-year follow-up period, 516 patients experienced at least one major cardiovascular event, resulting in an event rate of 15·6% (95% confidence interval 14·4–16·9%). Event rates varied across geographical region ($P < 0·001$), ranging from 13·0% in Latin America to 20·7% in North Africa. Unemployment status, living in a rural area, not living in fully serviced accommodation (i.e., house or apartment with its own electricity, toilet and water supply), no health insurance coverage, and low educational level (less than two-years of schooling) were predictors of major vascular events. Major vascular event rates steeply increased with the number of low-quality living/socioeconomic conditions (from 13·4% to 47·9%, adjusted *P* value for trend <0·001).**
Conclusion **Vascular risk in stroke patients in low- and middle-income countries varies not only with the number of arterial beds involved but also with socioeconomic variables.**
Key words: atherothrombotic, countries, epidemiology, ischemic stroke, risk factors, socioeconomic factors

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Introduction

Atherosclerotic disease and its complications such as stroke and myocardial infarction (MI) are globally epidemic in developed and low- and middle-income countries (1). In the INTERSTROKE study, high blood pressure (BP), waist-to-hip ratio, cigarette smoking, physical inactivity, and ratio of apolipoprotein A1 to apolipoprotein B were the most important contributors to stroke risk (2). In low- and middle-income countries, all these factors are highly prevalent (3–8). Epidemiological transition probably explains the increase in risk factor prevalence (9). As populations age and progress economically, the nature of diseases shifts from those related to poverty (infection, malnutrition, perinatal disease) to noncommunicable diseases including diabetes and stroke. However, low socioeconomic status (e.g., poverty; lack of formal housing – i.e., not living in a house or apartment with its own electricity, toilet and water supply; low level of education; insufficient or absent health care coverage) may also increase the risk factors for stroke, either independently or through an impact on other risk factors such as those identified in the INTERSTROKE study (10–12). Such socioeconomic risk factors may have a significant impact on stroke and have not been evaluated in large registries or case–control studies such as the REACH registry and the INTERSTROKE study (which included very few countries in the Middle East and Latin America and no countries in North Africa).

The Outcomes in Patients with TIA and Cerebrovascular Disease (OPTIC) registry was designed to evaluate the determinants of the risk of recurrent stroke and other vascular events in patients treated for secondary prevention of atherothrombotic stroke. Analysis of the baseline characteristics showed a high prevalence of traditional vascular risk factors, as well as socioeconomic factors such as indicators of poverty (8). We now present the two-year risk of stroke and other major vascular events according to these variables and risk factor control.

Methods

The OPTIC study is a prospective observational registry with a follow-up period of 24 months. Design and baseline characteristics of patients enrolled in this registry have been described in detail elsewhere (8).

In brief, between January 2007 and December 2008, over 3635 eligible patients were recruited to the registry from over 17 low-income and middle-income countries across the regions of Latin America (Brazil, Chile, Colombia, Dominican Republic, Ecuador, Mexico, Peru, Venezuela), the Middle East (Egypt, Iran, Jordan, Lebanon, Saudi Arabia), North Africa (Algeria, Morocco, Tunisia), and South Africa (13).

A questionnaire was sent to all potential sites to collect data on the type of institution (public, private, teaching), its location, the number of patients with stroke treated, and the services offered. The affiliates in each country then provided a list of centers that represented their country as completely as possible. The final list of investigators (including neurologists and internists) was then randomly generated by the trial manager. Physicians who declined to participate were replaced by the following physician on the list. The aim was to enroll approximately 20 patients per site, with five to 20 sites per country according to the size of the country.

For inclusion, patients had to be 45 years of age or older and were required to have one of the following three criteria, covering the whole spectrum of patients qualifying for secondary prevention of ischemic stroke: (1) transient ischemic attack (TIA) within the last 2 weeks, (2) minor ischemic stroke (National Institutes of Health Stroke Scale ≤3) of less than 24 h in duration, and (3) first ever ischemic stroke (modified Rankin ≤4) less than 6 months previously and confirmed by imaging.

Patients with any stroke defined as category 3 in the TOAST classification (stroke associated with cardiac embolism source) (14), already in a clinical trial, or who might have difficulty returning for a follow-up visits were excluded from enrollment. Patients' management was neither delayed nor altered by their inclusion in the OPTIC registry, and no specific treatment modification regimen was instituted as part of the study.

Standard protocol approval, registration, and patient consent

The study was conducted according to the principles of the Declaration of Helsinki (Edinburgh Amendment, 2000), and signed informed consent was obtained for all patients.

Data collection

All data were collected using standardized international case report forms and entered into a central database. Patient demographics, physical examination findings (weight, height, and current BP reading), medical history (medical treatments, atherothrombotic and cardiac history), socioeconomic profile, and laboratory measurements (fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein-cholesterol, triglycerides, and hemoglobin A1c) were recorded at baseline. Clinical events or hospitalizations that occurred were recorded every six-months (SD one-month) during the two-year follow-up period. Patient treatment and any change in employment status were also recorded at each follow-up visit. Conventional risk factor definitions have been reported elsewhere (8).

Living and socioeconomic conditions

Indicators of low living and socioeconomic conditions were living alone, not living in fully serviced accommodation (defined as not living in a house or apartment with its own electricity, toilet and water supply), location (living in a rural versus urban/suburban area), unemployment (excluding social pensioners on disability grant and old-age pensioners), no health insurance coverage, and low educational level (defined as less than two-years of schooling). Number of years of education is an important measure of socioeconomic status, with fewer years being strongly associated with death from cardiovascular diseases, and is probably an index of socioeconomic factors in early life, which have a particular influence on subsequent cardiovascular risk. The relationship is linear, fewer years being associated with increasing risk. We chose

a lower cutoff point for years of education to capture the higher risk (15,16).

Outcome definitions

The primary study endpoint was the time from inclusion in the study to the first nonfatal stroke, first nonfatal MI, or cardiovascular death. Cardiovascular death included fatal stroke, fatal MI, and "other cardiovascular death." "Other cardiovascular death" included other death of cardiac origin; pulmonary embolism; any sudden death, including unobserved and unexpected death (e.g., while sleeping), unless proven otherwise by autopsy; death following a vascular operation, vascular procedure, or amputation (except for trauma or malignancy); death attributed to heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause or hemorrhage. There was one prespecified secondary composite outcome, defined as the first occurrence of nonfatal stroke, nonfatal MI, cardiovascular death, hospitalization for peripheral vascular interventions (angioplasty/stenting, artery bypass graft, amputation affecting lower limbs), or hospitalization for atherothrombotic event [peripheral artery disease (PAD), worsening of claudication related to PAD, or unstable angina].

Statistical analysis

The analysis was performed on all patients with at least one post-baseline follow-up assessment. Cumulative event curves were constructed using the Kaplan–Meier method, and event rates were determined from two-year Kaplan–Meier rates. For a given endpoint, deaths that were not included in the endpoint were treated as censoring events. Events that occurred after the two-year follow-up period (the prespecified end of study) were not included in the analysis. In age-, sex-, and qualifying event-adjusted analysis, we identified the predictors of two-year cardiovascular events in Cox proportional-hazard regression models. As the proportional hazard assumption was not satisfied for qualifying event types, Cox regression models were stratified by qualifying event (stroke versus TIA or minor stroke). Continuous predictors were analyzed as such, as well as after categorization by quartiles and prespecified cutpoints. Geographic regions were analyzed as a four-level categorical variable and were further analyzed as binary variables (Latin America versus Middle East, North Africa, and South Africa) based on the OPTIC results. The assumptions of proportional hazards were checked by introducing time-dependent variables into the models. Variables that were associated at P value <0·20 with the primary endpoint were implemented in a stepwise-selection Cox regression model stratified by qualifying event, including age and sex as forced variables, and using entry and removal values set to 0·10. Candidate variables were hypertension, diabetes, current smoking, current physical activities, current alcohol consumption, prior history of TIA, history of coronary artery disease (CAD), history of PAD or ankle–brachial index (ABI) <0·9, history of congestive heart failure (CHF), high admission BP (systolic/diastolic ≥160/100 mmHg), living and socioeconomic characteristics (living alone, living in a rural area, living in a house/flat, unemployment, poor health insurance coverage, low educational level), and geographical region (Latin America versus other regions). Low-density lipoprotein cholesterol and glucose were not considered as candidate variables due to the high rate of missing data (>25%). The C-statistics and a global test for the proportional hazard assumption were calculated for the final model. In sensitivity analysis, we performed multiple imputation using the Markov-chain Monte Carlo method to handle missing data; five data sets were imputed and analyzed. We further investigated the impact of presence and number of living and socioeconomic indicators in Cox regression models stratified by qualifying event and adjusted for prespecified variables [age, sex, country, hypertension, diabetes, dyslipidemia, current smoking, current physical activities, current alcohol consumption, CAD and PAD (prior history or ABI <0·9)]. The Cox-regression models were refit using the Human Development Index (17) to adjust for country-level factors. Comparison between number of indicators was made using a trend test in a Cox regression model. Adjusted event rates were calculated using the corrected group prognosis method (18); adjustment for age was made using the quartile values. Statistical testing was done at the two-tailed α level of 0·05. Data were analysed with SAS version 9·2 (SAS Institute, Cary, NC).

Results

Of the 3635 patients enrolled in the OPTIC registry, 148 (4·1%) patients with no follow-up information were excluded from the present analysis; four patients withdrew their consent, 130 patients did not return after baseline visit, and 14 withdrew for other reasons. Among 3487 patients who contributed to the two-year outcome data, 2893 patients completed the two-year follow-up visit; 268 died before the two-year visit, and 326 did not attend the two-year visit (the last available visit was the 18-month visit for 98 patients, the 12-month visit for 95 patients, and the six-month visit for the remaining 133 patients). The median duration of follow-up was 24 months (range among survivors 3 to 34). Baseline characteristics of the 3487 included patients are shown in Table 1. Secondary prevention medications taken at discharge and at follow-up visits are shown in Table 2. Although we do not have data about compliance with specific medications, the overall rate of medication use was relatively high during the follow-up period.

At two-years, there were 187 cardiovascular deaths, 88 nonfatal MIs, and 290 nonfatal strokes. A total of 516 patients experienced at least one major cardiovascular event, resulting in a primary endpoint event rate of 15·6% (95% CI 14·4–16·9%). Geographical differences in the primary endpoint event rates were seen, with an age-, sex-, and qualifying event-adjusted event rate ranging from 13·0% in Latin America to 20·7% in North Africa (Table 3, $P < 0·001$). Using patients from Latin America as reference, the age/sex-adjusted hazard ratio (HR) was 1·24 (95% CI 0·99–1·54) for the Middle East, 1·31 (95% CI 0·91–1·90) for South Africa, and 1·67 (95% CI 1·34–2·07) for North Africa.

The two-year primary endpoint event rates by baseline characteristics are shown in Table 1 after adjustment for age, sex, and qualifying event; continuous variables were dichotomized using prespecified cutpoints in order to simplify the data presentation. As expected, the triple ischemic endpoint was strongly dependent

Table 1 Baseline characteristics of patients and associated two-year cardiovascular risk

Variable	*n* (%)	Two-year cardiovascular risk (%)*		*P* value*
		Present	Absent	
Demographic characteristics				
Age >60 years	2300 (66·0)	17·6	11·8	<0·001
Male sex	1978 (56·7)	15·8	15·4	0·76
Medical history				
Hypertension	2879 (82·6)	16·3	12·4	0·02
Diabetes	1266 (36·3)	17·5	14·7	0·03
Dyslipidemia	2556 (73·3)	16·1	14·6	0·30
Current smoking	722 (21·4)	18·1	15·0	0·07
Current physical activities	928 (26·6)	13·8	16·3	0·09
Current alcohol consumption	425 (12·2)	19·9	15·1	0·01
Prior known TIA	784 (23·0)	13·5	16·3	0·07
Prior known CAD	443 (12·8)	29·2	14·1	<0·001
Prior known PAD or ABI <0·9	905 (26·0)	19·5	14·2	<0·001
Prior known CHF	120 (3·5)	37·8	14·9	<0·001
Examination findings				
BMI ≥30 kg/m^2	859 (25·4)	14·9	16·2	0·41
Systolic/diastolic BP ≥160/100 mmHg	1041 (29·9)	19·1	14·2	<0·001
Fasting glucose ≥126 mg/dL	938 (36·2)	17·0	15·1	0·21
Total cholesterol ≥200 mg/dL	1055 (44·0)	15·2	15·3	0·91
LDL cholesterol ≥130 mg/dL	764 (38·2)	16·9	14·0	0·08
HDL cholesterol <40 mg/dL	956 (46·0)	15·9	13·7	0·19
Triglycerides ≥150 mg/dL	991 (43·0)	14·8	16·2	0·40
Living and socioeconomic characteristics				
Living alone	292 (8·4)	19·3	15·4	0·08
Living in rural area	440 (12·8)	23·2	14·6	<0·001
Living in house/apartment	3170 (92·5)	14·5	32·4	<0·001
Unemployed†	1084 (31·1)	18·2	14·5	0·02
No health insurance coverage	799 (23·0)	21·5	14·0	<0·001
Low educational level (<2 school years)	902 (26·2)	20·9	14·1	<0·001

*Primary Endpoint Event rates and *P* values are reported after adjustment for age,sex and qualifying event.
†Excluding social pensioners on disability grant and old-age pensioners.
ABI, ankle–brachial index; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral arterial disease; TIA, transient ischemic attack.

on age (with a gradual increase across decades; sex- and qualifying event- adjusted HR = 1·26; 95% CI 1·16–1·37) and baseline risk features. Among examination findings, only high admission BP level was associated with a significant increase in combined risk of cardiovascular death, nonfatal MI and nonfatal stroke. However, in quartile analysis, a significant trend toward a higher risk with increasing glucose quartile was found (adjusted HR per log-increase 1·52; 95% CI 1·17–1·95), whereas a threshold effect near the upper quartile of systolic BP (≥160 mmHg) was found [using the first quartile as reference, the adjusted HR was 0·86 (95% CI 0·66–1·12) for the second quartile, 1·01 (95% CI 0·77–1·31) for the third, and 1·38 (95% CI 1·09–1·74) for the upper]. Except for some nonsignificant differences, low-quality living and socioeconomic conditions were associated with an increased risk of combined primary events. For example, patients without health insurance coverage had a primary endpoint event rate of 21·5% in comparison with 14·0% in patients with health insurance coverage (adjusted HR 1·61; 95% CI 1·33–1·94).

In multivariate analysis, 12 baseline characteristics were considered as independent predictors of two-year cardiovascular death, nonfatal MI, and fatal stroke (Table 4). These included four living/socioeconomic characteristics (living alone, not living in fully serviced accommodation, lack of health insurance coverage, and low level of education) in addition to a geographical region effect. Similar results were found after handling missing data by multiple imputations (data not shown). When the secondary endpoint (combined primary events and hospitalization for atherothrombotic events or peripheral vascular interventions) was examined, two additional independent predictors were found: diabetes (HR 1·19, 95% CI 1·00–1·42; $P = 0·05$) and current smoking (HR 1·25, 95% CI 1·01–1·54; $P = 0·04$).

Figure 1 shows the primary endpoint event rates as a function of low-quality living and socioeconomic conditions after adjustment for conventional risk factors and country. In separate multivariate analysis (one variable at a time), five living/socioeconomic characteristics [living in rural area, not living in serviced accommodation (i.e., house or apartment with its own electricity, toilet and water supply), unemployment, lack of health insurance coverage, and low level of education] were associated with an increased cardiovascular risk (all adjusted *P* values <0·005). The absolute additional risk of having cardiovascular death, nonfatal MI, or nonfatal stroke ranged between 4·8% for unemployed patients (excluding social pensioners on disability grant and old-age pensioners) to 11·3% for patients not living in

Table 2 Medication use at baseline and self-reported utilization 6, 12, 18, and 24 months thereafter

Medication (%)	Baseline (n = 3487)	6 months (n = 3290)	12 months (n = 3053)	18 months (n = 2974)	24 months (n = 2893)
Antiplatelet drug	95·4	94·2	94·7	94·0	93·5
Acetylsalicylic acid	77·7	75·8	75·6	74·4	74·0
ADP receptor antagonists	38·0	8·2	7·0	6·1	6·0
Other agents	12·3	38·2	38·4	39·0	39·5
Oral anticoagulant drug	7·1	7·0	6·1	7·2	7·3
Antihypertensive drug	79·3	79·7	80·7	80·4	80·1
ACE inhibitors	41·7	40·3	40·5	39·0	38·1
Calcium channel blockers	27·7	28·9	29·4	29·6	29·7
Diuretics	25·8	25·9	26·8	26·3	26·6
Beta-blockers	20·2	21·4	22·1	21·9	21·8
Angiotensin II receptor blockers	15·7	17·9	18·2	19·5	21·0
Other agents	6·1	6·4	6·2	6·1	6·3
Lipid-lowering drug	71·9	70·1	69·3	68·1	67·9
Statins	69·7	67·9	66·9	65·5	65·1
Other agents	5·9	5·5	5·5	5·8	6·4
Antidiabetic drug	34·2	32·6	32·5	32·2	32·0
Insulin	11·6	10·6	11·0	10·9	11·1
Oral agents	26·4	25·8	25·2	25·6	25·4

Some patients used more than one of a particular class of drug.
ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate.

Table 3 Two-year event rates for the total sample and geographical regions*

	Geographical region				
CV events, number* (%)	All (n = 3487)	Latin America (n = 1510)	Middle East (n = 1013)	North Africa (n = 756)	South Africa (n = 208)
All-cause mortality	266 (8·0)	102 (6·5)	46 (5·5)	94 (13·1)	24 (11·7)
CV death, nonfatal MI, or nonfatal stroke	516 (15·6)	192 (13·0)	149 (15·8)	142 (20·7)	33 (16·7)
CV death	187 (5·7)	59 (3·9)	40 (4·8)	72 (10·3)	16 (8·0)
Nonfatal MI	88 (2·8)	29 (2·2)	42 (3·9)	14 (2·3)	3 (1·7)
Nonfatal stroke	290 (9·0)	113 (7·9)	85 (9·0)	75 (11·6)	17 (9·0)
CV death, nonfatal MI, nonfatal stroke, hospitalization for atherothrombotic events, or peripheral vascular intervention	610 (18·5)	233 (15·9)	189 (19·9)	150 (21·8)	38 (19·3)
Atherothrombotic events†	142 (4·4)	62 (4·5)	51 (5·1)	22 (3·6)	7 (3·8)
Peripheral vascular intervention‡	33 (1·0)	11 (0·8)	14 (1·6)	6 (0·9)	2 (1·1)

Event rates for geographical regions were adjusted for age, sex and qualifying event.
*Only the first event for each patient is counted.
†Atherothrombotic events leading to hospitalization includes unstable angina and new diagnosis/worsening of claudication.
‡Peripheral vascular intervention includes amputation affecting lower limbs, peripheral artery bypass graft and peripheral angioplasty/stenting.
CV, cardiovascular; MI, myocardial infarction.

fully serviced accommodation. In analysis of event rates as a function of the number of low quality-of-living and socioeconomic conditions, the primary endpoint event rates increased in stepwise fashion with the number of indicators (Fig. 1; adjusted HR per number increase 1·29, 95% CI 1·18–1·40). Similar results were found when models were refit using human development indices (adjusted HR per number increase 1·34, 95% CI 1·24–1·44).

Discussion

The OPTIC registry investigated atherothrombotic events and risk factors in stroke patients from low- and middle-income countries with a two-year follow-up period. It illustrates key challenges to be addressed in the global prevention and control of stroke risk factors in these countries after epidemiological transition.

The major finding of this study was the significant association between indicators of low socioeconomic status and recurrence of all cardiovascular events, even after adjustment for age, sex, and a group of defined conventional risk factors that might be significant. Furthermore, this association was higher in patients with all five indicators of low socioeconomic profile than in those with only one indicator. Previous studies using different study designs and various definitions of socioeconomic status have shown that people with lower socioeconomic status are at increased stroke risk (19–22), even in well-developed countries with a high

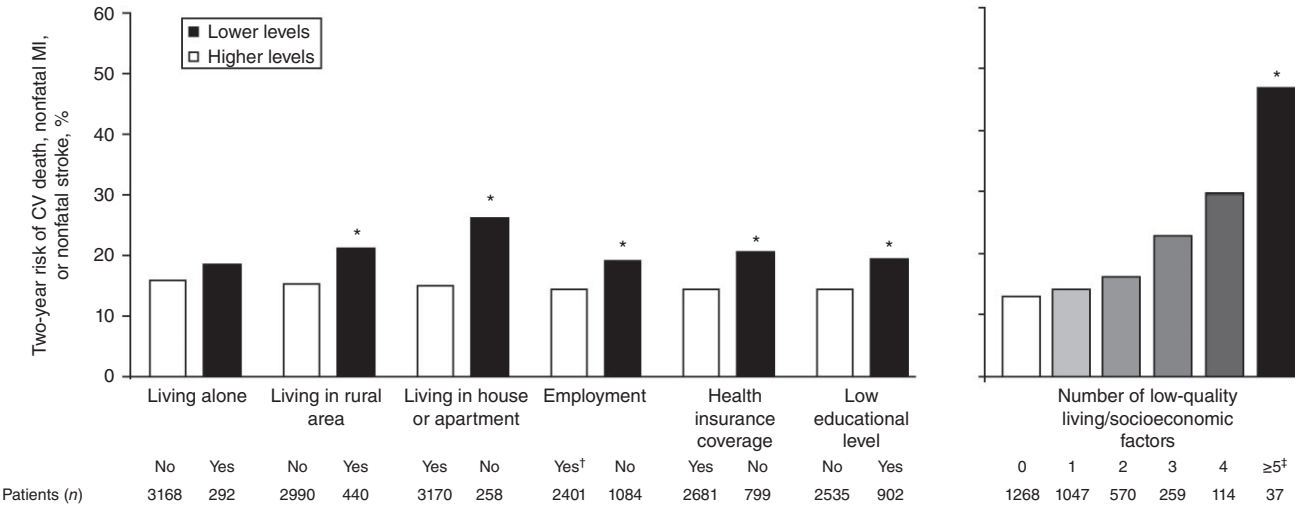

Fig. 1 Adjusted risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke as a function of low-quality living and socioeconomic conditions. Event rates were adjusted by age, sex, qualifying event, country, and other conventional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, current smoking, current physical activities, current alcohol consumption, coronary artery disease, peripheral artery disease). *$P < 0{\cdot}005$. †Including social pensioners on disability grant and old-age pensioners. ‡Including one patient with six indicators of low socioeconomic level.

Table 4 Multivariate analysis of predictors of two-year cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

Variable	Hazard ratio (95% CI)	*P* value
Age (per 10-year increase)	1·26 (1·15–1·37)	<0·001
Prior known CAD, yes versus no	1·82 (1·44–2·31)	<0·001
Living in house/apartment, no versus yes	1·97 (1·49–2·60)	<0·001
Current alcohol consumption, yes versus no	1·58 (1·21–2·06)	<0·001
Prior known CHF, yes versus no	1·83 (1·25–2·67)	0·002
Latin America versus other regions	0·76 (0·61–0·93)	0·01
Health insurance coverage, no versus yes	1·33 (1·08–1·65)	0·01
Low educational level, yes versus no	1·31 (1·04–1·64)	0·02
Living alone	1·42 (1·06–1·91)	0·02
Prior known TIA	0·76 (0·60–0·96)	0·02
Prior known PAD or ABI <0·9, yes versus no	1·25 (1·03–1·53)	0·02
Systolic/diastolic BP ≥160/100 mmHg, yes versus no	1·25 (1·03–1·51)	0·03
Unemployment, yes versus no*	1·26 (0·99–1·58)	0·05

Calculated from stepwise-selection Cox-model stratified by qualifying event and including age and sex as forced variables, on the basis of the 3065 patients with nonmissing candidate variables; the *C*-statistic for the final model was 0·67 (95% CI 0·64–0·70), and the *P* value for global test of proportional hazard assumption was 0·98.
*Excluding social pensioners on disability grant and old-age pensioners.
ABI, ankle–brachial index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; PAD, peripheral arterial disease.

standard of medical care (19,23). However, the mechanism by which socioeconomic status influences stroke and the recurrence of vascular events is not entirely understood. Potential explanations may be related to inadequate access to health-care service (19,24), differences in treatment and use of secondary prevention therapies among the different socioeconomic groups (25,26), disparities in access to specialist care (23), medication adherence, and other unmeasured factors (27) (e.g., urban versus rural geographic location, the overall economic rating of the country concerned) (28). We used a combination of measures because each of these indicators do not measure the same thing, as they capture different aspects of socioeconomic status that are not interchangeable; however, they were consistently asociated with increased cardiovascular risk in our study (19). Furthermore there is conflicting evidence regarding rural/urban effect on stroke and cardiovascular disease. There is evidence that patients in rural or underserved areas of high-income countries and in medium- and low-income countries have lower education, income, and access to care and higher risk of stroke and mortality (28,29). But there is also evidence that urbanization in developing countries increases the prevalence of cardiovascular risk factors such as obesity and hypertension (30,31). In our study, living in a rural area increased the cardiovascular risk, and this could be the result of less awareness of stroke symptoms and less access to care, prevention, and rehabilitation (32–34).

The rate of major vascular events (vascular deaths, nonfatal MI, and stroke) was 15·6% at two-year follow-up. If hospitalizations for atherothrombotic events or peripheral vascular intervention were to be added to this composite endpoint, an event occurred in nearly one patient in every five. However, there were marked geographical variations in recurrence rates, with the highest rate seen in North Africa and the lowest in Latin America.

These differences may be partially explained by differences in health care systems and health insurance coverage, by the impact of socioeconomic factors, perhaps by genetic variations, and by an increased prevalence of risk factors in these regions, such as diabetes (29%, 46%, 28%, and 35% in Latin America, the Middle East, North Africa, and South Africa, respectively) (8). North Africa had the worst socioeconomic profile, with 12% of patients

not living in serviced accommodation, 18% living in rural areas, 36% unemployed, 42% without health insurance coverage (as compared with 15%, 23%, and 20% in Latin America, the Middle East, and South Africa, respectively), and 62% with less than two-years of schooling (as compared with 12%, 26%, and 2·3% in Latin America, the Middle East, and South Africa, respectively) (8).

A high percentage of patients in this registry were treated with secondary prevention drugs. Nearly 80% were on antihypertensive medication, 72% were on a lipid-lowering therapy, and more than 95% received at least one antiplatelet agent or were taking oral anticoagulants. Compliance with antihypertensive medication, statins, and aspirin treatment was excellent in the OPTIC registry. A higher awareness of stroke risk recurrence by these patients and their physicians and the possibility of directly assessing treatment effects (i.e., measuring BP and cholesterol level) may have accounted for patient adherence to the recommended medication. In contrast, only 7·5% of patients discharged on ADP receptor antagonists were on this medication at six-months. The much higher costs for ADP receptor antagonists and differences in medical health care systems across countries may have accounted for some changes in treatment.

By design we excluded patients younger than 45 years and those with cardioembolic stroke, which might well be more prevalent in developing countries with epidemiological transition from infectious disease to atherothrombotic risk factors, particularly at younger ages. We have also excluded patients who might have had difficulty returning for follow-up visits, which may have accounted for the rather low proportion of patients from rural areas. Therefore our study was centered on urban populations, possibly accounting for differences observed with the PURE study, where the uptake of recommended secondary prevention drugs was lower than 25% for antiplatelet agents, antihypertensive drugs, or statins in rural and low-income countries (26). Nevertheless, our study has shown that socioeconomic status has a strong impact on the two-year recurrent vascular risk.

One major limitation that is common in large multiregional registries was the lack of formal adjudication by a critical event committee, and diagnosis of components of the primary endpoints was based on chart summaries. This may have led to underdiagnosis of nonfatal, nonhospitalizing MI and stroke. However, if there was a systematic underevaluation in incident MI and stroke, it likely does not invalidate the main result of this study, as diagnosis rates should be higher and not lower in countries with lower socioeconomic level, and underestimation was similar between groups.

Vascular risk recurrence in stroke patients in low- and middle-income countries such as South Africa and those in North Africa, the Middle East, and Latin America varies not only across geographical regions and with the number of arterial beds involved but also with socioeconomic variables, particularly poor health insurance cover, not living in serviced accommodation, and low level of education. Not only measures aiming to control classic risk factors but also strategies that address socioeconomic issues at a political level (e.g., economic status of populations; improvement in social security and health care systems, particularly for the poor and indigent) are essential to reduce the burden of vascular disease recurrence after ischemic stroke.

Contributors

PA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PA, HA, and JL drafted the manuscript. JL and EV did the statistical analyses. PA, EV, AA, AB, PGL, AM, MMC, PGS, and BIY were responsible for the study concept, design, and supervision. PA, EV, AA, AB, PGL, AM, MMC, PGS, BIY, JL, and HA analyzed and interpreted the data. All authors revised the manuscript for important intellectual content.

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