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on behalf of the Italian Project on Stroke in Young Adults (IPSYS) Investigators

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Predictors of Long-Term Recurrent Vascular Events After Ischemic Stroke at Young Age
The Italian Project on Stroke in Young Adults

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Background—Data on long-term risk and predictors of recurrent thrombotic events after ischemic stroke at a young age are limited.

Methods and Results—We followed 1867 patients with first-ever ischemic stroke who were 18 to 45 years of age (mean age, 36.8±7.1 years; women, 49.0%), as part of the Italian Project on Stroke in Young Adults (IPSYS). Median follow-up was 40 months (25th to 75th percentile, 53). The primary end point was a composite of ischemic stroke, transient ischemic attack, myocardial infarction, or other arterial events. One hundred sixty-three patients had recurrent thrombotic events (average rate, 2.26 per 100 person-years at risk). At 10 years, cumulative risk was 14.7% (95% confidence interval, 12.2%–17.9%) for primary end point, 14.0% (95% confidence interval, 11.4%–17.1%) for brain ischemia, and 0.7% (95% confidence interval, 0.4%–1.3%) for myocardial infarction or other arterial events. Familial history of stroke, migraine with aura, circulating antiphospholipid antibodies, discontinuation of antiplatelet and antihypertensive medications, and any increase of 1 traditional vascular risk factor were independent predictors of the composite end point in multivariable Cox proportional hazards analysis. A point-scoring system for each variable was generated by their β-coefficients, and a predictive score (IPSYS score) was calculated as the sum of the weighted scores. The area under the receiver operating characteristic curve of the 0- to 5-year score was 0.66 (95% confidence interval, 0.61–0.71; mean, 10-fold internally cross-validated area under the receiver operating characteristic curve, 0.65).

Conclusions—Among patients with ischemic stroke aged 18 to 45 years, the long-term risk of recurrent thrombotic events is associated with modifiable, age-specific risk factors. The IPSYS score may serve as a simple tool for risk estimation. (***Circulation***. 2014;129:1668-1676.)

Key words: brain ischemia ■ prognosis ■ stroke

Patients who survive an ischemic stroke (IS) are at particularly high risk for subsequent cardiovascular events, including recurrent brain ischemia, myocardial infarction (MI), and death from vascular causes.[1] Although it is well documented that such a risk is much lower in young patients with stroke than in elderly patients, information on what specific factors may predict recurrent events in younger age groups are limited. Most data derive from single-center studies enrolling several hundred patients or less,[2] using different thresholds of age to define young, and sometimes being biased by the inadequate capture of cases, the inclusion of different ethnic groups, and the high number of patients lost to follow-up.[3] This makes such studies somewhat heterogeneous and their findings poorly comparable. In addition, the influential effect of some specific factors is missing in most previous studies. This is the case, for example, of patients' adherence to secondary prevention therapies, which is likely to impact the recurrence of potentially avoidable vascular events. The Italian Project on Stroke in Young Adults (IPSYS) provides the opportunity to investigate these issues owing to its large sample size, the homogeneous demographic characteristics and clinical phenotype of the subjects included, and the standard diagnostic workup. Therefore, in the present study we aimed at (1) elucidating the predictors of long-term recurrent vascular events after first-ever IS, and the extent to which these factors can be modified, which implicates the potential of reducing this risk, and (2) developing a tool for estimating the risk of recurrence, in a cohort of Italian IS patients aged 18 to 45 years.

Methods

Patients and Study Design

The IPSYS is a countrywide network of neurological centers with special interest in cerebral ischemia at young age across Italy, aimed at recruiting white patients with first-ever acute stroke who fulfill the following criteria: (1) age 18 to 45 years, (2) computed tomography– or magnetic resonance imaging–proven cerebral infarction, in the setting of a hospital-based, multicenter, observational study.[4] Centers are included in the network provided that the recruitment process of stroke cases takes place prospectively. The study was approved by the local Ethics Committee. Informed consent was provided by all study participants. For the purpose of the present analysis, we screened data sets from patients consecutively admitted to 22 hospitals. The recruitment period was January 2000 through January 2012, and follow-up was completed January 2013. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for >24 hours with a probable vascular cause.[5] IS due to sinus venous thrombosis, vasospasm after subarachnoid hemorrhage, cardiac surgery, occurring as an immediate consequence of trauma, and iatrogenic strokes were excluded.

Risk Factor Definition

The following risk factors for premature cerebral ischemia were retained: hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, migraine, oral contraceptive use, excessive alcohol consumption, and family history of stroke. These variables were defined and dichotomized as follows: hypertension, systolic blood pressure ≥140 mm Hg and diastolic pressure ≥90 mm Hg in 2 separate measurements after the acute phase or use of antihypertensive drugs before recruitment; diabetes mellitus, history of diabetes mellitus, use of hypoglycemic agent or insulin, or fasting glucose ≥7.0 mmol/L; current smoking, including former smokers who had quit smoking for 6 months before the index event; hypercholesterolemia, cholesterol serum levels ≥5.7 mmol/L or use of cholesterol-lowering drugs; migraine (personal history of headache was assessed in all patients by study physicians during a face-to-face interview in both acute-phase and follow-up evaluations), as migraine without aura and migraine with aura (MA) according to the diagnostic criteria of the International Headache Society[6]; heavy alcohol consumption, weekly consumption >14 drinks for men and > 7 drinks for women; oral contraceptive use, current use (including former users who had quit taking these medications for 1 month before the index event); and family history of stroke, stroke recorded in first-degree relatives by interviewing probands or family members. We also collected information on atrial fibrillation (medical history or electrocardiographic findings at admission).

Clinical and Laboratory Investigations

All patients underwent an etiologic workup including complete blood cell count, biochemical profile, urinalysis, 12-lead ECG, chest roentgenography, Doppler ultrasonography with frequency spectral analysis and B-mode echotomography of the cervical arteries, transcranial Doppler ultrasonography, and computed tomography and magnetic resonance angiography to investigate extracranial and intracranial vessels. Coagulation testing included prothrombin and activated partial thromboplastin times, circulating antiphospholipid antibodies (aPLs), fibrinogen, protein C, protein S, activated protein C resistance, antithrombin III, genotyping to detect factor V Leiden and the G20210A mutation in the prothrombin gene. aPLs were analyzed as an all-or-none variable (ie, subjects who were persistently positive for lupus anticoagulant,[7] or IgG anticardiolipin antibodies,[8] or IgG anti–β_2-glycoprotein I,[9] or any combination of these were considered aPL+ [aPL=1], whereas subjects who were negative were aPL– [aPL=0]). Transthoracic and transesophageal echocardiography were performed to rule out cardiac sources of emboli. Based on the results of such investigations, patients were classified according to a classification based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, accommodated and validated for the cause of stroke in the young[10] and divided into 5 etiologic categories: (1) atherosclerotic vasculopathy, (2) nonatherosclerotic vasculopathy, (3) small-vessel disease, (4) cardioembolism, and (5) other: cerebral infarction that did not meet the criteria for one of the categories outlined.

Outcomes

Only patients who survived the index event were entered into the present analysis. Death was considered due to the index stroke if it occurred within 30 days of the onset of symptoms. Subjects were included in the subgroup of patients who did not experience recurrence if they had at least a 1-year follow-up. Follow-up evaluations were conducted at 3 months and then annually, and outcome events were classified by using information from interviews (directly during follow-up visits or by telephone) with patients, next of kin, witnesses, and attending physicians or from hospital/general practitioner records.

Long-term vascular recurrence was defined as any event of fatal/nonfatal IS, transient ischemic attack (TIA), fatal/nonfatal MI, or other arterial thrombotic event. Recurrent IS was defined by using

the same criteria applied for the definition of the index event. MI was diagnosed when at least 2 criteria among (1) ischemic chest pain, (2) characteristic ECG changes, and (3) cardiac enzyme abnormalities[11] were present. Diagnosis of TIA was made when the patient had reliably observed transient (<24 hours) neurological deficit of abrupt onset, without evidence of an underlying nonvascular cause, according to the consulting neurologist or the attending physician who evaluated the event by clinical and imaging methods.[12] Deaths were classified by using death certificates, medical records, and family interviews. In the cases in which it was difficult to make a precise determination of the cause of death, consensus was reached based on the best available information. If >1 recurrent event occurred, the first was used for calculation of the disease-free survival time. The primary end point was a composite of IS, TIA, MI, or other arterial events. Secondary end points were (1) brain ischemia (IS or TIA) and (2) MI or other arterial events, as well.

Long-term antithrombotic therapy and other treatment for secondary prevention were administered in accordance with published guidelines.[13] Adherence to secondary prevention medication (oral anticoagulants, aspirin or other antiplatelet agents, antihypertensive agents, oral hypoglycemic agents or insulin, and statins) during follow-up was ascertained in the same way as for recurrent vascular events. Patients were considered persistent medication users if they were still using treatments prescribed at hospital discharge at the end of follow-up, and nonpersistent medication users if they discontinued a medication regardless of the reason. Medication discontinuation was considered to influence recurrence and, thus, was entered into the analysis when it was detected before the occurrence of the recurrent event.

Statistical Analyses

Duration of follow-up was calculated in person-months by using the follow-up of each participant from baseline examination until death, recurrent event, or most recent censored follow-up assessment. We computed a cumulative index (from 0 to 4) based on the number of traditional risk factors (hypertension, diabetes mellitus, smoking, and hypercholesterolemia). To evaluate the cumulative influence of these markers, they were all included in the risk predictor set, regardless of their independent effect on the risk of recurrence. Kaplan-Meier survival analysis was used to estimate the cumulative incidence of recurrent events by follow-up time.[14] Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed by Cox proportional hazards models in univariate analyses to compare demographic variables and risk factor prevalence at baseline, and in stratified multivariable analysis, as well, to detect the independent predictors of recurrence (with baseline hazard functions varying according to the strata defined by the TOAST categories). In each model, predictors of the overall primary and secondary end points were identified. The first model included the following covariates: age, sex, traditional risk factors, migraine without aura and MA, patent foramen ovale, atrial fibrillation, alcohol consumption, factor V Leiden, the G20210A mutation in the prothrombin gene, circulating aPLs, family history of stroke, and discontinuation of medications prescribed at discharge. The same analysis was performed entering the cumulative index instead of each single traditional factor into the model.

For the selection of predictors we used the lasso method proposed by Tibshirani[15] in survival analysis. This is a penalized variable selection technique, which shrinks β-coefficients [β=ln(HR)] and produces some β-coefficients that are exactly zero. The variables whose β-coefficient is zero are then automatically deleted from the predictor set. Model screening was performed by tuning penalized parameter by K-fold cross-validation,[16] with K=10 roughly equal-sized subsets. The nonzero β-coefficients of each predictor variable from the multivariable survival model with minimum lasso penalty were used to generate a weighted scoring system of the predictors. An overall continuous individual risk score (IPSYS score, s) for each patient (i) was calculated by summing up its β-coefficients × predictor values (x_i) [$s(i)=\sum_j \beta_j x_j$]. $\eta(i)=\exp(s(i))$ represents the hazard score for each subject. Higher values of $\eta(i)$ correspond to a higher level of hazard and a shorter survival time based on the predictors.

To assess the predictive validity of the IPSYS score we used the receiver operating characteristic curves, the area under the receiver operating characteristic curve (AUC), and the discrimination C statistic (overall AUC), which takes into account the timing of events from survival data.[17–19] AUC and C summaries are 0 to 1 values, where 50% is the null value of worse scenario for decision making. To account for the fact that we evaluated the risk score function on the same data on which it was developed, overall AUC in predicting events that occur in a time range 0 to t was validated by K-fold cross-validation with K=10, each fold evaluating a test sample (n=187) by using scores obtained from the β-coefficients trained by the other learning sample (n=1867−187=1680). In this way, we corrected for potential overoptimism in the assessment of the score performance.

Additionally, we estimated the prediction error of the variables built in the IPSYS score by weighted time-dependent Brier score curve,[20] that is, the weighted mean of the squared difference of the patient status (recurrence versus no recurrence) and the risk prediction of all observations at each time point, with weights that account for right censoring. Brier score values range between 0 and 1, the smaller values indicating good performance of the risk prediction model at given time points (a useful risk prediction model should not have a value >0.25). Three prediction errors were compared, as suggested by Gerds et al[21]: (1) 0.632+ prediction error estimate, a weighted combination of the apparent error on the full data set and the bootstrap cross-validation error estimate with K=10 parts and B=100 bootstrap samples; (2) null model prediction error, an estimation of fit without the prognostic variables by using the Kaplan-Meier estimate; and (3) no-information error of the full data set, an evaluation of the prognostic variables in artificially permuted data where the recurrence response is independent of the predictors. Two-sided values of *P*<0.05 were considered significant. Statistical analyses were conducted with the software R (version 3.02, R Development Core Team, 2013).

Results

Study Group

A cohort of 1906 patients with first-ever IS was included in the IPSYS registry. Of these, 1867 were followed-up for a total of 86 491 person-months. The median follow-up time in patients who did not experience recurrence was 42.0 months (25th to 75th percentile, 54.0). Recurrent events were recorded in 163 patients (average rate, 2.26 per 100 person-years at risk), of which 86 had an IS, 8 had a MI, 67 had a TIA, and 2 had other arterial thrombotic events. The median interval between the index stroke and the outcome event was 22.0 months (25th to 75th percentile, 27.0). Baseline characteristics of the study group are summarized in Table 1.

Cumulative risk of combined outcome was 3.6% (95% CI, 2.9%–4.6%) at 1 year, 11.5% (95% CI, 9.8%–3.5%) at 5 years, and increased to 14.7% (95% CI, 12.2%–17.9%) at 10 years (Figure 1A). A similar trend was observed for recurrent cerebral ischemic events, whose cumulative risk was 3.2% (95% CI, 2.5%–4.2%) at 1 year, 10.9% (95% CI, 9.3%–12.9%) at 5 years, and 14.0% (95% CI, 11.4%–17.1%) at 10 years (Figure 1B). Conversely, the cumulative risk of MI or other arterial events was 0.5% (95% CI, 0.2%–0.9%) at 1 year, increased negligibly up to 0.7% at 5 years (95% CI, 0.4%–1.3%), and then did not change further (Figure 1C).

Patients whose index stroke etiology was large-artery atherosclerosis had the highest cumulative risk of recurrence, corresponding to a 10-year risk of composite end point >4 times higher than that of nonatherosclerotic vasculopathies (24.7% versus 5.7%; Figure 2), although differences across the TOAST categories were not significant (log-rank test (df) = 8.9 (4); *P*=0.06).

Table 1.   Demographics and Clinical Characteristics of the Study Group According to Recurrence Status

Variable	No Vascular Recurrence (n=1704)	Recurrent Vascular Event (n=163)	HR (95% CI)	P Value
Age, y, mean±SD	36.7±7.1	37.1±7.1	1.01 (0.99–1.04)	0.21
Men, n (%)	869 (50.9)	83 (50.9)	0.98 (0.72–1.33)	0.89
Hypertension, n (%)	382 (22.4)	45 (27.6)	1.34 (0.95–1.89)	0.09
Diabetes mellitus, n (%)	62 (3.6)	9 (5.5)	1.66 (0.85–3.26)	0.14
Current smokers, n (%)	632 (37.0)	76 (46.6)	1.40 (1.03–1.91)	0.03
Hypercholesterolemia, n (%)	417 (24.4)	46 (28.2)	1.18 (0.84–1.65)	0.35
One major risk factor or more, n (%)	1000 (58.6)	114 (69.9)	1.23 (1.05–1.44)	0.011
History of migraine, n (%)*				
No migraine	1221 (75.2)	112 (70.0)	1	…
MO	282 (17.3)	29 (18.1)	1.15 (0.76–1.73)	0.50
MA	120 (7.3)	19 (11.9)	1.70 (1.05–2.77)	0.03
Oral contraceptives, n (%)†	284 (35.1)	23 (28.8)	1.25 (0.77–2.03)	0.38
Family history of stroke, n (%)	434 (25.4)	60 (36.8)	1.65 (1.20–2.28)	0.002
Patent foramen ovale, n (%)	516 (30.3)	48 (29.4)	1.00 (0.71–1.40)	0.10
Atrial fibrillation, n (%)	32 (1.9)	3 (1.8)	1.06 (0.34–3.32)	0.92
Heavy alcohol consumption, n (%)	145 (8.5)	12 (7.4)	0.89 (0.49–1.60)	0.69
Therapy at discharge, n (%)				
Antiplatelets	1260 (76.8)	119 (73.9)	0.89 (0.62–1.26)	0.50
Oral anticoagulants	346 (21.1)	39 (24.2)	1.14 (0.79–1.63)	0.49
Antihypertensive	382 (22.4)	45 (27.6)	1.34 (0.95–1.89)	0.09
Statins	282 (16.5)	39 (23.9)	1.62 (1.13–2.33)	0.009
Nonpersistent medication users, n (%)	172 (10.2)	28 (17.2)	1.51 (1.00–2.26)	0.049
Medication discontinuation, n (%)				
Antiplatelets	47 (3.5)	18 (14.8)	3.40 (2.08–5.55)	<0.001
Oral anticoagulants	104 (29.1)	9 (23.0)	0.72 (0.37–1.41)	0.34
Antihypertensive	4 (1.0)	4 (8.8)	9.96 (3.69–26.93)	<0.001
Statins	23 (8.1)	2 (5.1)	0.96 (0.24–3.88)	0.96
FV $_{G1691A}$, n (%)				
GG	1604 (96.0)	154 (95.0)	1	…
AG	66 (4.0)	8 (5.0)	0.83 (0.41–1.68)	0.60
AA	0	0 (0.0)	–	…
PT $_{G20210A}$, n (%)				
GG	1597 (96.6)	153 (94.4)	1	…
AG	55 (33.2)	9 (5.6)	0.71 (0.36–1.39)	0.32
AA	1 (0.2)	0 (0.0)	–	…
Antiphospholipid antibodies	98 (5.7)	22 (13.5)	2.74 (1.75–4.30)	<0.001

HRs (95% CI) and P values were obtained by univariate Cox model. CI indicates confidence interval; FV, factor V Leiden; HR, hazard ratio; MA, migraine with aura; MO, migraine without aura; PT prothrombin gene; and SD, standard deviation.

*Eighty-four missing.

†In women (25 missing).

Overall, 200 (10.7%) patients stopped at least 1 class of medications for secondary prevention prescribed at hospital discharge (5.7% at 1 year, 8.9% at 5 years, and 10.2% at 10 years). By medication class, persistence was highest for antihypertensive drugs (98.1%), followed by antiplatelet (95.3%), lipid-lowering (92.3%), and oral anticoagulant (71.2%) medications, whereas we did not detect discontinuation of oral antidiabetic drugs or insulin. Median interval between the index stroke and medications discontinuation was 12.0 months (25th to 75th percentile, 21.0) (5.0 months [25th to 75th percentile,

24.0] for antihypertensive agents; 12.0 months [25th to 75th percentile, 30.0] for antiplatelets; 12 months [25th to 75th percentile, 17.0] for statins; 6.5 months [25th to 75th percentile, 7.75] for oral anticoagulants). Recurrent events occurred after a median interval of 2.0 months (25th to 75th percentile, 22.0) after the patients had stopped taking at least 1 drug (6.5 [25th to 75th percentile, 15.2] for antihypertensive agents; 3.5 [25th to 75th percentile, 21.0] for antiplatelets; 6.5 [25th to 75th percentile, 11.0] for statins; 6.5 [25th to 75th percentile, 21.5] for oral anticoagulants). Nonadherence to secondary
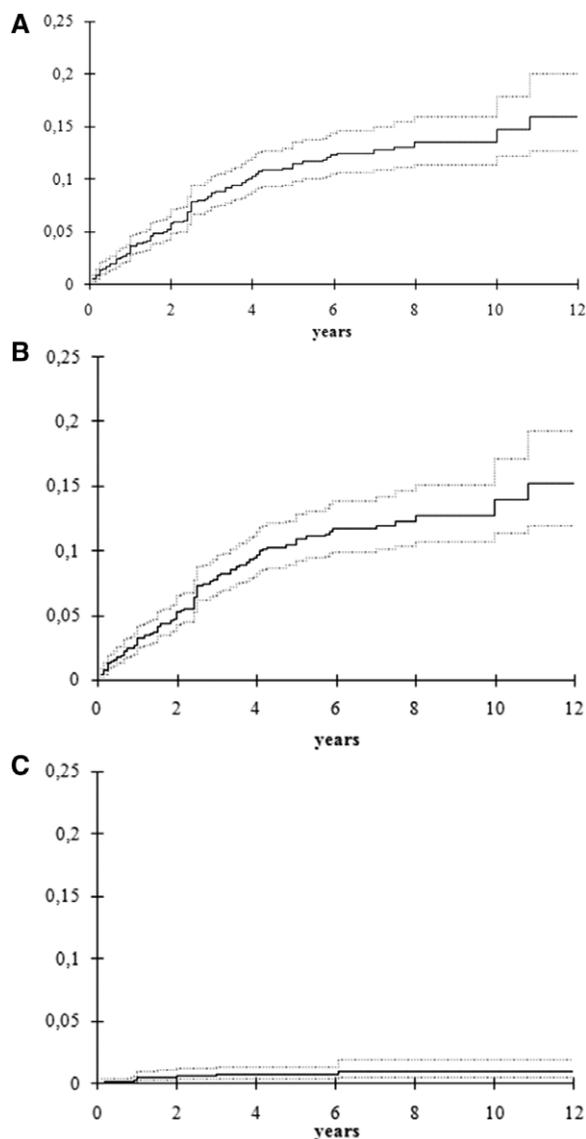
Figure 1. Cumulative risk (with 95% confidence intervals) of composite outcome event (**A**), brain ischemia (**B**), and myocardial infarct or other arterial thrombotic event (**C**).

prevention medication was associated with an increased risk of primary end point (HR, 1.51; 95% CI, 1.00–2.26) in univariate analysis.

Variable Selection for Risk Prediction Model

In multivariable stratified Cox proportional regression analysis, 5 covariates predicted independently the risk of recurrence at any follow-up time (Table 2): familial history of stroke (HR, 1.44; 95% CI, 1.02–2.04), MA (HR, 2.02; 95% CI, 1.21–3.36), aPL (HR, 2.36; 95% CI, 1.45–3.82), and discontinuation of antiplatelet (HR, 2.92; 95% CI, 1.65–5.14) and antihypertensive (HR, 5.80; 95% CI, 1.58–21.25) medications, whereas there was a trend toward an independent effect for smoking (HR, 1.34; 95% CI, 0.96–1.85). The cumulative index was also independently associated with recurrence when included in the model instead of each traditional risk factor (HR, 1.23; 95% CI, 1.04–1.45 for any increase of 1 risk factor). The model with brain ischemia as an outcome measure gave
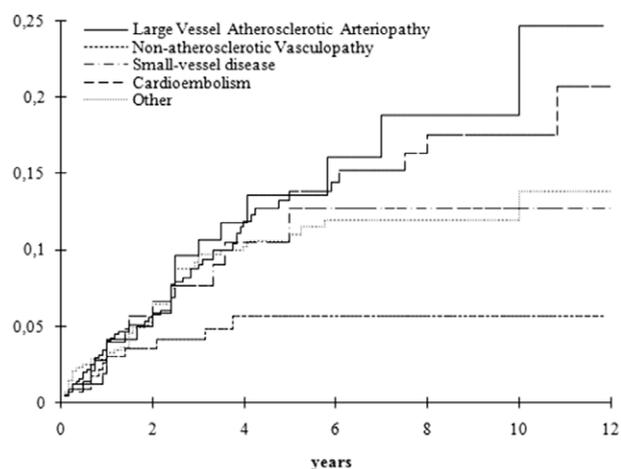
Figure 2. Cumulative risk of composite outcome event stratified by stroke subtype (modified Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria). χ^2 (*df*)=8.9(4); *P*=0.063.

similar results, whereas the low number of MIs and other arterial events did not allow for separate multivariable analysis.

The lasso technique for variable selection confirmed the nonzero β-coefficients of familial history of stroke, MA, aPL, discontinuation of antiplatelet and antihypertensive medications, and the cumulative index, as independent predictors of recurrence. The IPSYS score was generated by using 5 of the 6 predictor variables reported above. Antihypertensive medication discontinuation was not entered into the score as a separate variable because of its low prevalence (8 patients) and was combined with the variable antiplatelet medication discontinuation. To derive a value for each parameter of the IPSYS score, β-coefficients were rounded to the closest decimal (Table 3). The sum of the weighted scores was used to estimate the overall score. This gave a continuous score whose values range between 0 and 4.

Assessment of Model Performance

The IPSYS score offered moderate discrimination for the long-term risk of ischemic recurrence. In particular, AUCs were 0.62 (95% CI, 0.53–0.71) at 1 year, 0.67 (95% CI, 0.62–0.72) at 5 years, and 0.66 (95% CI, 0.59–0.73) at 10 years (Figure I in the online-only Data Supplement). Overall AUC (C statistics) for the prediction of events that occur in the time range of 0 to 5 years was 0.66 (95% CI, 0.61–0.71). Mean 10-fold cross-validated AUC was 0.65, suggesting that the bias coming from predicting on the same data set used for fitting was ≈1%. The 0.632+bootstrap prediction errors of the variables included in the IPSYS score were lower than those of the null model and those of the no-information model over the entire follow-up time, with all values <0.25 (Figure II in the online-only Data Supplement), indicating good predictive performance of our model.

Figure 3 contrasts the estimated 1-year and 5-year risks of thrombotic recurrence in patients with varied combinations of predictors. For each combination, the 5-year model gives risk estimates that are 2 to 3 times higher than those of the 1-year model. For example, the 1-year risk for a patient with MA and aPL, who discontinues secondary preventive medications is ≈30%, but the corresponding 5-year risk reaches ≈70%.

Table 2.   Multivariable Cox Proportional Hazard Model Stratified by TOAST Categories for Predicting Composite Outcome Events and Brain Ischemia

	Composite End point		Brain Ischemia	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.00 (0.97–1.02)	0.80	1.00 (0.97–1.02)	0.80
Sex (female)	0.88 (0.63–1.23)	0.48	0.87 (0.62–1.24)	0.46
Hypertension	1.12 (0.75–1.67)	0.57	0.96 (0.63–1.48)	0.88
Diabetes mellitus	1.49 (0.71–3.12)	0.29	1.49 (0.68–3.26)	0.31
Smoking	1.34 (0.96–1.85)	0.08	1.23 (0.88–1.74)	0.21
Hypercholesterolemia	1.15 (0.79–1.66)	0.45	1.24 (0.85–1.81)	0.25
History of migraine*				
No migraine	1	–	1	–
MO	1.16 (0.76–1.78)	0.47	1.28 (0.83–1.97)	0.26
MA	2.02 (1.21–3.36)	0.007	1.98 (1.15–3.39)	0.012
FV $_{G1691A}$	1.12 (0.53–2.36)	0.75	0.87 (0.37–2.04)	0.75
PT $_{G20210A}$	1.15 (0.57–2.33)	0.68	1.27 (0.62–2.58)	0.50
Family history of stroke	1.44 (1.02–2.04)	0.034	1.61 (1.13–2.30)	0.007
Patent foramen ovale	0.65 (0.41–1.04)	0.08	0.67 (0.41–1.09)	0.11
Atrial fibrillation	0.57 (0.17–1.92)	0.37	0.63 (0.18–2.11)	0.46
Heavy alcohol consumption	0.96 (0.52–1.76)	0.90	1.04 (0.56–1.90)	0.89
Medication discontinuation				
Antiplatelets	2.92 (1.65–5.15)	<0.001	2.89 (1.60–5.20)	<0.001
Oral anticoagulants	1.06 (0.50–2.27)	0.86	1.00 (0.45–2.25)	0.98
Antihypertensive	5.80 (1.58–21.25)	0.007	6.67 (1.79–24.83)	0.004
Statins	0.60 (0.13–2.62)	0.50	0.68 (0.15–3.00)	0.62
Antiphospholipid antibodies	2.36 (1.45–3.82)	<0.001	2.40 (1.46–3.94)	<0.001

CI indicates confidence interval; FV, factor V Leiden; HR, hazard ratio; MA, migraine with aura; MO, migraine without aura; and PT prothrombin gene.

Discussion

Approximately 10% of ISs occur at ages ≤45 years,[3] with a worrisome trend toward increasing incidence over time[22] and obvious socioeconomic consequences in terms of life-years with disability and life-years lost. The burden of disease raises even more in the case of recurrent events. Our findings indicate that subjects aged 18 to 45 years who survive the first 30 days after an IS are at substantial risk of recurrent arterial thrombosis over time and that such a risk is partly attributable to modifiable factors. In particular, the ≈15% cumulative risk over 10 years emphasizes the need for appropriate prevention therapies and the importance of age-specific approaches.

Most of the studies conducted so far on the long-term prognosis after premature stroke were clearly underpowered for multivariable analysis because of the rather modest number of patients involved.[2] To our knowledge, this is the largest study population of IS patients aged 18 to 45 years and the first to include long-term adherence to secondary prevention medications in the recurrence prediction models. Notably, the 2 large studies on young stroke with extended follow-up recently conducted in Finland[23] and in the Netherlands[24] included a number of patients with IS aged <45 years which is about one-third of those enrolled in our registry. Furthermore, differences in inclusion criteria, definition of variables and outcome measures, and the peculiarity in the lifestyle, and the genetic background of the studied population, as well, should be also taken into

account when comparing the results of these studies, because they might contribute to the explanation of some discrepancies. Our study provides, therefore, essential new information on the long-term risk of recurrence after stroke at younger ages.

As a huge number of epidemiological analyses have clearly indicated, even among subjects experiencing premature stroke, ageing is associated with the accumulation of traditional vascular risk factors and an etiologic spectrum resembling that seen in elderly patients.[25,26] Age difference (baseline mean age, 36.8 years in our cohort versus 40.3 years in the

Table 3.   Prognostic IPSYS Score for the Calculation of the Probability of Recurrent Thrombotic Events After Ischemic Stroke at Young Age

	HR (P Value)	β-Coefficient	Score Points
Cumulative risk factor index*	1.21 (0.020)	0.192	0.2
History of MA	1.87 (0.011)	0.626	0.6
Family history of stroke	1.63 (0.003)	0.489	0.5
Circulating antiphospholipid antibodies	2.39 (<0.001)	0.869	0.9
Medication discontinuation†	3.33 (<0.001)	1.202	1.2

HR indicates hazard ratio; and MA, migraine with aura;

*Values ranging from 0 to 0.8 (presence/absence of arterial hypertension, diabetes mellitus, smoking, or hypercholesterolemia).

†Antiplatelets or antihypertensive agents.
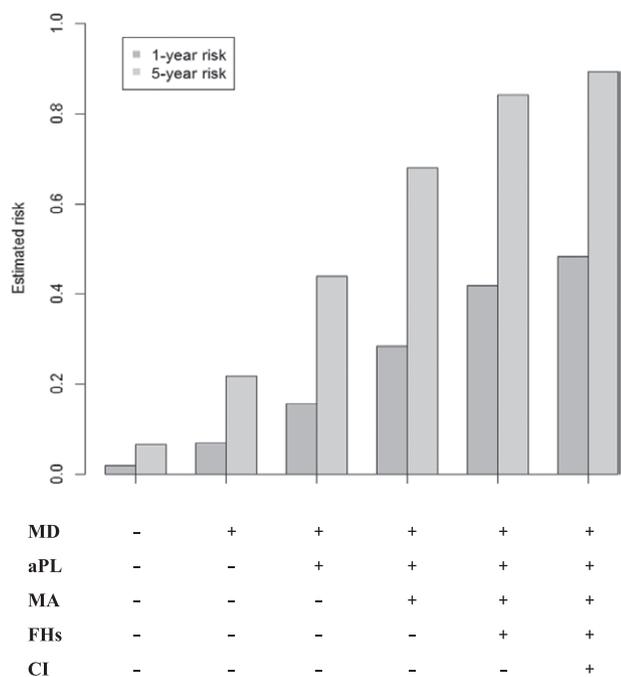
Figure 3. One-year vs 5-year risk of recurrent ischemic events for subjects with different risk profiles. No risk factors profile: cumulative index, 0 (normotensive; nonhypercholesterolemic; nonsmoker; nondiabetic); no personal history of migraine with aura; no family history of stroke in first-degree relatives; no circulating antiphospholipid antibodies; no discontinuation of antiplatelets or antihypertensive agents over follow-up. aPL indicates circulating antiphospholipid antibodies; CI, cumulative index (at least 1 among arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia); FHs, family history of stroke in first-degree relatives; MA, migraine with aura; MD, medication discontinuation (antiplatelets or antihypertensive drugs); –, absent; +, present. 1-year risk=$1 - 0.97^{\exp(\text{IPSYS score})}$; 5-year risk=$1 - 0.93^{\exp(\text{IPSYS score})}$.

Dutch study[24] and 41.3 years in the Helsinki Young Stroke Registry)[23] is, therefore, the most likely explanation for the lower prevalence of traditional risk factors in our series in comparison with the other 2, and might account for the different independent contribution of these factors to the risk of recurrence.[23,24] Demographic characteristics might also partly explain the relative influence of additional factors in our cohort, as opposed to what was observed in earlier reports. This is the case, for example, of MA, whose independent effect on post-stroke recurrence was not consistently found in the longitudinal studies conducted so far. A reason for this might be that the effect of MA as risk factor for stroke decreases with age,[27] whereas the effect of traditional risk factors becomes prominent. Furthermore, the low prevalence of migraine and the lack of characterization of migraine subtypes in some of the previous studies prompt the speculation that several possible biases in the assessment of individual migraine history were also operant.[28–35] As an indirect support to our findings, Gioia and coworkers[36] recently found a higher prevalence of MA in young patients with stroke with silent ischemic lesions on brain MRI, an independent predictor of recurrence, in comparison with those with no evidence of brain abnormalities. This reinforces the hypothesis that MA might also predict clinical recurrent events. Most of the considerations reported above also apply to the observed effect of individual

family history of stroke, a condition with well-established age-dependent influence on the risk of disease.[37]

Another important finding of our study is that the discontinuation of secondary preventive medications prescribed at discharge strongly predicts the long-term risk of recurrence. Data of literature provide evidence that the discontinuation of drugs prescribed after a stroke leads to potentially avoidable disease recurrences, disability, and death independent of the patient's age. However, because juvenile strokes have been largely underrepresented in trials on secondary prevention over the past 50 years,[38] the ideal duration, safety, and efficacy of these medications in younger age groups is still unclear, and there is virtually no demonstration from longitudinal studies that long-term adherence to prescribed treatments might reduce the risk of recurrence.[39] In this regard, both the Helsinki Young Stroke Registry[23] and the FUTURE study[24] recorded data on secondary preventive medications at discharge, but did not provide information on the eventual discontinuation of these drugs during follow-up, leaving the issue unsolved.

Finally, our data also indicate that part of the long-term risk of recurrent thrombotic events after the index stroke is attributable to aPL. This is not surprising when considering the well-known prothrombotic effects of these molecules, and it is even more likely if we take into account the controversy on the most adequate treatment approach in these cases.[30,40]

The assessment of factors we identified as predictors of arterial thrombotic recurrence is part of the routine clinical investigation of patients with ischemic stroke at a young age. Therefore, the risk score we developed based on such factors is a simple prediction algorithm for the estimation of the individual long-term risk in this age category in a clinical setting. Effective risk communication is another reason why our long-term risk prediction score might be helpful. Patients are more likely to adopt lifestyle changes on hearing that their 5-year risk of recurrence is >70% than when they are told it is ≈30%.

Several strengths of the present study should be noted, including the large number of participants, the homogeneous demographic characteristics and clinical phenotype of the cohort, the standardized diagnostic workup and evaluation of risk factors, and the systematic assessment of recurrent events. Some limitations also should be considered. First, because the IPSYS is a hospital-based study, the results might be susceptible to hospital referral selection bias. However, inaccurate capture of the incident cases is highly unlikely because young patients with stroke are usually referred to academic centers during the course of the disease. Second, TIA is a less clear-cut end point than stroke and has a number of mimicking conditions, particularly in younger individuals. However, at least biologically, TIAs represent reliable markers of failed secondary prevention just as major strokes or any other thrombotic events, and, as such, they should not be excluded from long-term prediction models. Third, because the therapeutic decision on antiphospholipid syndrome was left to the discretion of the investigator in charge of the patients, we cannot exclude that treatment variability might have influenced the recurrent rate in this category. Fourth, because we did not assess migraine frequency and severity, and the frequency of auras, as well, at baseline or during follow-up, we cannot evaluate whether the observed association differs according to specific migraine

patterns. However, whether migraine frequency is a measure of migraine severity remains to be demonstrated. Fifth, in the assessment of the IPSYS score performance, we accounted for the overoptimism introduced by evaluating the model on the same data on which it was developed by using 10-fold cross-validation. Although this technique is well suited for this purpose, it cannot be equated with the preferred method of validation in a different cohort. Finally, we cannot rule out that other factors, not included in the present analysis, might have influenced the results. This is the case, for example, with illicit drugs use, a common risk factor for ischemic stroke at a young age,[41] for which we did not obtain consent to specific tests from most of the patients included in the registry, and for specific genotypes, as well, that might have an impact on stroke biology. Similarly, because our findings were obtained from a homogeneous Mediterranean white population, they cannot be generalized to other groups of different racial-ethnic origin, because of disparities in risk factor distribution, access to stroke services, and overall recurrence risk.

In conclusion, our study showed that in patients with IS aged 18 to 45 years, the risk of long-term recurrent arterial thrombotic events is associated with age-specific risk factors whose effect is largely modifiable. The risk score we developed based on the combination of these factors might serve as a tool in the clinical and public health setting for the estimation of individual risk of recurrence. Our findings, in particular, emphasize the importance of extending the use of secondary prevention treatments beyond the acute and early postacute phase of brain ischemia into the long term. Implementation of appropriate therapeutic and lifestyle treatment strategies in this age category is likely to impact the individual susceptibility to recurrence.

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CLINICAL PERSPECTIVE

Data on long-term risk of recurrent thrombotic events in young adults with first-ever ischemic stroke are limited, and scarce information is available on what factors may predict such a risk. In the present investigation, we evaluated the impact of age-specific risk factors on thrombotic recurrence in a cohort of 1867 patients with ischemic stroke aged 18 to 45 years, in the setting of the multicentric Italian Project on Stroke at Young Age (IPSYS). The average rate of recurrence was 2.26 per 100 person-years at risk. The 14.7% cumulative risk of recurrence we observed 10 years after the index event suggests that young adults are at substantial risk of further thrombotic episodes over a long-term follow-up. Our findings also indicate that a familial history of stroke, circulating antiphospholipid antibodies, discontinuation of antiplatelet and antihypertensive medications for secondary prevention, and a personal history of migraine with aura, as well, and, to a lesser extent, of traditional vascular risk factors (arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia) are independent predictors of this risk. This emphasizes the need for appropriate prevention therapies and the importance of specific lifestyle treatment strategies in this age category. Additionally, we generated and internally validated a risk prediction algorithm (the IPSYS score, whose values range between 0 and 4 depending on the combination of these predictors) which might serve as a tool in the clinical and public health setting for estimating the individual propensity to long-term thrombotic recurrence of young ischemic stroke patients.

Figure 1

Area under the receiver operating characteristic (AUC) curve (with 95% confidence intervals) of the prognostic variables included in the *IPSYS score* over follow-up.

Figure 2

Prediction error curves over follow-up.

The prediction error (by the expected Brier score) based on the prognostic variables set built-in the *IPSYS score* is compared with that from the Kaplan-Meyer estimates without prognostic variables, and from an artificially permuted prognostic variables data set independent of recurrences.

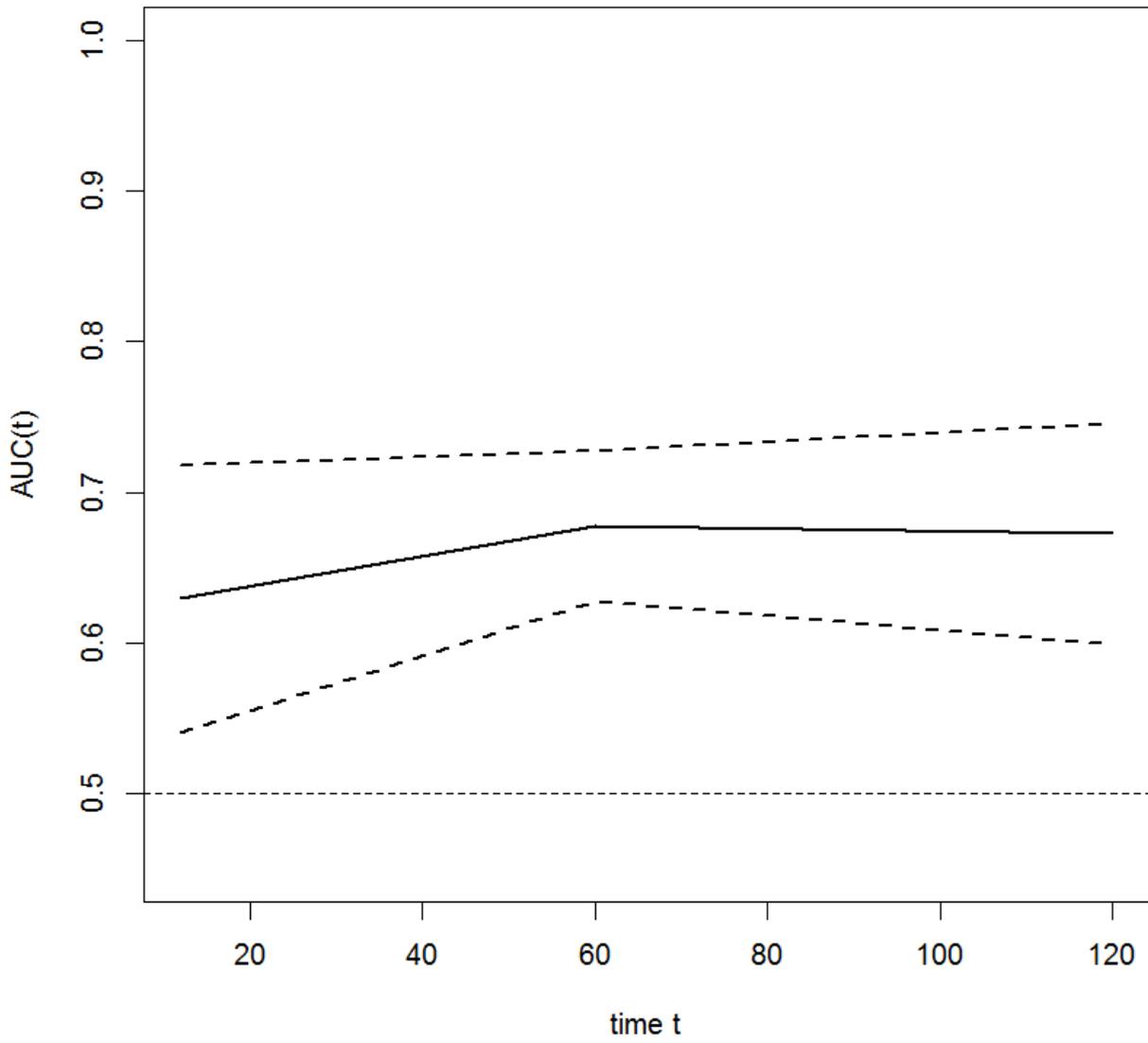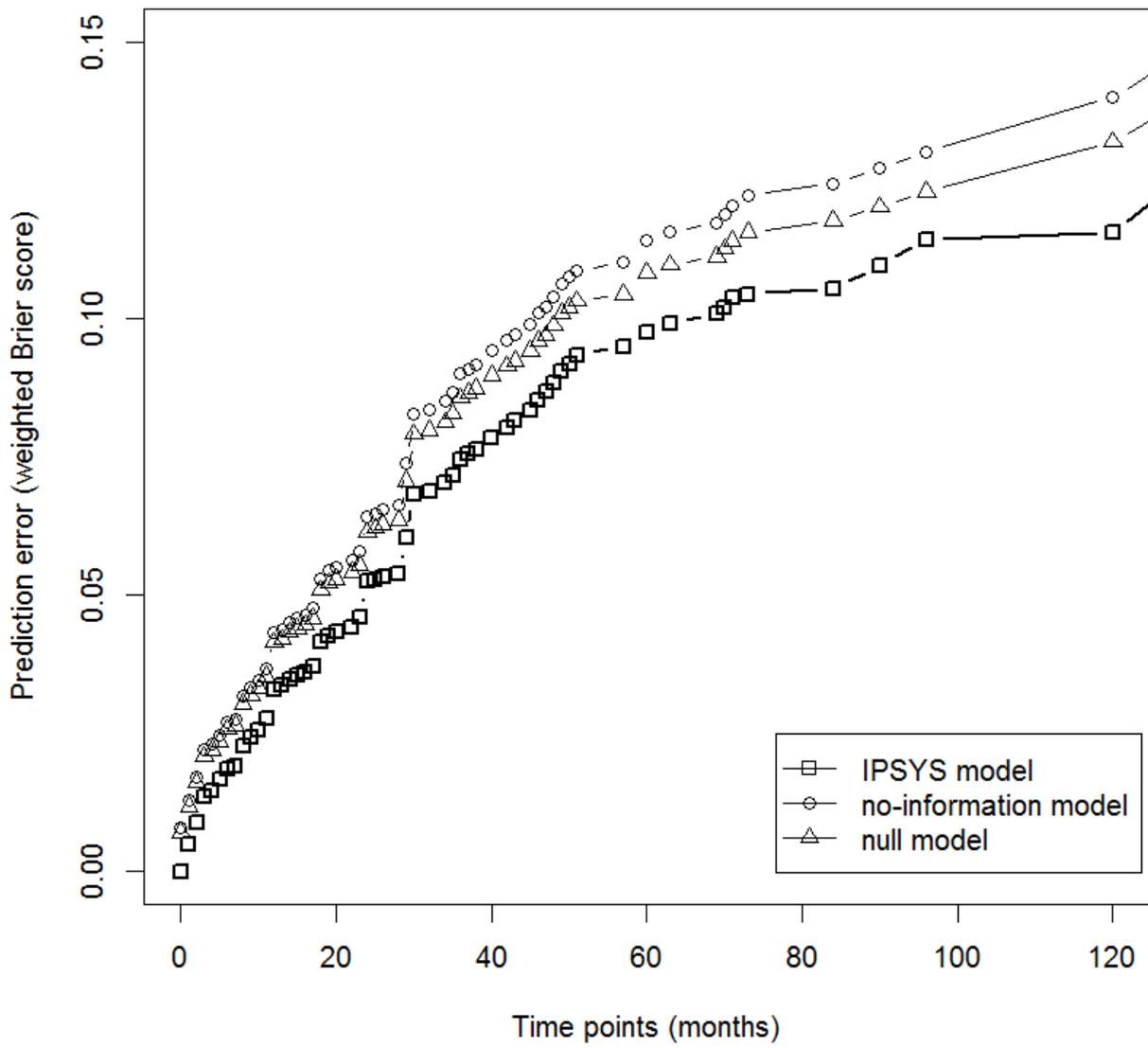**IPSYS Co-investigators (listed by participating centers)**

Figure 1

Figure 2

IPSYS Co-investigators (Listed by Participating Centers)

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