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

Running title: Pezzini et al.; Recurrence after ischemic stroke at young age

Alessandro Pezzini, MD; Mario Grassi, PhD; Corrado Lodigiani, MD, PhD; Rosalba Patella, MD; Carlo Gandolfo, MD; Andrea Zini, MD; Maria Luisa DeLodovici, MD; Maurizio Paciaroni, MD; Massimo Del Sette, MD; Antonella Torriello, MD; Rossella Musolino, MD; Rocco Salvatore Calabrò, MD; Paolo Bovi, MD; Alessandro Adami, MD; Giorgio Silvestrelli, MD; Maria Sessa, MD; Anna Cavallini, MD; Simona Marcheselli, MD; Domenico Marco Bonifati, MD; Nicoletta Checcarelli, MD; Lucia Tancredi, MD; Alberto Chiti, MD; Elisabetta Del Zotto, MD, PhD; Alessandra Spalloni, MD; Alessia Giossi, MD; Irene Volonghi, MD; Paolo Costa, MD; Giacomo Giacalone, MD; Paola Ferrazzi, MD; Loris Poli, MD; Andrea Morotti, MD; Maurizia Rasura, MD; Anna Maria Simone, MD; Massimo Gamba, MD; Paolo Cerrato, MD; Giuseppe Micieli, MD; Maurizio Melis, MD; Davide Massucco, MD; Valeria De Giuli, MD; Licia Iacoviello, MD; Alessandro Padovani, MD, PhD on behalf of the Italian Project on Stroke in Young Adults (IPSYS) Investigators


Address for Correspondence:
Alessandro Pezzini, MD
Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica
Università degli Studi di Brescia
P.le Spedali Civili, 1
25123 Brescia, Italia
Tel: +39.030.3384086
Fax: +39.030.3384086
E-mail: ale_pezzini@hotmail.com, alessandro.pezzini@med.unibs.it

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Abstract

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

**Methods and Results**—We followed 1,867 first-ever IS patients aged 18 to 45 years (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). Primary endpoint was a composite of IS, transient ischemic attack (TIA), myocardial infarction (MI) or other arterial events. 163 patients had recurrent thrombotic events (average rate, 2.26 per 100 person-years at risk). At 10 years, cumulative risk was 14.7% (95% CI, 12.2–17.9%) for primary endpoint, 14.0% (95% CI, 11.4–17.1%) for brain ischemia, and 0.7% (95% CI, 0.4–1.3%) for MI or other arterial events. Familial history of stroke, migraine with aura, circulating anti-phospholipid antibodies, discontinuation of antiplatelet and anti-hypertensive medications, and any increase of 1 traditional vascular risk factor were independent predictors of composite endpoint in multivariable Cox proportional hazard analysis. A point-scoring system for each variable was generated by their β-coefficients and a predictive score (*IPSYS score*) calculated as the sum of the weighted scores. The area under the receiver operating characteristic curve (AUC) of the 0- to-5-year score was 0.66 (95% CI, 0.61-0.71; mean 10-fold internally cross-validated AUC, 0.65).

**Conclusions**—Among patients with IS 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.

**Key words:** stroke in young adults, prognosis, brain ischemia
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\(^1\). Though it is well documented that such a risk is much lower in young stroke patients than in the elderly, 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 of patients or less\(^2\), using different thresholds of age to define “young”, and sometimes 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) CT- or MRI-proven cerebral infarction, in the setting of a hospital-based, multicentre, observational study. 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. 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 two separate measurements after the acute phase or use of antihypertensive drugs before recruitment; diabetes mellitus, history of diabetes, 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
(MO) and migraine with aura (MA) according to the diagnostic criteria of the International Headache Society (IHS); heavy alcohol consumption, weekly consumption > 14 drinks for males and > 7 drinks for females; oral contraceptive use, current use (including former users who had quit taking these medications for one 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 CT and/or MR angiography to investigate extracranial and intracranial vessels. Coagulation testing included prothrombin and activated partial thromboplastin times, circulating anti-phospholipid antibodies (aPL), 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. aPL were analyzed as an all-or-none variable [i.e., subjects who were persistently positive for lupus anticoagulant (LA), or IgG anticardiolipin antibodies (aCL), or IgG anti-β2-glycoprotein I (anti-β2 GPI) or any combination of these were considered aPL+ (aPL=1), whereas subjects who were negative were aPL- (aPL=0)]. Transthoracic and/or 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.
and divided into 5 etiologic categories: 1) atherosclerotic vasculopathy, 2) non-atherosclerotic 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 symptoms onset. Subjects were included in the subgroup of patients who did not experience recurrence if they had at least a one-year follow-up. Follow-up evaluations were conducted at 3 months and then annually, and outcome events classified 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/non-fatal IS, transient ischemic attack (TIA), fatal/non-fatal myocardial infarction (MI), or other arterial thrombotic event. Recurrent IS was defined using the same criteria applied for the definition of the index event. MI was diagnosed when at least two criteria among 1) ischemic chest pain, 2) characteristic ECG changes, and 3) cardiac enzyme abnormalities were present. Diagnosis of TIA was made when the patient had reliably observed transient (<24 hours) neurologic 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. Deaths were classified using death certificates, medical records, and family interviews. In those 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 more than one recurrent event occurred, the first was used for calculation of the disease-free survival time.
Primary endpoint was a composite of IS, TIA, MI or other arterial events. Secondary endpoints were 1) brain ischemia (IS or TIA) as well as 2) MI or other arterial events.

Long-term antithrombotic therapy and other treatment for secondary prevention were administered in accordance with published guidelines. 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 non-persistent medication users if they discontinued a medication regardless of the reason.

Medication discontinuation was considered to influence recurrence and, thus, 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. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed by Cox proportional hazard models in univariate analyses to compare demographic variables and risk factors prevalence at baseline, as well as in stratified multivariable analysis 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 endpoints were identified. The first model included the following covariates: age, sex, traditional risk factors, migraine without aura (MO) and with aura (MA), patent foramen ovale, atrial fibrillation, alcohol consumption, factor V Leiden, the G20210A mutation in the prothrombin gene, circulating anti-phospholipid antibodies (aPL), 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 in survival analysis\(^\text{15}\). This is a penalized variable selection technique, which shrinks \(\beta\)-coefficients \([\beta = \ln(\text{HR})]\) and produces some \(\beta\)-coefficients that are exactly zero. The variables whose \(\beta\)-coefficients is zero are then automatically deleted from the predictor set. Model screening was carried out tuning penalized parameter by K-fold cross-validation\(^\text{16}\), with K=10 roughly equal sized subsets. The non-zero \(\beta\)-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 (\(\text{IPSYS score, s}\)) for each patient (i) was calculated summing up its \(\beta\)-coefficients \(\times\) predictor values \((x_j)\) \(\eta(i) = \exp[s(i)]\) represents the hazard score for each subject. Higher values of \(\eta(i)\) correspond to a higher level of hazard and shorter survival time based on the predictors.

To assess the predictive validity of the \(\text{IPSYS score}\) we used the receiver operating characteristic (ROC) curves, the area under the ROC curve (AUC), and the discrimination C statistic (overall AUC), which takes into account the timing of events from survival data\(^\text{17-19}\). 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 - t
was validated by K-fold cross-validation with K=10, each fold evaluating a “test” sample (n =
187) using scores obtained from the β-coefficients trained by the other “learning” sample (n =
1,867–187 = 1,680). In this way, we corrected for potential over-optimism in the assessment of
the score performance.

Additionally, we estimated the prediction error (PE) of the variables built-in the IPSYS
score by weighted time-dependent Brier score curve20, that is, the weighted mean of the squared
difference of the patient status (recurrence vs 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 above 0.25).

Three PE were compared, as suggested by Gerds et al21: 1) 0.632 + PE estimate, a weighted
combination of the apparent error on the full data set and 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 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 1,906 patients with first-ever IS was included in the IPSYS registry. Of these, 1,867
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 a MI, 67 a TIA, and 2 other arterial thrombotic events. 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). 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 endpoint more than 4-times higher than that of non-atherosclerotic vasculopathies (24.7% vs 5.7%; Figure 2), though differences across the TOAST categories were not significant (log-rank test (df) = 8.9(4), p = 0.06).

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; 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 anti-diabetics 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 anti-hypertensive 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 anti-hypertensive 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]. Non-adherence to secondary prevention medication was associated to an increased risk of primary endpoint (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 anti-hypertensive (HR, 5.80; 95% CI, 1.58–21.25) medications, while 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 to recurrence when included in the model instead of each traditional risk factors (HR, 1.23; 95% CI, 1.04–1.45 for any increase of 1 risk factor). The model with brain ischemia as outcome measure gave similar results, while the low number of MI and other arterial events did not allow for separate multivariable analysis.

The “lasso” technique for variable selection confirmed the non-zero β-coefficients of familial history of stroke, MA, aPL, discontinuation of antiplatelet and anti-hypertensive
medications, and the cumulative index, as independent predictors of recurrence. The IPSYS score was generated using the 5 of the 6 predictor variables reported above. Anti-hypertensive medications discontinuation was not entered into the score as a separate variable because of its low prevalence (8 patients), and was combined with the variable anti-platelet medications 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, 0.66 (95% CI, 0.59-0.73) at 10 years (Figure S1, online-only Data Supplement). Overall AUC (C statistics) for the prediction of events that occur in the time range 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 dataset used for fitting was approximately 1%. The 0.632 + bootstrap PEs 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 below 0.25 (Figure S2, 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%.
Discussion

Approximately 10% of ISs occur at ages ≤ 45 years [3], with a worrisome trend toward increasing incidence over time and obvious socio-economic consequences in terms of life-years with disability and life-years lost. The burden of disease raises even more in 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. 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 two large studies on young stroke with extended follow-up recently conducted in Finland and in the Netherlands 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, as well as peculiarity in the life-style and the genetic background of the studied population should be also taken into account when comparing the results of these studies, as they might contribute to explain 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 epidemiologic analyses have clearly indicated, even among subjects suffering premature stroke ageing is associated with accumulation of traditional vascular risk
factors and an etiologic spectrum resembling that seen in elderly patients\textsuperscript{25,26}. Age difference (baseline mean age, 36.8 years in our cohort \textbf{vs} 40.3 years in the Dutch study\textsuperscript{24} and 41.3 years in the Helsinki Young Stroke Registry\textsuperscript{23}) is, therefore, the most likely explanation for the lower prevalence of traditional risk factors in our series as compared to the other two, and might account for the different independent contribution of these factors on the risk of recurrence\textsuperscript{23,24}. Demographic characteristics might also partly explain the relative influence of additional factors in our cohort, as opposed to what 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\textsuperscript{27}, while that 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 to speculate that several possible biases in the assessment of individual migraine history were also operant\textsuperscript{28-35}. As an indirect support to our findings, Gioia and co-workers recently found a higher prevalence of MA in young stroke patients with silent ischemic lesions on brain MRI, an independent predictor of recurrence, compared to those with no evidence of brain abnormalities\textsuperscript{36}. 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\textsuperscript{37}.

Another important finding of our study is that discontinuation of secondary preventive medications prescribed at discharge strongly predicts the long-term risk of recurrence. Data of literature provide evidence that discontinuation of drugs prescribed after a stroke leads to potentially avoidable disease recurrences, disability, and death independent of the patient’s age.
However, since juvenile strokes have been largely underrepresented in trials on secondary prevention over the last 50 years, 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.

In this regard, both the Helsinki Young Stroke Registry and the FUTURE study 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.

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 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 more than 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 work-up 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 as young stroke patients 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, since therapeutic decision on anti-phospholipid 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. Forth, because we did not assess migraine frequency and severity, as well as frequency of auras, 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 over-optimism introduced by evaluating the model on the same data on which it was developed 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, of illicit drugs use, a common risk factor for ischemic stroke at young age\textsuperscript{41}, for which we did not obtain consent to specific tests from most of the patients included in the registry, as well as for specific genotypes which might have an impact on stroke biology. Similarly, since our findings were obtained from a homogeneous Mediterranean Caucasian population, they cannot be generalized to other groups of different racial-ethnic origin, because of disparities in risk factors 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 post-acute 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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Conflict of Interest Disclosures: None.

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Table 1. Demographics and clinical characteristics of the study group according to recurrence status. HRs (95% CI) and p-values were obtained by univariate Cox model. MO, migraine without aura; MA, migraine with aura.* 84 missing. † in women (25 missing).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No vascular recurrence (n = 1704)</th>
<th>Recurrent vascular event (n = 163)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean ± SD</td>
<td>36.7 ± 7.1</td>
<td>37.1 ± 7.1</td>
<td>1.01 (0.99 - 1.04)</td>
<td>0.21</td>
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<td>Men</td>
<td>1221 (75.2)</td>
<td>112 (70.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>382 (22.4)</td>
<td>45 (27.6)</td>
<td>1.34 (0.95 - 1.89)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (3.6)</td>
<td>9 (5.5)</td>
<td>1.66 (0.85 - 3.26)</td>
<td>0.14</td>
</tr>
<tr>
<td>Current smokers</td>
<td>632 (37.0)</td>
<td>76 (46.6)</td>
<td>1.40 (1.03 - 1.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>417 (24.4)</td>
<td>46 (28.2)</td>
<td>1.18 (0.84 - 1.65)</td>
<td>0.35</td>
</tr>
<tr>
<td>History of migraine*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no migraine</td>
<td>1221 (75.2)</td>
<td>112 (70.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>282 (17.3)</td>
<td>29 (18.1)</td>
<td>1.15 (0.76 - 1.73)</td>
<td>0.50</td>
</tr>
<tr>
<td>MA</td>
<td>120 (7.3)</td>
<td>19 (11.9)</td>
<td>1.70 (1.05 - 2.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Oral contraceptives†</td>
<td>284 (35.1)</td>
<td>23 (28.8)</td>
<td>1.25 (0.77 - 2.03)</td>
<td>0.38</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>434 (25.4)</td>
<td>60 (36.8)</td>
<td>1.65 (1.20 - 2.28)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patent Foramen Ovale</td>
<td>516 (30.3)</td>
<td>48 (29.4)</td>
<td>1.00 (0.71 - 1.40)</td>
<td>0.10</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>32 (1.9)</td>
<td>3 (1.8)</td>
<td>1.06 (0.34 - 3.32)</td>
<td>0.92</td>
</tr>
<tr>
<td>Heavy alcohol consumption</td>
<td>145 (8.5)</td>
<td>12 (7.4)</td>
<td>0.89 (0.49 - 1.60)</td>
<td>0.69</td>
</tr>
<tr>
<td>Therapy at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>1260 (76.8)</td>
<td>119 (73.9)</td>
<td>0.89 (0.62 - 1.26)</td>
<td>0.50</td>
</tr>
<tr>
<td>Oral anti-coagulants</td>
<td>346 (21.1)</td>
<td>39 (24.2)</td>
<td>1.14 (0.79 - 1.63)</td>
<td>0.49</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>382 (22.4)</td>
<td>45 (27.6)</td>
<td>1.34 (0.95 - 1.89)</td>
<td>0.09</td>
</tr>
<tr>
<td>Statins</td>
<td>282 (16.5)</td>
<td>39 (23.9)</td>
<td>1.62 (1.13 - 2.33)</td>
<td>0.009</td>
</tr>
<tr>
<td>Non-persistent medication users</td>
<td>172 (10.2)</td>
<td>28 (17.2)</td>
<td>1.51 (1.00 - 2.26)</td>
<td>0.049</td>
</tr>
<tr>
<td>Medication discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>47 (3.5)</td>
<td>18 (14.8)</td>
<td>3.40 (2.08 - 5.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral anti-coagulants</td>
<td>104 (29.1)</td>
<td>9 (23.0)</td>
<td>0.72 (0.37 - 1.41)</td>
<td>0.34</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>4 (1.0)</td>
<td>4 (8.8)</td>
<td>9.96 (3.69 - 26.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>23 (8.1)</td>
<td>2 (5.1)</td>
<td>0.96 (0.24 - 3.88)</td>
<td>0.96</td>
</tr>
<tr>
<td>FV G1691A§</td>
<td>1604 (96.0)</td>
<td>154 (95.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>66 (4.0)</td>
<td>8 (5.0)</td>
<td>0.83 (0.41 - 1.68)</td>
<td>0.60</td>
</tr>
<tr>
<td>AA</td>
<td>0</td>
<td>0 (0.0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PT G20210A§</td>
<td>1597 (96.6)</td>
<td>153 (94.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>55 (33.2)</td>
<td>9 (5.6)</td>
<td>0.71 (0.36 - 1.39)</td>
<td>0.32</td>
</tr>
<tr>
<td>AA</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anti-phospholipids antibodies</td>
<td>98 (5.7)</td>
<td>22 (13.5)</td>
<td>2.74 (1.75 - 4.30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2. Multivariable Cox proportional hazard model stratified by TOAST categories for predicting composite outcome events and brain ischemia. MO, migraine without aura; MA, migraine with aura.

<table>
<thead>
<tr>
<th></th>
<th>Composite Endpoint</th>
<th>Brain Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.97 - 1.02)</td>
<td>0.80</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.88 (0.63 - 1.23)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.12 (0.75 - 1.67)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.49 (0.71 - 3.12)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.34 (0.96 - 1.85)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.15 (0.79 - 1.66)</td>
<td>0.45</td>
</tr>
<tr>
<td>History of migraine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No migraine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>1.16 (0.76 - 1.78)</td>
<td>0.47</td>
</tr>
<tr>
<td>MA</td>
<td>2.02 (1.21 - 3.36)</td>
<td>0.007</td>
</tr>
<tr>
<td>FV G1691A</td>
<td>1.12 (0.53 - 2.36)</td>
<td>0.75</td>
</tr>
<tr>
<td>PT G20210A</td>
<td>1.15 (0.57 - 2.33)</td>
<td>0.68</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.44 (1.02 - 2.04)</td>
<td>0.034</td>
</tr>
<tr>
<td>Patent Foramen Ovale</td>
<td>0.65 (0.41 - 1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.57 (0.17 - 1.92)</td>
<td>0.37</td>
</tr>
<tr>
<td>Heavy alcohol consumption</td>
<td>0.96 (0.52 - 1.76)</td>
<td>0.90</td>
</tr>
<tr>
<td>Medication discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>2.92 (1.65 - 5.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral anti-coagulants</td>
<td>1.06 (0.50 - 2.27)</td>
<td>0.86</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>5.80 (1.58 - 21.25)</td>
<td>0.007</td>
</tr>
<tr>
<td>Statins</td>
<td>0.60 (0.13 - 2.62)</td>
<td>0.50</td>
</tr>
<tr>
<td>Anti-phospholipids antibodies</td>
<td>2.36 (1.45 - 3.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Prognostic IPSYS score for the calculation of the probability of recurrent thrombotic events after ischemic stroke at young age. * values ranging from 0 to 0.8 (presence/absence of arterial hypertension, diabetes mellitus, smoking, or hypercholesterolemia). † anti-platelets or anti-hypertensive agents.

<table>
<thead>
<tr>
<th></th>
<th>HR (p-value)</th>
<th>β-coefficient</th>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative risk factor index*</td>
<td>1.21 (0.020)</td>
<td>0.192</td>
<td>0.2</td>
</tr>
<tr>
<td>History of MA</td>
<td>1.87 (0.011)</td>
<td>0.626</td>
<td>0.6</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.63 (0.003)</td>
<td>0.489</td>
<td>0.5</td>
</tr>
<tr>
<td>Circulating anti-phospholipids antibodies</td>
<td>2.39 (&lt;0.001)</td>
<td>0.869</td>
<td>0.9</td>
</tr>
<tr>
<td>Medication discontinuation†</td>
<td>3.33 (&lt;0.001)</td>
<td>1.202</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Figure Legend:

Figure 1. Cumulative risk (with 95% confidence intervals) of composite outcome event (A), brain ischemia (B), myocardial infarct and/or other arterial thrombotic event (C).

Figure 2. Cumulative risk of composite outcome event stratified by stroke subtype [modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria]. $X^2(\text{df}) = 8.9(4); p = 0.063$

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; non-hypercholesterolemic; non-smoker; non-diabetic); no personal history of migraine with aura; no family history of stroke in first-degree relatives; no circulating anti-phospholipid antibodies; no discontinuation of anti-platelets or anti-hypertensive agents over follow-up. MD, medication discontinuation (anti-platelets or anti-hypertensive drugs); aPL, circulating anti-phospholipid antibodies; MA, migraine with aura; FHs, family history of stroke in first degree relatives; CI, cumulative index (at least 1 among arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia); -, absent; +, present. 1-year risk = $1 - 0.97^{\exp(\text{IPSY3 score})}$; 5-year risk = $1 - 0.93^{\exp(\text{IPSY3 score})}$. 

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Figure 2
Predictors of Long-Term Recurrent Vascular Events after Ischemic Stroke at Young Age: The Italian Project on Stroke in Young Adults

Alessandro Pezzini, Mario Grassi, Corrado Lodigiani, Rosalba Patella, Carlo Gandolfo, Andrea Zini, Maria Luisa DeLodovici, Maurizio Paciaroni, Massimo Del Sette, Antonella Toriello, Rossella Musolino, Rocco Salvatore Calabrò, Paolo Bovi, Alessandro Adami, Giorgio Silvestrelli, Maria Sessa, Anna Cavallini, Simona Marcheselli, Domenico Marco Bonifati, Nicoletta Checcarelli, Lucia Tancredi, Alberto Chiti, Elisabetta Del Zotto, Alessandra Spalloni, Alessia Giossi, Irene Volonghi, Paolo Costa, Giacomo Giacalone, Paola Ferrazzi, Loris Poli, Andrea Morotti, Maurizia Rasura, Anna Maria Simone, Massimo Gamba, Paolo Cerrato, Giuseppe Micieli, Maurizio Melis, Davide Massucco, Valeria De Giuli, Licia Iacoviello and Alessandro Padovani

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

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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)

Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, Brescia (Alessandro Pezzini, Paolo Costa, Andrea Morotti, Loris Poli, Valeria De Giuli, Alessandro Padovani); U.O di Recupero e Rieducazione Funzionale, IRCCS Fondazione Don Gnocchi, Milano (Elisabetta Del Zotto); U.O Neurologia, Istituto Clinico “S. Anna”, Brescia (Alessia Giossi, Irene Volonghi); Stroke Unit, Neurologia Vascolare, Spedali Civili di Brescia, Brescia (Massimo Gamba, Nicola Gilberti, Mauro Magoni); Centro Trombosi (Corrado Lodigiani, Paola Ferrazzi, Elena Banfi, Luca Librè, Lidia Luciana Rota) and Neurologia d’Urgenza and Stroke Unit (Simona Marcheselli), IRCCS Istituto Clinico Humanitas, Rozzano; Stroke Unit, Azienda Ospedaliera Sant’Andrea, Roma (Alessandra Spalloni, Rosalba Patella, Maurizia Rasura); Istituto di Ricovero e Cura a Carattere Scientifico, Centro Neurolesi Bonino-Pulejo, Policlinico Universitario, Messina (Rocco Salvatore Calabrò, Placido Bramanti); Dipartimento di Neuroscienze, Scienze Psichiatriche e Anestesiologiche Clinica Neurologica, Università di Messina, Messina (Paolo La Spina, Rossella Musolino); Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università di Genova, Genova (Cinzia Finocchi, Maurizio Balestrino, Chiara Bruno, Davide Massucco, Carlo Gandolfo); Unità di Neurologia, Ospedale S. Andrea, La Spezia (Elisabetta Traverso, Elisa Giorli, Massimo Del Sette); Unità di Neurologia, Ospedale di Circolo, Università dell’Insubria, Varese (Maria Luisa DeLodovici, Elena Pinuccia Verrengia, Federico Carimati, Giorgio Bono); Stroke Unit, Clinica Neurologica, Nuovo Ospedale Civile “S. Agostino Estense”, AUSL Modena (Anna Maria Simone, Andrea Zini, Guido Bigliardi, Maria Luisa Dell’Acqua, Livio Picchetto, Roberta Pentore, Silvia Olivato, Paolo Frigio Nichelli); Stroke Center, Dipartimento di Neurologia, Ospedale Sacro Cuore Negrar, Verona (Alessandro Adami); U.O Neurologia, Azienda Ospedaliera-Universitaria Borgo Trento, Verona (Monica Carletti, Giampaolo Tomelleri, Paolo Bovi); Dipartimento di Neuroscienze, Stroke Unit, Università di
Torino, Torino (Paolo Cerrato); Laboratorio di Epidemiologia Molecolare e Nutrizionale, Dipartimento di Epidemiologia e Prevenzione, IRCCS Istituto Neurologico Mediterraneo, NEUROMED, Pozzilli (Licia Iacoviello, Augusto Di Castelnuovo, Giovanni de Gaetano);
Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Unità di Statistica Medica e Genomica, Università di Pavia, Pavia, (Mario Grassi); U.O.C. Neurologia, A.O Universitaria “San Giovanni di Dio e Ruggi d’Aragona”, Salerno (Antonella Toriello, Nicola Pugliese); Stroke Unit, Divisione di Medicina Cardiovascolare, Università di Perugia, Perugia (Maurizio Paciaroni, Valeria Caso, Cataldo D’Amore, Giancarlo Agnelli); U.O.C Neurologia, Ospedale Valduce, Como (Nicoletta Checcarelli, Mario Guidotti); U.O Neurologia, Azienda Ospedaliera Ospedale Sant’Anna, Como (Lucia Tancredi, Marco Arnaboldi); Stroke Unit, U.O Neurologia, IRCCS Ospedale S. Raffaele, Milano (Maria Sessa, Giacomo Giacalone, Elisa Zanoli); Stroke Unit, Fondazione Istituto “C. Mondino”, Pavia (Anna Cavallini, Alessandra Persico, Giuseppe Micieli);
U.O Neurologia, Azienda Ospedaliera Universitaria Pisana, Pisa (Alberto Chiti, Giovanni Orlandi); Stroke Unit, Azienda Ospedaliera “G. Brotzu”, Cagliari (Piernicola Marchi, Maurizio Melis); Stroke Unit, U.O Neurologia, Azienda Ospedaliera “C. Poma”, Mantova (Giorgio Silvestrelli, Alessia Lanari, Alfonso Ciccone); Stroke Unit, U.O Neurologia, Ospedale “S. Chiara”, Trento (Marco Domenico Bonifati)