**Comparison of risk scores for the prediction of the overall cardiovascular risk in patients with ischaemic stroke: The Athens Stroke Registry**

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**Disclosures**

None related to this paper.

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**Abstract**

**Background**: Stratification of overall vascular risk in patients with ischemic stroke is important as it may guide management decisions. Currently available schemes have only modest prognostic accuracy. The TRA2°P score aids in vascular risk stratification in patients with previous myocardial infarction (MI). **Aim**: We investigated whether the prognostic performance of TRA2°P can be extended in patients with ischemic stroke and whether it can improve the risk stratification made by CHA2DS2VASc and Essen-Stroke-Risk-Score (ESRS) scores.

**Methods**: We analyzed the Athens Stroke Registry using Kaplan-Meier survival and Cox-regression analyses to assess if TRA2°P (in different categorizations) predicts the composite endpoint of stroke recurrence, MI or cardiovascular death. We compared its incremental predictive value over CHA2DS2-VASc and ESRS and calculated continuous net reclassification indices (cNRI).

**Results:** In 2833 patients (followed for 9278 patient-years) and 776 events, there was decreased survival probability for TRA2°P-based high-risk patients compared to low-risk (log-rank-test p<0.001), but the discriminatory power for the occurrence of the composite endpoint was only modest (Harrell’s-C:0.566, 95%CI:0.545-0.587). Combined with ESRS, TRA2°P conferred incremental discrimination (Harrell's-C:0.544, 95%CI:0.513-0.574 versus 0.574, 95%CI:0.543-0.605 respectively, p=0.049) and reclassification value (cNRI=9.8%, p=0.02). Combined with CHA2DS2-VASc, TRA2°P did not improve discrimination (Harell’s-C:0.578, 95%CI: 0.547-0.608 versus 0.585, 95%CI:0.554-0.616, p=0.738).

**Conclusion**: The currently available prognostic scores have generally low performance to predict the overall cardiovascular risk in ischemic stroke patients. Further research is needed to improve vascular risk stratification in ischemic stroke patients.

**Key words:** risk stratification; TRA2°P; Essen-Stroke-Risk-Score; CHA2DS2-VASc

**Introduction**

Patients with established cardiovascular disease are at very high risk for recurrent cardiovascular events and mortality[[1](#_ENREF_1)]. Nevertheless, within this very high risk group, there is significant variation of the underlying risk with some patients being at the extreme edge of the spectrum[[2](#_ENREF_2), [3](#_ENREF_3)].

The identification of these patients is of utmost importance as it may have implications for management strategies such as prioritization of high-cost strategies like PSCK9 inhibitors and aggressive treatment of modifiable risk factors like arterial hypertension and dyslipidemia. Refined risk stratification may also guide treatment decisions in situations where the balance between the expected benefit and the risk of serious adverse events is borderline like in patients with high bleeding risk who need aggressive antithrombotic treatment, or patients with intracranial bleeding and an indication for antithrombotic treatment[[4](#_ENREF_4)]. In addition, it may allow identify those patients who may benefit more from an intensive follow-up schedule. Finally, improved risk stratification may have a positive impact on the motivation of the patient to adhere to secondary prevention strategies.

Identification of patients at greater risk of secondary vascular events after ischaemic stroke is challenging because stroke is an etiologically heterogeneous syndrome which may be caused by a diverse set of pathophysiologically discrete diseases like atrial fibrillation (AF), small vessel disease, atherosclerosis and others[[5](#_ENREF_5)]. The CHA2DS2VASc score has been shown to predict long-term stroke outcomes in patients with ischaemic stroke, both with and without AF[[6-8](#_ENREF_6)]. The Essen Stroke Risk score (ESRS) was derived from patients with ischaemic stroke in the CAPRIE trial and was shown to stratify the 1-year risk of stroke recurrence or major vascular events[[9](#_ENREF_9)]. However, the discriminatory performance of both scores in patients with ischemic stroke was modest (c-statistic approximately 0.55 for 1-year stroke recurrence and cardiovascular events) and further refinements are required for clinical application[[10](#_ENREF_10)].

Recently, a risk stratification tool was developed among placebo-treated patients with stable ischemic heart disease and previous myocardial infarction (MI) in the TRA2°P-TIMI50 trial[[11](#_ENREF_11)]. This score is an integer-based scheme which consists of 9 easily assessed clinical parameters (age, diabetes mellitus,hypertension, smoking, peripheral arterial disease, previous stroke, previous coronary bypass grafting, heart failure and renal dysfunction) and showed a strong graded relationship with the rate of the composite outcome of cardiovascular death, MI and ischaemic stroke, as well as its individual components[[11](#_ENREF_11)].

Stroke and ischaemic heart disease share many risk factors and the INTERHEART and INTERSTROKE studies have shown that the 9 or 10 common cardiovascular risk factors account for > 90% of MI or stroke[[12-14](#_ENREF_12)]. In this context, several risk stratification models have been introduced to predict the overall cardiovascular risk (rather than its components like myocardial infarction or stroke), mainly in the general population at the primary care level[[15-18](#_ENREF_15)].

In this context, we aimed to investigate whether the prognostic performance of the TRA2°P score in patients with previous MI can be extended also to patients with ischemic stroke. We sought to assess whether the TRA2°P score would improve risk stratification performed by the CHA2DS2VASc and the ESRS scores in patients with ischemic stroke.

**Methods**

The dataset was derived from the Athens Stroke Registry which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece between June 1992 and August 2012[[19](#_ENREF_19)]. Patients with transient ischaemic attack (TIA) or recurrent stroke are not included in the registry. Εthics approval was obtained from the local institutional review board and written informed consent was obtained from patients.

Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, stroke mechanism, clinical-laboratory findings and vital signs at admission, laboratory investigations and medication at discharge. Hypertension was defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90mmHg diagnosed at least twice before stroke or if patient was already on antihypertensives[[20](#_ENREF_20)]. Diabetes mellitus was defined if patient was already on antidiabetic drugs and/or insulin, or if fasting blood glucose level was >6.0mmol/l before stroke[[21](#_ENREF_21)]. Dyslipidemia was defined as cholesterol concentration >6.5mmol/l the day after admission, or if patient had a previous diagnosis of dyslipidemia[[22](#_ENREF_22)]. Coronary heart disease was assessed by questionnaire and relevant medical confirmation. Heart failure was defined according to the criteria recommended by the working group on heart failure of the European Society of Cardiology[[23](#_ENREF_23)].

Patients were followed-up prospectively at the outpatient clinic at 1, 3 and 6 months after hospital discharge and yearly thereafter for up to 10 years or until death. For those patients who were unable to attend the outpatient clinic, follow-up was assessed over a telephone interview with the patient or proxies, or at the patient’s residence.

*Statistical analysis*

Continuous variables are presented as mean±standard deviation or median (interquartile range) for variables not following the normal distribution in descriptive analyses. Normal distribution of all continuous variables was graphically assessed by histograms and normal-quantile plots. Nominal variables are represented by count and valid percentages. We compared baseline characteristics of the study population across ascending categories of the TRA2°P score by implementing analysis of variance or non-parametric Kruskall Wallis test for continuous variables and chi squared test for nominal variables. A test for linear trend across ascending categories was used in certain parameters such as the incidence of the study's primary endpoint.

The TRA2°P score was calculated as previously described[[11](#_ENREF_11)]. In brief, 9 independent baseline clinical risk indicators [i.e. age ≥75years, hypertension, diabetes mellitus, chronic heart failure (CHF), current smoking, peripheral artery disease (PAD), estimated glomerular filtration rate (eGFR) <60ml/min, prior coronary artery by-pass grafting (CABG) and previous stroke] were summed to obtain a total risk score (i.e. TRA2°P score), ranging from 0 to 9. Due to limited number of patients with very high scores, subjects with scores 6 to 9 were grouped in a single risk score category. Risk indicators were identical to the original ones proposed and were used to calculate the TRA2°P score, independently of their association with the composite survival outcome in our data. We performed a sensitivity analysis by excluding baseline predictors not associated with the composite outcome (smoke, PAD, previous CABG and previous stroke) and calculating a simplified atherothrombotic risk score, extending from 0 to 5 (age ≥75years, hypertension, DM, CHF, eGFR<60ml/min). Risk categories were selected on the basis of the number of risk indicators as follows: low risk (0-1), intermediate (2), high-intermediate (3) and high risk (≥4).

The main outcome of the study was the composite endpoint of stroke recurrence, MI or cardiovascular death, including also in-hospital events. Data were censored at the time of the last visit. Patients that experienced more than one cardiovascular events during the follow-up period were censored at the time of the first event.

According to their TRA2°P score patients were grouped using three different classifications: a) by the nominal value of the score (6 categories: 0, 1, 2, 3, 4, 5, ≥6); b) by risk categories (low, intermediate, high intermediate and high); and c) by tertiles of their score. The Kaplan-Meier product limit method was used to estimate the probability of survival for discrete subgroups of patients. Kaplan-Meier curves were generated to show the cumulative cardiovascular event-free survival for each subgroup of interest. Cox proportional-hazards models were used to examine the association between the TRA2°P score and the composite endpoint. The proportional hazard assumption of Cox model was assessed using the appropriate graph and statistical test (Schoenfeld residuals). Associations are presented as hazard-ratios (HR) with 95% confidence intervals (CI).

We compared incremental predictive value of the TRA2°P score over the CHA2DS2-VASc and the ESRS scores by the Harrell’s C-index for censored time-to event data[[24](#_ENREF_24)]. The components of these three scores are presented in the supplemental table 1. Harrell’s c of inverse hazard ratio was used as a measure of the predictive power of survival regression models after splitting data into training and test sets to avoid over-optimistic estimates. Moreover, we calculated the continuous net reclassification index (NRI) (cNRI), a category-free version of the NRI, as an estimate of the correct reclassification of patients into risk categories for the incidence of the composite endpoint by the TRA2°Pscore[[25](#_ENREF_25)]. Finally, we implemented decision curve analysis and calculated the net benefit (NB) over a wide range of threshold probabilities (up to 80%) associated with the use of the TRA2°P, the CHA2DS2-VASc and the ESRS scores for the prediction of the composite endpoint[[26](#_ENREF_26)]. In order to calculate 95% confidence intervals for NBs at specific thresholds and to correct for overfit, we applied bootstrap methods with 2,000 replications as previously described[[27](#_ENREF_27)]. Provided values for NBs are mean (2.5th – 97.5th centile) of 2000 replications. Finally, we conducted a sensitivity analysis and assessed the diagnostic performance of the TRA2°P, the CHA2DS2-VASc and the ESRS scores by calculating the Area Under the receiver operating characteristic Curve (AUC) for prediction of the composite outcome in biologically plausible subgroups of the registry (males-females and across distinct TOAST classification, i.e. cardioembolic, lacunar, atherosclerotic and cryptogenic strokes). We implemented bootstrapping with 500 replicates to calculate 95% CI around AUCs and used one-way analysis of variance with post hoc pairwise comparisons corrected by the Dunnett’s method to compare these estimates among the TRA2°P, the CHA2DS2-VASc and the ESRS score in each subgroup.

Type I error was predefined at 0.05 for power considerations. Statistical analysis was conducted with STATA package, version 12.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at a=0.05. All reported P values are two sided.

**Results**

The dataset comprised of 2833 patients (median age 71 years, 38.79% women). Baseline characteristics of patients are outlined in Table 1. Patients distributed in higher simplified categories of the TRA2°P score were older and presented a worse risk factors profile (Table 1). Ascending categories of TRA2°P score were correlated with increasing ESRS and CHA2DS2-VASc risk scores (p<0.001 for both, Table 1).

During an overall follow-up period of 9278 patient-years (mean follow-up 39.3 months), the composite end-point occurred in 776 (27.4%) patients. The primary endpoint gradually increased across ascending categories of TRA2°P (p for trend=0.004) (figure 1). The TRA2°P score, in all categorizations, predicted the composite endpoint with the Kaplan-Meier curves showing a decreased survival probability for high risk patients (log-rank test for all: p<0.001, figure 2).

On univariate Cox regression analysis, ascending strata of TRA2°P score showed increased HR for the composite end-point (Figure 3). Simplified TRA2°P risk categories (low, intermediate, intermediate high and high risk) displayed a more smooth, graded increase in hazard in comparison to the categorization of the study population in 6- or 3-groups of TRA2°P score (Figure 3, plot). In terms of survival analysis, our sample size of 2833 subjects with 776 events provided over 90% power to establish a 1.5-fold alteration in HR for Cox proportional hazards models.

The TRA2°P score had modest discrimination (Harrell’s C: 0.566, 95% CI 0.545-0.587) for the occurrence of the composite endpoint. It conferred incremental discrimination (Harrell's C: 0.544, 95% CI 0.513-0.574 versus 0.574, 95% CI 0.543-0.605, p=0.049) and reclassification (cNRI=9.8%, p=0.02) value over the ESRS score for the prediction of the composite end-point (Table 2). The results of the sensitivity analysis of the scores’ AUCs in males/females and TOAST categories is presented in supplemental table 2.

In contrast, the TRA2°P score did not improve the prognostic value of the CHA2DS2-VASc score in terms of discrimination and reclassification (p>0.05 for both, Table 2). TRA2°P score incorrectly re-classified (-8.24% and -10.3%) subjects that experienced the composite endpoint into lower risk categories and was able to accurately classify (18.04% and 11.7%) only low risk patients in comparison to ESRS and CHA2DS2-VASc, respectively (Table 2).

Decision curve analysis indicated that the use of the TRA2°P, the CHA2DS2-VASc and the ESRS scores to inform clinical decisions would lead to superior outcomes only for a range of threshold probabilities between 35% and 65% (Figure 4). The CHA2DS2-VASc score led to the highest net benefit in comparison to the TRA2°P and the ESRS score to a range of threshold probabilities near 35% to 55%, but only added small non-significant value (40% threshold : ΔΝΒ as compared to the TRA2°P, 2.7%, 95% CI -4.1 to 9.3 and ΔNB to the ESRS score, 3%, 95% CI -3.9 to 9.5; 50% threshold: ΔΝΒ as compared to the TRA2°P, 1.9%, 95% CI -4.7 to 8.5 and ΔNB to the ESRS score: 2.1%, 95% CI -4.5 to 8.4). The TRA2°P score was shown to be related with higher NB in respect to other scores only with a (high) threshold probability of ≥ 60% (Figure 4).

**Discussion**

The considerable advance in the treatment and control of common cardiovascular risk factors provides the opportunity to significantly reduce the risk of recurrent events in patients with vascular disease. However, new drugs are often very expensive and carry a risk of side effects that often result in treatment discontinuation. This makes it crucial to identify patients at the greatest risk of future vascular events in order to prioritize available resources and provide the physician with useful tools to motivate patients and improve their compliance. As current prediction tools provided only limited advances in risk stratification of patients with a previous stroke, in this study we assessed for the first time the capacity of the TRA2°P score to identify patients with cerebrovascular disease at highest risk of recurrent vascular events or death. Using a large population of 2833 consecutive patients during an overall follow-up period of 9278 patient-years, we showed that theTRA2°P score has only modest accuracy to stratify the risk of cardiovascular outcomes and mortality in patients with acute ischaemic stroke. Compared to other schemes, it conferred only a marginal incremental discrimination and reclassification over the ESRS, but not over the simpler CHA2DS2-VASc score.

The TRA2°P score performed less accurately in our cohort of ischemic stroke patients compared to the cohort of patients with previous MI in the original publication, with the c-statistics being 0.57 and 0.67 respectively[[11](#_ENREF_11)]. The most plausible explanation for this is that although there is sufficient commonality of risk factors to warrant the development of a single prognostic scheme which could predict the overall vascular risk as well as the risk of individual components, the weighs of risk factors probably varies between specific vascular diseases, especially for stroke which is a pathophysiologically heterogeneous syndrome [[5](#_ENREF_5), [28](#_ENREF_28)].

The accuracy of the TRA2°P score in our stroke cohort was comparable to the CHA2DS2-VASc score and conferred only a borderline incremental discrimination and reclassification over the ESRS. A plausible explanation for this finding is that there are strong similarities between the scores’ components: all three scores include age, arterial hypertension, diabetes mellitus, previous stroke and other vascular disease as their components. Nevertheless, our results also show that these three clinical factor based risk stratifications schemes only have modest prognostic ability to predict the overall vascular risk in patients with ischemic stroke, both in the overall stroke population as well as in males/females and TOAST subgroups. Hence, further research is needed to improve vascular risk stratification in this patient population. Inclusion of biomarkers, imaging parameters and genetic studies in the existing or future models may increase accuracy but may also decrease generalizability and applicability.

The strengths of this analysis include the large population of consecutive patients which minimizes the risk for selection bias, the prospective registration of patients and their data, the long follow-up and the rigorous assessment of outcome events by visits at the outpatient clinic, telephone calls or visits at home. We also performed several analyses using different categorizations of the TRA2°P score. On the contrary, the study is limited by its retrospective nature and single-center design.

In conclusion, the TRA2°P score has only modest accuracy to stratify the risk of cardiovascular outcomes and mortality in patients with acute ischaemic stroke. Compared to other schemes, it conferred only marginal incremental discrimination and reclassification over the ESRS, but not over the simpler CHA2DS2-VASc score. Given the generally low performance of all scores in this stroke population, the results of this study indicate that further research is needed to improve vascular risk stratification in patients with ischemic stroke.

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**Table legends**

**Table 1.** Descriptive characteristics of the study population per TRA2°P score category.

**Table 2.** TRA2oP score performance over ESRS and CHA2DS2-Vasc scores in terms of discrimination and reclassification for long-term cardiovascular outcomes (CV death, non-fatal MI and recurrent stroke)

**Figure legends**

**Figure 1:** Event rates per 100 patient-years in different strata of the TRA2oP score (Panel A: 6 categories; Panel B: 3 categories; Panel C: tertiles)

**Figure 2:** Kaplan-Meier curves of cumulative composite event-free survival (Panel A: 6 categories of the TRA2oP score; Panel B: 3 categoriesof the TRA2oP score; Panel C: tertiles of the TRA2oP score)

**Figure 3:** Cox regression analysis of the association between the TRA2°P score and the risk for stroke recurrence, myocardial infarction or cardiovascular death.

**Figure 4:** Decision curves for the TRA2°P, the CHA2DS2-VASc and the ESRS scores applied in 2,833 patients enrolled in Athens Stroke Registry for prediction of all-cause death, stroke recurrence and non-fatal myocardial infarction across a 10-years follow-up period. Correction for overfit has been performed by bootstrap. Grey line: Assume no patients are treated, net benefit is zero (no true-positive and no false-positive classifications); Solid line: assume all patients are treated; Dashed lines: patients are treated if predictions exceed a threshold, with risk predictions based on the TRA2°P, the CHA2DS2-VASc and the ESRS score, respectively. The graph gives the expected net benefit per patient relative to no treatment in any patient (‘Treat none’).