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# Élaboration d'un score prédictif téléphonique d'occlusion proximale d'artère cérébrale : the stroke triage alpha rescue score (STARS)

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**DESIGN OF A PREDICTIVE TELEPHONE SCORE FOR  
CEREBRAL LARGE VESSEL OCCLUSION :  
THE STROKE TRIAGE ALPHA RESCUE SCORE (STARS)**

THÈSE PRÉSENTÉE POUR L'OBTENTION DU TITRE DE  
DOCTEUR EN MÉDECINE

-

DIPLÔME D'ÉTAT

**Hugo MERLIN**

*[Données à caractère personnel]*

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Le 02/04/2021

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# Glossary

AF - Atrial Fibrillation

AIS - Acute Ischemic Stroke

AUC - Area Under Curve

BA - Basilar Artery

CHAL - Alpes Léman Hospital Center

CHANGE - Annecy Genevois Hospital Center

CHUGA – Grenoble Alpes University Hospital

CHMS - Métropole Savoie Hospital Centre

CSC - Comprehensive Stroke Center

CT-scan - Computerized Tomography scanner

DS - Drip and Ship

ECC - Emergency Medical Communication Centers

EVT - Endovascular Thrombectomy

HBP - High Blood Pressure

ICA - Internal Carotid Artery

ICH - Intracranial Haemorrhage

IQR - Interquartile Range

IVT - Intravenous Thrombolysis

LVO - Large Vessel Occlusion

MCA – Middle Cerebral Artery

MRI – Magnetic Resonance Imaging

MS - MotherShip

NIHSS - National Institute of Health Stroke Scale

NPV – Negative Predictive Value

OR - Odds Ratio

PPV – Positive Predictive Value

PSC - Primary Stroke Center

RENAU - Northern French Alps Emergency Network

ROC - Receiver Operating Curve

TIA - Transient Ischemic Attack



## Résumé

La thrombectomie mécanique (TM) est devenue la référence pour le traitement de l'accident vasculaire cérébral ischémique (AVCi) secondaire à une occlusion proximale d'une artère cérébrale (OPAC). Son bénéfice est d'autant plus important que la recanalisation est précoce. Mais l'accès à la TM reste limité à certains centres rendant difficile la régulation préhospitalière. Pour la faciliter, nous avons élaboré un score téléphonique préhospitalier de prédiction d'OPAC. Nous avons étudié rétrospectivement les caractéristiques cliniques et radiologiques des patients régulés par le SAMU centre 15 pour une suspicion d'AVC de moins de 24 heures, sur le territoire du réseau nord alpin des urgences (RENAU) : Isère, Savoie, Haute-Savoie, en 2014 et 2016. Le diagnostic d'OPAC était retenu après relecture des imageries cérébrales. La pondération des items du score correspond aux odds ratio des variables significatives après analyse multivariée. Nous avons établi les performances du score par validation interne. Parmi 3 452 patients inclus, 1643 (48%) avait un AVCi, 496 (14%) un accident ischémique transitoire, 368 (11%) une hémorragie intracérébrale et 945 (27%) un « stroke mimics ». Une OPAC a été retrouvée chez 315 patients, soit 19% des AVCi (9% de la population totale). Les items retenus sont : 2 points pour la parésie du membre supérieur, 2 pour la parésie du membre inférieur, 2 pour un trouble du langage, 2 pour la paralysie faciale, 3 pour un trouble de la conscience et 2 pour le tabagisme. Avec un cut-off final  $\geq 6$ , la sensibilité était de 0.78, la spécificité de 0.56, la VPP à 0.15, la VPN à 0.96. L'aire sous la courbe était de 0,75. Nous avons conçu un score téléphonique préhospitalier prédictif d'OPAC à la fois simple et performant. Sa validation externe est en cours de réalisation via une étude prospective. Mots-clés : score préhospitalier ; régulation téléphonique ; occlusion proximale d'artère cérébrale ; thrombectomie ; thrombolyse ; STARS.

## Abstract

Endovascular thrombectomy (EVT) has become the gold standard for the treatment of acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). Its benefit is even more important as recanalization is early. However, access to EVT remains limited to a few centers, which complicate pre-hospital triage. To make it easier, we developed a prehospital telephone score predictive of LVO. We retrospectively studied baselines clinical and radiological data of all adult patients calling to Emergency Medical Communication Centers for a suspected stroke within 24 hours in the North Alps network (RENAU) territory (Isère, Savoie, Haute-Savoie) in 2014 and 2016. The LVO was confirmed by expert stroke neurologists. The items weighting was based on Odds Ratio of significant variables after multivariate analysis. The score's performances were established thanks to an internal validation. Of 3452 patients, 1643 (48%) had an AIS, 496 (14%) had a transient ischemic attack, 368 (11%) had intracerebral haemorrhage, and 945 (27%) had stroke mimics. An LVO was found in 315 patients (9% overall, 19% of AIS patients). The items retained were: 2 points for upper limb paresis, 2 for lower limb paresis, 2 for language impairment, 2 for facial palsy, 3 for disorders of consciousness and 2 for active smoking. We chose the cut off  $\geq 6$  for a sensitivity at 0.78 and a specificity at 0.56. The PPV was 0.15 and the NPV, 0.96. The AUC was 0.75. We designed a simple and efficient pre-hospital telephone score useful to predict LVO in stroke alerts. A prospective study is currently underway to establish an external validation. Key words: prehospital score; stroke triage; large vessel occlusion; thrombectomy; thrombolysis; STARS.

# Introduction

Stroke is a leading cause of acquired adult disability and death worldwide (1). Its management is a major public health and economic issue (2).

Historically, treatment with intravenous thrombolysis (IVT), aiming at early reperfusion, has been proven effective for patients with acute ischemic stroke (AIS) when they are treated within 4.5 hours after stroke onset (3,4). Approximately 30% of the AIS are caused by a proximal occlusion (5). In these patients the effect of IVT is limited and recanalization is obtained in less than 30% (6).

Since 2015, according to six studies (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND IA and THRACE) (7–12), endovascular thrombectomy (EVT) is becoming the leading treatment for the management of AIS due to a large vessel occlusion (LVO). Whether associated with IVT or not, it improves the functional outcome (13).

Stroke is a time dependent disease and vascular recanalization (by EVT or IVT) is all the more efficient as it is realised early (3,14,15). While IVT is widely spread in the care system and available in most of primary stroke centers (PSCs), EVT is restricted to comprehensive stroke centers (CSCs). The diagnosis of LVO cannot be ascertained with clinical assessment alone but requires brain imaging. AIS suspected patients are often transferred to the nearest hospital (often a PSC) to start IVT as soon as possible. Thus, discovering an LVO in a PSC is a common situation, leading to inter hospital transfers to CSC, that delay EVT.

Two prehospital triage paradigms have been developed. In the Drip and Ship (DS) model (mostly used) , patients are referred to the closest PSC to perform neuroimaging and early IVT in AIS patients. Eligible patients are secondarily transferred to the CSC for EVT. In the MotherShip (MS) model, patients suspected of LVO are directly brought to the CSC.

The main advantage of DS model is to administrate early IVT, using a large network of PSCs. When EVT is needed, interhospital transfer remains an important cause of delay and is associated with worse outcomes (17,18).

The MS model reduces the access time for EVT but increases the delay of IVT. Moreover, this model quickly leads to the overload of the emergency care system in CSCs.

Nowadays, benefits of one model over another is still debated. The MS model appears to be superior (19–21). Studies are underway to compare cost-effectiveness of each model, e.g. PRESTO-F a French multicenter study (22). In urban area, MS paradigm is generally more efficient, while in rural areas or suburban areas, with large distances to the CSC, DS paradigm can be beneficial (23).

This situation generated a transport dilemma in the triage of suspected AIS patients: when is it reasonable to bypass a nearby PSC, thereby potentially delaying IVT, in favour of direct transport to an EVT-capable hospital?

The prehospital identification of patient with a high probability of LVO may be one of the solutions, referring high-risk patient directly to the CSC, while low risk patents would be referred to the nearest PSC.

Accordingly, several predictive scales of LVO have been designed. National Institute of Health Stroke Score (NIHSS) was originally proposed as a predictive score for proximal occlusion, but the threshold was debated and its feasibility in the pre-hospital setting was difficult (16). Other scores, derived from NIHSS items, were proposed. Among the most commonly accepted : the Rapid Arterial occlusion Evaluation (RACE) (24), Los Angeles Motor Scale (LAMS) (25), Prehospital Acute Stroke Severity (PASS) (26), Cincinnati Prehospital Stroke Scale (CPSS) (27), the gaze-face-arm-speech-time test (G-FAST) (28) and the Field Assessment Stroke Triage for Emergency Destination (FAST-ED) (29).

These scores are performed "on scene" by trained paramedics. None of them were based on data from the telephone call to Emergency Medical Communication Centers (ECC). In fact, this call can be made by any witness, mostly without medical experience, or even by the patient himself.

Moreover, some have been validated in the hospital setting by emergency physicians, or even on patients with confirmed AIS, in stroke units by a neurologist (30). These study populations are not representative of those where LVO prediction is required (i.e a pre-hospital population including AIS, but also intracerebral haemorrhages or stroke mimics [migraine, epilepsy, functional disorders...]).

There is currently a lack of stroke triage scores based on a representative population in the pre-hospital field (30).

The objective of this study was to create a phone-based prehospital tool for LVO identification in a suspected stroke population using phone-based neurological impairment and medical history.

# Material and Methods

## Study Design and Population

We retrospectively analysed data from an observational prospective registry of a regional French north alps emergency stroke network (RENAU) collected from 01/01/2014 to 31/12/2014 and from 01/01/2016 to 31/12/2016. This network covers a set of 3 departments (Isère, Savoie and Haute-Savoie) with an area of 17,500 km<sup>2</sup> of mountainous land, involving a population of 2 million inhabitants. It is composed by one CSC (Grenoble-Alpes University Hospital [CHUGA]), 3 other stroke units (Annecy Genevois Hospital Center [CHANGE], Métropole Savoie Hospital Center in Chambéry [CHMS] and Alpes Léman Hospital Center [CHAL]) and a telestroke network (Salanches, Voiron, Thonon-Les-Bains, Albertville, Bourg Saint Maurice, Saint Jean de Maurienne, Belley). Admission to stroke unit, multimodal Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) are available 24 hours a day every day. The RENAU registry includes all patients hospitalised in one of the forementioned stroke unit and all patients who called the ECC with a suspected stroke. It contains baseline demographical data, ECC call characteristics including initial telephonic clinical assessment, final diagnosis, stroke-related data (imaging information, outcome parameters) and patient past medical history.

The study population was defined as all patients 18 years of age or older who called the ECC for clinical suspicion on an acute stroke within 24 hours from symptoms onset in the territory of the RENAU. There were no exclusion criteria other than not satisfying the inclusion criteria.

## Clinical data

The following data were systematically collected in the ECC call registry:

- Demographical data (age and sex)
- ECC call data: time and place of the patient's call, the date and hour of symptoms onset, delay between symptoms onset and ECC call, who made the ECC phone call (patient, caregivers or witness), data from a simplified NIHSS (supplemental data - Table 1) completed by emergency physicians at the time of the ECC call, including motor deficit, detailed in upper or lower limb, speech disability, facial palsy, vision impairment, and consciousness disorder.
- Relevant comorbidities : diabetes (defined by known diabetes or anti diabetics treatment use), dyslipidaemia (defined by known dyslipidaemia or lipo-lowering treatment use), embolic heart disease (defined by known atrial fibrillation or flutter), high blood pressure (HBP) (defined by known HBP or hypotensive drugs use), smoking (defined by active smoking or smoking cessation for less than 2 years), and known vascular disease (coronary artery disease, lower limb arteriopathy, ischemic stroke, transient ischemic stroke, chronic kidney failure from vascular disease) (see supplemental data -Table 2).
- Final diagnosis at the end of the emergency management, and if realised, after cerebral imagery. Cerebral imagery was not required for a stroke mimic diagnosis.

In the case of missing data on the medical history or on the final diagnosis, we completed the files with the registry of the stroke care unit or retrospectively with the hospital medical file. On the contrary, the clinical data were collected exclusively from the initial telephone clinical assessment, without being completed secondarily.



## Imaging data

Multimodal brain MRI or CT was performed according to the availability of each center, prioritising access to MRI when possible. LVO was defined as the complete occlusion of the intracranial internal carotid artery (ICA), the first portion of the middle cerebral artery (M1), the junction of the first and second portion of the middle cerebral artery (M1-M2) and the basilar artery (BA), with or without association of extracranial occlusion (tandem).

All images were first interpreted by a radiologist at the time of the imaging procedure. A re-reading was carried out for all images concluding to an arterial occlusion (whatever its level). In addition, this review was also performed on images that did not show any occlusion in the first interpretation, but in which the patient had a simplified NIHSS greater than 10. This second review was carried out by a senior neurologist with stroke expertise.

## Statistical analysis

We aimed to find the highly predictive items of an LVO in all the available data, then combine the most clinically and statistically relevant ones to create the predictive score.

A  $p < 0.05$  was considered statistically significant. Continuous variables are presented as median  $\pm$  interquartile range (IQR). Categorical variables were reported as proportions (%) and absolute values.

Patients were dichotomized into a LVO group and a non LVO group (nLVO). Then we performed the descriptive statistics of our study population. After the preliminary test for normality with Kolmogorov-Smirnov test, univariate comparisons were assessed

using Mann-Whitney test for the quantitative items and chi-squared test or Fisher test, as appropriate, for the qualitative items.

We also tested the interactions between the data from the telephonic neurological assessment, by simple interaction tests.

Then, a cross-validation procedure was performed, by splitting the sample randomly into 2 groups. We performed the logistic regression model on derivation cohort (set of 2/3 of overall population), and the internal validation, applying the resulting prediction equation, to the validation cohort (set of 1/3 of overall population). The comparability of the two groups was achieved by chi-squared test.

With the first population, univariate analyses were performed to select predictor variables for the multivariate model. Missing data were assumed indicative of their true absence. We categorized the continuous variables that were statistically significantly associated with LVO. Significance was assessed by using the chi-square test or Fisher test for nominal categorical variables. We included in a multivariate logistic regression model all the variables that were significantly associated with LVO ( $p < 0.05$ ) in univariate analysis. Multiple associations of significant variables were tested to obtain different score tries. Points of scores were assigned by rounding the regression Odds Ratio (OR) of each variable. The prediction scales were compared using receiver operating curve (ROC) analysis, calculating the area under the curve (AUC). We finally selected the score with the best combination between statistical performance and clinical relevance.

The optimal cut-off was selected by optimising the balance between the specificity and sensitivity.

Once the best score and threshold were chosen, we carried out the internal validation on the validation cohort to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

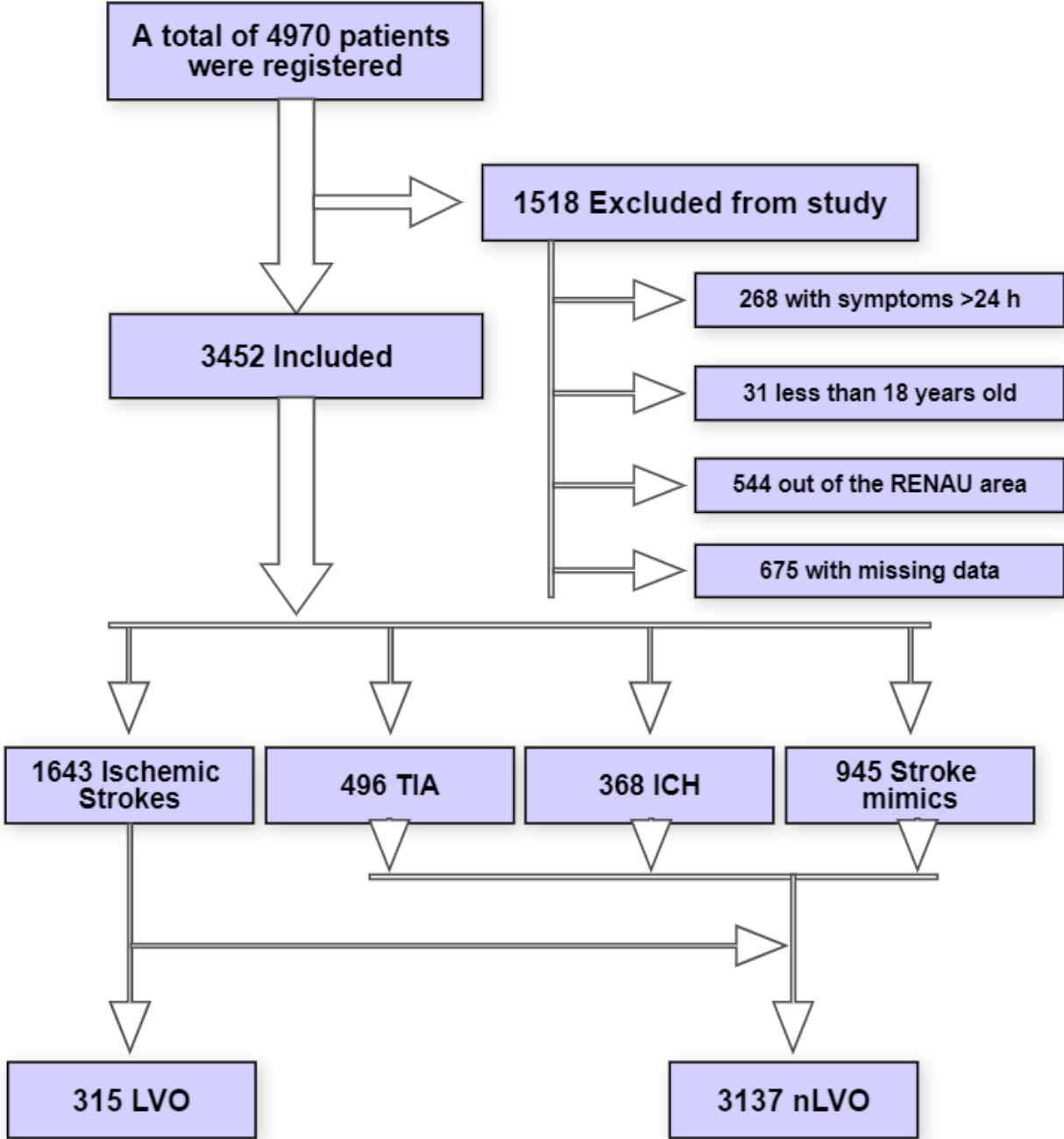
For statistical analysis, SPSS version 26.0 (IBM software) was used.

## Results

Of 4970 patients registered, we excluded 268 patients from the analysis because they had symptoms for more than 24 hours. 31 were less than 18 years old. 544 were hospitalised out of the RENAU area. Finally, we had 675 missing data (14% of the total).

A total of 3452 patients were included, 1701 were women (49.3%) and median age was 75.5 years (IQR 62.2 - 84.3). Acute ischemic stroke (AIS) was diagnosed for 1643 patients (47.6%), stroke mimics for 945 (27.4%), transient ischemic attack (TIA) for 496 (14.4%) and intracerebral haemorrhage (ICH) for 368 (10.7%). Among the 1643 AIS patients, 315 (19.2%) had an LVO. It represented 9.1% of the overall population (Figure 1). Table 1 details the characteristics of the study population.

Figure 1 - Flow chart of participants



TIA: Transient Ischemic Attack  
 LVO: Large Vessel Occlusion

ICH: Intra Cerebral Haemorrhage  
 nLVO: no Large Vessel Occlusion

Table 1 - Descriptive analysis of our study population

	Non LVO Group (n= 3137)	LVO Group (n = 315)	Total (n= 3452)	p
<b>Baseline characteristics</b>				
Age, Mean (IQR)	75.5 (61.9 - 84.3)	75.8 (64.8 - 83.6)	75.5 (62.2 - 84.3)	0.99
Gender Woman, n (%)	1549 (49.4%)	152 (48.3%)	1701 (49.3%)	0.70
<b>Comorbidities n (%)</b>				
Diabetes	521 (16.6%)	48 (15.2%)	569 (16.5%)	0.53
HBP	1856 (59.2%)	189 (60.0%)	2045 (59.2%)	0.77
Smoking	395 (12.6%)	55 (17.5%)	450 (13.0%)	<b>0.01</b>
Dyslipidaemia	1020 (32.5%)	96 (30.5%)	1116 (32.3%)	0.46
Vascular Disease	1153 (36.8%)	82 (26.0%)	1235 (35.8%)	<b>&lt; 10<sup>-3</sup></b>
Atrial Fibrillation or Flutter	590 (18.8%)	72 (22.9%)	662 (19.2%)	0.08
Number of risk factor				0.80
0	624 (19.9%)	61 (19.4%)	685 (19.8%)	
1	853 (27.2%)	90 (28.6%)	943 (27.3%)	
2	727 (23.2%)	73 (23.2%)	800 (23.2%)	
3	582 (18.6%)	63 (20.0%)	645 (18.7%)	
4	278 (8.9%)	23 (7.3%)	301 (8.7%)	
5	68 (2.2%)	5 (1.6%)	73 (2.1%)	
6	5 (0.2%)	0 (0.0%)	5 (0.1%)	
<b>Telephone neurological assessment</b>				
Simplified NIHSS <sup>1</sup> , median (IQR)	4.00 (2-6)	8.00 (6-12)	4.00 (2-8)	<b>&lt; 10<sup>-3</sup></b>
Left Arm Motor Function				<b>&lt; 10<sup>-3</sup></b>
0	2242 (71.5%)	178 (56.5%)	2420 (70.1%)	
2	620 (19.8%)	62 (19.7%)	682 (19.8%)	
4	275 (8.8%)	75 (23.8%)	350 (10.1%)	
Right Arm Motor Function				<b>&lt; 10<sup>-3</sup></b>
0	2331 (74.3%)	189 (60%)	2520 (73.0%)	
2	520 (16.6%)	43 (13.7%)	563 (16.3%)	
4	286 (9.1%)	83 (26.3%)	369 (10.7%)	
Arm Motor Impairment	1672 (53.3%)	256 (81.3%)	1928 (55.9%)	<b>&lt; 10<sup>-3</sup></b>
Left Leg Motor Function				<b>&lt; 10<sup>-3</sup></b>
0	2511 (80.0%)	195 (61.9%)	2706 (78.4%)	
2	402 (12.8%)	50 (15.9%)	452 (13.1%)	



	4	224 (7.1%)	70 (22.2%)	294 (8.5%)	
Right Leg Motor Function	0	2585 (82.4%)	213 (67.6%)	2798 (81.1%)	<b>&lt; 10<sup>-3</sup></b>
	2	313 (10.0%)	29 (9.2%)	342 (9.9%)	
	4	239 (7.6%)	73 (23.2%)	312 (9.0%)	
Leg Motor Impairment		1137 (36.2%)	217 (68.9%)	1354 (39.2%)	<b>&lt; 10<sup>-3</sup></b>
Arm and Leg Simultaneous Impairment		1011 (32.2%)	212 (67.3%)	1223 (35.4%)	<b>&lt; 10<sup>-3</sup></b>
Language	0	1474 (47.0%)	85 (27.0%)	1559 (45.2%)	<b>&lt; 10<sup>-3</sup></b>
	2	1098 (35.0%)	122 (38.7%)	1220 (35.3%)	
	4	565 (18.0%)	108 (34.3%)	673 (19.5%)	
Facial Palsy	0	1993 (63.5%)	133 (42.2%)	2126 (61.6%)	<b>&lt; 10<sup>-3</sup></b>
	2	1144 (36.5%)	182 (57.8%)	1326 (38.4%)	
Vision Trouble	0	2837 (90.4%)	296 (94.0%)	3133 (90.8%)	<b>0.04</b>
	2	300 (9.6%)	19 (6.0%)	319 (9.2%)	
Awareness	0	2780 (88.6%)	231 (73.3%)	3011 (87.2%)	<b>&lt; 10<sup>-3</sup></b>
	2	303 (9.7%)	59 (18.7%)	362 (10.5%)	
	4	54 (1.7%)	25 (7.9%)	79 (2.3%)	
<b>Phone call characteristics</b>					
Center of triage	Haute-Savoie	997 (31.8%)	109 (34.6%)	1106 (32.0%)	0.50
	Savoie	958 (30.5%)	89 (28.3%)	1047 (30.3%)	
	Isère	1182 (37.7%)	117 (37.1%)	1299 (37.6%)	
Caller location	Home	2328 (74.2%)	253 (80.3%)	2581 (74.8%)	0.07
	Health structure	485 (15.5%)	31 (9.8%)	516 (14.9%)	
	Public highway or building	276 (8.8%)	27 (8.6%)	303 (8.8%)	
	Working place	36 (1.1%)	2 (0.6%)	38 (1.1%)	
	Unknown	12 (0.4%)	2 (0.6%)	14 (0.4%)	
Patient calling from home?	Yes	2328 (74.2%)	253 (80.3%)	2581 (74.8%)	<b>0.02</b>
	No	809 (25.8%)	62 (19.7%)	871 (25.2%)	
Caller	Witness	1825 (58.2%)	232 (73.7%)	2057 (59.6%)	<b>&lt; 10<sup>-3</sup></b>
	Doctors /Nurse	791 (25.2%)	54 (17.1%)	845 (24.5%)	
	Patient himself	417 (13.3%)	18 (5.7%)	435 (12.6%)	
	Ski Patrol and First Aiders	71 (2.3%)	8 (2.5)	79 (2.3%)	

Unknown		33 (1.1%)	3 (1.0%)	36 (1.0%)	
Is the caller a caregiver*?	Yes	862 (27.8%)	62 (19.9%)	924 (27.0%)	<b>&lt; 10<sup>-3</sup></b>
	No	2242 (72.2%)	250 (80.1%)	2492 (73.0%)	
Is the caller the patient himself?	Yes	417 (13.4%)	18 (5.8%)	435 (12.7%)	<b>&lt; 10<sup>-3</sup></b>
	No	2687 (86.6%)	294 (94.2%)	2981 (87.3%)	
Is the caller a witness?	Yes	1825 (58.8%)	232 (74.4%)	2057 (60.2%)	<b>&lt; 10<sup>-3</sup></b>
	No	1279 (41.2%)	80 (25.6%)	1359 (39.8%)	
<b>Delays</b>					
Categories of delay	Quantified Delay	1964 (62.6%)	185 (58.7%)	2149 (62.2%)	0.20
	Unknown	1173 (37.4%)	130 (41.3%)	1303 (37.7%)	
Delay between onset of symptoms and call (mins)	Percentiles 25	12.0	7.0	11.0	<b>&lt; 10<sup>-3</sup></b>
	Median	34.5	17.0	33.0	
	Percentiles 75	110.0	62.5	105.5	
"Wake up" Stroke	Yes	241 (7.7%)	37 (11.7%)	278 (8.1%)	<b>0.012</b>

<sup>1</sup> See supplemental data- Table 1

<sup>2</sup> Caregivers could be doctors, nurses, ski patrol and first aiders

### Baseline characteristics

There was no significant difference for the age and sex between the two groups.

### Comorbidities

Smoking was significantly related to the presence of LVO (17.5% versus 12.6%,  $p = 0.01$ ) while confirmed vascular disease was linked to its absence (26.0% for the LVO group, 36.8% for the nLVO group,  $p < 0.05$ ). We did not find any association between the other comorbidities and the risk of LVO (diabetes, dyslipidaemia, cardio-embolic diseases, HBP). Number of comorbidities was not statistically different in both groups.

## Telephone-based neurological assessment

Each variable in the clinical assessment showed a significant difference in distribution between the two groups. Compared to nLVO patients, LVO patients had significantly more arm paresis (81.3% versus 53.3%,  $p < 10^{-3}$ ), more leg paresis (68.9% versus 36.2%,  $p < 10^{-3}$ ), more hemiparesis (67.3% versus 32.2%,  $p < 10^{-3}$ ), more language impairment ( $p < 10^{-3}$ ), more facial paralysis ( $p < 10^{-3}$ ), more consciousness impairment ( $p < 10^{-3}$ ). On the contrary, vision impairment was more present in patients without LVO (9.6% versus 6.0%,  $p = 0.04$ ).

The simplified NIHSS score was significantly higher in the LVO group compared to the nLVO group (respectively 8 [IQR 6-12] and 4 [IQR 2-6],  $p < 0.05$ ).

## Caller location and characteristic

There was no significant difference between the two groups on the distribution between call centers and on the place of call. Isolating only the call from home from all other locations, we found a significant difference (74.2% in the non LVO group versus 80.3% in the LVO group,  $p=0.02$ ).

In the LVO group, there were significantly more calls by a witness and less by the patient himself or a caregiver ( $p < 10^{-3}$ ).

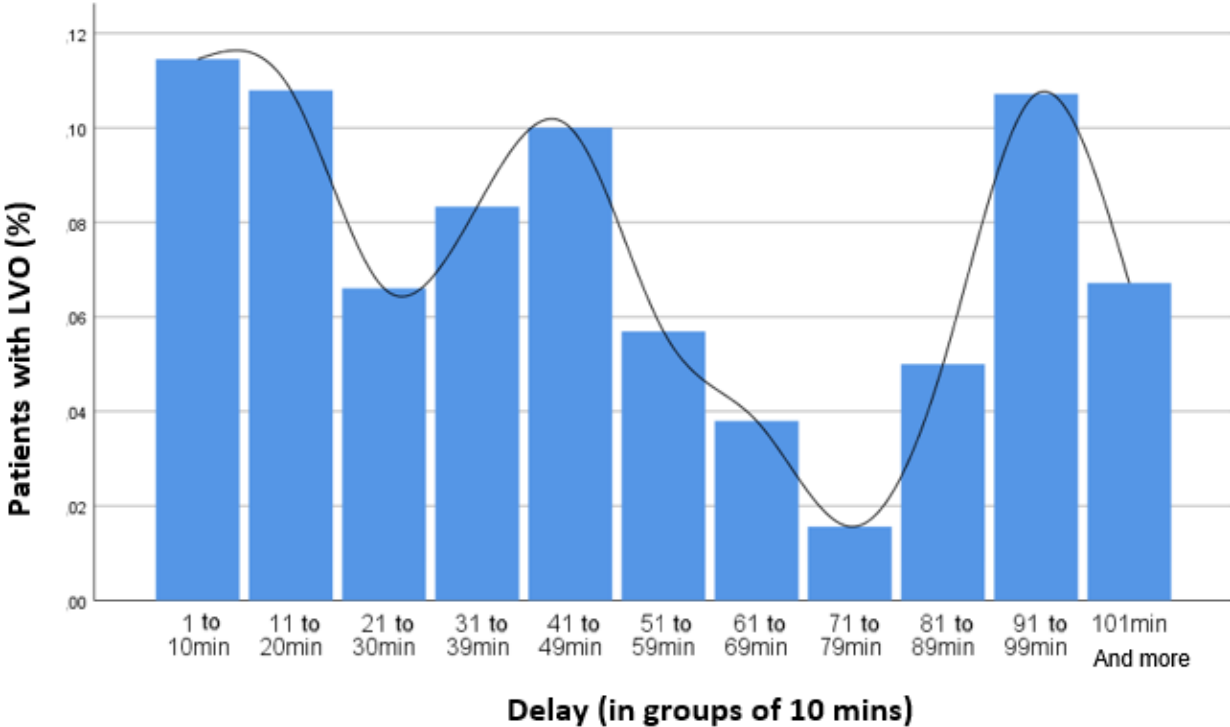
## Delay

We were able to have a precise delay between the onset of symptoms and the call for 2149 patients (62.2%). For the 1303 others (37.7%) no exact time could be determined. The distribution of a quantified delay and unknown delay was not significantly different between the two groups ( $p=0.20$ ).

The median time from symptoms onset to the first ECC call was shorter in the LVO group than in the non LVO group (17 mins vs 34.5 mins,  $p < 10^{-3}$ ). However, the distribution of delays was not linear in the LVO group (Figure 2). This delay was significantly lower in the LVO group, whatever the threshold chosen (supplemental data – Table 3).

Wake-up strokes (patients last seen well the night before bed) were significantly more common in patients with LVO (11.7% versus 7.7%,  $p = 0.012$ ).

Figure 2 - Distribution of number of LVO patients as a function of time



## Imaging data

An LVO was detected in 315 of 3452 patients (9.1%), 192 (60.9%) were M1 occlusions, 60 (19.0%) ICA occlusions, 31 (9.8%) M1-M2 occlusions, 29 (9.2%) were BA occlusions and 3 (0.9%) combined occlusions (ICA and M1-M2, BA and M1, ICA and BA). Of the M1 occlusions, 37 were tandems (i.e. a combination of a M1 branch and internal carotid artery occlusion).

## STARS design

Once the significant items were identified from the univariate analysis, we randomly split the study population to obtain the derivation population (2/3 of the overall population) and the validation population (remaining 1/3). There was no significant difference in the distribution of the variables between the two cohorts (supplemental data - Table 4).

A total of 2281 patients, 2075 nLVO (91.0%) and 206 LVO (9.0%), was selected for the derivation population to perform the multivariate analysis via logistic regressions.

The area under the curve (AUC) of different combinations of these items was determined by receiver operating curve (ROC) analysis (supplemental data – Figure 1). Items were selected for their clinical relevance and the power of their ORs. The ORs were rounded to the nearest whole number to create the score (supplemental data – Table 5).

For an easier achievement of the ECC neurological assessment, we chose a binary rating (presence or absence of impairment). The item « absence of vascular disease », that is difficult to determine, was excluded although it had a high correlation with LVO.

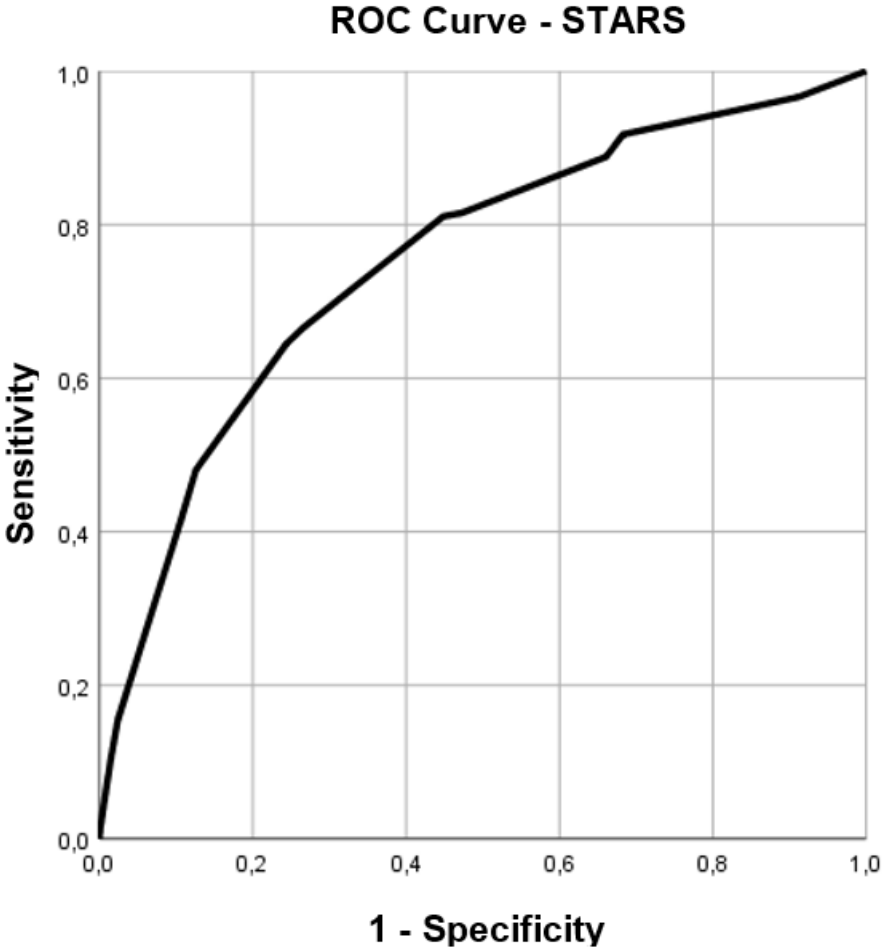
After multivariate analyses via logistic regression, the item “delay” was no longer significant and has been excluded for further analyses (supplemental data – Table 5).

A high global accuracy was obtained with the combination of 6 items that finally built the STARS: Arm motor function Injury, leg motor function injury, speech disability, facial palsy, alertness disorders and smoking. Table 2 resumes the OR and the characteristics of the STARS. The area under the curve of the STARS is 0.75 (Figure 3).

Table 2 - Univariate and multivariate analysis for the six items chosen

	<b>Univariate analysis</b>	<b>Multivariate Analysis</b>	<b>STARS</b>
	OR [95%CI]	OR [95%CI]	Points
Arm motor function Injury	<b>4.56</b> [3.11 – 6.68]	<b>2.35</b> [1.48 – 3.72]	<b>2</b>
Leg Motor Function Injury	<b>4.11</b> [3.01 – 5.62]	<b>2.45</b> [1.68 – 3.57]	<b>2</b>
Speech Disability	<b>2.01</b> [1.47 – 2.75]	<b>1.67</b> [1.21–2.32]	<b>2</b>
Facial Palsy	<b>2.84</b> [2.11 – 3.81]	<b>2.19</b> [1.61 – 2.99]	<b>2</b>
Alertness disorders	<b>2.62</b> [1.85 – 3.71]	<b>2.75</b> [1.89 – 4.00]	<b>3</b>
Smoking	<b>1.49</b> [1.01 – 2.19]	<b>1.77</b> [1.17 – 2.67]	<b>2</b>

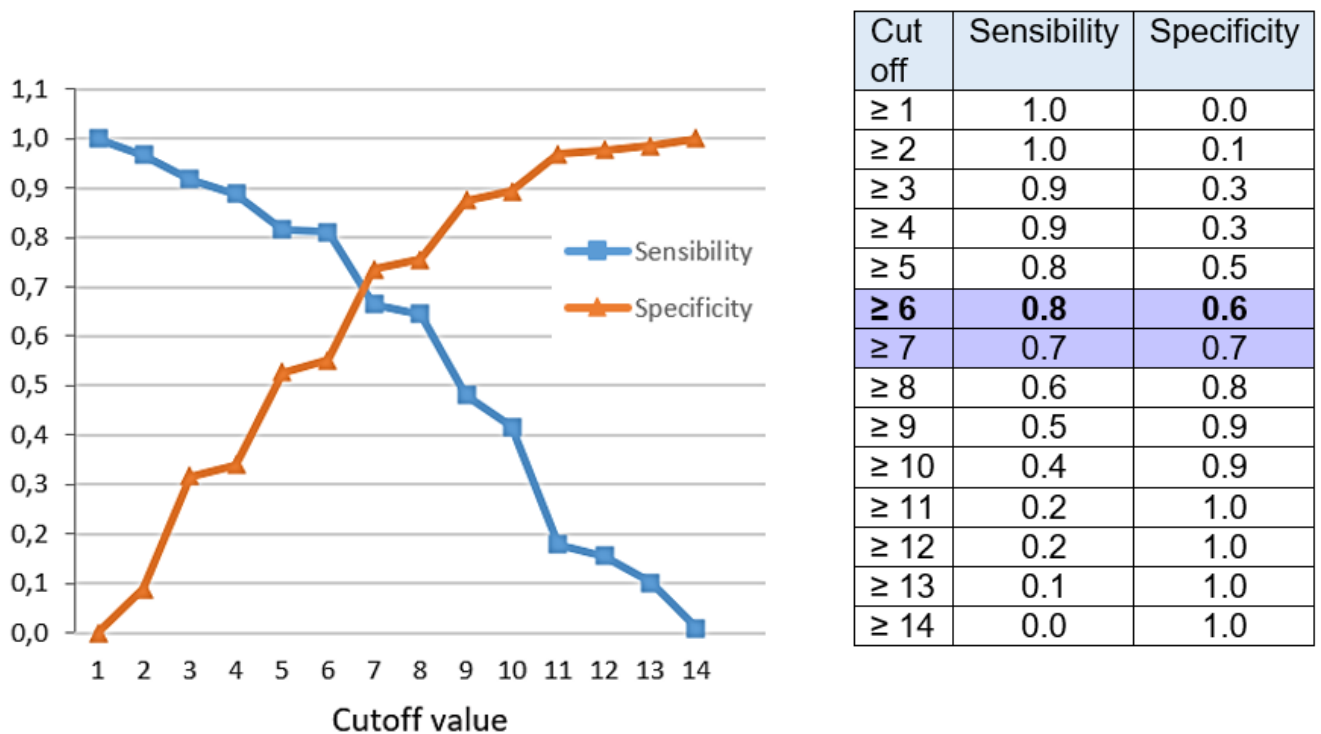
Figure 3 - ROC curve of the STARS for the LVO detection



The specificity and sensitivity values were calculated for the different cut offs (Figure 4).

We compared two cut-offs for which the sensitivity and specificity values seemed interesting:  $\geq 6$  and  $\geq 7$  (Table 3). We chose the cut off  $\geq 6$ .

Figure 4- Sensitivity and Specificity of different cut-off values of the STARS for the detection of LVO (table and corresponding graph)



Cut off	Sensibility	Specificity
≥ 1	1.0	0.0
≥ 2	1.0	0.1
≥ 3	0.9	0.3
≥ 4	0.9	0.3
≥ 5	0.8	0.5
<b>≥ 6</b>	<b>0.8</b>	<b>0.6</b>
<b>≥ 7</b>	<b>0.7</b>	<b>0.7</b>
≥ 8	0.6	0.8
≥ 9	0.5	0.9
≥ 10	0.4	0.9
≥ 11	0.2	1.0
≥ 12	0.2	1.0
≥ 13	0.1	1.0
≥ 14	0.0	1.0

Table 3 - Statistical performances of STARS depending on the threshold chosen, calculated on the derivation cohort

Proportions are reported to the total of the LVO and nLVO group.

	Cut Off 6		Cut Off 7		Total
	< 6	≥ 6	< 7	≥ 7	
LVO	39 (18.9%)	167 (81.1%)	69 (33.3%)	137 (66.6%)	206
nLVO	1145 (55.2%)	930 (44.8%)	1525 (73.5%)	550 (26.5%)	2075
Total	1184 (51.9%)	1097 (48.1%)	1594 (69.9%)	687 (30.1%)	2281
Sensibility	<b>0.81</b>		0.67		
Specificity	<b>0.55</b>		0.73		
PPV	<b>0.15</b>		0.20		
NPV	<b>0.97</b>		0.96		
Accuracy	<b>0.57</b>		0.76		



### Internal validation

To realise the internal validation of the score, we applied the final STARS to the validation cohort (remaining third of the overall population) (Table 4). This population was composed of 1171 patients, with 109 LVO (9.3%) and 1062 nLVO (90.7%).

With a cut-off  $\geq 6$ , we determined a sensitivity of 0.78, a specificity of 0.56, a PPV of 0.15 and a NPV of 0.96 (accuracy 0.58).

Table 4 - Internal validation and Performance of STARS

	<b>&lt; 6</b>	<b><math>\geq 6</math></b>	<b>Total</b>		
LVO	24 (22.0%)	85 (78.0%)	109	<b>Sensitivity</b>	<b>0.78</b>
nLVO	594 (55.9%)	468 (44.1%)	1062	<b>Specificity</b>	<b>0.56</b>
Total	618 (52.8%)	553 (47.2%)	1171	<b>PPV</b>	<b>0.15</b>
				<b>NPV</b>	<b>0.96</b>
				<b>Accuracy</b>	<b>0.58</b>

## Discussion

The STARS shows a high sensitivity (78%) and specificity (56%) to identify LVO when considering a cut-off point  $\geq 6$ , or even higher specificity with lower sensitivity with a higher cut-off point  $\geq 7$  (Table 3 and 4). This scale is the first phone scale to detect patients with AIS due to LVO in prehospital setting at the time of the first ECC call.

This study is a continuum of Dr Alphane Baquerre's work who proposed in 2017 a score, the Alpha Stroke Score (ASS) (31) (supplemental data -Table 7 and 8). This study focused on the 2014 registry and included only neurological deficits within 6 hours of evolution. Our survey aimed to enrich this work by increasing its population and updating the EVT recommendations. According to DEFUSE 3 and DAWN study, published in 2018, all stroke alerts less than 24 hours were considered. This studies demonstrated the effectiveness of thrombectomy on patients with delays until 16 and 24 hours, but also on "wake up strokes" (32,33). These choices are in line with AHA guidelines (21).

The prevalence of LVOs in our study population (9.1%) is in line with previous reports using a similar reference group of suspected stroke (i.e. also including haemorrhagic strokes and stroke mimics) (34–36). The same is true for the distribution between AIS, haematoma, TIA and stroke mimic (35,37) and site of LVO (13,38). The rate of LVO per confirmed AIS is in the low range of studies (19.2% in the STARS population, compared to values between 13% and 46% in the literature; with 30% average rate) (5).

## LVO and population definition

Cerebral infarctions related to the posterior circulation present a much more heterogeneous and atypical clinical presentation than those of the anterior circulation making the NIHSS poorly performing at its screening (39). Indeed, symptoms can associate disorders of alertness, damage to cranial nerves or vertiginous sensations. Including the BAO in our definition of the LVO probably leads to a decrease in the performance of the score (reduced sensitivity). To explore this hypothesis, we analysed the STARS sensitivity and specificity results on the internal validation population, removing the BAO from the LVO group. We improved the sensitivity to 83% (compared to 78%), while maintaining specificity at 56% (supplemental data - Table 9). The rate of recanalization after thrombolysis for BAO is low (from 4% to 30%) (40,41) and the prognosis poor. The few studies that have been carried out show that EVT associated with IVT is more effective than thrombolysis alone (42,43). Given the poor prognosis of this occlusion, we accepted a slight decrease in sensitivity performance to consider BAO in the LVO definition. This attitude is supported by the official guidelines (16,44) and other predictive scores also included it, e.g. RACE (24) and FAST-ED (29).

The indication of EVT for patients with M2 segment occlusions is subject to debate. Although EVT appears to be as effective and safe for M2 as for M1 occlusions (45), its contribution to patient outcome is discussed (13,46). Literature data are still limited, only one study has directly compared the contribution of EVT with best medical management for the M2 occlusion (47). IVT is challenged by M1 and ICA occlusions but offers good results for M2 occlusions (6). It seemed interesting to find a predictive score for LVO with a high risk of failure with IVT. We therefore chose to include the M1-M2 junction occlusions but not the distal M2 occlusions.

### Neurological items associated with LVO

All clinical items were significantly different between the two groups (arm motor function, leg motor function, speech disability, facial palsy, vision impairment and alertness disorder), underlining the importance of the clinical presentation in predicting LVO.

As the neurological assessment was carried out by telephone, this score had to be as simple as possible, achievable without any medical training. Accordingly, a dichotomous rating (absence or presence) was chosen to improve the feasibility.

The feasibility of the main predictive scores has been tested in a recent large cohort study (37). It highlights the importance of a good static performance coupled with a high feasibility rate.

Some studies have shown that cortical signs (aphasia and neglect) are better markers than motor impairment and increase the specificity of the tests (35,48). Contrary to the STARS, some of the previous pre-hospital scales ignored the evaluation of aphasia (25,26). However, neglect was deliberately excluded from the STARS due to its low inter-rater reliability of evaluation in emergency conditions, though it was reported to be associated with large cortical infarct. Indeed, some pre-hospital scores loose in feasibility by including the evaluation of neglect (e.g. FAST ED) (37).

### Non neurological factors associated with LVO

Active smoking or smoking that has been stopped for less than 2 years, appears to be an important risk factor for LVO. This importance has already been proven in another study (49).

By contrast, other cardiovascular risk factors (diabetes, dyslipidaemia and HBP) are not predictive of LVO. The presence of a known vascular disease (supplemental data – Table 2) is even a protective factor for LVO. These data are concordant with the literature (50,51). We hypothesise that these pathologies were mainly responsible of cerebral small vessel disease and lacunar infarction (52). While significant, the item "absence of vascular disease" was deliberately not included in the final score, because its rating may induce scoring errors (not instinctive for clinicians). Moreover, recording this comorbidity is complicated for ECC physicians because it is based on several questions (searching for five past medical histories).

In our study, cardio-embolic diseases were not linked to a high risk of LVO while this was evidenced in a large study (53). Atrial fibrillations (AFs) responsible for LVO are those that are not treated with anticoagulant treatment or those that are discovered during the hospitalisation (54,55). In our study, we were interested in known embolism arrhythmia at the moment of the ECC call, without any indication of the use of anticoagulant treatment. It seems reasonable to assume that known AFs are treated. Therefore, we probably did not detect AF at risk of LVO.

The evaluation of the delay between the symptoms onset and the EEC call for the prediction of an LVO is an originality of our study. Whatever the threshold chosen, it was significantly shorter in the LVO group, in the univariate analysis but not in the multivariate ones. We explained this by the interaction between an early call and a serious clinical presentation. The more severe the clinical presentation is, the faster the ECC is called by the patient or witness. The delay is therefore a confounding factor with the clinical presentation.

In descriptive analyses of the general population, wake up stroke was also associated with a significant risk of LVO. However, this significance was lost when the population was randomized due to a lack of power.

From the descriptive statistics, if the ECC had been called by a witness, there was a significantly higher probability of LVO, whereas if the caller had been the patient himself the risk of LVO was reduced. This significance was preserved in some of the scores tested in the multivariate analyses (supplemental data – Table 5). Nevertheless, including these variables did not improve the final score and decrease the specificity (supplemental data – Table 10). To preserve the simplest possible score, we therefore decided not to retain them.

In the line with this, a call to the ECC by a caregiver was significantly less likely to result in a diagnosis of LVO. We can suppose that a caregiver is more aware of subtle clinical presentation, and therefore of small infarctions (no LVO). This univariate significance has not been retained the univariate and multivariate analysis on the derivation cohort, secondarily to a lack of statistical power (lack of population size).

### Choice of the best cut off

We compared two cut-offs for which the sensitivity and specificity values seemed interesting:  $\geq 6$  and  $\geq 7$  (Table 3).

We chose to privilege the sensitivity, to limit as much as possible the rate of false negatives (and thus the under-diagnosis of LVO). Considering a cut-off value of STARS  $\geq 6$ , ECC physicians would identify 78% of patients with LVO. Coupled with a specificity of 0.56, this was the best compromise.

Using a scale with a low specificity involves a risk to exceed the capacity of most CSC. Lowering the severity of the cut-off also enables the detection of LVO associated with a low NIHSS or with an atypical clinical presentation. The morbidity and disability of these patients are consequent and initial presentation may worsen in a second step (36). Approximately one third of patients with LVO but low NIHSS (<7) will worsen despite IVT performing (56). The thrombus length and the occlusion site have been proposed as a predictive factor of poor outcome for this population (57). There is no high grade recommendation for the indication of thrombectomy in these patients with low NIHSS LVO (NIHSS <6) (16) but studies are in progress (58,59). In the near future, they should probably be considered as potential strong candidates.

### Comparison of the STARS with other predictive scores

The optimal threshold for LVO detection by the NIHSS is a matter of debate. Usually values of 6 to 10 are used (60). AUC values range from 0.70 to 0.86 with sensitivity from 0.73 to 0.64 and specificity from 0.79 to 0.84 (respectively depending on the cut off at 8 or 10, and on the population) (16,35). These values are better than those of the STARS, but these results were obtained thanks to emergency doctor or neurologist assessment on the patient's bedside. Several studies therefore consider that the NIHSS cannot be performed in the pre-hospital field, as it is too complex and time-consuming (30,61).

Two recent large prospective cohort studies comparing the efficiency of the main predictive scores (RACE, LAMS, PASS, G-FAST, FAST-ED) have just been published. (35,37). AUC of these scores range from 0.72 to 0.83. With a value of 0.75, the STARS AUC is in line with these results. All the scores have a good specificity and a mild

sensitivity (specificity varies from 0.80 to 0.93, against a sensitivity of 0.38 to 0.67). In our cohort the STARS has a sensitivity of 0.78 but at the cost of a mild specificity of 0.56. The NPVs are identical for all scores and for the STARS with values from 0.95 to 0.96. But we have the lowest PPV at 0.15 (from 0.21 to 0.32 depending on the score).

The spontaneous recanalization of LVOs or migration of the thrombus decrease the statistical performances of the STARS. As far as the clinical items were assessed only by phone at the time of the first ECC call, if a spontaneous recanalization happened between the time of the telephone call and the neuroimaging exam, the patient will not be classified as having LVO. It is possible that STARS may lose specificity because the association of a clinical presentation of LVO will be made without discovery of an LVO on imaging, because it is already resolving.

### In practice

Many questions have emerged around the choice of the best pre-hospital predictive scale with the challenging question: when is it reasonable to bypass a nearby primary stroke center, thereby potentially delaying IV thrombolysis, in favour of direct transport to an EVT-capable hospital?

The answer is probably that there is no universal best score. The efficiency of each score depends on local geographical constraints, the prevalence of LVOs, differences in transport times between hospitals, regional characteristics, the organisation of the healthcare system, etc (16,62). The solution is probably that everyone should create their own self-driven processes (63).



Predictive scores can be defaulted by atypical clinical presentations and none of them allows to have a good sensitivity and specificity (30,64). This can lead to a loss of chance for more than 20% of LVOs (65).

In the near future, the indications for EVT may become increasingly broad, especially on more distal occlusions and low NIHSS LVO strokes (66). Pre-hospital scores based only on the clinical assessment will be challenged even more. Other pre-hospital tools must be found to help improve triage, based on relevant and rapid paraclinical examinations, all under financial constraints (67).

Transcranial ultrasonography (68), electroencephalography (69), biomarkers (70), and even the mobile stroke unit with an on-board CT-scan (71) are some of the ways of reflection.

The emergence of smartphones and video-based clinical assessments in medicine is a potential way forward, and one that STARS can support.

### Limits

Our study has some limits. First, the STARS scale was derived and validated from a single cohort. The retrospective and observational design inherits potential for bias. A prospective multi-centre study starting in March 2021 is currently confirming these results (supplemental data – Figure 2).

It is possible that we may have a slight underestimation of LVOs in our population for TIA or minor stroke patients. In these patients, non-vascular imaging was always performed. Although, the number of these patients remains limited. We have chosen not to exclude these patients and to consider them as infarctions without LVO.

Due to its retrospective design, our study suffers from missing data. We excluded 675 patients (14%) because of missing data. They were mainly represented by medical past histories and final diagnoses.

### Strength of the study

This study has many strengths. Firstly, to our knowledge, this cohort is the largest pre-hospital suspected stroke telephone population. Unlike many studies, our cohort contains the full spectrum of stroke suspicion including AIS, ICH, TIA and stroke mimics occurring less than 24 hours delay, including “wake up” strokes. Secondly, we tested the contribution of the delay from the symptom’s onset to the ECC call, patient commodities, and call characteristics that are rarely studied. We thus proved the confounding nature of the delay between the onset of symptoms and the call for ECC, which no other study had done to our knowledge.

We validated the predictive link of smoking on the risk of LVO, which is a variable easily accessible by phone assessment. We highlighted the importance of the caller in the risk of LVO, demonstrating that if the caller was not the patient himself, the risk increased. Finally, we have performances that are close to the already well-established scores while preserving ease of use.

## **Conclusion**

In summary, STARS could be a simple and effective tool to identify high-risk patients of LVO, and therefore eligible for EVT, allowing them to be transferred quickly to a CSC. The accuracy and feasibility of the STARS to predict LVOs in the pre-hospital setting needs to be tested in a prospective study. This external validation is already underway through a multi-center prospective study.

## **THÈSE SOUTENUE PAR HUGO MERLIN**

### TITRE: DESIGN OF A PREDICTIVE TELEPHONE SCORE FOR CEREBRAL LARGE VESSEL OCCLUSION: THE STROKE TRIAGE ALPHA RESCUE SCORE (STARS)

#### Conclusion:

Endovascular thrombectomy (EVT) has become the gold standard for the treatment of acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). Its benefit is even more important as recanalization is early. However, access to EVT remains limited to a few centers, the Comprehensive Stroke Centers (CSC), making pre-hospital triage difficult.

There are currently two competing paradigms: The Drip and Ship model, which consists in referring to the nearest center and then performing a secondary transfer if a thrombectomy is required, and the Mothership model, in which all patients are referred to a CSC.

Another approach is to differentiate in prehospital field, high-risk LVO patients, who are referred to a CSC, and low-risk LVO patients, referred to the nearest hospital.

Accordingly, several clinical scores for LVO prediction were proposed. Most of them have been performed on emergency room patient populations and even on patients in stroke units with known AIS. These populations do not represent the population of interest because the triage is carried out at an earlier stage, at the first call to the Emergency Medical Communication Centers (ECC). Furthermore, these scores are largely based on a pre-hospital clinical assessment by a medical emergency

technician, which is difficult to achieve and time consuming. None of which was created for telephone use.

In this study, we aimed to create a simple and robust pre-hospital LVO predictive telephone score using RENAU prospective registry (Northern French Alps Emergency Network) of the years 2014 and 2016. This registry collect data from all the ECC call for a suspected stroke, and data from all the patients hospitalised in the four stroke units of the area: Grenoble, Annecy, Chambéry and Annemasse.

We included 3452 patients. 1643 (47.6%) had an ischemic stroke, 945 (27.4%) a stroke mimic, 496 (14.4%) a TIA and 368 (10.7%) an intracerebral haemorrhage. Among the 1643 patients attended by an ischemic stroke, 315 (19.2%) had an LVO. It represented 9.1% of the total population.

Using different multivariate significant item associations, we designed several score which we then compared using Receiver Operating Curve analysis (ROC) and their associated area under curve (AUC). We finally chose the score that presented the best compromise between statistical performance, feasibility, and clinical relevance.

A high global accuracy was obtained with the combination of 6 items that finally built the STARS scale: 2 points for upper limb impairment, 2 for lower limb impairment, 2 for language impairment, 2 for facial paralysis, 3 for alertness disorders and 2 for an active smoking or stopped less than 2 years ago. A low severity threshold has been favoured to prioritize sensitivity, in order to detect as many LVO patients as possible (i.e a low false negative rate).

The cut off  $\geq 6$  was chosen to carry out the internal validation. This cut-off value showed sensitivity 0.78 and specificity 0.56 (AUC 0.75).

Globally, the risk of LVO was related to the severity of the clinical presentation and particularly to the simplified NIHSS. One of the innovations compared to the other scores is the association we demonstrated between smoking and the risk of LVO. Another remarkable notion is that the type of caller is also predictive of LVO. In fact, there is an excess risk in the situation where the ECC is called by someone other than the patient himself.

On the contrary, we thought that the delay between the onset of the symptoms and the call would be predictive of LVO, but this appeared to be a confounding factor with the clinical presentation.

In total, we have succeeded in developing a prehospital LVO prediction telephone score that is both efficient and simple to perform, including clinical and non-clinical concepts: the STARS.

Its external validation is being carried out as a prospective and multicentric study.

**VU ET PERMIS D'IMPRIMER, Grenoble, le 09/03/21 :**

**LE DOYEN**

Pour le Président  
et par délégation  
-----  
Le Doyen de Médecine  
Pr. Patrice MORAND  
**Pr. Patrice MORAND**

**LE PRÉSIDENT DE LA THÈSE**

**Pr. Guillaume DEBATY**

Pour le Président  
et par délégation  
-----  
Le Doyen de Médecine  
Pr. Patrice MORAND

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# Supplemental data

Table 1 - Simplified NIHSS used by ECC physician

If you are unable to check an item, check and count 0.

	0	2	4	Score
<b>RIGHT Arm motor Function</b>	Normal	Impaired	Total Paralysis	
<b>LEFT Arm motor Function</b>	Normal	Impaired	Total Paralysis	
<b>RIGHT Leg Motor Function</b>	Normal	Impaired	Total Paralysis	
<b>LEFT Leg Motor Function</b>	Normal	Impaired	Total Paralysis	
<b>Language</b>	Normal	Impaired	Mutism	
<b>Facial Palsy</b>	Absent	Present		
<b>Vision Impairment</b>	Absent	Present		
<b>Awareness</b>	Normal	Impaired	Coma	
<b>Total</b>				

Table 2 - Dictionary of variables

<u>Variables</u>	<u>Definition</u>
<u>Baseline characteristic</u>	
Age	Age at the time of the call
Gender	Gender at the time of the call
<u>Comorbidities</u>	
Diabetes	Known diabetes or anti diabetics treatment use
HBP	Known HBP or hypotensive drugs use
Smoking	Active smoking or smoking cessation for less than 2 years
Dyslipidaemia	Known dyslipidaemia or lipo-lowering treatment use
Vascular disease	Presence of at least one known history of coronary artery disease, lower limb arteriopathy, ischemic stroke, transient ischemic stroke, chronic kidney failure from vascular disease
Embolic disease	Known atrial fibrillation or flutter
Number of risk factor	Number of items associated above

Table 3 - Distribution of the LVO patients according to the delay cut-off

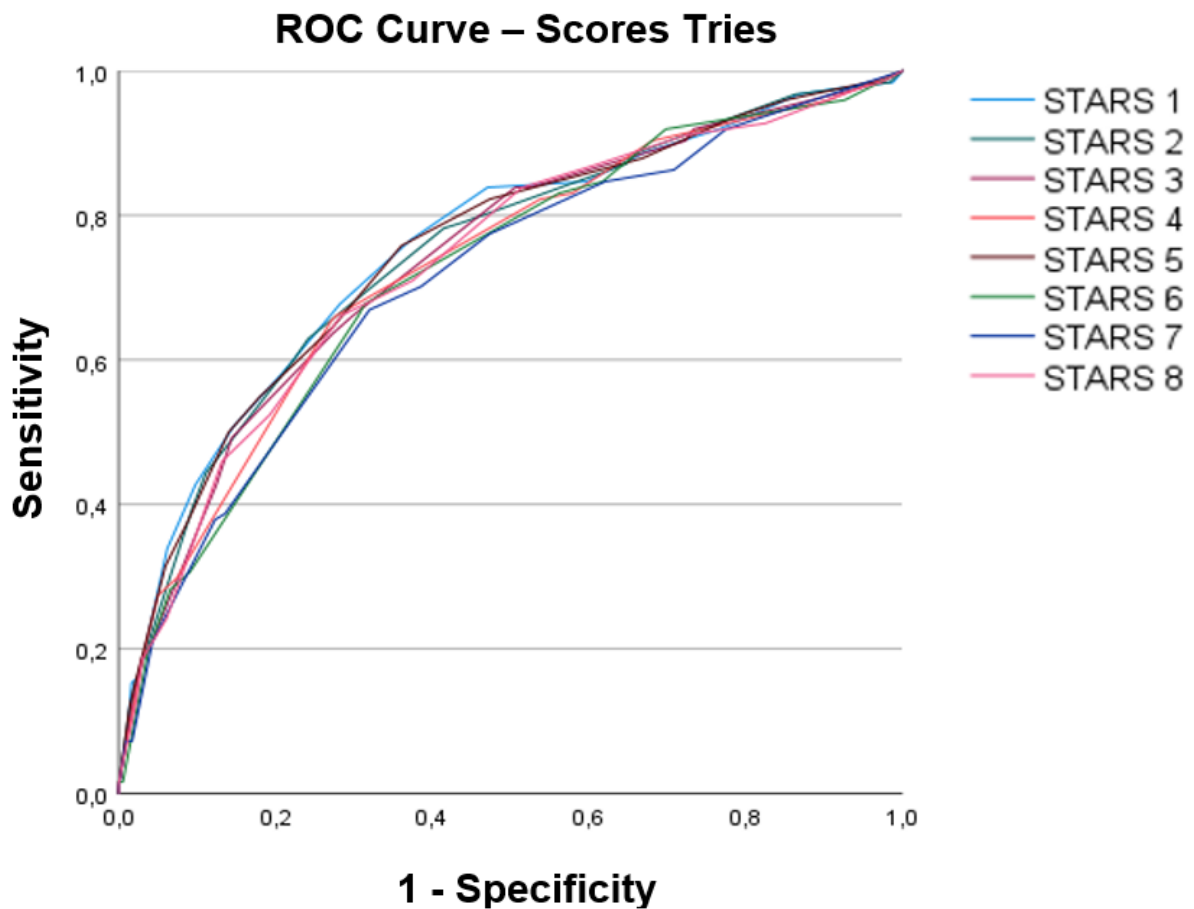
	<b>No LVO Group (n= 1964)</b>	<b>LVO Group (n = 185)</b>	<b>Total (n= 2149)</b>	<b>p</b>
≤ 15 mins	599 (30.5%)	86 (46.5%)	685 (31.9%)	<b>&lt; 10<sup>-3</sup></b>
15 mins < time ≤ 35 mins	394 (20.1%)	32 (17.3%)	426 (19.8%)	
> 35 mins	971 (49.4%)	67 (36.2%)	1038 (48.3%)	
≤ 30 mins	933 (47.5%)	114 (61.6%)	1047 (48.7%)	<b>&lt; 10<sup>-3</sup></b>
> 30 mins	1031 (52.5%)	71 (38.4%)	1102 (51.3%)	
≤ 40 mins	1036 (52.7%)	122 (65.9%)	1158 (53.9%)	<b>0.01</b>
> 40mins	928 (47.3%)	63 (34.1%)	991 (46.1%)	

Table 4 - Comparability between the score development population (two thirds of the total) and the internal validation population (remaining third)

<b>Variable</b>	<b>p</b>
Woman	0.91
Categories of delay	0.21
Caller	0.12
Left Arm motor Impairment	0.75
Right Arm motor Impairment	0.88
Left Leg Motor Impairment	0.53
Right Leg Motor Impairment	0.93
Arm motor impairment	0.51
Leg Motor impairment	0.45
Both Arm and Leg impairment	0.66
Language	0.19
Facial Palsy	0.95
Vision Trouble	0.57
Alertness disorder	0.10
Diabetes	0.85

HBP	0.43
Smoking	0.23
Dyslipidaemia	0.30
Vascular Disease	0.11
Cardio-embolic disease	0.75
LVO	0.79
Wake Up stroke	0.22
The caller is a care giver	0.16
The caller is not the patient	0.08
Place of call is patient's home	0.051
Delay < 30 mins	0.96
Delay < 45 mins	0.58

Figure 1 - ROC curves for each scale tries



**Table 5 - Testing of several STARS according to different combinations of items**

Data are **rounded OR** (OR original) [95% CI]

	<b>STARS 1</b>	<b>STARS 2</b>	<b>STARS 3</b>	<b>STARS 4</b>	<b>STARS 5</b>	<b>STARS 6</b>	<b>STARS 7</b>	<b>STARS 8</b>	<b>STARS 9</b>
Arm Paresis	<b>2</b> (2.15) [1.16–4.00]	<b>2</b> (2.40) [1.51 – 3.80]	<b>2</b> (2.35) [1.48 – 3.72]	<b>3</b> (2.70) [1.72 – 4.26]		<b>2</b> (2.72) [1.72 – 4.29]	<b>2</b> (2.70) [1.71 – 4.27]	<b>2</b> (2.35) [1.48 – 3.73]	<b>2</b> (2.17) [1.16–4.07]
Leg Paresis	<b>3</b> (2.52) [1.53–4.14]	<b>2</b> (2.41) [1.65–3.52]	<b>2</b> (2.45) [1.68 – 3.57]	<b>2</b> (2.49) [1.72 – 3.61]		<b>2</b> (2.45) [1.68 – 3.57]	<b>2</b> (2.50) [1.71 – 4.27]	<b>2</b> (2.43) [1.67 – 3.55]	<b>2</b> (2.47) [1.51–4.10]
Both Arm and Leg motor function Injury									
Speech Disability	<b>2</b> (1.61) [1.06–2.46]	<b>2</b> (1.71) [1.23–2.80]	<b>2</b> (1.67) [1.21–2.32]	<b>2</b> (1.88) [1.37–2.60]	<b>2</b> (1.57) [1.03 – 2.39]	<b>2</b> (1.78) [1.29 – 2.46]	<b>2</b> (1.78) [1.29 – 2.46]	<b>2</b> (1.60) [1.15 – 2.23]	<b>1</b> (1.50) [0.98–2.91]
Facial Palsy	<b>2</b> (1.97) [1.32–2.94]	<b>2</b> (2.14) [1.56–2.92]	<b>2</b> (2.19) [1.61 – 2.99]		<b>2</b> (1.98) [1.33 – 2.95]			<b>2</b> (2.15) [1.57 – 2.94]	<b>2</b> (1.90) [1.27–2.83]
Alertness disorders	<b>3</b> (2.56) [1.57–4.16]	<b>3</b> (2.75) [1.88–54.0]	<b>3</b> (2.75) [1.89 – 4.00]	<b>3</b> (2.69) [1.86–3.90]	<b>2</b> (2.49) [1.53 – 4.05]	<b>3</b> (2.63) [1.81 – 3.81]	<b>3</b> (2.69) [1.86 – 3.90]	<b>3</b> (2.71) [1.86 – 3.95]	<b>3</b> (2.44) [1.50–3.98]
Smoking	<b>2</b> (2.01) [1.21–3.35]	<b>2</b> (1.77) [1.17–2.67]	<b>2</b> (1.77) [1.17 – 2.67]	<b>2</b> (1.75) [1.17–2.63]	<b>2</b> (2.00) [1.20 - 3.33]	<b>2</b> (1.88) [1.24 – 2.83]	<b>2</b> (1.78) [1.18 – 2.68]	<b>2</b> (1.88) [1.24 – 2.85]	<b>2</b> (2.13) [1.27–3.57]
No vascular disease	<b>2</b> (1.86) [1.12–2.94]	<b>2</b> (1.78) [1.26–2.52]			<b>2</b> (1.84) [1.16 - 2.90]				<b>2</b> (1.87) [1.18–2.96]
Call delay ≤ 30 mins	<b>1</b> (1.23) [0.83–1.83]				<b>1</b> (1.24) [0.84 - 1.85]				<b>1</b> (1.25) [0.84–1.87]
Caller is not a caregiver									<b>2</b> (2.44) [0.95 – 6.27]
Caller is not the patient himself						<b>2</b> (1.97) [1.04 – 3.75]			
Caller is a Witness							<b>2</b> (1.57) [1.12 – 2.18]	<b>1</b> (0.57) [0.30 – 1.08]	
AUC	<b>0.75</b>	<b>0.76</b>	<b>0.75</b>	<b>0.74</b>	<b>0.75</b>	<b>0.73</b>	<b>0.72</b>	<b>0.75</b>	<b>0.75</b>



Table 7 - The Alpha Stroke Scale

<b>Alpha Stroke Score</b>					
Caller is not the patient himself	Left Leg Motor Function Injury	Right Leg Motor Function Injury	Speech Disability	Call delays < 30 mins	Smoking
<b>3</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>3</b>

Table 8 – The performance of the Alpha Stroke Scale

<b>Alpha Stroke Score</b>		
Cut off	Sensibility	Specificity
> 7	0.48	0.85
6-7	0.72	0.51
< 6	0.93	0.18

Table 9 – Statistical performances of STARS during internal validation excluding basilar artery occlusions of LVO definition

	< 6	≥ 6	Total	Sensitivity	<b>0.83</b>
LVO	17 (17.3%)	81 (82.7%)	98	Specificity	<b>0.56</b>
nLVO	594 (55.9%)	468 (44.1%)	1062	PPV	<b>0.15</b>
Total	611 (52.7%)	549 (47.3%)	1160	NPV	<b>0.96</b>

Table 10 – Statistical performance of the no-patient caller-inclusive score (STARS 6)

	<b>&lt; 6</b>	<b>≥ 6</b>	<b>Total</b>
LVO	510 (48.4%)	543 (51.6%)	1053
nLVO	15 (14.0%)	92 (86%)	107
Total	525 (45.3%)	635 (54.7%)	1160

Sensitivity	<b>0.86</b>
Specificity	<b>0.48</b>
PPV	<b>0.14</b>
NPV	<b>0.97</b>
AUC	<b>0.73</b>

Figure 2 – French inclusion document for the STARS prospective study

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**STARS : Score Téléphonique Alerte AVC par Régulation Samu**

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**PATIENT :**

Nom : \_\_\_\_\_

Prénom : \_\_\_\_\_

Genre :

DDN : \_\_/\_\_/\_\_\_\_

**APPELANT :**

Patient :

Témoin :  Précision (famille, soignant) : \_\_\_\_\_

Date et Heure de l'appel : \_\_\_\_\_

Localisation du patient : Domicile :  Autre :

Numéro d'appel régulation: \_\_\_\_\_

**HORAIRES :**

Date et heure du début des symptômes (si connu) : \_\_\_\_\_

Si inconnu : date et heure vue normal pour la dernière fois : \_\_\_\_\_

**SCORE STARS : symptômes au moment du 1<sup>er</sup> appel (de l'APPELANT)**

Items	Quotation	Cocher
Déficit moteur membre supérieur	Absent	
	Partiel ou total	
Déficit moteur membre inférieur	Absent	
	Partiel ou total	
Paralysie faciale	Absence	
	Partielle ou totale	
Trouble du langage (aphasie/dysarthrie)	Absent	
	Partiel ou total	
Trouble de la vigilance <i>Somnolence ou coma</i>	Absent	
	Partiel ou total	
Tabagisme actif	Non	
	Ne sait pas	
	Oui	

**AUTRES SYMPTOMES :**

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**TRAITEMENTS au long cours :**

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**ORIENTATION DU PATIENT :** \_\_\_\_\_

**MODE DE TRANSPORT :** \_\_\_\_\_

<b>Critères d'inclusions</b>
<ul style="list-style-type: none"><li>- Tout appel au centre 15 pour un <b>probable AVC</b> datant de <b>moins de 24 heures</b> :<ul style="list-style-type: none"><li>o Quel que soit la gravité ou les symptômes (vertige atypique/flou visuel à l'hémiplégie/coma brusque)</li><li>o AVC du réveil</li><li>o Probable accident vasculaire rétinien</li></ul></li></ul>
<b>Critères d'exclusions</b>
<ul style="list-style-type: none"><li>- Patients mineurs</li><li>- Régression totale des symptômes, situation évocatrice d'un probable AIT</li><li>- Patients non régulés par le centre 15 du SAMU 38 et 73</li><li>- Symptômes de plus de 24 heures au moment de l'appel</li><li>- AVC intra-hospitaliers</li><li>- Transfert primo-secondaire intra hospitalier pour un AVC</li></ul>

# Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

**“ Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. ”

# Abstract

## DESIGN OF A PREDICTIVE TELEPHONE SCORE FOR CEREBRAL LARGE VESSEL OCCLUSION: THE STROKE TRIAGE ALPHA RESCUE SCORE: (STARS)

### Background:

Since 2015, endovascular thrombectomy (EVT) has become the gold standard for the treatment of acute ischemic stroke (AIS) caused by a large vessel occlusion (LVO). Safety and efficacy are timely dependant, resulting in new pre-hospital triage challenges.

We aim to establish a prehospital telephone score predictive of LVO.

### Methods:

We performed an observational multicentric study on stroke alert database of the Northern French Alps Emergency Network (RENAU) registry in 2014 and 2016.

Telephone-based neurological assessment, characteristics of the phone call and medical history of all patients calling Emergency Medical Communication Centers for a suspected stroke within 24 hours were retrospectively analysed. The items weighting was based on Odds Ratio of significant variables after multivariate analysis. The score's performances were established after internal validation.

### Results:

Of 3452 patients included, 1643 (48%) had an AIS, 496 (14%) had a transient ischemic attack, 368 (11%) had intracerebral haemorrhage, and 945 (27%) had stroke mimics. A LVO was found in 315 patients (9% overall or 19% of AIS patients).

In multivariate analysis upper limb paresis (OR = 2.35, 95% confidence interval [1.48 - 3.72]), lower limb paresis (OR = 2.45, [1.68 - 3.57]), language impairment (1.67, [1.21 - 2.32]), facial palsy (2.19, [1.61 - 2.99]), consciousness disorder (2.75, [1.89 - 4.00]) and active smoking (1.77, [1.17 - 2.67]) were significantly associated with presence of LVO. After rounding, all items had a value of 2 points, except for the disturbed consciousness item, which was a 3. We chose the cut off  $\geq 6$  for a sensitivity and specificity of 0.78 and 0.56, respectively. The PPV was 0.15 and the NPV, 0.96. The AUC was 0.75.

### Conclusion:

We have designed a pre-hospital telephone score for the prediction of LVO in a suspected stroke population that is both simple and efficient. A prospective study is underway to evaluate the external validation.