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A. ter Schiphorst, Claire Duflos, I. Mourand, N. Gaillard, C. Dargazanli, L. Corti, P. Prin, A. Lippi, X. Ayrignac, M. Charif, et al.

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Ter Schiphorst Adrien, MD[1], Duflos Claire, MD, PhD[2], Mourand Isabelle, MD[1], Gaillard Nicolas, MD[1], Dargazanli Cyril, MD[3], Corti Lucas, MD[1], Prin Pauline, MD[1], Lippi Anaïs, MD[1], Ayrignac Xavier, MD[1], Charif Mahmoud, MD[1], Wacongne Anne, MD[4], Bouly Stéphane, MD[4], Lalu Thibault, MD[5], Sablot Denis, MD[6], Blanchet-Fourcade Genevieve, MD[7], Landragin Nicolas, MD[8], Jacob François, MD[9], Sayad Christophe, MD[10], Derraz Imad, MD[3], Cagnazzo Federico, MD[3], Lefevre Pierre-Henri, MD[3], Gascou Grégory, MD[3], Beaufils Olivier, MD[11], Costalat Vincent, MD, PHD[3], Arquizan Caroline, MD[1*]

1: Department of Neurology, CHRU Gui de Chauliac, Montpellier, France; 2: Clinical Research and Epidemiology Unit, CHU Montpellier, University Montpellier, Montpellier, France, 3: Department of Neuroradiology, CHRU Gui de Chauliac, Montpellier, France; 4: Department of Neurology, CHRU Carémeau, Nîmes, France; 5: Department of Neurology, CH de Béziers, France; 6: Department of Neurology, CH de Perpignan, France; 7: Department of Neurology, CH de Narbonne, France; 8: Department of Neurology, Clinique du Millénaire, Montpellier, France; 9: Emergency Department, CH de Millau, France, 10: Emergency Department, CH de Mende, France, 11: Emergency Department, CHRU Gui de Chauliac, Montpellier, France

***Corresponding Author:**

Full name: Caroline Arquizan

Address: Service de Neurologie, 80 Avenue Augustin Fliche, 34295 Montpellier, France

Email: c-arquizan@chu-montpellier.fr

Telephone number: 0033467337413

ABSTRACT:

Background and Purpose: The best transportation strategy for patients with suspected large vessel occlusion (LVO) is unknown. Here, we evaluated a new regional strategy of direct transportation to a Comprehensive Stroke Center (CSC) for patients with suspected LVO and low probability of receiving intravenous thrombolysis (IVT) at the nearest Primary Stroke Center (PSC).

Methods: Patients could be directly transported to the CSC (bypass group) if they met our pre-hospital bypass criteria: high LVO probability (i.e., severe hemiplegia) with low IVT probability (contraindications) and/or travel time difference between CSC and PSC <15 minutes. The other patients were transported to the PSC according to a "drip-and-ship" strategy. Treatment time metrics were compared in patients with pre-hospital bypass criteria and confirmed LVO in the bypass and drip-and-ship groups.

Results: In the bypass group (n=79), 54/79 (68.3%) patients met the bypass criteria and 29 (36.7%) had confirmed LVO. The positive predictive value of the hemiplegia criterion for LVO detection was 0.49. In the drip-and-ship group (n=457), 92/457 (20.1%) patients with confirmed LVO met our bypass criteria. Among the 121 patients with bypass criteria and confirmed LVO, direct routing decreased the time between symptom discovery and groin puncture by 55 minutes compared with the drip-and-ship strategy (325 vs 229 minutes, $p<0.001$), without significantly increasing the time to IVT ($p=0.19$).

Conclusions: Our regional strategy led to the correct identification of LVO and a significant decrease of the time to mechanical thrombectomy, without increasing the time to IVT, and could be easily implemented in other territories.

Keywords: Stroke, Fibrinolysis, Thrombectomy, Brain ischemia, Endovascular Treatment

ABBREVIATIONS:

AIS: Acute Ischemic Stroke

CSC: Comprehensive Stroke Center

EMS: Emergency Medical Services

ICH: Intracranial Hemorrhage

IVT: Intravenous Thrombolysis

LVO : Large Vessel Occlusion

MT : Mechanical Thrombectomy

NIHSS: National Institutes of Health Stroke Scale

PSC: Primary Stroke Center

PPV: Positive Predictive Value

mTICI: modified Thrombolysis In Cerebral Ischemia

TTC: Tele-Thrombolysis Center

1. INTRODUCTION

Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) are recommended for patients with acute ischemic stroke (AIS), but their benefit for disability reduction is highly time-dependent[1–10]. International guidelines recommend the development of regional stroke care systems to administer IVT, and possibly MT, with the shortest possible delay[1,11]. The current most used pre-hospital organization model is the 'drip-and-ship strategy' in which patients are transported to the closest primary stroke center (PSC) for IVT initiation, followed by a rapid transfer to a comprehensive stroke center (CSC) with an MT facility for patients with large vessel occlusion (LVO).

An ongoing question concerns the potential advantage of the direct transfer to the CSC (mothership strategy) to shorten MT times[11–14]. Indeed, the drip-and-ship strategy might cause a considerable delay to MT[10,14,15], with door-in to door-out times up to 106 minutes at the PSC[12], leading to ineligibility for MT in up to 45% of patients with AIS[16,17]. Conversely, the mothership strategy could increase the time to IVT and reduce the percentage of patients eligible for IVT. Observational studies in which the two strategies were compared reported controversial results concerning the patient outcomes[14,15,18,19], and the findings of ongoing randomized controlled trials are not available yet. Nevertheless, patients with high suspicion of LVO and known IVT contraindication in the pre-hospital setting could benefit most from direct transportation to the CSC, as suggested by the Society of Neurointerventional Surgery, regardless of travel times[20]. However, no study has evaluated this strategy. In addition, this strategy is based on the pre-hospital selection of patients with high suspicion of LVO, to prevent overflow of interhospital transport and CSC, but an accurate and widely used pre-hospital clinical scale to screen patients eligible for MT is lacking [21–24].

In this study, we present our regional strategy based on the direct transfer to the CSC of all patients with high pre-hospital suspicion of LVO ("hemiplegia criterion") and low probability of IVT at the nearest PSC or low time difference between transportation to the CSC and the PSC. Our primary objective was to assess the positive predictive value (PPV) of our pre-hospital "hemiplegia criterion" to detect LVO. The second aim was to compare time metrics between stroke onset and recanalization treatments (IVT, MT) in patients with LVO transported directly to the CSC and in patients with LVO who followed the drip-and-ship strategy.

2. MATERIAL AND METHODS

For this retrospective study, data were extracted from our prospective database of consecutive patients admitted to the Montpellier CSC between January 2016 and December 2017. This study was approved by the local institutional review board of University Hospital Center of Montpellier, France (IRB-MTP-2020-01-201900270). Informed consent was waived by the local institutional review board due to the study observational design.

2.1. Regional pre-hospital strategy

The Occitanie-East region in the South of France extends over 36 216 km² and has an estimated population of 3 million inhabitants. During the study period, Montpellier University Hospital Center was the only CSC with neuro-interventional facilities. IVT could be administered in five other PSCs and in two tele-thrombolysis centers (TTC) in community hospitals (Figure 1).

The drip-and-ship strategy was used for patients outside the Montpellier area. Patients with suspected AIS ("stroke alert") were first transported to the closest PSC/TTC, and then to the CSC if LVO was detected by imaging. Since 2016, a partnership between emergency medical services (EMS), CSC and PSC/TTC led to a new regional protocol that includes also a "direct CSC" strategy for patients outside the Montpellier area who meet our pre-hospital bypass criteria. These bypass criteria, designed for non-medical emergency services, are: autonomous patient living at home (i.e., a patient living at home, being independent in everyday life, walking without human assistance, corresponding to a pre-stroke modified Rankin scale ≤ 2) with suspected LVO, defined as a patient "suddenly not moving half of his/her body" ("hemiplegia criterion") within 6 hours of symptom discovery AND one of the following criteria: a) known pre-hospital contraindication to IVT (e.g. anticoagulant therapy, recent surgery with presumed high risk of bleeding, hemorrhage), b) estimated time between stroke onset and arrival at the PSC >3h30, leading to low chance of receiving IVT, c) unknown stroke onset time, d) time difference between direct transport to the CSC and transport to the nearest PSC/TTC <15 minutes, with the best available transport (e.g. helicopter, ambulance).

Patients fulfilling the pre-hospital bypass criteria should be directly transferred to the CSC.

2.2. Access to MT at the CSC

All patients referred for a “stroke alert” to the CSC (i.e., patients from the Montpellier area or patients in the “direct CSC” group) were admitted to the emergency room, with immediate neurological evaluation (National Institutes of Health Stroke Scale -NIHSS-, and screening for IVT contraindications), blood testing, ECG and vital parameters. Cerebral and non-invasive vascular imaging (computed tomography angiography or contrast-enhanced magnetic resonance angiography) were quickly performed. For patients with LVO, MT was discussed between the stroke neurologist and the interventional neuroradiologist. If indicated, according to international guidelines [1], IVT was performed in the angiosuite, as a bridging therapy.

Patients in the drip-and-ship group with LVO confirmation at the PSC/TTC were directly transferred to the angiosuite after NIHSS evaluation by the stroke neurologist upon arrival at the CSC. Imaging was performed again if the time between initial imaging and CSC admission was >3 hours, or for patients with a significant clinical change during transfer (defined by a NIHSS score change ≥4 points). Patients in the direct CSC group without LVO confirmation and patients in the drip-and-ship group without confirmation of the MT indication at the CSC were transferred to the PSC/TTC on the same day. After MT, patients were initially hospitalized at the CSC for 24 hours, and then rapidly transferred to the PSC/TTC.

2.3.Assessment of bypass criteria by expert reviewing

During the implementation phase of the regional bypass criteria, procedural violations were observed. Specifically, some patients outside the Montpellier area who met the bypass criteria were admitted to the PSC/TTC instead of being directly transported to the CSC, and some patients were directly transported to the CSC, although not filling the criteria. Two investigators (ATS, CA), blinded to the final diagnosis of the stroke alert for the “Direct CSC” group and to the recanalization treatment, classified all patients in the “direct CSC” and “drip-and-ship” groups as meeting or not the bypass criteria (hemiplegia and presence of an associated condition), based on the pre-hospital evaluation. Any discrepancy between investigators was resolved by consensus adjudication.

2.4.Patient population

All consecutive patients admitted to the CSC for a stroke alert or transferred from a PSC/TTC because of LVO-related AIS between January 2016 and December 2017 were included in the registry (Figure 2). LVO was defined as an occlusion of the intracranial carotid artery, M1 or

proximal M2 segments of the middle cerebral artery, or basilar artery. As this study aim was to assess the pre-hospital regional strategy and the reliability of the bypass criteria, patients with a stroke alert occurring in the Montpellier area (and thus directly admitted to the CSC), and patients with in-hospital AIS were excluded.

The remaining patients (drip-and-ship strategy, and direct CSC) were divided in three groups: i) Group A or "direct CSC" group: all patients directly admitted to the CSC. In this group, the positive predictive value (PPV) of the pre-hospital "hemiplegia criterion" for LVO, the adherence to the bypass criteria (i.e. the hemiplegia criterion and one associated condition), and the final diagnosis were evaluated; ii) Group B: patients with a drip-and-ship strategy and pre-hospital bypass criteria confirmed by expert review (ATS, CA), time between symptom discovery and EMS call <6 hours, and confirmed LVO; and iii) Group C: patients from Group A with pre-hospital bypass criteria confirmed by expert review (ATS, CA), time between symptom discovery and EMS call <6 hours, and confirmed LVO. The patients' characteristics, treatments, and time metrics between stroke onset and recanalization treatments (IVT, MT) were compared in groups B and C (second study aim).

2.5.Data collection

The following data were systematically recorded:

* Group A: bypass criteria (i.e. the hemiplegia criterion and one associated condition); final diagnosis of the stroke alert: AIS, intracranial hemorrhage (ICH), or stroke mimic.

* Groups B and C: a) clinical data: age, sex, NIHSS score at the PSC/TTC (Group B) and at the CSC for all patients; b) imaging data: imaging modality at the PSC/TTC and CSC, LVO side and site, recanalization or thrombus migration between PSC/TTC and CSC; c) treatments: IVT, MT, or reasons for not performing these treatments, time metrics, modified Thrombolysis In Cerebral Ischemia (mTICI) score[25]; d) NIHSS score at 24 hours.

2.6.Statistical analysis

Dichotomous data are presented as percentages, and continuous variables as medians with first and third quartiles (Q1 and Q3). Univariate analysis was performed using the non-parametric Wilcoxon-Mann-Whitney test for continuous variables, and the Fisher's exact test for categorical variables.

All tests were considered significant for a bilateral $\alpha < 0.05$, and data were analyzed using SPSS Statistics Version 25 (IBM, Armonk, NY) and SAS9.4.

The mean times were computed in groups B and C, and time differences between groups, adjusted for confounding factors, were evaluated using the mixed procedure and the LSMEANS statement (SAS 9.4). Potential confounding factors were preselected following univariate comparison of groups and clinical features. Age, sex, area of origin, unknown stroke onset time, estimated time between known stroke onset and arrival at the PSC/TTC >3h30, additional transport time to CSC <15 minutes, known IVT contraindication, first NIHSS score, and LVO side, were included in all models. In addition, IVT was included in the three models that analyzed the times from symptom discovery/first imaging/CSC arrival to groin puncture. Finally, potential confounders were kept in the models if their adjusted p-value was <0.10. Confidence intervals (95% CI) for the adjusted time metrics and differences are provided.

3. RESULTS

Between January 2016 and December 2017, 3056 consecutive patients were admitted to the Montpellier CSC for a stroke alert (patients from the Montpellier area and "direct CSC" patients) or were transferred from a PSC/TTC when LVO was confirmed by imaging (drip-and-ship strategy) (Figure 2).

3.1.Direct CSC patients (Group A).

Among the 79 patients admitted directly to the CSC instead of the closest PSC/TTC (Group A), the final diagnosis was AIS in 49 (62%), caused by LVO in 30 (38%), ICH in 18 (23%), and stroke mimics in 12 (15%). Among the 54 patients (69%) who met both pre-hospital bypass criteria (i.e. hemiplegia and associated condition), 37 (69%) had AIS among whom 29 (54%) due to LVO, 14 (26%) had ICH, and 3 (6%) stroke mimics. Twenty-five patients did not meet the direct CSC criteria: 18 patients (72%) had no pre-hospital hemiplegia, and 11 (44%) did not have the second criterion (4 patients had none of these criteria). Among these patients, 12 (48%) had AIS caused by LVO in one (4%), 9 (36%) had stroke mimics, and 4 (16%) ICH.

Among the 61 "Direct CSC" patients with hemiplegia (77%), 30 (49%) had LVO, thus giving a PPV for LVO identification of 49%. None of the 18 patients without hemiplegia had LVO.

The associated condition in Group A was: known pre-hospital IVT contraindication (n=31 patients, 39%: n=29 anticoagulation treatment, n=1 recent femur fracture surgery, n=1 recent ankle fracture), unknown stroke onset time (n=23, 29%), additional transport time <15

minutes (n=21; 27%), estimated delay between stroke onset and arrival to PSC >3h30 (n=9; 11%). Multiple associated conditions were possible. Eleven patients (14%) had no associated condition.

Among the 31 patients with pre-hospital IVT contraindication, oral anticoagulants intake was the cause, in 29 patients. Among them, 9 patients had ICH (of whom 8 (89%) had effective anticoagulation), 4 had stroke mimic. Among the 16 patients with AIS and pre-hospital anticoagulation, 8 (50%) had a biological contra-indication to IVT due to anticoagulants intake, 3 (19%) were treated by IVT) and 5 had no biological contra-indication but a contra-indication to IVT (2 had recent stroke on imaging, 2 had FLAIR positive wake-up stroke, one patient was recanalized with thrombectomy before the biological results).

3.2.Patients with bypass criteria and LVO: characteristics, times and recanalization treatment in Groups B and C

Among the 457 patients transferred from a PSC/TTC to the CSC for LVO-related AIS, 92 (20%) fulfilled the pre-hospital bypass criteria, although first admitted to the closest PSC/TTC (Group B) (Figure 2). In Group A, 29 patients fulfilled the bypass criteria and had LVO-related AIS (Group C). These 121 patients had LVO-related AIS outside the Montpellier area, with pre-hospital bypass criteria confirmed by expert review. Comparison of Groups B and C (Table 1 and Figure 3) did not highlight any significant difference in terms of age, sex and NIHSS score. Six (21%) patients in “Group C” and 25 (27%) in “Group B” received IVT at the CSC and at the PSC/TTC, respectively. The most frequent pre-hospital associated criterion for “direct CSC” was low probability of IVT (90% of “Group C” and 92% of “Group B” patients). The criterion “Additional transport time to the CSC ≤15 minutes” was retained for 31% and 12% of patients in Group C and Group B, respectively.

Comparison of the different time metrics in Groups B and C (Table 2) showed that during the study period, the “direct CSC” strategy allowed reducing the time between symptom discovery and groin puncture by about 55 (adjusted) and 100 minutes (unadjusted metrics), compared with the drip-and-ship strategy, without any significant increase of the time to IVT (n=6 patients, 21%, in Group C, and n=25, 27%, in Group B). The time between first symptoms and arrival to the CSC was reduced by approximately 100 minutes in Group C compared with Group B. The time between first imaging and thrombolysis was similar in both groups. Concerning MT, 16 “Group B” patients did not have MT (17%), among whom 7 (8%) had recanalization (n=5 of the 25 (20%) drip-and-ship patients treated by IVT). In

Group C, 24 (83%) patients underwent MT and 5 did not (n=2 without clinical-imaging or diffusion-perfusion mismatch, and n=3 with large infarct).

4. DISCUSSION

To the best of our knowledge, this is the first large study about a new regional strategy for selecting patients with suspected LVO and low probability of having IVT or short time difference between transportation to the CSC and PSC to be directly transported to the CSC. During the study period, our regional strategy led to the correct identification of LVO and a significant MT time decrease in the group of directly transported patients, without increasing the time to IVT or decreasing the proportion of patients treated by IVT compared with patients in the drip-and-ship group. Specifically, the "direct CSC" strategy (group C) reduced the time from symptom discovery to groin puncture by approximately 100 minutes, compared with the "drip-and-ship" strategy (group B), thanks to a drastic reduction of the pre-CSC time. We think that this time reduction was not due to differences in the initial management of the stroke alerts between CSC and TTC/PSC, because the times between first imaging (usually MRI in our region) and IVT were similar between group C and B. As MT benefit is time-dependent[8,9], this strategy could reduce the proportion of patients with disability and the costs for society[9,10,26].

There are two (drip-and-ship and mothership) strategies for patients with AIS and pre-hospital suspicion of LVO. The optimal strategy is unknown, but some observational studies suggest that the mothership strategy leads to faster MT times and better outcomes[14,18,27,28]. However, only patients treated by MT were included in one study, thus excluding patients recanalized after IVT at the PSC[14]. Moreover, other studies were performed in urban settings or in areas where PSC and CSC were not more than 20 minutes away[27,28]. Another study compared time metrics before and after stroke care re-organization, and the time reduction could be explained by the improved management[18]. The large randomized clinical trial RACECAT (NCT02795962) is currently testing the hypothesis that outcome is better in patients with suspected LVO managed according to the mothership strategy than the drip-and-ship strategy. Currently, the mothership strategy is not recommended for this population because of the lack of high-quality evidence.

4.1.Pre-hospital LVO prediction

Many scales have been developed to detect LVO-related AIS, essentially based on motor symptoms, aphasia, and/or other cortical symptoms[23]. However, none of them can detect LVO with high sensibility and sensitivity[23], and only few scales have been tested in pre-hospital settings, without head-to-head comparisons[27–35]. Thus, currently, there is no optimal instrument for LVO prediction[11,21,36]. Moreover, these scales require skilled personnel with prior training and are often time-consuming. In France, most pre-hospital transports are made by non-medical staff (ambulance drivers, firemen), without specific stroke training. Therefore, we chose "not moving one side of the body", a simple and pragmatic criterion for measuring the deficit severity, to identify LVO-related strokes. This pre-hospital criterion allowed the correct identification of LVO in 49% patients (PPV=0.49). Similar PPV values for LVO prediction (0.21 to 0.61) have been reported for more complicated scales tested in pre-hospital settings (all patient types with stroke alert, including stroke mimics and ICH, like in our study)[27–35] (**Table 3**). It should be noted that none of the 18 'direct CSC' patients without the "hemiplegia" criterion had LVO in our study, which suggests the need to respect this criterion, although some patients with LVO can present only minor deficits[37]. Our study was not designed to assess the specificity and sensitivity of our "hemiplegia" criterion for LVO identification (as data were not available for all patients without massive deficit in the pre-hospital setting), and we cannot exclude a lower sensitivity than other scales. A recent monocentric study in a PSC showed that this criterion can predict LVO with a sensibility of 0.88 and a specificity of 0.53. However, it only included highly selected patients with AIS admitted to the PSC and treated with IVT or transferred to the CSC for LVO[38].

Our results, suggesting that our strategy reduces the time to MT, are in favor of a strict respect of our criteria. Nevertheless, during the study period, many patients outside the Montpellier area were directly transferred to the CSC, although they did not meet the bypass criteria (to note, LVO was rare in these patients). Moreover, too many patients with pre-hospital bypass criteria were first admitted to a PSC/TTC. Indeed, only 24% of the 121 patients with LVO and bypass criteria (Group B + Group C) were directly transported to the CSC. To increase the proportion of patients with correct pre-hospital triage, the different involved actors (EMS, PSC and CSC) and dispatch officers must be regularly informed on procedures and better trained to identify LVO. If all patients filling the bypass criteria were transferred, assuming a constant PPV of 0.49, about 250 patients would have been sent directly to the CSC during the study period (2 years). In addition, because patients not

undergoing MT are transferred to the PSC/TTC the same day and patients with MT are transferred the day after, this number of patients would not have exceeded our CSC capacity.

4.2.Pre-hospital strategy

The innovative aspect of our study is that our strategy can be applied regardless of the results of the RACECAT study because we focus only on the population with suspected LVO and low IVT probability to avoid futile admissions to a PSC/TTC. During the study period, 79 patients (Group A) were selected for the “direct CSC" procedure. The Society of Neurointerventional Surgery suggests to bypass patients with suspected LVO and known pre-hospital contraindications to IVT[20], but no study has tested this strategy yet.

Patients on anticoagulants were selected for direct transportation, based on the hypotheses that AIS is more frequent in these patients and that MT would be indicated and IVT contraindicated in most of them. This choice implies that some of the selected patients taking anticoagulants had ICH, and thus their direct transport to the CSC was not necessary. Among the 29 patients on anticoagulants in group A, 9 (31%) had ICH and 16 (55%) had AIS. These data comforted the choice of this criterion for bypass. However, among the 16 AIS patients wo were treated with anticoagulants, only 8 (50%) patients had effective anticoagulation after biological evaluation, and 3 (19%) were treated with IVT. To improve this criterion, it could be very interesting to add in our bypass decision the date of last medication-intake or values and date of the last INR to estimate the probability of the biological efficacy of these treatments.

A known hemorrhagic risk (i.e. recent surgery) and an estimated arrival time after the therapeutic window for IVT are ideal conditions to bypass patients, because the only possible treatment is MT. Other conditions included in our bypass strategy are more questionable. For instance, patients with unknown time of stroke onset were directly sent to the CSC, based on the hypothesis that most of them will not receive IVT, although IVT can be performed in patients with diffusion-weighted imaging-FLAIR mismatch[3]. Interestingly, the recent WAKE-UP trial, which demonstrated IVT benefit, showed that more than half of patients with wake-up stroke had FLAIR-positive stroke or other contraindications and did not receive IVT[3]. Similarly, in our population, 62% of patients with wake-up stroke did not receive IVT. Moreover, MT superiority compared with the best medical treatment has been demonstrated in selected patients with wake-up stroke and is highly time-dependent[6,7]. Therefore, we think that the “direct CSC” strategy might be more suitable for patients with

wake-up stroke because the risk of receiving neither IVT nor MT would be higher with the drip-and-ship strategy.

Another bypass criterion was similar or additional transport time to the CSC <15 min compared with the PSC/TTC. This 15-minute cut-off was based on the hypothesis that a small additional delay for IVT would be compensated by the reduction of the time to MT. This was comforted by the recent American Stroke Association recommendation update of direct transport to a CSC in case of additional travel time <15 minutes [36]. Some studies even suggest extending this cut-off. Using a mathematical model, Schlemm et al suggested to send patients directly to a CSC if the additional delay to IVT is <30 minutes in urban and 50 minutes in rural settings[39]. This cut-off could be increased to 56 minutes in patients with symptom onset <24h [40], and even to 32 or 99 minutes for patients with high suspicion of LVO [41].

4.3.Limitations

Our study has some limitations. First, it was a retrospective study, although data were extracted from a prospective database. Second, not all patients fulfilling the bypass criteria were directly transported to the CSC. This could be explained by mistakes linked to the recent implementation of the pre-hospital criteria, but also by the initial characteristics of the patients, thus suggesting that groups B and C may not be comparable. However, the initial characteristics (i.e. severity of the deficit at admission, ASPECT score, site of occlusion) were comparable between these groups. To reduce this bias, some baseline characteristics, although not significantly different between groups, were included in the multivariate analyses that confirmed the results of the univariate analysis. Third, the PPV for LVO was estimated using only the data of patients who went directly to the CSC (Group A). Indeed, LVO was confirmed in all patients in the drip-and-ship category, but data were missing for patients with pre-hospital bypass criteria addressed to a PSC/TTC and without LVO. Thus, PPV was calculated using data from a subgroup of all patients with bypass criteria, and this could have led to an overestimation of its value. Fourth, as our strategy was evaluated only in one region, our results can only be generalized in similar regions where most of the PSC/TTC are located at less than 90 minutes from the CSC. Fifth, the potential benefit for AIS patients with our strategy could be counterbalanced with the potential deleterious influence on the functional outcome of patients with ICH, as time between symptoms and first imaging was increased between 46 minutes (unadjusted analysis) and 60 minutes (adjusted analysis), thus delaying the specific management of these patients (anti-hypertensive drugs, anticoagulation

antagonization, surgery). This important question needs to be evaluated on future studies focusing on mothership strategies. Finally, our sample was relatively small, although extracted from a large database.

5. CONCLUSION

Our regional strategy, based on the direct transport to the CSC of all patients with high pre-hospital suspicion of LVO (hemiplegia), and low probability of IVT or low additional transport time to the CSC led to the correct identification of LVO in half of them and a significant decrease of the time to MT, without increasing the time to IVT. Independently of the RACECAT study findings, as our criteria for direct transport are very simple, our strategy could be easily implemented elsewhere and immediately, without the need of long and expensive training of the personnel involved in the pre-hospital management. Nevertheless, it requires a good stroke care organization, close coordination between EMS, PSC, CSC, and strict respect of the bypass criteria.

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Declarations of interest

None

Authors' contributions

Caroline Arquizan and Adrien ter Schiphorst planned the study data collection, identified the patient cohort, gathered the data and drafted the manuscript; Claire Duflos did the statistical analysis. All authors contributed to data collection, made suggestions on analysis and approved the final manuscript. They all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and material

The data supporting the study findings are available from the corresponding author upon reasonable request.

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TABLES

Table 1: Comparison of Group B and Group C (univariate analysis)

	Drip-and-ship patients with "direct CSC" criteria (Group B, 92 patients)	"Direct CSC" patients with "direct CSC" criteria and LVO (Group C, 29 patients)	p-value
Age, median (Q1-Q3), years	77 (66-83)	72 (61-79)	0.16
Women, n (%)	52 (57)	14 (48)	0.52
First NIHSS (Q1-Q3)	19 (15-22)	19 (13-23)	0.86
Type of large vessel occlusion, n (%)			0.28
Middle cerebral artery (M1 or M2)	61 (66)	15 (52)	
T- or L- occlusion	28 (30)	13 (45)	
Basilar artery	3 (3)	1 (3)	
Second "Direct CSC" criterion†, n (%)			
Known contraindication to IVT	26 (28)	13 (45)	0.11
Estimated delay between known stroke onset and arrival to PSC/TTC >3h30	7 (8)	4 (14)	0.29
Unknown stroke onset time	56 (61)	12 (41)	0.09
Additional transport time to Montpellier CSC <15 minutes	11 (12)	9 (31)	**0.023**
Area of origin (see Figure 1), n (%)			**0.001**
Nîmes	33 (36)	19 (66)	
Perpignan	22 (24)	1 (3)	
Narbonne	14 (15)	1 (3)	
Béziers	8 (9)	1 (3)	
Millénaire	8 (9)	1 (3)	
Mende	3 (3)	6 (21)	
Millau	4 (4)	0 (0)	
Thrombolysis, n (%)	25 (27)	6 (21)	0.63

Reasons of no thrombolysis, n (%):			-
Wake-up stroke without diffusion-weighted imaging-FLAIR mismatch or without MRI	34 (36)	8 (28)	
Effective anticoagulation	20 (22)	8 (28)	
Stroke symptoms >4.5h	7 (8)	5 (17)	
Large infarct	5 (5)	3 (10)	
Other‡	5 (5)	3 (10)	
Mechanical thrombectomy, n (%)	76 (83)	24 (83)	0.55
mTICI 2b-3, n (%)	75 (74)	16 (67)	0.60
Causes of no thrombectomy, n (%)§			-
Recanalization or thrombus migration	7 (8)	-	
Absence of clinical-imaging or diffusion-perfusion mismatch	5 (5)	2 (7)	
Clinical trial – medical group	4 (4)	0 (0)	
Large infarct	2 (2)	3 (10)	
Time metrics, median (Q1-Q3), minutes			
Symptom discovery - first imaging	128 (93-185)	174 (146-236)	**0.001**
Symptom discovery - CSC admission	265 (222-355)	142 (110-206)	**<0.001**
Symptom discovery - thrombolysis	165 (130-195)	185 (168-212)	0.19
Symptom discovery - groin puncture	325 (251-415)	229 (200-314)	**<0.001**
First imaging - thrombolysis	33 (21-50)	29 (24-46)	0.93
First imaging - groin puncture	184 (151-218)	53 (42-67)	**<0.001**
CSC admission - groin puncture	49 (29-70)	78 (57-96)	**<0.001**

†The total number can exceed the number of patients because they could have more than one second criterion. ‡Other includes recent stroke, bleeding, fracture, blood glucose >22 mmol/L. §The total number can exceed the number of patients because they could have various contraindications to IVT. The number of drip-and-ship patients with only "known contra-indication for IVT" was 23 (25%) in the Group B and 11 (38%) in the Group C. Abbreviations: CSC = Comprehensive Stroke Center, NIHSS = National Institutes of Health Stroke Scale, PSC = Primary Stroke Center, mTICI = modified Thrombolysis in Cerebral Infarction, TTC = Tele-Thrombolysis Center.

Table 2: Adjusted time metrics in 'Group B' and 'Group C'

	Group B	Group C	Difference		
Time, minutes	mean±SD	mean±SD	mean±SD	95% CI	p-value
Symptom discovery - First imaging†	209 ± 11	269 ± 15	60 ± 14	[33;87]	**<0.0001**
Symptom discovery - CSC arrival†	360 ± 13	251 ± 17	-109 ± 15	[-140;-79]	**<0.0001**
Symptom discovery - Thrombolysis	160 ± 10	190 ± 19	30 ± 22	[-14;74]	0.18
Symptom discovery - Groin puncture†	394 ± 19	339 ± 22	-55 ± 21	[-96;-13]	**0.01**
First imaging - Thrombolysis‡	49 ± 6	39 ± 9	-10 ± 10	[-31;11]	0.33
First imaging - Groin puncture§	200 ± 7	82 ± 12	-118 ± 12	[-142;-93]	**<0.0001**
CSC arrival - Groin puncture	54 ± 4	82 ± 6	29 ± 7	[14;43]	**0.0002**

†Models adjusted for area of origin, estimated time between known stroke onset and arrival to PSC/TTC >3h30, known contraindication to IVT, and LVO side; in addition, time from symptom discovery to groin puncture was adjusted for IVT. ‡Model adjusted for known contraindication to IVT. §Model adjusted for area of origin. Other models were not adjusted. Group B: "drip-and ship" strategy; Group C: "direct CSC" strategy. Abbreviation: CSC = Comprehensive Stroke Center.

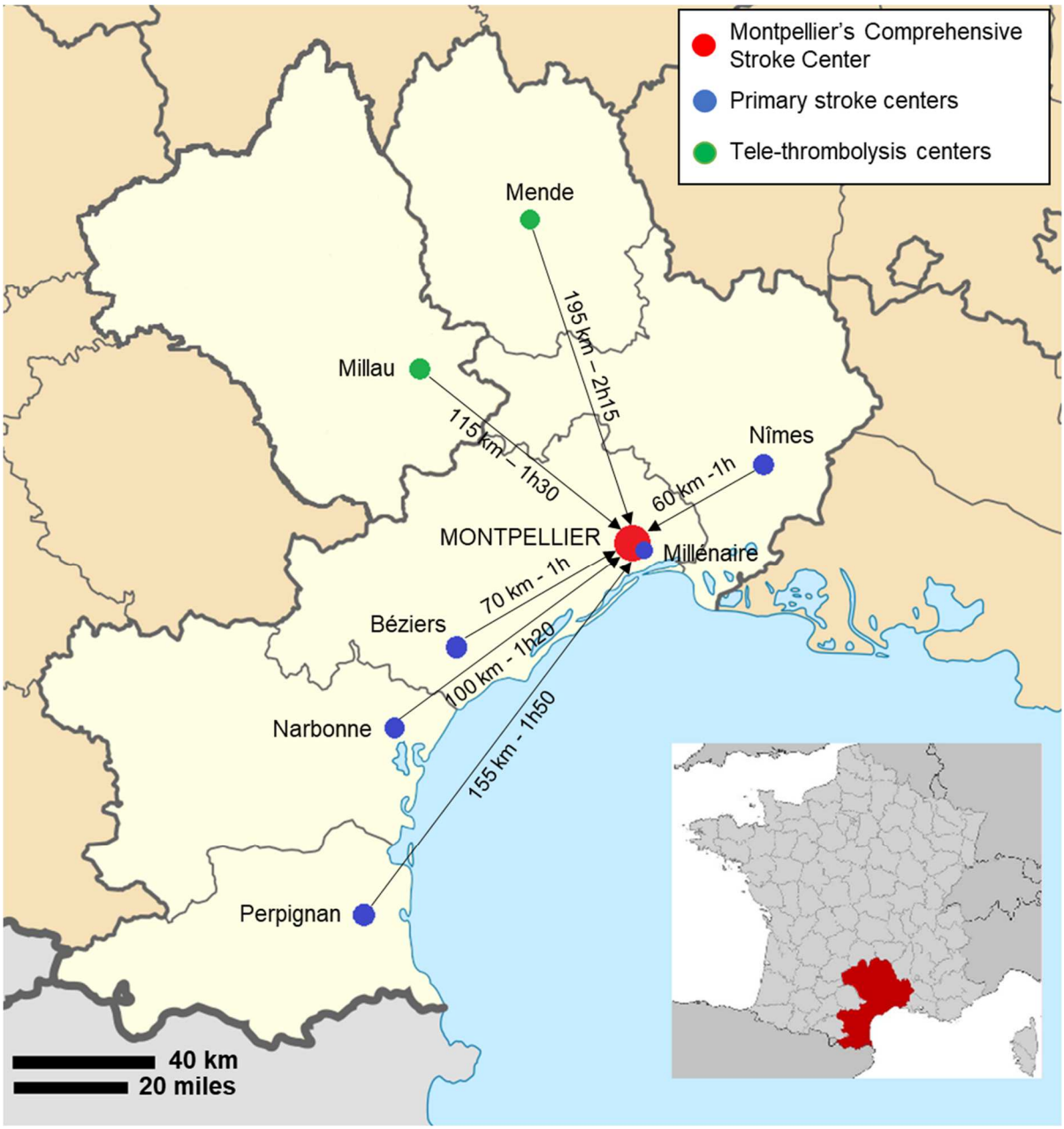
Table 3: Positive predictive value of prehospital scales for LVO in the field.

Scale, cut-off	Study, year	PPV for LVO
RACE ≥5	Pérez de la Ossa, 2014[29]	0.42
	Zaidi, 2017[27]	0.21
	Carrera, 2018[30]	0.35
	Dickson, 2019[31]	0.29
	Jumaa, 2019[32]	0.37
LAMS ≥4	Noorian, 2018[33]	0.48
	Helwig, 2019[34]	0.35
C-STAT ≥2	McMullan, 2017[35]	0.13
M-DIRECT ≥2	Rodríguez-Pardo, 2020[28]	0.61
"Hemiplegia criterion"	This study, 2021	0.49

Abbreviations: RACE = Rapid Arterial oCclusion Evaluation; LAMS = Los Angeles Motor Scale; C-STAT = Cincinnati Stroke Triage Assessment Tool; M-DIRECT = Madrid-Direct Referral to Endovascular Center; PPV = Positive predictive value

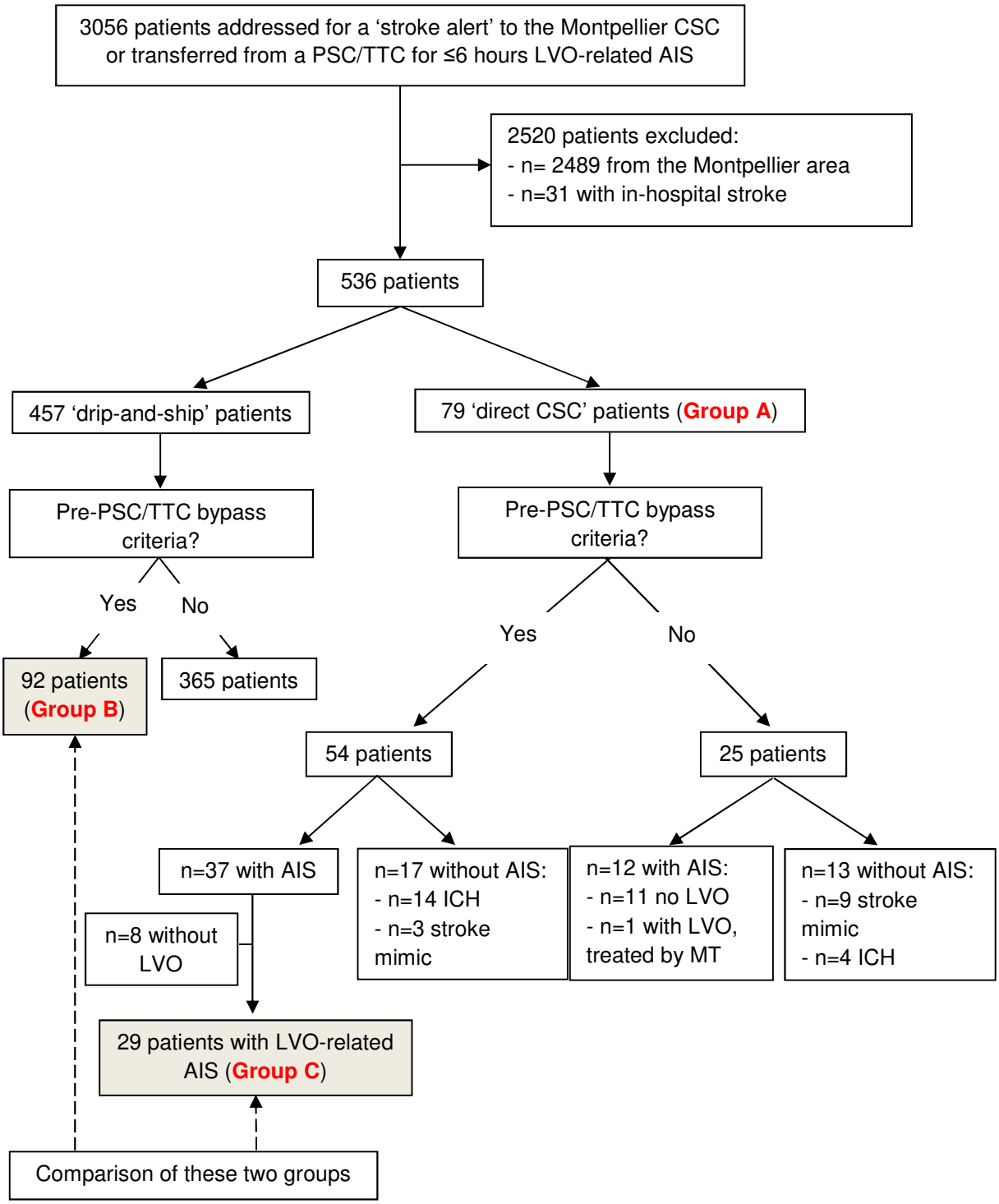
FIGURES

Figure 1: Map of the Occitanie-East region that includes five PSC, two TTC, and one CSC in Montpellier, and the distances with the estimated travel time by road (calculated using GoogleMaps®) between the PSC/TTC and CSC.



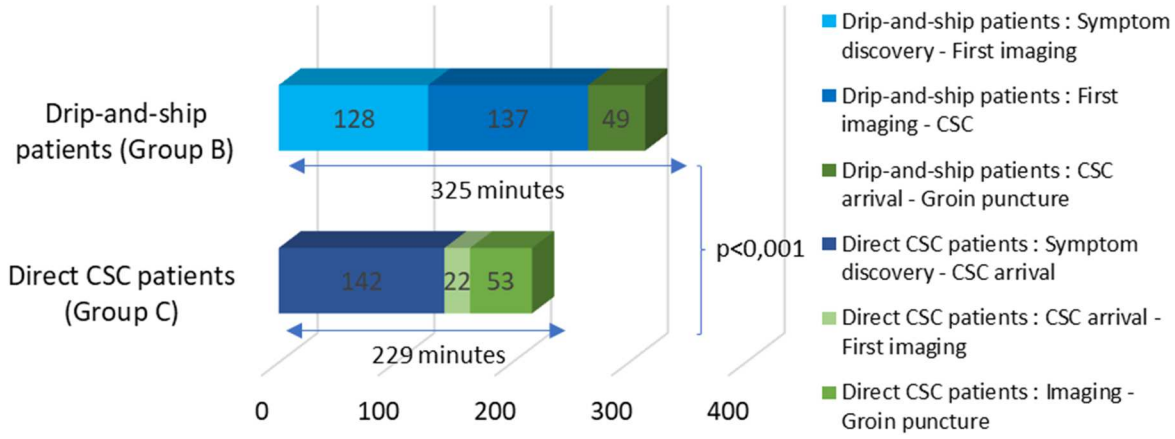
Abbreviations: CSC = Comprehensive Stroke Center; PSC = Primary Stroke Center; TTC = Tele-Thrombolysis Center

Figure 2: Study flow-chart



Abbreviations: AIS = Acute ischemic stroke; CSC = Comprehensive Stroke Center; ICH = Intracranial Hemorrhage; LVO = Large vessel occlusion; MT = Mechanical Thrombectomy; PSC = Primary Stroke center; TTC = Tele-Thrombolysis center

Figure 3: Median Times from stroke onset to groin puncture



Abbreviation: CSC = Comprehensive Stroke Center.