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ASSESSING THE EFFECTIVENESS OF OPTIMIZATION STRATEGIES IN HOSPITAL CARE FOR STROKE CODE: IMPLICATIONS FOR DOOR-TO-NEEDLE TIMES

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ABSTRACT:

Introduction: Time plays a crucial role in the success of reperfusion treatments for acute ischemic stroke. Despite clinical guidelines recommending prompt intervention, only about one-third of patients receive fibrinolysis within ≤ 60 minutes. This study aims to outline our experience in implementing a specific protocol for acute ischemic stroke treatment and assess its impact on door-to-needle times.

Methods: Starting at the conclusion of 2015, a series of measures were gradually introduced to reduce response times and optimize care for acute ischemic stroke. This included the implementation of a dedicated neurovascular team. Performance times were compared before (2013-2015) and after (2017-2019) the introduction of the protocol.

Results: A total of 182 patients were included before and 249 after the implementation of the protocol. With the introduction of all measures, the overall median door-to-needle time reduced to 45 minutes (previously 74 minutes, a 39% reduction, $p < 0.001$). Notably, 73.5% of patients were treated within ≤ 60 minutes, representing a 47% increase compared to the pre-protocol period ($p < 0.001$). The overall time to treatment (symptom-to-needle onset) decreased by an average of 20 minutes ($p < 0.001$).

Conclusions: The measures incorporated into our protocol led to a significant and sustained reduction in door-to-needle times, though opportunities for further improvement persist. Established mechanisms for outcome monitoring and continuous enhancement will pave the way for ongoing progress in acute ischemic stroke care.

KEYWORDS: Cerebrovascular Accident, Ischemic Stroke, Acute Stroke, Door-To-Needle Time, Intravenous Fibrinolysis

INTRODUCTION:

In recent years, there have been various advances in the treatment of acute ischemic stroke, including the implementation of mechanical thrombectomy and the expansion of the therapeutic window for reperfusion treatments. However, the aphorism "time is brain" remains valid since time continues to be a determining variable in the result. In the case of intravenous fibrinolysis (FBL-IV), every minute counts, with a number needed to treat (NNT) of 4 to achieve functional independence at 3 months in patients treated within the first hour and a half of starting treatment. Symptoms, compared to 14 for those treated 4.5 hours after onset (Kolls et al., 2024).

In this sense, clinical guidelines recommend performing FBL-IV within 60 minutes of the patient's arrival at the hospital (door-to-needle time [DPA]). Despite these recommendations, only approximately one-third of patients with acute ischemic stroke are treated in this time interval3-6. Recently, several studies have shown that implementing a specific protocol for treating acute ischemic stroke leads to a significant improvement in door-to-needle times and, consequently, in the functional prognosis of these patients at 3 months (Oostema et al., 2024).

With the arrival of clinical studies that have reliably demonstrated the benefit of endovascular treatment (EVT) in acute ischemic stroke at the Miguel Servet University Hospital (HUMS), it was decided to implement a series of measures in a protocolized manner to optimize care. The stroke code (IC) improves access times to the FBL-IV. It establishes the VTE as the autonomous community's reference centre (Roper, Cerilo, Bena, Morrison, & Siegmund, 2024).

OBJECTIVE:

The objective of this research is to describe these measures, our experience in their implementation, and evaluate their impact on hospital care times in the IC.

METHODOLOGY:

Study design and population Descriptive before-after, non-controlled study, consisting of a pre-implementation period of the protocol and its measures (pre-IC period, from January 1 2013 to September 30 2015) compared to the post-implementation period of all its measures (post-CI period, from March 1, 2017, to December 31 2019). All patients with an acute neurological focus who arrived at the HUMS emergency department and were treated with FBL-IV between January 1, 2013, and December 31, 2019, were included. Patients transferred from another hospital or with acute ischemia were excluded from hospital stroke since, in both cases, the care circuits are structured in different and variable ways (for example, a patient transferred from another centre with already a brain CT scan done) (Kim et al., 2024; Paolucci et al., 2023).

Intervention:

In the present study, the intervention consisted of implementing a series of planned measures (Table 1) for the treatment of IC at the HUMS between October 2015 and March 2017, the date on which the intervention was implemented. The last planned measure is the unified Neurovascular-Aragonese Guard, composed of a pool of neurologists coming from the different hospitals of Aragon, who work personally at the HUMS until 9 pm and then locally until 8 am the following day, going as far as managing the care of all ICs arriving at our hospital, including endovascular VTEs and also telestroke care from other hospitals in the autonomous community (Hwong et al., 2024).

MEASURES/ACTIONS	PRE-CI	POST-CI
Population Awareness	There are no scheduled activities.	Semi-annual activities with the patient association. Promotion of recognizing warning signs and disseminating the stroke code in the population and through the media regularly.
Staff Training	There are no scheduled activities.	Regulated training for 061 personnel, emergencies and on-call equipment
Establishment Of Neurovascular Guard-Aragón	A general neurologist treats stroke codes in addition to other neurological emergencies.	CIs are cared for by neurologists from the Neurovascular Guard-Aragón.
Pre-Notification	The ambulance (061) calls the hospital's Emergency Service. Once the Emergency doctor sees the patient, the general neurologist is called, notifying him of the stroke code.	061 directly calls the neurovascular neurologist on call, and activation
Medical Record	The patient's data and history are collected upon arrival at the Emergency Room.	Collect all possible data and a checklist of contraindications for FBL-IV before the patient arrives at the emergency room.
TC Registration And Request	Brain CT is ordered only after the patient has arrived at the hospital and been seen by an emergency doctor.	Advance notice and reservation of CT room. Data logging and TC request as soon as the patient arrives simultaneous with its evaluation
Laboratory	Blood tests are obtained in the emergency room before starting FBL-IV, r-tPA is administered with blood glucose results, and INR is only waited for in cases of known or suspected anticoagulation.	061 directly calls the neurovascular neurologist on duty to notify and activate the stroke code
Route IV	If not inserted in the emergency room, the IV line is usually available upon arrival.	Without changes
Direct To TC	Upon arrival, the patient is moved to an emergency room bed before beginning care.	The patient goes on the ambulance stretcher directly to the CT.
FBL-IV On CT Table	After the brain CT, the patient returns to the emergency room, where FBL-IV is indicated and begins to prepare medication and doses to administer.	r-tPA and material are brought to prepare and administer FBL-IV on the CT table (it is prepared and administered once the decision to FBL-IV has been made)
FBL-IV: intravenous fibrinolysis; post-IC: post-protocol implementation period. CT: computed tomography; pre-IC: period protocol pre-implementation; r-tPA: recombinant tissue plasminogen activator. Of the proposed measures, it was the only one that could not be implemented on a continuous basis.		

Table 1 Comparison of measures and actions for stroke code (IC) care between the pre-and post-implementation periods of CI protocol

Data Collection And Definitions:
From January 1, 2013, to December 31, 2019, data were prospectively collected on all fibrinolysis performed in our hospital, the time of onset of symptoms (in strokes with known time of onset), the time of arrival at the emergency room rescue, brain CT scan, administration of FBL-IV and the intervals derived from these times: out-of-hospital time (ETH, time from the onset of symptoms, in those with known onset time, until arrival at hospital), door time -to-CT (cTPT, time from when the patient arrives at the emergency room until he arrives at the brain CT) and APT (time from when the patient arrives at the emergency room until the administration of the FBL bolus) (Härkönen et al., 2024; Shinoda et al., 2023).

IV) and the onset of symptoms needle time (TSA, time from the onset of symptoms to administration of the FBL-IV bolus). Among the essential characteristics recorded, we included age, sex, NIHSS scale score on arrival at the emergency room, whether or not VTE was present in addition to the FBL-IV, type of arrival at the emergency room (ambulance or own vehicle), whether the attention was paid during on-call hours and whether it was a working day or holiday (Daniel, Maillie, & Dhamoon, 2024).

Outcome Variables:
The primary outcome variable was the effect of implementing the stroke code protocol on ADT (median percentage of patients treated with ADT of 60 minutes or less). The percentage of patients treated with a TPA less than or equal to 45 minutes, TEH, TPTc, and TSA in the pre-CI and post-CI periods were determined as secondary variables. Additionally, we sought to determine which variables influenced the percentage of fibrinolyzed patients with a TPA less than or equal to 60 minutes (Kurniawan et al., 2024).

Statistic Analysis:
The qualitative variables were described using the frequency distribution of the percentages of each category. For the quantitative variables, indicators of central tendency (mean or median) and dispersion (standard deviation or interquartile range [IQR]) were used, depending on whether or not they followed a normal distribution, determined using the Kolmogorov-Smirnov test (Aziz & Khatri, 2024).

For inferential analysis, we used the following hypothesis contrast tests: chi-square to compare proportions when both were qualitative. Student's t-test or ANOVA to compare means when one was quantitative (Mann-Whitney or Kruskall U test -Wallis if they have done so, they do not follow a normal distribution) (Mayer-Suess et al., 2024).

Data were processed using SPSS 21 statistical packages (IBM SPSS Statistics 21.0.0.0, New York, NY, USA).

RESULTS:
During the study period (January 2013-December 2019), 607 patients were fibrinolysed in our hospital; 543 met the inclusion criteria and did not have the previously mentioned exclusion criteria. Of these, 182 (33.5%) were performed in the pre-IC period and 249 (45.9%) in the post-IC period (Fig. 1) (Strilciuc, Ruban, Kalinin, Kalinin, & Khasanova, 2024).

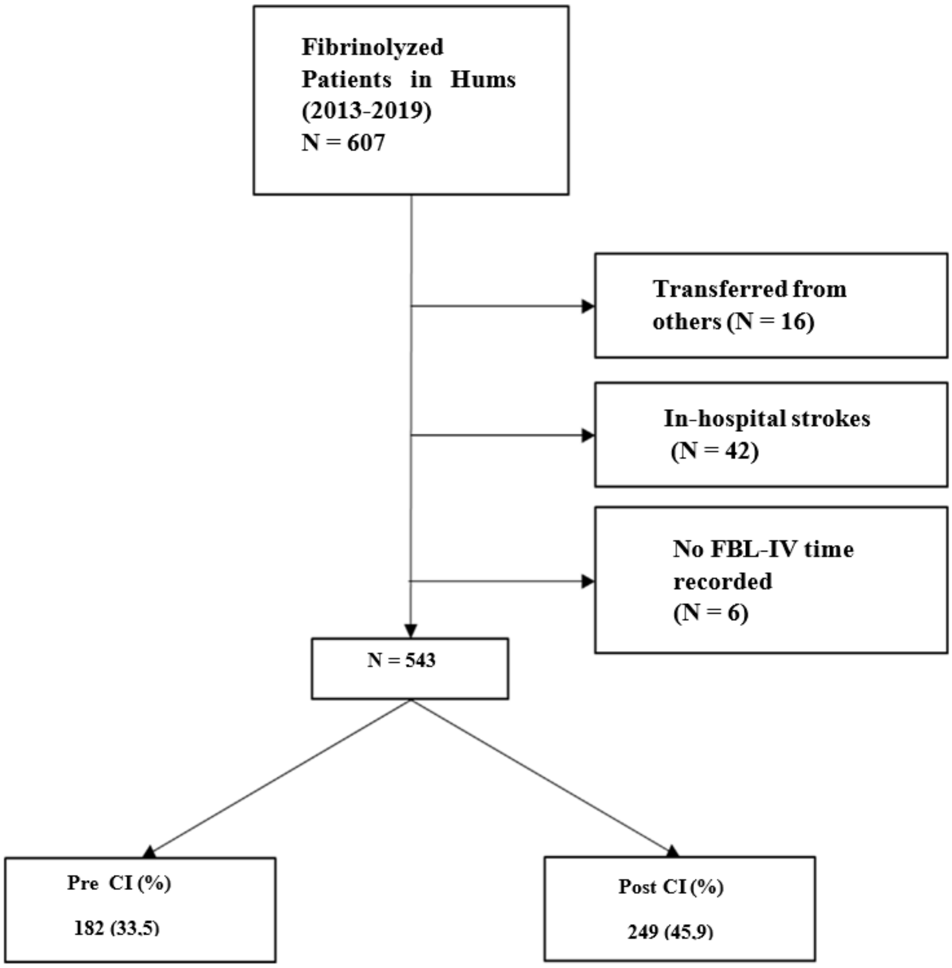

Figure 1 Flow chart of patients included in the HUMS study: Miguel Servet University Hospitalpost-IC: post-protocol implementation period; pre-IC: pre-implementation period of the protocol; Fbl-IV: intravenous fibrinolysis.

During the implementation period of the IC protocol, the only measure that was not performed regularly was "do not change stretchers and go directly to brain CT".

	Pre-CI n=182	**Post-CI n=249**	**p**
Age In Years	76,5 (68-84)	79 (67,5-86)	0,27
Over 80 Years Old	65 (35,7)	105 (42,2)	0,17
Male Sex	96 (52,7)	114 (45,8)	0,15
Holidays	65 (35,7)	74 (29,7)	0,19
Attention During On-Call Hours	130 (71,4)	181 (72,7)	0,77
Brought By Ambulance (061)	74 (40,7)	169 (67,9)	< 0,001
NIHSS	11 (6-17)	10 (6-16)	0,18
Mechanical Thrombectomy	1 (0,5)	80 (32,1)	< 0,001
NIHSS: National Institute of Health Stroke Scale; post-CI: protocol post-implementation period; pre-CI: pre-protocol implementation period; RIQ: interquartile range.			

Table 2 Baseline Characteristics

Table 2 describes the characteristics of the sample, which, as can be seen, presents a higher percentage of thrombectomized patients (0.5% vs 32.1%, $p < 0.001$) and those transported by ambulance (40.7% vs 67.9%, $p < 0.001$) during the post-IC period. Since the implementation of the IC protocol, there has been a progressive improvement in median ADT per year but not in cTPT (Fig. 2) (Harrigan & Deveikis, 2024).
Median ADT decreased statistically significantly ($p < 0.001$) from 74 minutes (IQR 59-97.3) in the pre-IC period to 45 minutes in the post-IC period (IQR 33-62.5); A significant improvement ($p = 0.001$) was also observed in the median TSA, which increased from 155 (126.3-195) to 135 (94.3-190) min (Table 3) (Yu et al., 2024).
Furthermore, a statistically significant increase was observed in the proportion of patients fibrinolysed in the first 60 minutes of their arrival at the emergency department (26.4% vs 73.5%, $p < 0.001$) and in that of patients with ADT of 45 minutes or less (8.8% vs 51.8%, $p < 0.001$), regardless of whether or not they were brought by the 061 emergency and medical transport service. This improvement in TPA has been progressively observed every year since the implementation of the CI protocol (Table 4) (Fig. 3). However, compared to TSA, a statistically significant improvement was achieved only in the proportion of patients fibrinolysed within the first 90 minutes of symptom onset (4% vs 24.0%, $p < 0.001$) (Table 4) (Meza, Inda, Ponz, Ara, & Moreno, 2023).
Among the variables that influenced a more significant percentage of fibrinolized patients with 60-minute ADT, both in the pre-IC and post-IC period, a statistically significant association was found with patients brought by the emergency room and by medical transports 061, 26 (35.1%) versus 22 (20.4%) and 136 (80.5%) versus 47 (58.8%), residual pending (Stamm et al., 2023).
Treatment during a workday was independently associated with a higher rate of 60-minute ADT only in the post-IC period, 135 (77.1%) vs. 48 (64.9%) (table 5). In the pre-IC period, patients with 60 minutes of ADT had a higher median TEH, 90 minutes (IQR 55.3-103.4), compared to those treated with more than 60 minutes of ADT, 73 minutes (IQR 47,8). -103.3) ($p = 0.016$), a phenomenon that was called "end of window effect", disappeared in the post-IC period, 82.5 min (IQR 52-136.5) vs. 85 minutes (IQR 54.5-138.5) ($p = 0.906$) (Kolls et al., 2024).

DISCUSSION:

This is well known in treating ischemic stroke: "Time is the brain." In congruence with this motto, clinical guidelines recommend establishing objectives in the TPA that allow us to monitor and improve patient care. The recommendation to perform FBL-IV in the first 60 minutes dates back to 1995,12 Since then, efforts have been made to ensure that most patients are treated within this time frame. In 2010, the American Heart Association/American Stroke Association launched the initiative «Target: Stroke» to achieve a 60-minute ADT in at least 50% of fibrinolysed patients2, an initiative which moved to a second phase in 2014, changing the target in at least 75% of these patients with a TPA of 60 minutes and establish as a secondary objective that at least 50% of fibrinolysed patients have a TPA of 45 minutes or less13. Along the same lines, the "Angels" initiative, launched in 2016, supports the optimization of the quality of reperfusion treatment in centres that treat acute ischemic stroke, promoting the adoption of various measures that shorten ADT and allow achieve these objectives (De Mase et al., 2023; Souza Leite et al., 2023)

	Pre-CI		**Post-CI**		
	N	**Median (RIA)**	**N**	**Median (RIA)**	**p**
TEH	176	75 (49-115)	220	84 (52-138)	0,033
TPTc	182	24 (17-39)	249	26 (16,5-35,5)	0,842
TPA	182	74 (59-97,3)	249	45 (33-62,5)	< 0,001
TSA	176	155 (126,3-195)	220	135 (94,3-190)	0,001

post-IC: post-protocol implementation period; pre-IC: pre-implementation period of the protocol; IQR: interquartile range; TEH: out-of-hospital time, APT: door-to-needle time; TPTc: gate-CT time; TSA: time of onset of symptoms-to-needle.

Table 3 Comparative analysis of the different time intervals (expressed in minutes)

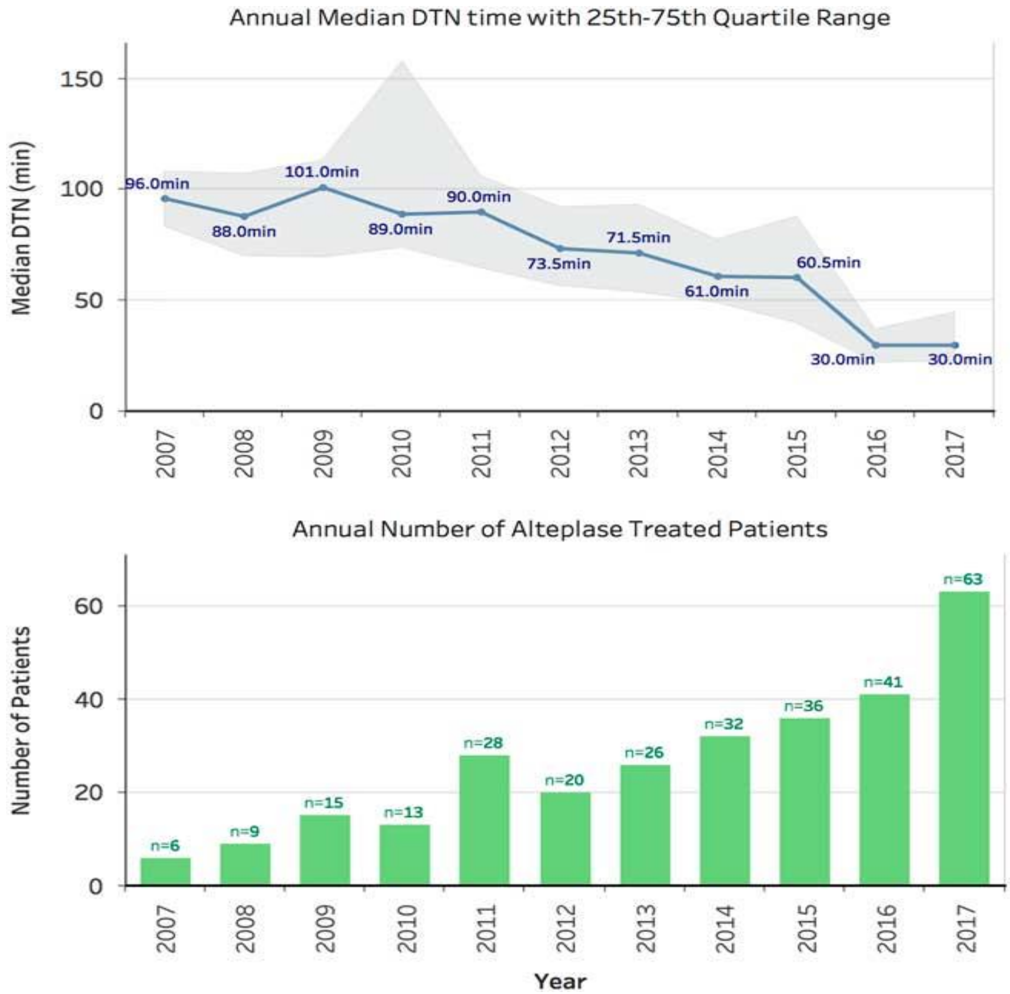

Figure 2 Comparative graph of door-to-needle and door-to-CT times of all patients included in the study, with their medians per year.

	Pre-CI (%)	Post-CI (%)	p
TPA ≤ 60 min	48 (26,4)	183 (73,5)	<0,001
TPA ≤ 45 min	16 (8.8)	129 (51,8)	<0,001
TPA ≤ 180 min	123 (69,9)	160 (72,7)	0,909
TPA ≤ 90 min	7 (4,0)	51 (23,2)	<0,001
Post-CI: post-protocol implementation period; pre-IC: pre-implementation period of the protocol; TPA: door-needle time; TSA: time of onset of symptoms-needle. A correct Model for “brought from 061”.			

Table 4 *Comparative analysis of the proportion of fibrinolysis patients in the different intervals*

In our work, median TPA decreased significantly, from 74 minutes (IQR 59-97.3) in the pre-IC period to 45 minutes (33-62.5) in the post-IC period. This sustained improvement began when the implementation of the IC protocol began in our hospital at the end of 2015, reaching 41 min (IQR 31-57) in 2019, with a constant and progressive increase in the percentage of fibrinolized patients in the first 60 and 45 minutes from their arrival to the Emergency Department each year, reaching the objectives of phase 2 of the "Target: Stroke" initiative in 2019. This is in line with what was found in other similar studies, which describe their results after the implementation of a protocol aimed at improving treatment times (Man et al., 2023).

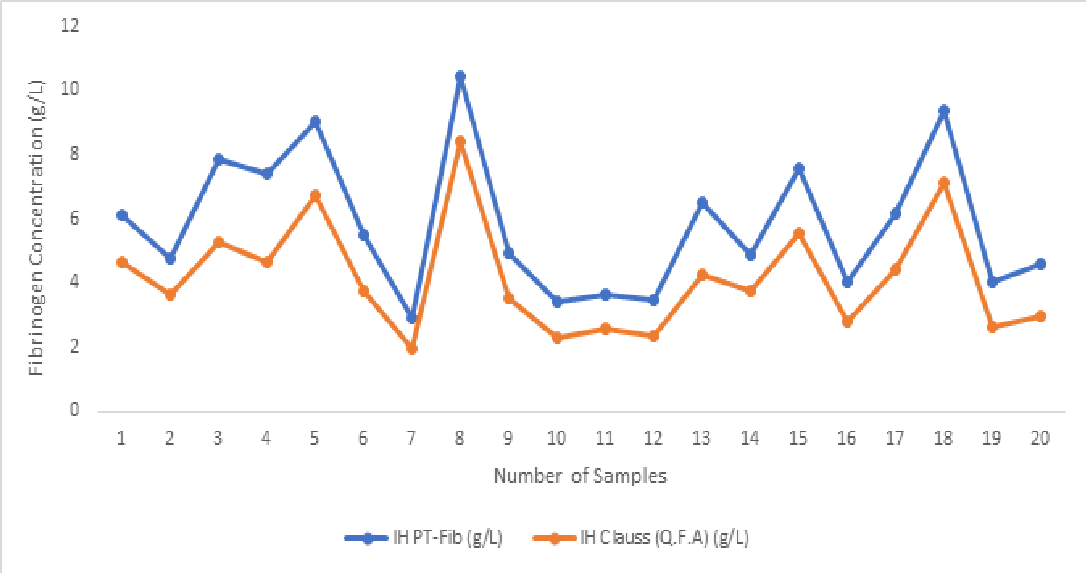

Figure 3 *Comparative graph of the percentage of patients who received fibrin*

This improvement in TPA resulted in better TSA, 135 minutes (IQR 94.3-190) in the post-IC period, compared to 155 minutes (IQR 126.3-195) in the pre-IC period. <0.001). Therefore, despite having a higher TEH, the percentage of patients who received FBL-IV in the first hour and a half after the onset of symptoms increased significantly (23.2% vs 4.0%). -IV1 is described (Oostema et al., 2024). Establishing action protocols that allow optimization of TPA is a recommendation that remains in force in every update of the clinical guidelines15-17. However, implementing a care protocol in IC is not easy, as it is a multidisciplinary process. It requires adequate coordination and collaboration on all parts of the care "equipment", including those involved in the extra-hospital phase. The measures implemented by Meretoja et al. in Helsinki, which achieved 50% or more patients with a TPA of 20 minutes or less, were implemented progressively and systematically over approximately 13 years (Reziya et al., 2023; Thevenet et al., 2023).

Only about one-third of fibrinolyzed patients reach the goal of ADT 60 min3-6. Even after implementing the 10 recommendations of the "Target: Stroke" initiative in the USA, only 41.3% of patients were fibrinolyzed with ADT 60 minutes in the years following surgery and, subsequently. To evaluate the results after implementation phase 2 of this initiative, the median ADT achieved was 52.6 minutes, falling short of the goal of 75% of fibrinolysed patients with an ADT of 60 minutes (Inoue et al., 2023).

More recently, in the ADT post hoc analysis of the Thrombolysis Implementation in Stroke (TIPS) study, no significant differences were found between the proportion of fibrinolysed patients with a 60-minute ADT in the pre-and post-intervention periods, ultimately yielding a figure of 30%, which illustrates the difficulty of extending the excellent results of a single hospital, in this case Melbourne, to the whole of Australia (Boss, 2023).

		TPA ≤ 60 min in pre-IC	**p**	**TPA ≤ 60 min in post-IC**	**p**
Age in Years n (%)	Over 80	19 (29,2)	0,514	78 (74,3)	0,809
	80 or less	29 (24,8)		105 (72,9)	
Sex n (%)	Male	22 (22,9)	0,263	84 (73,7)	0,95
	Female	26 (30,2)		99 (73,1)	
Days of the Week n (%)	Holidays	20 (30,8)	0,316	48 (64,9)	0,045
	Labor	28 (23,1)		135 (77,1)	
Opening Hours n (%)	Guard	36 (27,7)	0,523	135 (74,6)	0,524
	Office	12 (23,1)		48 (70,6)	

Means of Transportation n (%)	Ambulance	26 (35,1)	**0,026**	136 (80,5)	0,001
	Own media	22 (20,4)		47 (58,8)	
NIHSS Score n (%)	≤ 15	32 (24,8)	0,454	129 (70,5)	0,083
	16 or more	16 (30,2)		53 (81, 5)	

NIHSS: National Institute of Health Stroke Scale; TPA: door-to-needle time; post-IC: post-protocol implementation period; pre-CI: pre-implementation period of the protocol.
Statistically significant results are highlighted in bold.

Table 5 Factors associated with APT less than or equal to 60 minutes in the pre-IC and post-IC periods

Unlike what was reported in the studies cited above, there were some interventions we did not incorporate or could not implement in our hospital that would be important to consider to shorten ADT further. We have not been able to continuously implement the transfer of the patient directly to the scanner after he arrived at our Emergency Departments, an intervention considered among those fundamental to reduce the TPA, and this is reflected in the slight variation in the TPTc that we obtained during of these years (Fig. 2) (Table 3) (Astasio-Picado et al., 2023).
However, as fundamental as it is, it is usually not easy to achieve. It is one of the most violated measures when analyzing the results after implementing phase 2 of the "Target: Stroke" initiative. We do not apply the recommendation to prepare the fibrinolytic before patient arrival for those cases highly suspected of ending up in this due to the economic implications for our healthcare system in those cases that have not been definitively fibrinolyzed. Another measure, described in other studies and which we did not apply, was to take blood samples after the start of rt-PA administration (Giorelli et al., 2023).
The availability of a neurologist in person is also reflected in a shorter delay in the administration of fibrinolytic treatment compared to the local one19. In our case, the «Guardia Neurovascular Aragón», a homogeneous group of neurologists trained in Neurovascular and constant training (meetings, monthly sessions, etc.), although it is mainly aimed at the management of endovascular treatment, has favored the improvement of ADT (Fig. 2 and 3) and probably contributed to the disappearance of the "end of the window" effect (patients with a shorter duration of symptoms, despite having "more time" to perform FBL-IV, are treated more slowly)11, which was seen in the pre-IC period. It is interesting to observe how attendance times have worsened on non-working days, which led us to decide to change the in-person Neurovascular on-call service, including on weekends, from January 2019 (Svobodová, Maršálková, Volevach, & Mikulík, 2023).
As in any process, some elements are more challenging to act on. Among these, it should be underlined that in cases where the patient arrives alone at the emergency room, the on-call team is not notified; therefore, in any program that aims to shorten hospital stays for acute ischemia and stroke, it is essential to inform the population not only on the symptoms of a stroke, but also on the importance of using the emergency service and medical transport 061 to go to hospital (Rawson, Petrone, & Adcock, 2023).
In our study, the percentage of patients transferred by ambulance to our emergency department increased from 40.7% in the pre-IC period to 67.9% in the post-IC period ($p < 0.001$). Although the decrease in TPA in our study was independent of whether the patient was brought by ambulance or by own means, the percentage of patients treated with TPA 60 min was much higher in those brought by 061 (35.1% versus 20, 4 in group 061). pre-CI period and 80.5% versus 58.8% in the post-CI period), confirming the importance of medical transport for intra-hospital times (Popa et al., 2023).
We also believe it is relevant to remember how important continuous training is and to periodically promote the motivation of the multidisciplinary team that participates in the treatment of the acute phase of IC, not only for the implementation but also to maintain the improvements achieved made also collected by other Spanish centres (Hu et al., 2023).
Finally, the already-known impact of time on the functional prognosis of ischemic stroke patients treated with FBL-IV forces us to set increasingly challenging goals for ADT. Recent studies suggest that the TPA target should be lowered to 30 minutes rather than 60 minutes21,22; however, few

published experiences establish these ultra-rapid protocols in our environment11. This year, the objectives of the "Target: Stroke" initiative have moved to a third phase, which requires at least 85% of patients treated with a 60-minute TPA, 75% of fibrinolized patients with a 45-minute TPA. and adds that 50% or more were done in 30 minutes or less (Alhajala et al., 2023).

In conclusion, TPA improvement must be a constant, organized and dynamic process in all hospitals treating acute ischemic strokes, and no "floor" value justifies accommodation (Wang et al., 2023).

Our study has several limitations. The study design (uncontrolled before and after) allows the possibility of overestimating the benefit of the analyzed intervention; therefore, to minimize this bias, we tried to determine the baseline characteristics and the presence of other factors that may have contributed to the decrease in APD, to ensure that they did not have an asymmetric distribution between the pre-and post-CI groups and, if so, adopt the comparative model taking these variables into account (Liberman et al., 2023).

We did not analyze the impact of the intervention on 3-month functional prognosis or post-FBL-IV bleeding complications; however, previous studies have shown that early initiation of FBL-IV in patients with acute ischemic stroke is associated with functional prognoses better, so we can assume that this benefit should be maintained in our sample1. Determining which intervention was most relevant in reducing APD (Mitsuhashi, Tokugawa, & Mitsuhashi, 2023) is difficult.

Although they were initially proposed simultaneously, the reality is that they came into force in secret, without keeping track of the specific moment when each of them was completed. The next one began, except the last one, implementing the unified guard of Neurovascular-Aragon (Shah & Diwan, 2023).

CONCLUSION:

Implementing the measures associated with our protocol resulted in a significant and sustained decrease in TPA and the number of patients fibrinolysed in 60 minutes or less. Furthermore, a dynamic of monitoring results and continuous improvement has been established, which we believe will allow us to continue to advance in this direction.

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