Futile Interhospital Transfer for Endovascular Treatment in Acute Ischemic Stroke

The Madrid Stroke Network Experience

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Background and Purpose—The complexity of endovascular revascularization treatment (ERT) in acute ischemic stroke and the small number of patients eligible for treatment justify the development of stroke center networks with interhospital patient transfers. However, this approach might result in futile transfers (ie, the transfer of patients who ultimately do not undergo ERT). Our aim was to analyze the frequency of these futile transfers and the reasons for discarding ERT and to identify the possible associated factors.

Methods—We analyzed an observational prospective ERT registry from a stroke collaboration ERT network consisting of 3 hospitals. There were interhospital transfers from the first attending hospital to the on-call ERT center for the patients for whom this therapy was indicated, either primarily or after intravenous thrombolysis (drip and shift).

Results—The ERT protocol was activated for 199 patients, 129 of whom underwent ERT (64.8%). A total of 120 (60.3%) patients required a hospital transfer, 50 of whom (41%) ultimately did not undergo ERT. There were no differences in their baseline characteristics, the times from stroke onset, or in the delays in interhospital transfers between the transferred patients who were treated and those who were not treated. The main reasons for rejecting ERT after the interhospital transfer were clinical improvement/arterial recanalization (48%) and neuroimaging criteria (32%).

Conclusions—Forty-one percent of the ERT transfers were futile, but none of the baseline patient characteristics predicted this result. Futility could be reduced if repetition of unnecessary diagnostic tests was avoided. **(*Stroke*. 2015;46:2156-2161. DOI: 10.1161/STROKEAHA.115.009282.)**

Key Words: endovascular treatment ■ neuroimaging ■ patient transfer ■ stroke ■ stroke networks

Mechanical thrombectomy is being implemented in clinical practice for the treatment of acute ischemic stroke (IS) because it has been shown to increase recanalization rates, improve outcomes, and is useful for patients who are contraindicated for intravenous thrombolysis (IVT) or who do not respond to it and for patients who arrive at the hospital >4.5 hours after stroke onset. The positive results of several recently published clinical trials that provided a high level of evidence for endovascular reperfusion treatment (ERT) reinforced the need to offer this treatment to every stroke patient with acute IS because of an intracranial artery occlusion, primarily in those cases in which IVT had failed.[1–5]

However, the complexity of this technique justifies the development of collaborative stroke center networks with interhospital transfers of eligible patients.[6] To date, these stroke care networks have been implemented in regional settings, connecting a comprehensive stroke center (CSC) with primary stroke centers and general hospitals.[6] This approach has been designed principally to improve the rates of IVT in IS, but it has also played an important role in patients eligible

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for ERT. Few studies have analyzed the effect of interhospital patient transfers on ERT rates. A delay in intra-arterial therapy has been reported for patients transferred from a community hospital to a CSC when compared with those who arrived directly at a CSC.[7] Delays in interhospital transfers for ERT also reduced the likelihood of performing angiography in an emergency setting, with a 2.5% decrease in the chances of performing intra-arterial therapy for every minute of transfer time.[8] It is therefore possible that this approach results in futile transfers (ie, the transfer of patients who ultimately do not undergo ERT), thus generating not only unnecessary costs but also compromising the treatment of those patients who were clear candidates for endovascular treatment when first arriving at hospitals that do not have ERT capability.

Thus, the question of who to transfer for ERT and how to organize equitable access to this treatment is an important issue that must be addressed by neurologists, neurointerventionalists, and policy makers.

Our aim was to analyze the frequency of these futile transfers and the reasons for denying ERT and to identify the possible associated factors in a collaborative program for ERT from 3 CSCs within the Madrid Stroke Network. Our experience could be useful for other CSCs in the process of establishing new facilities and networks to ensure the provision of ERT to patients with acute IS who could benefit from it.

Methods

Population and Study Protocols

The Madrid Stroke Network is composed of 7 hospitals with stroke units (SUs) and 17 community hospitals working together in a coordinated system to ensure specialized care for all patients with stroke in the Madrid region, regardless of their place of residence. This system covers almost the entire population of ≈6.3 million inhabitants. All the SUs share common stroke codes and protocols, including ERT for acute IS,[9] as well as registries and databases for clinical collaborative studies.

In February 2012, 3 of the CSCs from the Madrid Stroke Network established a weekly rotating shift during which one of the centers was on-call for ERT. This on-call center was responsible for the entire population in the area the 3 CSCs or ≈3 million inhabitants (Northeast Madrid ERT Network).[10] The other half of Madrid's population also has 24-hour/365-day ERT coverage, which has been provided by another CSC until August 2013 when the Southwest Madrid ERT Network was created with the participation of 3 CSCs. Occasionally, patients from other areas of Madrid are accepted if they meet the criteria and do not otherwise have access to ERT, which is often due to an overload at another network.

This collaborative system provides 24-hour/7-day access to the angiography suite, on-call neurologists, neuroradiologists, and all the facilities of the SU in each hospital during its on-duty period. A common protocol was established containing the indications and contraindications for treatment based on the available evidence, with the agreement of all the neurologists and neuroradiologists involved in the network.[9] An assessment of arterial occlusion at the referring hospital by means of a neurovascular sonography study or noninvasive angiography was recommended. The summarized criteria for ERT according to the consensus protocol of the Madrid Stroke Network are (1) acute IS because of occlusion of large intracranial arteries, (2) moderate to severe neurological impairment, and (3) at least one of the following conditions: (1) IVT failure (persistence of the arterial occlusion and neurological deficit) within the therapeutic window for an endovascular procedure, (2) contraindication for IVT, and (3) time from stroke onset >4.5 hours, ≤8 hours for anterior circulation stroke, ≤12 hours in maximum deficit from the start, or ≤24 hours for fluctuating or progressing stroke in cases of basilar occlusion.[9]

A protocol for interhospital transfer from the referring hospital to the on-duty ERT center was also implemented. This protocol establishes the pathways for rapid transmission of all the relevant information using available communication methods (including via the Internet). The protocol also involves prehospital emergency services to guarantee immediate transportation to the ERT center in ambulances provided by the Emergency Medical System of the Madrid Health Community (Servicio de Urgencia Médica de Madrid [SUMMA]-112) in a centralized system, ensuring the assignation of top priority to these transfers and the allocation of the closest ambulance to the referring hospital to avoid transfer delays.[9]

For this analysis, we included all the patients who were attended by the Northeast Madrid ERT Network from February 1, 2012 to May 7, 2013. When the attending neurologist indicated ERT for a patient with an acute IS with a proven or highly suspected intracranial artery occlusion, the neurologist at the on-duty hospital for this treatment was contacted by phone, and all the criteria for ERT were confirmed before the interhospital transfer. Prehospital emergency services were then requested for immediate transport to the ERT center in ambulances equipped with specialized life-support resources. On arrival, the patient was received by the neurologist, who evaluated the patient's neurological impairment and arterial status using transcranial Doppler or brain computed tomographic angiography. In some cases, it was requested a new brain computed tomographic (CT) scan (with or without computed tomographic angiography) or magnetic resonance imaging. Patients who had clinically significant improvement (a decrease of ≥8 points on the National Institute of Health Stroke Scale or a score of 0 points) or arterial recanalization on arrival at the ERT center were deemed ineligible for ERT and were admitted to the SU. In cases for which the second neuroimaging suggested poor odds of clinical improvement (Alberta Stroke Program Early CT score [ASPECTS] <7 or mismatch <20%), ERT was also ruled out.

Study Variables

Demographic, clinical, neuroimaging, and outcome data were recorded prospectively in a common, specific database that included, for the purpose of this analysis,[10] (1) the patient's baseline characteristics; (2) National Institute of Health Stroke Scale on admission; (3) neuroimaging data (ASPECTS, multimodal CT or magnetic resonance imaging, when available); (4) time elapsed from stroke onset to first hospital arrival and to arrival at ERT hospital; (5) frequency of interhospital transfers and their duration; (6) treatment or not with IVT and the reason for exclusion, where applicable; (7) indication for ERT; (8) complications during the interhospital transfer; and (9) outcome at 3 months according to the modified Rankin Scale Score. Patients who were considered for ERT treatment but who were ultimately excluded were also recorded, as well as the reasons for the exclusion.

Patient Consents

All patients, or their relatives in the case of patient incapacity, provided informed consent before inclusion in the ERT protocol, which specifically included consent for inclusion of their clinical data in a database. The study was conducted according to Good Clinical Practice guidelines and was approved by the La Paz University Hospital Ethics Committee for Clinical Research.

Data Analysis

The data are expressed as median and interquartile range (IQR) or mean±SD for continuous variables, or as absolute and relative frequencies for categorical variables. When necessary, comparisons among groups on outcomes were made using Pearson χ^2 test for categorical variables and the Kruskal–Wallis rank test or ANOVA for continuous measures, as appropriate. Statistical significance was set at $P<0.05$ for all contrasts of hypothesis. All the analyses were performed with SPSS package software, version 20.0.

Results

The ERT protocol was activated for 199 patients, 129 of whom ultimately underwent ERT (64.8%). A total of 120 (60.3%) patients required hospital transfer, 50 of whom (41%) ultimately did not undergo ERT (futile transfer).

The Table shows the baseline and outcome data comparing the 4 groups according to ERT and interhospital transfer. There were no differences in age, sex, vascular risk factors, times from stroke onset or interhospital transfer times, baseline National Institute of Health Stroke Scale, baseline ASPECTS, or rates of previous IVT among the groups, nor in the comparison of patients ineligible for ERT, with or without interhospital transfer. Patients who were ineligible for ERT and had no need for interhospital transfer had significantly higher times from stroke onset to arrival at the first attending hospital (Figure 1A). No differences were found in time from stroke onset to arrival at the ERT center (Figure 1B) or in time spent in interhospital transfers (54 [IQR, 17] and 57 [IQR, 36] minutes for the ERT and non-ERT groups, respectively; P=0.496; Figure 1C). There were no complications during the interhospital transfers.

No significant differences in the reasons for indicating ERT were found between the patients treated with ERT after an interhospital transfer and those whose transfer was futile: failure of IVT 60% versus 66.7%, respectively; contraindication for IVT 17.1% versus 11.1%, respectively; time from stroke onset >4.5 hours 17.1% versus 18.5%, respectively; and large arterial occlusion 5.7% versus 3.7%, respectively (P=0.856).

The primary reason for ineligibility was clinical improvement or arterial recanalization in the 48% of the patients (Figure 2). No significant differences were found between the patients who received IVT before transfer and those who did not in terms of clinical improvement (17.9% versus 18.2%) or in the frequency of arterial recanalization (28.6% versus 31.8%; P=0.317).

The second reason for ineligibility, involving 32% of the patients, was the finding in a second neuroimaging test of signs considered indicators of a low probability of recovery (Figure 2). Detailed information on the performance of a second imaging procedure before the final decision on ERT was available for only 2 of the 3 ERT hospitals, with data from a total of 107 patients, representing 54% of the total sample. A second neuroimaging procedure was ordered for 58 patients (54.2%) and was more frequently requested for patients who were transferred (86%) than for patients who underwent ERT without an interhospital transfer (10%) or who were excluded from this treatment without a transfer (7%; Figure 3). The most frequently requested neuroimaging procedure after arrival at the ERT center was CT. The median change in ASPECTS was 0 (IQR 1) for patients who underwent ERT after an interhospital transfer and −1 (IQR 2) for patients whose transfer was futile (P=0.109). The results of the ASPECTS in the second CT for the patients who were excluded from ERT after this second neuroimaging test were 6 for 1 patient, 5 for 4 patients, 4 for 2 patients, and 0 for 2 patients.

Other less frequent reasons for a futile transfer were clinical deterioration (8%), the presence of cervical internal carotid

Table. Baseline Data Classified Into 4 Groups According to the Performance of ERT and the Need for Interhospital Transfers

	ERT Without Interhospital Transfer, n=59	ERT After Interhospital Transfer, n=70	Futile Interhospital Transfer (no ERT), n=50	Rejected for ERT Without Interhospital Transfer, n=20	*P* Value
Demographics and vascular risk factors					
Age, mean (SD)	67.7 (11)	64.2 (14)	65.3 (12)	65.6 (13)	0.898
Male, n (%)	32 (54.2)	35 (50)	20 (74.1)	11 (61.1)	0.182
Hypertension, n (%)	36 (61)	44 (63.8)	14 (51.9)	11 (73.3)	0.551
Diabetes mellitus, n (%)	11 (18.6)	15 (21.7)	9 (33.3)	5 (35.7)	0.322
Hyperlipidemia, n (%)	26 (44.1)	33 (41.8)	13 (16.5)	7 (8.9)	0.969
Tobacco, n (%)	13 (22)	10 (14.3)	5 (18.5)	4 (33.3)	0.397
Atrial fibrillation, n (%)	27 (45.8)	22 (31.4)	7 (25.9)	2 (16.7)	0.104
Coronary artery disease, n (%)	8 (13.6)	9 (12.9)	6 (22.2)	2 (16.7)	0.685
Previous ipsilateral cerebral infarction, n (%)	3 (5.1)	4 (5.7)	3 (11.1)	1 (8.3)	0.357
Baseline data					
NIHSS, median (IQR)	17 (9)	16 (8)	19 (9)	16 (8)	0.441
ASPECTS; median (IQR)	9 (3)	8 (3)	9 (3)	8 (1)	0.356
Glycemia, mg/dL, mean (SD)	120 (29)	126 (50)	127 (34)	178 (79)	0.221
SBP, mm Hg, mean (SD)	145 (21)	146 (23)	152 (28)	155 (15)	0.389
IVT, n (%)	27 (46.6)	42 (60)	28 (56)	11 (55)	0.498
Outcome at 3 mo					
% death or dependence (mRS >2)*	39%	40.3%	60%	66.7%	0.032†

ASPECTS indicates Alberta Stroke Program Early CT score; ERT, endovascular revascularization treatment; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and SBP, systolic blood pressure.

*Follow-up data available for 183 patients (92%).

†For comparison between futile transfer and ERT patients after interhospital transfer.

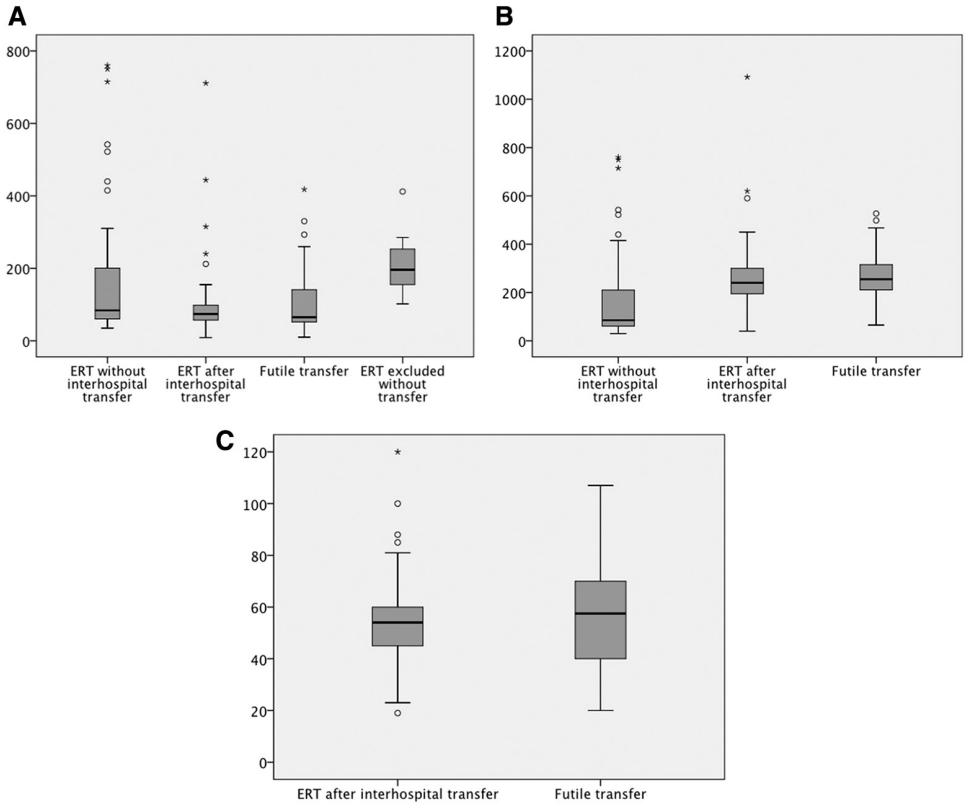

Figure 1. Comparison of times from stroke onset to first attending hospital and time from stroke onset to endovascular revascularization treatment (ERT) center and interhospital transfer times. **A**, Time from stroke onset to arrival at the first attending hospital (*y* axis: minutes); *P*=0.003 for comparison among all groups; *P*=0.884 for comparison among patients treated with ERT after an interhospital transfer and those with a futile transfer. **B**, Time from stroke onset to arrival at the ERT center (*y* axis minutes); *P*=0.000 for comparison among all groups; *P*=0.290 for comparison among patients treated with ERT after an interhospital transfer and those with a futile transfer. **C**, Time spent in interhospital transfer (*y* axis: minutes); *P*=0.496 for comparison among patients treated with ERT after an interhospital transfer and those with a futile transfer.

artery occlusion deemed as chronic and limiting the endovascular approach (4%), transport delay (2%), hemorrhagic transformation (2%), and revocation of consent (2%; Figure 2).

Patients in the futile transfer group had significantly poorer outcomes at 3 months than those who underwent ERT after transfer (Table).

Twenty-eight patients were transferred from 14 other hospitals in the Madrid region not belonging to this ERT network, as well as from another center from a neighboring region. Futile transfers were significantly more frequent when the referring center was not a member of the network (36% versus 60%; *P*=0.028), with a nonsignificant trend to be more frequent when the referring center was a hospital without an SU (39.4% versus 22.3%; *P*=0.119). However, no significant differences were shown in the time spent for interhospital transfers (median, 60 minutes; IQR, 28 minutes) or in the time from stroke onset to arrival at the ERT hospital (median, 240 minutes; IQR, 120 minutes) when compared with patients transferred from

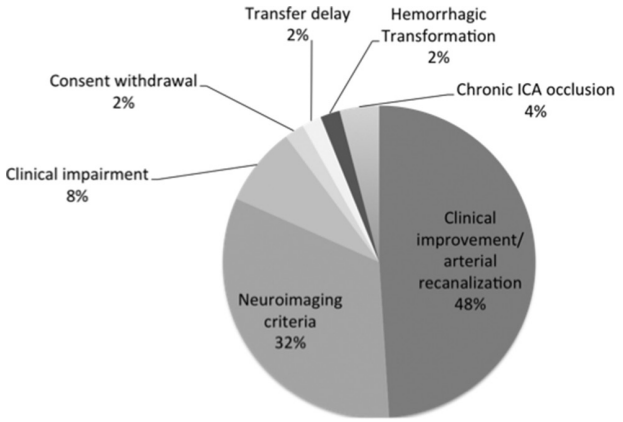

Figure 2. Reasons for the futile transfer. ICA indicates internal carotid artery.

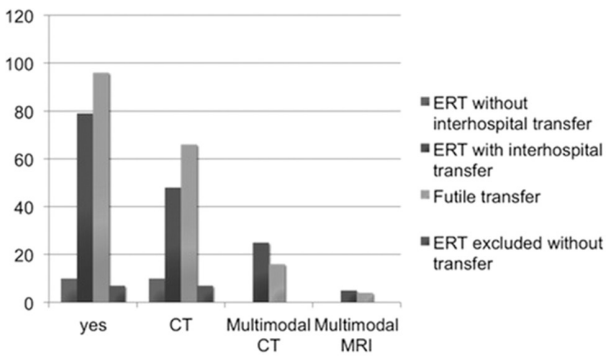

Figure 3. Frequency and type of second neuroimaging study performed at the endovascular revascularization treatment (ERT) center. *P*<0.001 for comparison among all groups. CT indicates computed tomography.

hospitals belonging to the ERT network (median of 56 minutes [IQR, 17 minutes] and 237 minutes [IQR, 106 minutes], respectively). Only 12 patients (6.3% of the total sample) who were transferred without any vascular neuroimaging were ultimately excluded from treatment; 9 of them had not been evaluated by the stroke team neurologist at the community hospital before interhospital transfer because of off-hours.

Discussion

Our study shows for the first time that the frequency of futile transfers in an ERT network is ≈41%. However, none of the patients' baseline characteristics were able to predict this event.

The most common reason for excluding a patient from ERT after a transfer was clinical improvement or arterial recanalization. These are positive outcomes but could not be predicted by previous IVT administration, given that the frequency was similar in treated and untreated patients.

The second most common reason for excluding a patient from ERT after a transfer was because of the results of a second neuroimaging study performed at the ERT center. Although this is not a per-protocol requirement unless there is clinical impairment or the time limit has been reached, the neuroradiologist who will perform the ERT usually requests it. Thus, our study raises the questions of where to perform the neuroimaging procedures (referring or receiving hospital) and whether it is necessary to repeat neuroimaging at the ERT hospital.

It has been suggested that complete neuroimaging procedures at the first attending hospital can help reduce door-to-groin puncture times to the 60-minute target and that repeated neuroimaging on arrival at the receiving hospital is only warranted in cases of clinical deterioration or significant delay in the interhospital transfer.[11] Is a new image worth the further delays for a patient who otherwise meets the ERT criteria? To date, very little information from clinical trials is available on this issue. Only the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT-PRIME) trials acknowledge that imaging was repeated for patients transferred from other hospitals, but no data on the number of patients excluded from those trials based on this repeated imaging was provided.[2,5]

Although further studies are warranted to address this question, we should take into account that the same patient would have been treated without a new CT scan had they been initially treated at the ERT center. In fact, in our study, only 10% of the patients who underwent ERT without an interhospital transfer had a repeated neuroimaging test when compared with 86% of the transferred patients.

As per protocol, patients with ASPECTS <7 were excluded from ERT in our study. This criterion was also applied to patients with baseline ASPECTS ≥7 but who scored lower on arrival at the ERT center. However, several analysis of ERT trials suggested that patients with ASPECTS <7 also derive some benefit in terms of outcome when treated with ERT.[12,13] In addition, the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial showed the efficacy of ERT in patients with acute IS within 6 hours from stroke onset in which enrollment was not limited according to ASPECTS.[1] MR CLEAN reinforces that this criterion should not be used to exclude patients for ERT who otherwise are candidates for this therapy.

No safety concerns have been indicated for patients with IS who are transferred between hospitals to undergo reperfusion therapies. Thus, the drip-and-ship and the drip-ship-and-retrieve methods are recommended models for distributing the administration of these therapies to all candidate patients, regardless of the type of hospital that initially treats them.

To our knowledge, no other studies have addressed the problem of futile transfers for ERT. In fact, a large ERT-treated cohort study in another region of Spain (Catalonia), based on a network of 7 CSCs that shared professional resources offering 24-hour service to cover the whole region, acknowledged as a limitation the fact that they could not report the total number of patients or the reasons why the patients thought to be ERT candidates eventually failed to undergo this treatment.[14] Similarly, an analysis from the Interventional Management of Stroke III that measured the effect of the patient transfer type (drip-and-shift; ship-and-drip; mother-ship) was restricted to patients randomized to the endovascular arm, with no information on the patients excluded from the trial after the interhospital transfer.[15]

The main limitation of this study is that it reflects a particular setup and organization of a network with specific features of this Spanish region, thus limiting the external validity of our results. However, our study can be considered an example of the search for new opportunities to improve IS management and to continually refine interhospital protocols to minimize delays and avoid unnecessary transfers. After this analysis, we implemented new strategies in our protocol, such as the recommendation for telemedicine, with online access to imaging studies from the referring hospital to help the ERT team at the recipient hospital to assess baseline neuroimaging studies and avoid repeating neuroimaging studies, thus providing more efficient patient evaluation. We have also implemented the position of the ERT Manager Neurologist who evaluates (via telemedicine or telephone) a patient who is initially treated at a hospital without an SU and is a candidate for ERT.[10]

In conclusion, the 41% of transfers for ERT are futile. However, none of the baseline patient characteristics are able to predict this event, and arterial recanalization and findings in the neuroimaging tests performed at the receiving hospital are the main reasons for ERT ineligibility. Thus, futility could be reduced if repetition of unnecessary diagnostic tests is avoided. Centers providing ERT should consider in their protocols which center (either the referring or the ERT-providing) is more feasible for performing the computed tomographic angiography imaging, avoiding repeated imaging in patients transferred to other centers who are otherwise candidates for this treatment.

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Disclosures

None.

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