

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Economic impact of the first pass effect in mechanical thrombectomy for acute ischemic stroke treatment in Spain: a cost-effectiveness analysis from the national health system perspective.
<b>AUTHORS</b>	González Diaz, Eva; Rodríguez-Paz, Carlos; Fernandez-Prieto, Andres; Martínez-Galdámez, Mario; Martínez-Moreno, Rosa; Ortega Quintanilla, Joaquín; Tomasello, Alejandro; Zamarro, Joaquín; Liebeskind, David; Zaidat, Osama; Mueller-Kronast, nils

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Abbasi, Mehdi United Kingdom of Great Britain and Northern Ireland
<b>REVIEW RETURNED</b>	06-Sep-2021

<b>GENERAL COMMENTS</b>	<p>This is an interesting research, as the authors have estimated the economical effect of FPE along with clinical outcomes in a large model cohort in the European community. Overall, the article is nicely written and organized. In my opinion, the manuscript is suitable for publication in the BMJ open, after the authors have addressed the following comments and questions:</p> <ol style="list-style-type: none"><li>1. To consider the results more significant within the population at risk I would include a specific analysis based on inpatient age. Cost-effectiveness comparison by age could bring a different perspective to the paper. We could consider an octogenarian population group where LVO cases rise and the clinical outcome is not the same as for the groups compared in this paper.</li><li>2. It would be important to include in the discussion more clinical data from the literature. I would recommend: Systematic review and meta-analysis of current rates of the first-pass effect by thrombectomy technique and associations with clinical outcomes, to address the importance of FPE and Per-pass analysis of recanalization and good neurological outcome in thrombectomy for stroke: Systematic review and meta-analysis, to address the neurological outcome after each pass of a thrombectomy device.</li><li>3. Adjustments of the currency (or mention of the dollar) might be reasonable as the established price of the Euro varies within time</li></ol>
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<b>REVIEWER</b>	Arling, Greg Purdue University, School of Nursing
<b>REVIEW RETURNED</b>	12-Sep-2021

<b>GENERAL COMMENTS</b>	<p>This study builds on a prior economic evaluation of MT + tPA vs. tPA alone in an observational study of stroke registry patients (STRATIS) in Spain (de Andrés-Nogales et. al., 2017). It is based on a sub-analysis of patients in the STRATIS registry who received MT. The objective of the study was to evaluate the health benefit and economic impact of achieving First Pass Effectiveness (FPE) by comparing MT patients who did have FPE with MT patients who did not (non-FPE). The base-case for the FPE group included all patients that achieved at least a final mTICI<math>\geq</math>2b, while the alternative scenario included all first pass patients regardless of their final mTICI (0-3). A lifetime Markov model was used to simulate incremental lifetime healthcare costs and health outcomes measured in quality-adjusted life-years [QALY] of patients that achieve FPE. Data from the STRATIS registry were analyzed to obtain degree of reperfusion achieved, mRS score at 90 days, and other clinical outcomes. Parameters for costs and mortality came from the authors' 2017 study of MT effectiveness. The authors found significantly better clinical outcomes (lower mRS score) at 90-days for the FPE group in both the base-case (mTICI <math>\geq</math> 2b) and alternative scenario (mTICI 0-3). Furthermore, the model estimated significant lifetime cost-savings and incremental gains in QALYs years for both FPE scenarios.</p> <p>This is an important study. Although several studies have found MT to be clinically effective and cost-beneficial, relatively little research has been conducted into the clinical or cost-effectiveness of FPE, an important development in MT treatment for stroke with large vessel occlusion. The objectives of the study were straightforward and the manuscript was generally well written. The study relied on what appeared to be good data on patient characteristics, clinical outcomes (particularly the mRS at 90 days) and healthcare costs. The Markov modeling and sensitivity analysis were competently carried out.</p> <p>Here are my concerns about the study.</p> <ol style="list-style-type: none"> <li>1. The comparison groups need to be more clearly described. The labels FPE and non-FPE used throughout the manuscript are confusing. There seem to be 3 groups: first pass effective (mTICI <math>\geq</math> 2b), first pass not effective (mTICI &lt; 2b) and non-first pass. In the base-case comparison of FPE and non-FPE, what happens to the first pass not effective group? Is it dropped from the base case comparison?</li> <li>2. The study results imply that a first pass, even without reperfusion (mTICI &lt; 2b), results in a better functional outcomes than non-first pass. That implication should be addressed in the discussion section. Also, it would be informative to compare directly the mRS scores or other outcomes between the first pass effective group and first pass not effective group.</li> <li>3. A major weakness of the study is its reliance on observational data where the conditions surrounding the intervention (FPE) are largely unknown. The FPE and non-FPE patients were similar demographically and clinically according to measured variables(A6-A9); yet there may have been unmeasured clinical differences or other characteristics between the groups that contributed to achieving both FPE and a better</li> </ol>
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	<p>mRS score. Also, there could have been differences in quality of stroke care between settings (e.g., clinical capacity or infrastructure, follow-up rehabilitation) that contributed both to FPE and subsequent outcomes. The limitations section should address the limitations of observational data and the validity threat of potentially unmeasured confounders.</p> <p>4. The difference between FPE and non-FPE groups in their mRS scores at 90 days is the main driver of the subsequent Markov modeling and simulation of costs, mortality, and QALYs. Little is known from the study about mRS transitions after 90 days post-stroke measurement point. The manuscript makes a questionable assumption: "Patients were assumed to remain in a given mRS score until they experienced a recurrent stroke or death. Other factors that may have an effect on mRS scores, such as comorbidities, were not included. However, this aspect should affect both patient cohorts equally." (In 328-334). There is also a reasonable possibility that the FPE and non-FPE patients will converge in their mRS scores as they age and are subject to more comorbidities. Convergence would narrow any differences in projected life-time costs and mortality rates.</p>
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## VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1

COMMENTS TO THE AUTHOR:

This is an interesting research, as the authors have estimated the economical effect of FPE along with clinical outcomes in a large model cohort in the European community. Overall, the article is nicely written and organized. In my opinion, the manuscript is suitable for publication in the BMJ open, after the authors have addressed the following comments and questions:

1. To consider the results more significant within the population at risk I would include a specific analysis based on inpatient age. Cost-effectiveness comparison by age could bring a different perspective to the paper. We could consider an octogenarian population group where LVO cases rise and the clinical outcome is not the same as for the groups compared in this paper.

Reply:

We appreciate the reviewer's thoughtful comment. A further data analysis and study focused on subgroup analyses including age, as well as time delays, would certainly add value to the analysis. Considering, that our main objective was to assess the impact of achieving FPE vs. non-FPE in the entire study population and the extension of the study, we consider that undertaking additional subgroup analyses would be better accomplished in a second study. As this is our first health economics study on the FPE effect, we would prefer to keep this study considering the overall population as in our initial objective.

On the other hand, in this study, we performed a one-way sensitivity analysis in which the starting age of the patients was varied. Considering that in our first analysis we considered an upper boundary of 75 years as the starting age, following the reviewer's comment, we increased the upper boundary to 81 years old to further investigate the effect in the model results. The model results remain consistent with the previous analysis after the suggested update: the net monetary benefit of the FPE is reduced, however, it remains positive and therefore, does not change the direction of the results.

The results of changes in the sensitivity analysis have been updated in line 271, figure 2 (tornado diagram), and the discussion section (line 356)

2. It would be important to include in the discussion more clinical data from the literature. I would recommend: Systematic review and meta-analysis of current rates of the first-pass effect by thrombectomy technique and associations with clinical outcomes, to address the importance of FPE and Per-pass analysis of recanalization and good neurological outcome in thrombectomy for stroke: Systematic review and meta-analysis, to address the neurological outcome after each pass of a thrombectomy device.

Reply:

We thank the reviewer for the suggested literature. In lines 292-302 we have added the key findings of the articles, and therefore we were able to stress that in terms of clinical outcomes our analysis was coherent with other research on the same topic.

3. Adjustments of the currency (or mention of the dollar) might be reasonable as the established price of the Euro varies within time

Reply:

In our study, we have mentioned the adjustment of the Euro currency to reflect Euros in 2020. Still, we tend to avoid conversion rates as this analysis is based on the Spanish context and costs. We would prefer to maintain lines 194-196, so to prevent the generalization of results to other countries with different health systems and factors influencing health service prices.

REVIEWER: 2

COMMENTS TO THE AUTHOR:

This study builds on a prior economic evaluation of MT + tPA vs. tPA alone in an observational study of stroke registry patients (STRATIS) in Spain (de Andrés-Nogales et. al., 2017). It is based on a sub-analysis of patients in the STRATIS registry who received MT. The objective of the study was to evaluate the health benefit and economic impact of achieving First Pass Effectiveness (FPE) by comparing MT patients who did have FPE with MT patients who did not (non-FPE). The base-case for the FPE group included all patients that achieved at least a final mTICI=2b, while the alternative scenario included all first pass patients regardless of their final mTICI (0-3). A lifetime Markov model was used to simulate incremental lifetime healthcare costs and health outcomes measured in quality-adjusted life-years [QALY] of patients that achieve FPE. Data from the STRATIS registry were analyzed to obtain degree of reperfusion achieved, mRS score at 90 days, and other clinical outcomes. Parameters for costs and mortality came from the authors' 2017 study of MT effectiveness. The authors found significantly better clinical outcomes (lower mRS score) at 90-days for the FPE group in both the base-case (mTICI  $\geq$  2b) and alternative scenario (mTICI 0-3). Furthermore, the model estimated significant lifetime cost-savings and incremental gains in QALYs years for both FPE scenarios.

This is an important study. Although several studies have found MT to be clinically effective and cost-beneficial, relatively little research has been conducted into the clinical or cost-effectiveness of FPE, an important development in MT treatment for stroke with large vessel occlusion. The objectives of the study were straightforward, and the manuscript was generally well written. The study relied on what appeared to be good data on patient characteristics, clinical outcomes (particularly the mRS at 90 days) and healthcare costs. The Markov modelling and sensitivity analysis were competently carried out. Here are my concerns about the study.

1. The comparison groups need to be more clearly described. The labels FPE and non-FPE used throughout the manuscript are confusing. There seem to be 3 groups: first pass effective (mTICI  $\geq$  2b), first pass not effective (mTICI < 2b) and non-first pass. In the base-case comparison of FPE and non-FPE, what happens to the first pass not effective group? Is it dropped from the base case

comparison?

Reply:

We thank the reviewer, as we agree that the definition of the groups compared in each scenario could be clearer. For this reason, in lines 153-156 we have modified the sentences to better define the intervention groups and to stress that the control group is always non-FPE in both scenarios.

Concerning the data on the “first pass not effective group”, as the reviewer noticed, in the base case scenario those with a final mTICI < 2b are not considered in the baseline study population and are therefore dropped from the analysis. Including this group in the base case could introduce a potential selection bias, as patients with mTICI < 2b have systematically worse clinical outcomes. Nevertheless, in order to explore the clinical and economic implications associated with lower mTICI scores, the alternative scenario was designed, and therefore includes all patients included in STRATIS registry regardless of the final mTICI (0-3).

2. The study results imply that a first pass, even without reperfusion (mTICI < 2b), results in a better functional outcome than non-first pass. That implication should be addressed in the discussion section. Also, it would be informative to compare directly the mRS scores or other outcomes between the first pass effective group and first pass not effective group.

Reply:

We thank the reviewer for this good observation. It is correct that functional outcomes improve in the first pass group when patients that did not achieve reperfusion (mTICI < 2b) are included in the analysis, yet, it is a slight improvement on the mRS 0-2: 66.2% in the first-pass group in patients that achieved mTICI ≥ 2b vs 66.9% when all patients are included (mTICI 0-3). The inclusion of patients with mTICI < 2b in the analysis, affected mainly the non-first pass group, and therefore the mRS 0-2 in this group changed from 54.6% in the base-case to 50.6% in the alternative scenario, widening the absolute difference in mRS score between FPE and non-FPE between the base case and alternative scenarios.

We have modified the paragraph in lines 310-316 to comment on this matter, as the reviewer kindly suggested.

3. A major weakness of the study is its reliance on observational data where the conditions surrounding the intervention (FPE) are largely unknown. The FPE and non-FPE patients were similar demographically and clinically according to measured variables (A6-A9); yet there may have been unmeasured clinical differences or other characteristics between the groups that contributed to achieving both FPE and a better mRS score. Also, there could have been differences in quality of stroke care between settings (e.g., clinical capacity or infrastructure, follow-up rehabilitation) that contributed both to FPE and subsequent outcomes. The limitations section should address the limitations of observational data and the validity threat of potentially unmeasured confounders.

Reply:

We thank the reviewer for this insight. In lines 349-352 we have added this limitation (“Moreover, the study reliance on observational data may limit the result’s interpretation due to the potential effect that unmeasured confounders (e.g. quality of stroke care, procedural technique) could have in the mRS score variation between groups”).

4. The difference between FPE and non-FPE groups in their mRS scores at 90 days is the main driver of the subsequent Markov modeling and simulation of costs, mortality, and QALYs. Little is known from the study about mRS transitions after 90 days post-stroke measurement point. The manuscript makes a questionable assumption: “Patients were assumed to remain in a given mRS score until they experienced a recurrent stroke or death. Other factors that may have an effect on mRS scores, such

as comorbidities, were not included. However, this aspect should affect both patient cohorts equally. “ (In 328-334). There is also a reasonable possibility that the FPE and non-FPE patients will converge in their mRS scores as they age and are subject to more comorbidities. Convergence would narrow any differences in projected life-time costs and mortality rates.

Reply:

We thank the reviewer’s comment on this point. We agree that in general there is limited evidence on mRS transitions after 90-days post-stroke, and probably is one of the potential reasons why many cost-effectiveness analyses on mechanical thrombectomy rely on the mRS score at 90 days and their modelling structure assumes that patients remain in the same health status unless an event that makes the patient transition to another health status occurs (generally a recurrent stroke or death due to any cause). To our knowledge, this is a limitation present in several of the published health economics studies related to mechanical thrombectomy. Please find below some references that support this statement.

- Matteo Ruggeri, Michele Basile, Andrea Zini, Salvatore Mangiafico, Elio Clemente Agostoni, Kyriakos Lobotesis, Jeffrey Saver, Silvia Coretti, Carlo Drago & Americo Cicchetti (2018) Cost-effectiveness analysis of mechanical thrombectomy with stent retriever in the treatment of acute ischemic stroke in Italy, Journal of Medical Economics, 21:9, 902-911, DOI: 10.1080/13696998.2018.1484748
- Kunz WG, Almekhlafi MA, Menon BK, Saver JL, Hunink MG, Dippel DWJ, Majoie CBLM, Liebeskind DS, Jovin TG, Davalos A, Bracard S, Guillemin F, Campbell BCV, Mitchell PJ, White P, Muir KW, Brown S, Demchuk AM, Hill MD, Goyal M; HERMES Collaborators. Public Health and Cost Benefits of Successful Reperfusion After Thrombectomy for Stroke. Stroke. 2020 Mar;51(3):899-907. doi: 10.1161/STROKEAHA.119.027874. Epub 2020 Jan 22. PMID: 31964289.

On the other hand, when we mention “Other factors that may have an effect on mRS scores, such as comorbidities, were not included. However, this aspect should affect both patient cohorts equally.”, we assume that based on the baseline characteristics, as there are no differences between both patient cohorts, it could be expected that both cohorts will be subject to the similar risk of comorbidities as they both age, although it is possible that one group could be subject to an increased risk of comorbidities in the future, nonetheless, we do not have long term follow up data to assume a greater risk being adjudicated to one of the groups.

In line with this, we modified the sentence in lines 360-362 to specify that this assumption is based on the baseline characteristics and added the need for long term data on mRS decline. The modified text is as follow: “Other factors that may have an effect on mRS scores, such as comorbidities, were not included. However, this aspect could affect both patient cohorts equally considering there are no differences in the baseline characteristics, nonetheless further studies on mRS decline in the long term are encouraged.”

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Arling, Greg Purdue University, School of Nursing
<b>REVIEW RETURNED</b>	23-Dec-2021

<b>GENERAL COMMENTS</b>	The reviewer completed the checklist but made no further comments.
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