Percutaneous mitral valve repair in severe secondary mitral regurgitation: Analysis of index hospitalization and economic evaluation based on the MITRA-FR trial

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(1) Title page

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(2) Structured abstract in English and French

Background: Percutaneous mitral valve repair (pMVR) is reimbursed in France for severe secondary mitral regurgitation (SMR) but French data regarding the hospitalisation index stay are lacking.

Aims: Our objectives were to describe the index hospitalisation stay and to evaluate the cost of hospital stay for pMVR used in SMR.

Methods: A secondary evaluation based on patients who were randomized to the intervention group of the Mitra-Fr study was undertaken. The economic evaluation was conducted according to the French hospital perspective. Medical resource use was estimated using specific data collected from patients enrolled in the Mitra-fr study and non-specific data from national statistics.

Results: The population was represented by 144 patients who underwent pMVR at 33 French centres. There was an average of 7.9±1.5 hospital staff during procedures. The average procedure duration was 154±68 minutes and increased with the number of implanted clips. Median total length of stay was 8 days. The occurrence of a serious adverse event was not associated with an increased risk of admission to CCU but was associated with an increased length of stay.

The mean total cost was 28,025± 3,424 €, which includes 21,547 € for the cost of medical devices used during pMVR and 6,478 € ± 3,424 € for costs outside devices.

Conclusion: The cost of pMVR is substantial for patients with secondary MR, which advocates for further efforts to identify the patients with SMR who are likely to derive a clear clinical benefit of the procedure.

List of key-words: percutaneous repair; secondary mitral regurgitation; economic evaluation; hospital; French health system

Rationnel : La réparation valvulaire mitrale percutanée (pMVR) est remboursée en France pour la régurgitation mitrale secondaire sévère (SMR) mais les données françaises sur le coût du séjour font défaut.

Objectifs : Décrire le séjour d'hospitalisation et évaluer le coût de l'hospitalisation après pMVR.

Méthodes : Une évaluation basée sur des patients randomisés dans l'étude Mitra-Fr a été réalisée. L'évaluation économique a été menée selon la perspective hospitalière. L'utilisation des ressources médicales a été estimée à l'aide de données spécifiques collectées dans Mitra-fr et des données non spécifiques issues de statistiques nationales.

Résultats : La population était représentée par 144 patients ayant eu une pMVR dans 33 centres français. Il y avait en moyenne 7,9 ± 1,5 personnels hospitaliers pendant les procédures. La durée moyenne de procédure était de 154 ± 68 minutes, ce chiffre augmentant avec le nombre de clips implantés. La durée totale médiane du séjour était de 8 jours. La survenue d'un événement indésirable grave n'a pas été associée à un risque accru d'admission en réanimation mais a été associée à une augmentation de la durée du séjour.

Le coût total moyen était de 28 025 ± 3 424 €, dont 21 547 € pour le coût des dispositifs médicaux spécifiques et 6 478 € ± 3 424 € pour le reste des coûts.

Conclusion : Le coût de la pMVR est notoire chez les patients présentant une IM secondaire. Des efforts supplémentaires sont nécessaires pour identifier les patients qui sont le plus susceptibles de tirer un bénéfice de la procédure.

Liste des mots-clés : réparation mitrale percutanée; évaluation économique; régurgitation mitrale secondaire ; hôpital ; système de santé français

(3) List of abbreviations

CRF: Case Report Form

CCAM: Common nomenclature of medical treatment/procedures

CCU: critical care unit

DRG: diagnosis related group

ERO: effective regurgitant orifice

ENCC: Étude nationale de coûts méthodologie commune

ICU: intensive care unit

MACE: major adverse cardiac event

MR: mitral regurgitation

NYHA: New York Heart Association

OR: Odds ratio

pMVR: Percutaneous mitral valve repair

SAE: serious adverse events

(4) Body of the text

Background

Percutaneous mitral valve repair (pMVR) using the MitraClip system (Abbot vascular, Santa Clara, US) has become an increasingly popular approach to treat patients with severe mitral regurgitation (MR).

Since 2008, date at which the first version of the device received CE marking, European centres have mainly adopted the technique to treat patients with severe secondary MR (SMR) despite the absence of a randomized trial evaluating its effectiveness on mortality and rehospitalisation for heart failure[1]. The first case performed in a French centre occurred in 2010 [1].

The Mitra-Fr study is a French clinical trial whose objective was to assess the impact of pMVR used in patients with SMR on all-cause mortality and unplanned hospitalisation for heart failure at 1 year. In 2018, the results of this trial were published and reported no improved outcomes with pMVR as measured by the primary endpoint. Similar findings were seen when patients were followed-up at 24 months [2].

Among the secondary objectives of the Mitra-Fr trial, one was to estimate the cost-effectiveness of pMVR over standard of care expressed as the cost per major adverse cardiac event (MACE) avoided at 12 months [3]. However, the numerically higher number of MACE observed in the pMVR group compared to the control group (86 vs 78 respectively out of 152 patients in each group with no statistical difference [4]), denoting that no MACE were avoided as a result of pMVR, has rendered futile this secondary objective.

Just one month after the first publication of the Mitra-Fr trial, the COAPT RCT, which was conducted in the US to support FDA approval of pMVR in SMR, reported conflicting

findings. Indeed, a major benefit was demonstrated for pMVR over medical therapy on the primary endpoint which was all hospitalisations for heart failure within 24 months [5].

Abbot Vascular, the MitraClip system manufacturer, has submitted a request to extend the reimbursement of the device to patients with severe SMR in France in 2019 based on the COAPT results. The reimbursement of the MitraClip had been already effective for primary MR for non-operable patients since December 2016.

For SMR, the target population has been restricted to patients the most resembling COAPT patients according to echocardiographic parameters (effective regurgitant orifice ERO area ≥ 0.3 cm^2 and left-ventricular end-diastolic ≤ 96 mL/m^2).

In November 2019, the MitraClip system received a positive opinion by the French Health Technology Assessment body, and ultimately, the formal reimbursement has been granted since September 2020.

Our objectives were: 1)- to describe the index hospitalisation stay for pMVR based on the Mitra-Fr trial; 2)- To evaluate the cost of hospital stay for pMVR using data collected in Mitra-Fr; 3)- To evaluate factors associated with higher medical resource use.

Methods

Study design and population

This is a secondary evaluation based on the population of patients who were randomized to the intervention group of the Mitra-Fr study. The design of Mitra-Fr has been previously described [2–4].

Briefly, the Mitra-Fr enrolled 304 patients at 34 French hospitals between December 2013 and March 2017. Eligible patients had severe secondary MR with a regurgitant volume >30 ml/beat or EROA >20 mm2 as assessed by echocardiography, in accordance with the 2012 guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery [6]. Patients were also required to have a left ventricular ejection fraction between 15% and 40% and to have chronic heart failure symptoms (assessed as New York Heart Association [NYHA] functional class II, III, or IV).

Here, we selected patients from the Mitra-fr study allocated to the intervention arm whether a clip was successfully implanted or not. This study adopts the hospital perspective with a cost analysis of the index hospital stay.

Identification, measure, and valuation of medical resource consumption

We proposed a similar approach to that used by Chevreul et al. [7].

The cost of hospitalisation stay has been determined first by estimating medical resource use, then by valuing corresponding costs based on rates for Year 2020. All costs are expressed in euros (€). No discount rate was applied to total costs.

Medical resource use has been estimated using specific data collected from patients enrolled in the Mitra-fr study (bottom-up microcosting method) and non-specific data.

Specific data were obtained from the Mitra-fr Case Report Form (CRF) which was designed to collect detailed information on the resource requirements for the procedure and the cost of the index hospital stay. Data of interest included: duration, staffing, and devices used during the procedure (including the location of the procedure), length of stay (total, critical care unit [CCU], intensive care unit [ICU]).

Procedural costs were determined: 1)- using hourly cost for each staff category, which were obtained from the human resources department of a French public University hospital, namely Hospices Civils de Lyon, France; 2)- using hourly cost of cath lab/ hybrid room usage which was determined following interview of biomedical engineer departments of three University hospitals and accounted for the costs of investment and maintenance of all equipment used in a conventional or hybrid cath lab (including the cost of peri-operative echocardiography). The cost of sterile medical devices other than the MitraClip system, which were used during the procedure and not tracked in the CRF, was determined by direct observation of devices used during a MitraClip implantation procedure performed within Hospices Civils de Lyon, France, and valued according to tariffs in place within this setting (appendix 1).

We added the cost of a trans-thoracic echocardiography which was systematically performed before discharge, based on the official rate (Common nomenclature of medical treatment/procedures [CCAM] "*Transthoracic doppler ultrasound of the heart and intrathoracic vessels*", code DZQM006). Last, we accounted for the number of packed red blood cells received per patient as documented in the CRF.

Nonspecific data correspond to the use of medical resources outside procedural costs, this includes the use of medical devices and medications used during the hospital stay. These were not recorded in the CRF. Hence, we used non-specific data associated with the hospital stay diagnosis related group (DRG) in which patients undergoing pMVR are grouped. To determine the DRG of patients undergoing pMVR, we extracted the national statistics of

DRGs for patients who underwent pMVR in France over the period 2017-2019 from the ATIH (Technical Agency for Information on Hospitalisation). This was done interrogating the database with the specific code related to pMVR (*DBBF198*) according to the CCAM nomenclature. Over the period, the main root DRG in which patients undergoing pMVR were grouped, was "*05K22" for "therapeutic procedure by vascular route on the orifices of the heart, age > 17 years*", with the four most frequently reported DRGs being (by order of frequency) 05K222, 05K221, 05K223, and 05K224 according to the level of severity.
Based on these four DRGs, which represented more than 91% of all DRGs, we collected the average cost per stay using data from the National hospital costs study database (ENCC, *Étude nationale de coûts méthodologie commune*) which is an annual survey conducted by the ATIH. This survey produces a cost repository, by establishing a national average cost per type of care provided by health facilities (appendix 2). To value these costs, we used the version of ENCC for Year 2019 (appendix 3).
The cost of DRG reported in the ENCC includes some of the specific costs that we valued from the consumption directly measured from Mitra-Fr patients. Hence, these specific costs were retrieved from DRG ENCC costs. The resulting costs were divided by the corresponding average length of stay to determine an average daily cost of hospital stay. Last, these were weighted according to the number of stays recorded in the national database.

The weighted average daily cost was then multiplied by the length of stay observed for each Mitra-fr patients, then specific costs previously calculated were added to determine a final hospitalisation stay per patient.
Last, the total cost of index hospitalisation, as measured according to the perspective of the hospital, was compared against the current tariff of DRG granted by the French Social Security as of January 2021.

Statistical analysis

Categorical variables were expressed as count (percentage) and continuous variables as mean ± standard deviation, except duration variables which were expressed as median, and 25-75 percentiles.

We differentiated centres with five or more patients enrolled in the MitraClip arm as opposed to those who enrolled fewer than five patients.

We also evaluated the impact of the number of implanted clips on the procedural time and procedural costs by differentiating patients in whom one, two, or ≥ three clips were implanted. To this end, a Kruskal-Wallis test was used.

The factors associated with increased medical use were assessed with a logistic regression for binary outcomes or with a gamma generalized linear model with log link for variables with skewed data. Regression analyses were conducted without (base-case) or with (scenario analysis) extreme values on stay duration.

The nature of periprocedural complications, and serious adverse events (SAE), variables which were chosen in the regression models, were reported in appendix 4. Other tested variables were the logistic EuroScore II, age, and the experience of centres.

We accounted for the uncertainty around our estimates by undertaking one-way deterministic sensitivity analyses. Variations were mostly performed by changing central values by ± 20%.

All analyses were carried out with Stata 16.0 (Stata corp, USA). A level of 0.05 was used to test for significance.

Results

Population and centres characteristics

Of the 152 patients randomised to the intervention group, 144 (94.7%) underwent the procedure at 33 centres and represent the population of interest (age 70.1±9.9 years ; Logistic EuroScore II: 8.8±7.3). Eighty patients (55.6%) were treated in six centres that included at least five cases during the trial (Group 1: six centres with an average of 13.3±4.5 cases) while 64 patients (44.4%) received the intervention in centres that performed fewer than five cases (Group 2: 27 centres with an average of 2.37±1.04 cases).

As previously published, technical success was achieved in 138 patients (95.8%). All six failed implantations occurred in group 1 centres.

Procedure characteristics

Seventy-point one percent of the procedures took place in a cath lab: 20 centres (60.6%) reported procedures being undertaken exclusively in cath labs and 10 (30.3%) in an hybrid room. In three centres (9.1%), procedures occurred either in a cath lab or an hybrid room.

During the procedure the team consisted of an average 7.9±1.5 (4.7±0.9 for medical and 3.2±0.9 for paramedical staff).

Medical team included at least one cardio-thoracic surgeon in 51.4% of procedures, at least one interventional cardiologist in 100% of procedures, at least one echocardiographer in 100% of procedure, and at least one anesthesiologist in 100% of procedures.

All procedures were undertaken with at least one technical proctor from Abbot Vascular [4], which did not incur additional cost to hospitals as this service is included in the tariff that hospitals pay to purchase the MitraClip device.

The average durations of anesthesia (all general) and procedure were 222±109 and 154±68 minutes respectively.

Procedure duration was not different depending on whether technical success was achieved (p=0.86). Durations were longer among the 21 procedures (14.6%) where periprocedural complications (Appendix 4) occurred during device implantation (median, 167 vs 136 minutes respectively; p=0.03).

Among the 121 implanted patients who had no periprocedural complications, procedure duration increased with the number of implanted clip (p= 0.0001) (figure 1).

In group 1 centres, procedure duration was shorter compared to group 2 centres in patients treated with one clip (median, 100 min. vs 140 min. respectively; p=0.039), was also shorter in patients who had two clips (median, 135 min vs 176 min respectively ; p= 0.0099), and did not differ in patients who had 3 or 4 clips (median, 225 vs 240 min. respectively ; p=0.73).

Overall hospital stay characteristics

Overall, 31 patients (21.7%) and 110 patients (76.4%) were admitted in critical care unit (CCU) and/or intensive care unit (ICU) during the index hospital stay, for a median duration of two days (IQR: 1-4) and two days (IQR: 1-3) respectively.

Median total length of stay was eight days (IQR:6-14).

SAE (Appendix 4) occurred in 35 patients (24.3%) during index stay. Although the rate of admission in CCU was numerically higher in patients who had at least one SAE compared to those who did not (31.4% vs 18.5% respectively), onset of at least one SAE was not associated with an increased risk of admission to CCU (Odds ratio [OR] 2.08, 95%CI 0.87 – 4.9). However, it was associated with an increased length of stay. No association were found for other tested variables.

Economic evaluation

Analyses were undertaken only for those patients who had a clip implantation with technical success (n=138).

The mean total cost of index hospitalisation was 28,025± 3,424 €, which includes 21,547 € for the cost of specific medical devices (21,100 € refundable in addition to DRG rate/447 € included into the DRG rate) and 6,478 € ± 3,424 € for costs outside those specifically related to the pMVR devices. Procedural costs outside those specific to pMVR devices were 1,377± 645€. The occurrence of a periprocedural complication, the growing number of implanted clips, or procedures that occurred in the hybrid room were associated with higher procedural costs (Table 2).

Patients who were admitted to CCU, who had at least one SAE during the hospital stay had higher costs of index hospitalisation outside those specific to pMVR devices (table 1).

Sensitivity analyses showed that the two main drivers of costs outside those related to pMVR devices were the daily rate of hospital stay and the length of hospital stay (figure 2). For example, the univariate change of daily rate of hospital stay by ± 20% led to a cost of index hospitalisation varying from 5,794 to 7,162 €.

To compare the cost of index hospitalisation stay with the reimbursement by the French Social Security, we added to the cost of 6,478 € previously estimated the cost of devices used during pMVR that are included into the DRG rate (447 €), which resulted in a cost of 6 925 € for hospital resource funded through the DRG rate.

The rate of reimbursement by the French Social Security, as of January 2021 (including supplements for days in CCU and ICU as observed in Mitra-Fr) was estimated at 6,492€ (see

details in appendix 5), hence the difference compared with the hospital cost was found at minus 433€.

Discussion

This paper corresponds to the first specific analysis of the characteristics and the economic evaluation of the index hospitalisation stay of Mitra-Fr patients who were enrolled in the pMVR arm.

Our data on hospital staff present during pMVR appear accurate to current practices from both a quantitative and qualitative viewpoint. Essentially, pMVR requires the presence of two main operators with interventional cardiology and/or cardio-thoracic surgery skills acting together with mandatory imaging guidance provided by the echocardiographist plus the presence of the anesthesiologist.

Our results based on French centres greatly comply with national requirements that were published in 2016 to regulate pMVR when it was originally validated to treat patients with severe primary MR [8].

The same guidance has specified that pMVR should be performed within centres with expertise in heart valve disease and that have technical equipment relevant to interventional cardiology and cardiothoracic surgery. In Mitra-Fr, pMVR mainly took place in a cath lab. There is no medical recommendation regarding the optimal setting / technical equipment relevant to pMVR. The decision to undergo pMVR in an hybrid room essentially depends on the availability of such equipment in the centre, which itself relies on each centre decision. The decision to involve a surgeon in the interventional team and to send all patients in ICU or CCU relies also on each centre policy. Conversely, transesophageal echocardiographic

capabilities with sonographers and access to 3D echocardiography is mandatory and present in every centre.

Last, as indicated in the French guidance, an anesthesiologist is present during pMVR, with procedures being mostly performed under general anesthesia since data reporting local anesthesia as primary anesthetic approach are currently very limited [9].

The procedure duration, which was measured at 154 ± 68 minutes is very similar to that reported in the COAPT trial, namely 163 ± 118 minutes [10]. However, the proportion of Mitra-Fr patients who had two clips or more, suggestive of more prolonged procedure, was slightly lower compared to that in COAPT (54.3% vs 61.8% respectively). We have observed that centres that have enrolled at least 5 patients in the MitraClip arm had a lower procedural time compared to those where fewer than 5 MitraClip devices were implanted, suggesting the potential impact of experience in achieving more expedited pMVR procedures. However, data from the large TVT Registry suggests that experience appears to be improved beyond 50 procedures [11]. Moreover, one may argue that “clipping faster is one thing but clipping better “ should be the pursued goal. Here, we have analysed only the link between number of implanted clips (i.e. technical success) and the duration of procedure, irrespective of whether a successful reduction of MR grade was achieved. As a consequence the mean number of implanted clips may tend to increase with the experience of the team due to a growing exigence on the quality of the final result.

Hence, it is likely that as of early 2021, the average procedure duration, after adjustment to the number of implanted clip (which may have increased over time) is lower compared to that reported here. One must notice that, irrespective of the number of clips implanted per patient, the cost of the MitraClip device is the same. Last, in addition to clinical practice and experience that have changed since the period 2013-2017, it is worth noting that the device

itself has known substantial evolutions too. Indeed, all Mitra-Fr procedures were performed with the first generation MitraClip system while the currently reimbursed version is the G4 one.

Admission to ICU appeared to be standard practice after pMVR, as described in other experience [12]. We found that the majority of patients were admitted in ICU, irrespective of the presence of a periprocedural complication.
Admission to CCU was less frequent but overall was pretty substantial. Our data did not allow us to determine the timing of admission to CCU post pMVR. Admission to CCU tended to be more frequent in patients who experienced at least one SAE. The rate of ICU/CCU is probably highly dependent on the local policy of each centre. It is likely that during this early phase the teams where over cautious and that this duration has largely decreased after.

The median length of stay was 8 days in the present study. Comparison of lengths of stay across health systems should be viewed cautiously because it can vary according to non-clinical organisational factors. Moreover, the enrollment of patients in the trial might have influenced the length of stay as a result of additional medical examinations required for the purpose of the trial. However the reported duration here is in line with other reported experiences in European centres [13,14]. In COAPT, the mean length of stay was 2.5 days [15] but it is not clear if patients were sent to a rehabilitation centre or back home after discharge.

The cost of pMVR herein reported is pretty similar to that estimated by Mahdjoub et al. in a French cohort of patients mainly presenting with primary MR [16] (28,025€ vs 30,039€ respectively), the difference being essentially related to a change in the MitraClip cost over

time. Informatively, the cost of index hospitalization for mitral valve repair or replacement was reported at 19,863€ by Trochu et al. [17].

As for length of stay, the comparison of costs beyond France should be undertaken with caution due to variations of costs across healthcare systems, including within the same continent. In COAPT, total index procedural costs were estimated at USD 35,755 (~29,741€), which includes the cost of MitraClip device, but these excluded physician fees [15]. Total index admission costs were estimated at USD 48,198 (~€40,091), which is higher than the cost reported in Mitra-Fr, even though the mean length of stay was shorter.

We found the tariff granted to hospitals by the National Social Security was slightly undervalued compared to the estimated hospital cost (minus 443€). However, this is consistent with differences in terms of length of stay. Indeed, the weighted mean length of stay for DRGs identified during Year 2020 was 7.4 days while mean length of stay was 10 days in Mitra-Fr patients. Reducing the length of stay should result in making even closer the cost of hospital stay with the revenue granted to hospitals. It is worth adding that the DRG rate which was identified for pMVR based on national statistics, is not specific to pMVR.

With regards to other valve disease, the cost of pMVR used for secondary MR patients appears slightly lower compared to the cost of TAVI as assessed by Chevreul et al [7], yet our economic evaluation suggests a substantial cost based on the hospital perspective, which is unsurprisingly mainly represented by the cost of the MitraClip system. As newer competitors of the clip will emerge in the future, such as the CE marked Pascal device [18], it is possible that the cost of pMVR will reduce over time.

As previously emphasized, the MitraClip system manufacturer has been successful to obtain a reimbursement of the device in patients with severe secondary MR with restrictions to those who have echocardiographic characteristics similar to those reported in COAPT. However, there is still uncertainty regarding the best eligibility criteria for pMVR in patients with severe SMR. Indeed, post-hoc analyses of the Mitra-Fr trial have demonstrated that the echocardiographic characteristics which were thought to be associated with improved outcome after pMVR in COAPT were not verified in the Mitra-Fr population [19,20].
Given the medical and economic consequences of these uncertainties [21], further efforts to reconcile the findings of the two trials should be encouraged.

This work presents several limitations. As any economic evaluation, the generalizability of our results beyond the French health system is questionable. The costs outside procedural costs were estimated using data extracted from national statistics, which may be unspecific to pMVR in general, and even more to pMVR for patients with secondary MR. However, these were used to calculate average daily costs which were multiplied by the observed stay duration in the Mitra-Fr trial.
As previously emphasized, these results are based on the initial experience of French centres over the period 2013-2017, which therefore may be less relevant to current practices as of 2021.
Moreover, we calculated the costs of pMVR using the prices observed in a limited number of participating centres. This should have little impact since the main driver of pMVR remains the cost of the device which is invariant nationally.
Our analyses to evaluate the factors associated with increased use of medical resource were limited to a few variables, essentially the logistic Euroscore, hence it doesn’t account for the multiple clinical and biological variables which were available in the Mitra-Fr CRF.

However, multiplying the number of analyses may have increased the risk to show a difference due to chance.

Last, as an inherent limitation of the objectives of the present work, there is no comparative data regarding the cost of follow-up of Mitra-Fr patients, including those enrolled in the control group. While the estimation of cost of care for severe SMR could be interesting to estimate in future works, there is no a priori reason to consider that pMVR could influence the cost of patients' care, as assessed in Mitra-Fr, given the absence of clinical benefit demonstrated against those patients who were medically treated.

Conclusions

This work represents an original economic study since it offers a first evaluation of the cost of stay for pMVR in patients with SMR by the MitraClip™ system, in the French context and carried out from the point of view of the hospital.

Giving the substantial cost of pMVR, it is of particular importance to clearly identify those patients who will benefit from the procedure which will help to avoid futile spending for the health care system.

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Declared competing interests of the authors:

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(6) Figure legends

Figure 1: Duration of the procedure according to the number of implanted clips

Caption: box upper and lower hinge indicate 75th and 25th percentile respectively and within box horizontal bar represent median ; upper and lower whiskers represent upper and lower adjacent values respectively ; outside values have not been represented

Figure 2: Tornado diagram (one-way deterministic sensitivity analyses)

Caption: The X-axis corresponds to euros with the central value of 6,478€ which is the cost of index hospitalisation stay (excluding the cost of devices used during pMVR). One-way sensitivity analyses are conducted to assess the impact that a fixed change in each parameter has on the cost of index hospitalization. Parameters are ranked from the most to the least influential on the cost of index hospitalisation stay. Univariate change by +/-20% of daily rate of hospital stay or univariate change by +/-20% of duration of hospital stay has strictly the same impact since the calculation of the cost uses these two variables which are multiplied.

(7) Tables

Table 1: Hospitalisation costs outside specific pMVR devices

Variable	N	Median	p25	P75	P-value
Total (€)	138	5,686	4,047	7,816	/
NO stay in CCU	109	4,815	3,727	7,070	<0.001
STAY in CCU	29	8,124	6,101	10,633	
No periprocedural complications	121	5,524	4,014	7,816	0.3372
Periprocedural complications *	17	6,280	4,815	7,536	
No SAE during stay	108	4,843	3,773	7,098	<0.001
SAE during stay	30	8,049	6,259	11,358	

**Procedural complications that were reported are recalled in Appendix 4*

Costs are expressed as euros

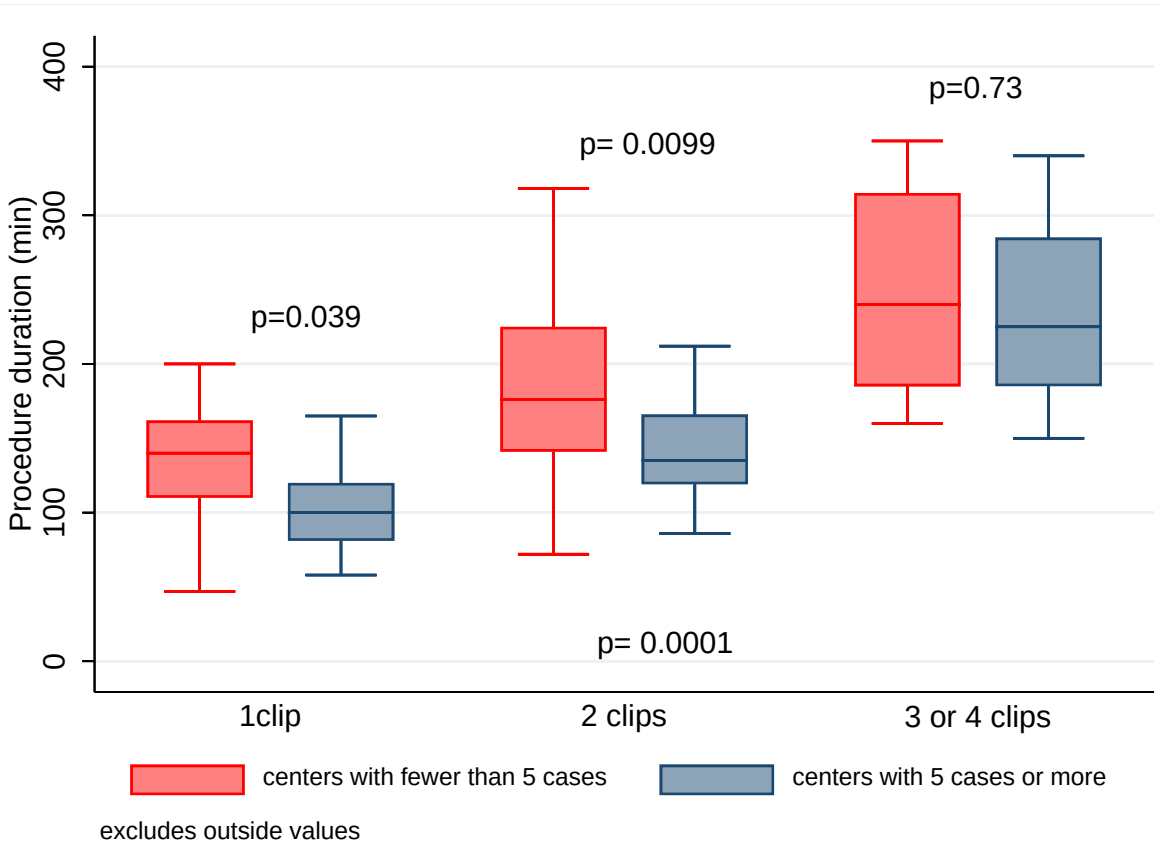
Table 2: Procedural costs outside specific devices

Variable	N	Median	p25	p75	P-value
Total (€)	138	1,213	891	1,712	/
No periprocedural complications	121	1,194	871	1,622	0.0162
Periprocedural complications*	17	1,477	1,241	2,017	
One clip implanted	63	922	724	1,223	<0.001
Two clips implanted	62	1,501	1,186	1,919	
3 or 4 clips implanted	13	1,948	1,477	2,565	
Location of procedure					
Cath lab	99	1,192	852	1,616	0.037
Hybrid room	39	1,398	1,102	1,805	

**Procedural complications that were reported are recalled in Appendix 4*

Costs are expressed as Euros

(8) Figures.



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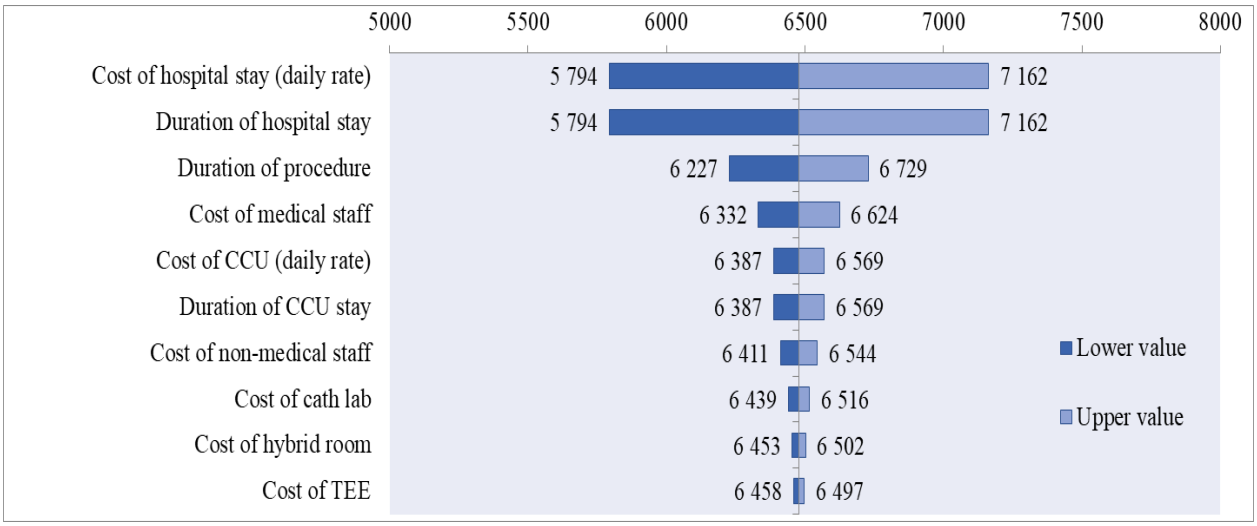

Figure 2: Tornado diagram (one-way deterministic sensitivity analyses)

Caption: The X-axis corresponds to euros with the central value of 6,478€ which is the cost of index hospitalisation stay (excluding the cost of devices used during pMVR). One-way sensitivity analyses are conducted to assess the impact that a fixed change in each parameter has on the cost of index hospitalization. Parameters are ranked from the most to the least influential on the cost of index hospitalisation stay. Univariate change by +/-20% of daily rate of hospital stay or univariate change by +/-20% of duration of hospital stay has strictly the same impact since the calculation of the cost uses these two variables which are multiplied.