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Cost-effectiveness analysis of mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation: a systematic review

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Abstract
To assess the cost-effectiveness of mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation and heart failure, a systematic literature search was conducted in various electronic databases to January 3, 2020. Eligibility criteria are the population (patients with mitral regurgitation (MR)), intervention (transcatheter mitral valve repair using the MitraClip), comparator (conventional medical treatment), outcomes, and designs (Model-based or trial-based full economic evaluations).The quality of included studies was assessed using the CHEERS checklist. Mortality and survival rate, quality-adjusted life year (QALY), life years gained (LYG), total cost, and the incremental cost-effectiveness ratio (ICER) regarding the use of MitraClip System were considered as the key outcomes. Eight articles were eligible for full-text assessment. Ultimately, a total of seven studies were considered in the current systematic review. Results demonstrated that MitraClip reduces mortality rate and increases survival rate. The mortality rate at 1 year and 10 years was 16.7% versus 29.77% and 70.9% versus 98.8%, respectively. Total cost data based on 2019 USD show that the MitraClip has the highest cost in the USA ($121,390) and the lowest cost in Italy ($33,062). The results showed that in all selected countries, willingness-to-pay (WTP) thresholds are upper than the cost per QALY; also, the highest ICER for the MitraClip is in the USA ($55,600/QALY) and the lowest in Italy ($10,616/QALY). To conclude, evidence from this systematic review suggests that MitraClip Delivery System improved both life expectancy and QALY compared with medical treatment in patients at high surgical risk and it was also a cost-effective treatment option for patients with mitral regurgitation.

Keywords Cost-effectiveness · Mitral valve repair · Mitral regurgitation · MitraClip · Systematic review

Introduction

Valve heart diseases (VHD) represent a serious public health concern, with an age- and sex-corrected prevalence rate of 2.5%, according to a recent population-based study [1]. Among VHD, mitral valve regurgitation (MVR), occurring when blood flows back through during the closure of the leaflets and the left ventricle contraction, is the most common VHD globally, in that it affects approximately up to 4 million people in the USA alone. Its prevalence rate increases with age and it is expected to increase further due to the aging of the population [2, 3]. Although declining in the Western population, mitral stenosis (MS) is still a frequent disease in the undeveloped and developing countries [4]. According to the Global Burden of Disease 2017 (GBD) study, 35,700 deaths and 1.1 million disability-adjusted life years (DALYs) were lost due to degenerative mitral valve diseases across the world, representing 0.12% of the total health lost from all diseases in 2017 [5].

In October 2013, the USA "Food and Drug Administration" (FDA) has approved the percutaneous edge-to-edge trans-catheter mitral valve repair (also known as the MitraClip system). Since then, this device has been utilized for the treatment of over 40,000 MVR patients worldwide [6]. The MitraClip system creates a double orifice mitral opening by a percutaneous approach via

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the femoral vein [4]. The MitraClip was evaluated in a randomized, controlled, prospective, multicenter study, EVEREST II (Endovascular Valve Edge-to-Edge Repair) [7].

In the last years, some experimentations are suggesting the feasibility of utilizing the MitraClip system also for the management of severe symptomatic tricuspid regurgitation, which, as well as MVR, imposes a significant burden, both from an epidemiological and economic perspective, in terms of morbidity, mortality, and generated costs.

Since resources are limited, a proper allocation is fundamental in ensuring equity in access to healthcare services. Cost-effectiveness analysis represents an economic analysis that enables the comparison of the relative costs and outcomes/effects of different types of interventions. Systematic reviews, by critically appraising the existing scholarly literature, provide health decision and policy makers with an updated, unbiased synthesis in order to make proper, evidence-based, and informed decisions.

Some studies have been conducted regarding the cost-effectiveness of the MitraClip system. However, to the best of our knowledge, there exists no systematic review of cost-effectiveness investigations of the use of the MitraClip system in MVR patients. Therefore, the present study was undertaken in order to fill this gap in knowledge.

Method

Identification of studies

A systematic literature search was conducted in PubMed, Scopus, Web of Science Core Collection, and Embase from inception to January 3, 2020. There was no restriction on language or date of publication. All full economic evaluation studies of MitraClip versus surgical repair for mitral regurgitation (MR) were identified using search strategies. Search strategy included a combination of keywords and medical subject headings (MeSH). Separate search strategies were developed for each database (Table 1). The reference lists of eligible articles were hand searched to find additional relevant studies. Search terms included MitraClip, "mitral valve clip*", "mitral valve insufficiency", "Mitral valve repair", "Transcatheter mitral valve repair", "Mitral regurgitation", "Heart Valve Prosthesis Implantation", "cost-benefit analysis", "cost-effectiveness analysis", "cost-utility analysis".

Eligibility criteria

The population, intervention, comparator, outcomes, and designs (PICOS) are described below.

- Population: patients with mitral regurgitation (MR);

Table 1 Search strategies and results for selected databases

Database	Date conducted	Search strategy	# Results
PubMed	January 3, 2020	(mitraclip [tiab] OR "mitral valve clip*" [tiab] OR "mitral valve insufficiency [tiab]" OR "Mitral valve repair" [tiab] OR "Transcatheter mitral valve repair" [tiab] OR "Mitral regurgitation" [tiab] OR "Heart Valve Prosthesis Implantation" [tiab]) AND ("cost-benefit analysis" [MeSH] OR "cost effectiveness analysis" OR "cost-utility analysis" OR economics [mesh] OR Cost* [tiab] OR Economic*[tiab])	238
Embase	January 3, 2020	('mitral valve clip'/exp OR 'mitral valve clip' OR 'mitraclip system'/exp OR 'mitraclip system' OR 'mitral valve regurgitation'/exp OR 'mitral valve regurgitation' OR 'mitral valve repair'/exp OR 'mitral valve repair' OR 'mitral valve repair device'/exp OR 'mitral valve repair device' OR 'transcatheter mitral valve repair'/exp OR 'transcatheter mitral valve repair') AND ('cost benefit analysis'/exp OR 'cost benefit analysis' OR 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR economic*:ab,ti)	340
Web of Science	January 3, 2020	TS=((mitraclip OR "mitral valve clip*" OR "mitral valve insufficiency" OR "Mitral valve repair" OR "Transcatheter mitral valve repair" OR "Mitral regurgitation") AND (cost* OR Economic* OR "cost-benefit analysis" OR "cost benefit analysis" OR "cost effectiveness analysis" OR "cost-effectiveness analysis" OR "cost utility analysis" OR "cost-utility analysis")) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI	293
Scopus	January 3, 2020	TITLE-ABS-KEY (mitraclip OR "mitral clip" OR "mitral valve clip*" OR "mitral valve insufficiency" OR "Mitral valve repair" OR "Transcatheter mitral valve repair" OR "Mitral regurgitation" OR "Heart Valve Prosthesis Implantation") AND TITLE-ABS-KEY ("cost benefit analysis" OR "cost-benefit analysis" OR "cost effectiveness analysis" OR "cost-effectiveness analysis" OR "cost utility analysis" OR "cost-utility analysis" OR cost*OR economic*)	108
Total			979
Total with duplicates removed			681

- Intervention: transcatheter mitral valve repair using the MitraClip;
- Comparator: conventional medical treatment;
- Outcomes: "Incremental Cost-Effectiveness Ratio" (ICER), "Incremental cost per Quality-Adjusted Life Year (QALY)", Net Monetary Benefit (NMB);
- Study design: model-based or trial-based full economic evaluations (cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA).

Exclusion criteria were

- Partial economic evaluation studies (cost-minimization analysis, cost-of-illness (CoI) studies, cost-analysis, cost outcome descriptions, cost descriptions)
- Reviews, commentaries, letters to the editors, editorials, protocols, abstracts
- Non-English language full-text studies
- Duplicates

Selection of studies

After removing duplicates, titles and abstracts of studies were screened independently by two authors for inclusion. Full text of selected studies was assessed by one author against the eligibility criteria and checked independently by a second author. Any disagreements were resolved by discussion. The agreement was reached on all included studies. EndNote ×7 was used for management of search results and removing duplications.

Data extraction and quality assessment of the studies

Two reviewers (SA and JA) independently extracted data using a predefined data extraction form. Disagreements were resolved by discussion at each step. Data extraction was performed in Microsoft Excel. Data extracted from each study included study/publication year, country, funding, comparators, health outcomes, perspective, time horizon, time follow up, number of patients, sensitivity analysis, discount rate, included costs, type of modeling, ICER threshold, base case analysis results and sensitivity analysis results.

The quality of included studies was assessed by two independent reviewers (SA and JA) using the CHEERS checklist [8, 9]. Any disagreements were resolved through consensus. The CHEERS tool consists of 24 items in six sections (title and abstract, introduction, methods, results, discussion, and other) and was scored using 'yes' (reported in full), 'partially reported', 'no' (not reported), and 'not applicable'. In order to estimate a score of reporting, we allocated a score of 1 for each item that was reported in full, 0.5 for partial report, and 0 otherwise. Therefore, the maximum score for each study was 24 [10].

Synthesis of results

The key characteristics and results of included studies were summarized and synthesized qualitatively using tables and complemented by a narrative description and comparison of the results among studies. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

Results

Study selection process

As shown in Fig. 1, the searches identified 979 records. After removal of duplicates and screening of title/abstract, eight articles were eligible for full-text assessment. Four studies were excluded because the studies were published as abstracts or had irrelevant outcomes and one article was excluded because percutaneous mitral valve repair was done with Carillon Mitral Contour System. Ultimately, a total of seven studies were considered in the current systematic review. The quality of included studies was assessed by using the CHEERS checklist (Table 2).

The seven studies were published between 2013 and 2019 in six different countries. All studies were conducted in developed countries; two studies were conducted in Canada, and one each in UK, France, Italy, USA, and Japan [12–18]. All studies focused on the economic evaluation of transcatheter mitral valve repair (TMVr) with MitraClip Delivery System compared with medical treatment (MT) in patients with severe MR.

Main characteristics of the studies are shown in Table 3. Six of seven studies were funded by Abbott Vascular, Inc. Most common health outcomes reported were QALYs and LYQs. Economic evaluations represented possible perspectives: health care system, provider, and third-party payer. The majority of the studies used a Markov model. The time horizons of the majority of studies are lifetime. Costs and benefits were discounted appropriately using country-specific guidance rates, ranging from 2% (Japan) to 5% (Canada). Also, all studies used sensitivity analysis to illustrate and assess the level of confidence that may be associated with the conclusion of an economic evaluation.

Table 4 summarizes the cost-effectiveness, QALYs, and other related economic evaluation parameters for each study. All studies reported the QALYs, except

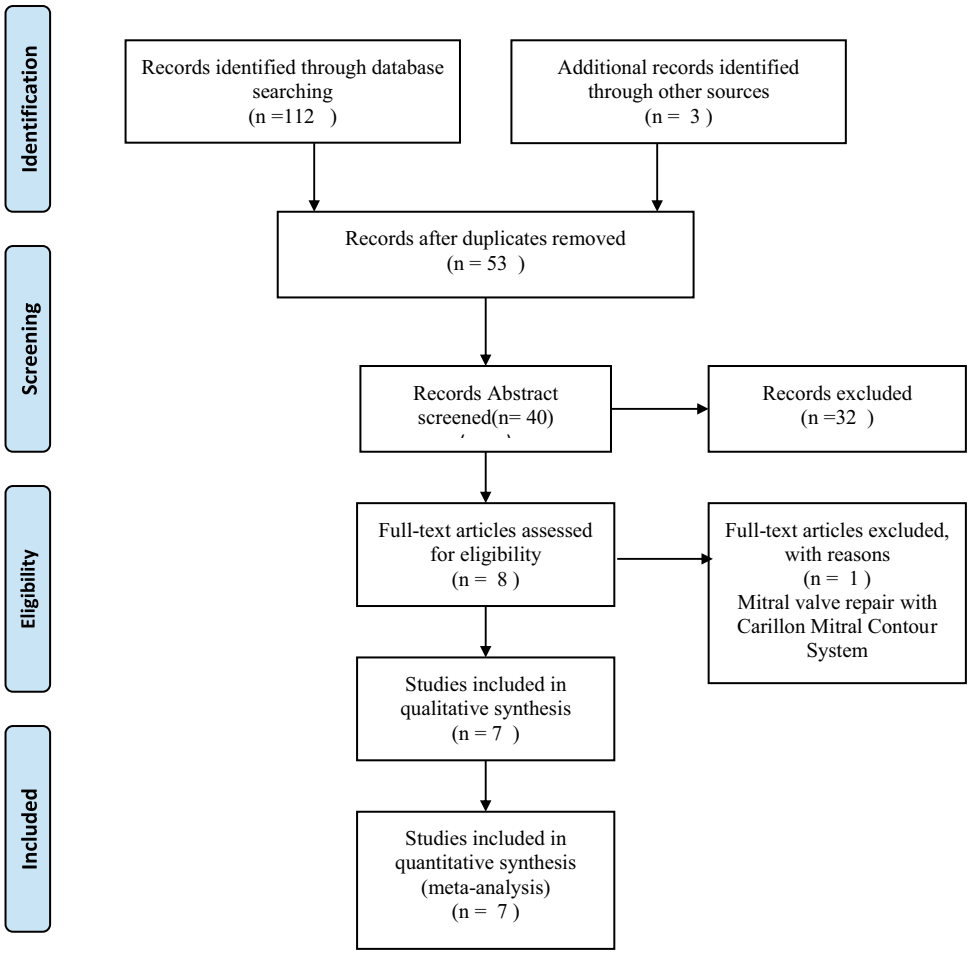

Fig. 1 PRISMA diagram

the French study, and in all cases, MitraClip created a greater improvement in QALYs. The least improvement was reported in Mealing et al. study (0.48) and the highest improvement in Cameron et al. study (1.73). As the QALY, MitraClip was associated with a greater improvement in LYQs, the least improvement was reported in Baron et al. study (1.13), and the highest improvement in Armeni et al. study (3.35). As shown in Table 2, in all studies, MitraClip vs medical treatment generated higher costs.

All of studies demonstrated that MitraClip reduces mortality rate and increases survival rate. Total cost data based on 2019 USD show that the MitraClip system has the highest cost in the USA, Canada, and Japan ($121,390, $78,619, and $70,887, respectively) and the lowest cost in Italy and France ($33,062 and $39,799, respectively). Results show that in all selected countries (UK, Canada, France, Italy, USA, and Japan), threshold for willingness to pay (WTP) is upper than cost per QALY, which means that at the current thresholds used by the health care systems, MitraClip system is cost-effective for patients with mitral regurgitation.

Discussion

This study represents the first published systematic review to assess the economic evolution analysis of MitraClip delivery system for mitral valve repair for patients with mitral regurgitation and heart failure. In case of disproportionate degree of mitral regurgitation to left ventricular chamber enlargement, the patients with chronic heart failure would benefit from TMVr [19]. Basis on a systematic review TMVr with MitraClip would provide lower all-cause mortality and hospitalization for heart failure and reduced need for unplanned mitral valve surgery and heart transplantation [20]. Overall, the analyses represented a broad range of health care systems, perspective, modeling, WTP thresholds, and costs.

In this article, we aimed to

1 Compare mortality and survival rate in MitraClip vs medical treatment
2 Total costs, incremental QALYs and LYQs in MitraClip vs medical treatment
3 Compare ICER and WTP threshold for selected countries.

Table 2 CHEERS checklist

Section/item	Item No	Recommendation	Mealing (2013)	Cameron (2014)	Guerin (2016)	Armeni (2016)	Asgar (2016)	Baron (2019)	Sakamaki (2019)
Title and abstract									
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared	Y	Y	Y	Y	Y	Y	Y
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	Y	Y	Y	Y	Y	Y	Y
Introduction									
Background and objectives	3	Provide an explicit statement of the broader context for the study	Y	Y	Y	Y	Y	Y	Y
		Present the study question and its relevance for health policy or practice decisions	Y	Y	Y	Y	Y	Y	Y
Methods									
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen	Y	Y	Y	Y	Y	Y	Y
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	Y	Y	Y	Y	Y	Y	-
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	Y	Y	Y	Y	Y	Y	Y
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	Y	Y	Y	Y	Y	Y	Y
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Y	Y	Y	Y	Y	Y	Y

Table 2 (continued)

Section/item	Item No	Recommendation	Mealing (2013)	Cameron (2014)	Guerin (2016)	Armeni (2016)	Asgar (2016)	Baron (2019)	Sakamaki (2019)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	11°	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Y	-	Y	Y	Y	Y	Y
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	Y	Y	-	Y	Y	Y	Y
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	Y	Y	Y	-	Y	Y	Y
Estimating resources and costs	13°	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	Y	Y	Y	Y	Y	Y	Y
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	Y	-	Y	Y	Y	Y	Y

Table 2 (continued)

Section/item	Item No	Recommendation	Mealing (2013)	Cameron (2014)	Guerin (2016)	Armeni (2016)	Asgar (2016)	Baron (2019)	Sakamaki (2019)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	Y	Y	Y	Y	Y	Y	Y
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	Y	Y	-	-	-	Y	Y
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model	N	Y	Y	N	Y	Y	Y
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	-	N	Y	Y	Y	Y	Y
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended	Y	Y	-	Y	Y	Y	Y

Table 2 (continued)

Section/item	Item No	Recommendation	Mealing (2013)	Cameron (2014)	Guerin (2016)	Armeni (2016)	Asgar (2016)	Baron (2019)	Sakamaki (2019)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	Y	Y	Y	Y	Y	Y	Y
Characterizing uncertainty	20°	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	N	Y	Y	N	Y	Y	Y
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	N	Y	Y	Y	Y	Y	Y
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	N	N	Y	N	-	-	N
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	Y	Y	Y	Y	Y	Y	Y
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	Y	Y	Y	Y	Y	Y	Y

Table 2 (continued)

Section/item	Item No	Recommendation	Mealing (2013)	Cameron (2014)	Guerin (2016)	Armeni (2016)	Asgar (2016)	Baron (2019)	Sakamaki (2019)
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	Y	Y	N	Y	Y	Y	Y

Mortality and survival rate

All of the studies demonstrated that MitraClip reduces mortality rate and increases survival rate.

Figure 2 shows that mean of mid-term and long-term mortality rate in MitraClip delivery system is lower than medical treatment. Mortality rate at 1 year and 10 years was 16.7% versus 29.77% and 70.9% versus 98.8%, respectively. These results are in line with the results of Larsen et al. study, which stated that the 1-year survival rate in the MitraClip method was 75–90% [21]. Also, Fig. 2 shows that 2-year mortality rate occurred in 33.33% for MitraClip and 62.9% for medical treatment, results in line with Stone et al. study that reports death from any cause within 24 months occurred in 29.1% of the patients in the transcatheter mitral-valve repair plus medical therapy (device group) as compared with 46.1% in the medical therapy alone (control group) [22].

Comparing total costs for MitraClip versus medical treatment

Figure 3 shows the cost for the MitraClip system and medical treatment in different countries, even though all studies have been conducted in developed countries. Despite inherent differences in health care systems, different costs, and WTP thresholds, in all selected countries, the MitraClip method is a more expensive intervention than the medical treatment method for mitral valve repair. Total cost data based on 2019 USD show that the MitraClip method, as a new method, has the highest cost in the USA, Canada, and Japan ($121,390, $78,619, and $70,887, respectively) and the lowest cost in Italy and France ($33,062 and $39,799, respectively). MitraClip system is not the only valve surgery method that is more expensive in the USA than the conventional method; for example, the transcatheter aortic valve implantation (TAVI) method

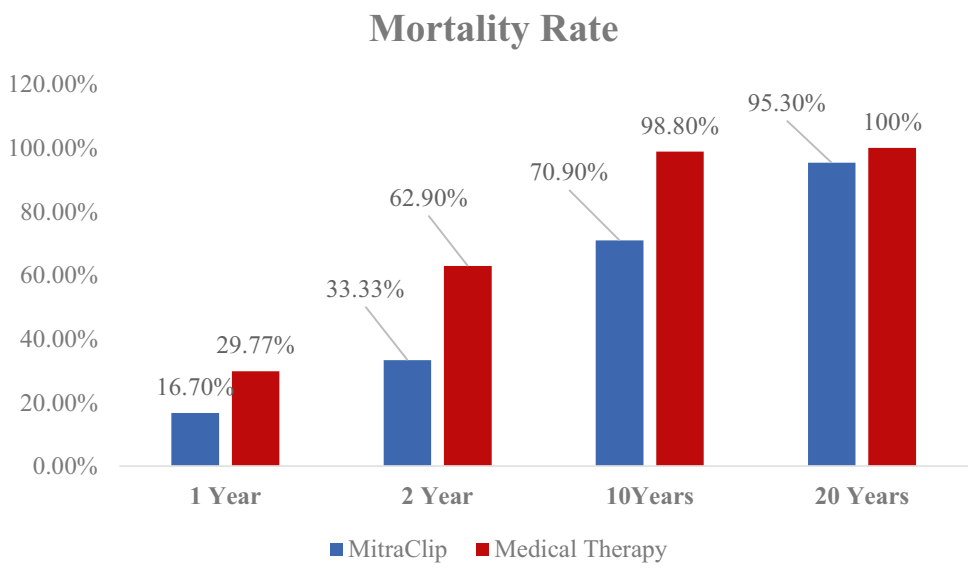

Fig. 2 Mean of mortality rate in MitraClip vs medical therapy

Table 3 Characteristics of included studies in the review

Study/publication year	Country	Funding	Comparators	Health outcomes	Perspective	Time horizon	Time follow-up	Number of patients	Mean age	Sensitivity analysis	Discount rate	Included costs
Mealing (12), 2013	UK	Oxford Outcomes Ltd. and Abbott Vascular	MitraClip vs conventional medical treatment	QALYs, survival	NHS Perspective	Lifetime	2 years	EVEREST II high-risk study	NA	Yes	3.5%	Total cost
Cameron (13), 2014	Canada	Cornerstone Research Group, Inc. and Abbott Vascular	MitraClip therapy vs medical treatment	LYQs, QALYs	Canadian healthcare payer	Lifetime horizon	-	EVEREST II high-risk study	77	Yes	5%	Total costs
Guerin (14), 2016	France	Abbott Vascular	MitraClip strategy vs medical treatment	Mortality, QALYs,	National Health Insurance perspective	Not mentioned	5 years	1000 patients	NA	Yes	4%	Direct medical costs
Armeni (15), 2016	Italy	Abbott Vascular and developed at CERGAS Bocconi	MitraClip + medical treatment vs medical treatment	Survival, QALYs, LYQs	Payer's perspective	Lifetime horizon	20 months	MitraClip = 232, medical treatment = 151	71	Yes	3.5%	Total costs
Asgar(16), 2016	Canada	Montreal Heart Institute Foundation	MitraClip vs medical treatment	Mortality, QALYs, LYQs	Canadian publicly funded health care system	10 years	22 months	MitraClip = 50, medical therapy = 42	MitraClip = 75.4 Medical therapy = 68.2	Yes	5% per year	Total costs
Baron (17), 2019	USA	Abbott	MitraClip vs medical treatment	Survival, QALYs, LYQs	US health care system	Lifetime horizon	2 years	COAPT trial: 614 patients	Medical therapy = 71.1 Medical therapy = 72.8	Yes	3% per year	Total costs
Sakamaki (18), 2019	Japan	Abbott Vascular Japan	MitraClip vs medical treatment	Survival, events, QALYs, LYQs	Public healthcare payer	Lifetime horizon	1 year	AVJ-514 Japan Trial	74 years old	Yes	2% per year	Total costs

QALY quality-adjusted life year, *LYQs* life year gained

Table 4 Summary results of included economic evaluation studies

Study/year	Patient population	Type of modeling	Mortality or survival rate	QALYs	LYQs	Cost	ICER	Threshold	Results
Mealing (12), 2013	Patients with severe mitral regurgitation, ineligible for surgery	Markov model	Survival rate 2Y (MC = 67%, MT = 33.2%), 10Y (MC = 29.1%, MT = 1.2%), 20Y (MC = 4.7%, MT = 0%)	2 years: 0.92 (MC), 0.43 (MT), incremental QALY = 0.48 5 years:1.84 (MC), 0.62 (MT), incremental QALY = 1.22	-	2 years: £28,725 (MC), £3,156 (MT), incremental cost 2Y: £25,565, 5 years: £31,593 (MC), £4,610 (MT), incremental cost 5Y: £26,989	2 years: £52,947 per QALY, 5 years: £22,153 per QALY	£20,000–£30,000 per QALY gained	At the current thresholds used by the NICE in the UK (£20,000 and £30,000 per QALY gained), the probability that MitraClip is cost-effective is approximately and 37% and 93%, respectively
Cameron (13), 2014	High surgical risk patients with significant mitral regurgitation	A decision analytic model	-	MC = 3.24, comparator = 1.51, incremental QALYs = 1.73	LYQs for patient in MC = 3.93, in concurrent comparator = 2.09, incremental LYQs = 1.84	Total costs MC per patient ($CDN) = 62,510, comparator = 21,893, incremental cost = 40,617	23,433 per QALY	$50,000 per QALY gained	MitraClip therapy is likely a cost-effective option for the treatment of patients at high risk for mitral valve surgery with significant mitral regurgitation
Guerin (14), 2016	Mitral regurgitation	Markov model	-	-	MC = 3,255.35, MT = 1,541.7, incremental LYQs = 1 713,64	MC = €29,984, MT = €8,557	€20,720 per death avoided, €15,741 per life year gained	€30,000 per life year gained	The probability of being cost-effective for a threshold of €30,000 per life year gained is 80%
Armeni (15), 2016	Patients with moderate to severe functional mitral regurgitation	Markov model	Survival at 12 months (%), MC = 91.4%, MT = 82.1%	Incremental QALYs = 3.01	Incremental life years = 3.35	MC = € 25,272, MT = € 3,444, incremental cost = 23,342 €	7908 €/QALY	10,000 €/QALY	Compared with MT alone and given conventional threshold values, MitraClip can be considered a cost-effective procedure

Table 4 (continued)

Study/year	Patient population	Type of modeling	Mortality or survival rate	QALYs	LYQs	Cost	ICER	Threshold	Results
Asgar (16), 2016	Patients with heart failure and moderate to severe mitral regurgitation	Markov model	12 months mortality, MC = 18%, MT = 24%	MC = 2.76, MT = 1.13, incremental QALYs = 1.63	MC = 3.6, MT = 1.87, incremental LYQs = 1.74	MC = $88,200, MT = $35,600, incremental cost = $52,600 Canadian dollars	$32,300 per QALY gained	$50,000 and $100,000	In heart failure patients with symptomatic moderate-severe mitral regurgitation, therapy with the MitraClip is associated with superior survival and is cost-effective compared with medical therapy
Baron (17), 2019	Heart failure and secondary mitral regurgitation	NA	24-month mortality, MC = 29.1%, MT = 46.1%	MC = 3.32, MT = 2.5, incremental QALYs = 0.82	Incremental LYQs = 1.13y	MC = $121,390, MT = $75,742, incremental cost = $45,648	$55,600 per QALY gained	$50,000–$100,000/QALY	M increases life expectancy and quality-adjusted life expectancy compared with MT at an incremental cost per QALY gained that represents acceptable economic value based on current US thresholds
Sakamaki (18), 2019	Patients with symptomatic severe MR at high surgical risk	Markov model	Mortality (/month), MC = 1.96%, (/month), MT = 3.16%, (/month)	MC = 3.23, MT = 1.78, incremental QALYs = 1.45	MC = 3.85, MT = 2.42, incremental QALYs = 1.43	MC = 7,541,151 JPY, MT = 4,699,692 JPY, incremental cost = 2,841,459□	1,968,389 JPY/QALY, 1,996,778 JPY/LYQs	5 million JPY/QALY	MitraClip procedure improved life years and quality of life in patients at high surgical risk and it was also a cost-effective treatment option

QALY quality-adjusted life year, *LYQs* life year gained *MC* MitraClip, *MT* medical therapy

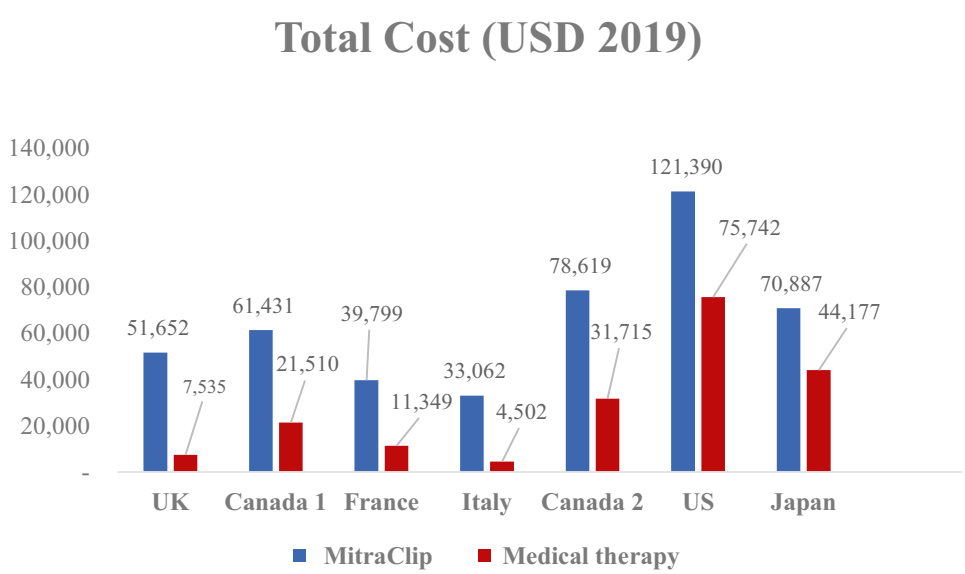

Fig. 3 Total cost of MitraClip and medical therapy in selected countries

total costs more than $70,000 in the USA, while in European countries such as Italy and France, it costs about $35,000.

As such, the key economic question is whether or not the MitraClip system offers enough benefit to offset the additional costs incurred by treatment. The data of the present study show that despite the higher costs of the MitraClip system, it creates upper QALYs and LYQs and lower mid-term (1 year) and long-term (10 years and 20 years) mortality rates for patients compared with medical treatment. In all studies that present QALYs and LYQs indicators, MitraClip system has generated higher values, meaning that MitraClip procedure increased life expectancy and quality of life in patients at high surgical risk, which is consistent with lower mortality rates and higher survival rates of the MitraClip method vs medical treatment.

Comparing threshold and ICER for selected countries

All seven final included studies reported cost per QALY and threshold in the current study. Figure 4 shows that the highest ICER for the MitraClip system is in the USA ($55,600/QALY) and the lowest in Italy ($10,616/QALY). One of the reasons for the high cost per QALY in the USA is the higher cost of this surgical procedure compared with European countries, such as Italy. Of course, despite the high costs in the USA for MitraClip system, this country has the highest threshold for willingness to pay ($100,000 per QALY), while the threshold in a country like Italy is only €10,000/QALY ($11,800/QALY). Figure 4 shows that in all six selected countries (UK, Canada, France, Italy, USA, and

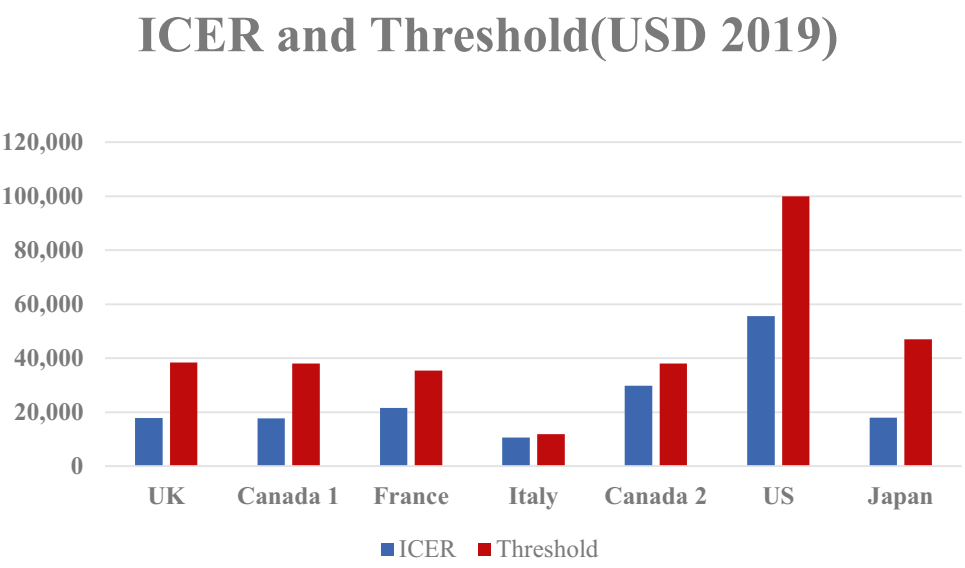

Fig. 4 Cost per QALY and WTP threshold in selected countries

Japan), threshold for willingness to pay is upper than cost per QALY, which means that at the current thresholds used by the health care systems in selected countries such as NICE in the UK (£30,000 per QALY gained) and in the Japan (5 million JPY/QALY), MitraClip is cost-effective, the only country where ICER and threshold are close to each other being Italy (€7908/QALY for ICER and €10,000/QALY for threshold), which has both lower costs and lower thresholds compared with other European countries; also, Japan has the largest difference in threshold values and cost per QALY (1,968,389 JPY/QALY for ICER and 5 million JPY/QALY for threshold 0.38 = 1,968,389/5,000,000), which indicates the high probability of cost-effectiveness of the MitraClip method in this country.

Limitation

- Given that the US "Food and Drug Administration" (FDA) has approved the percutaneous edge-to-edge trans-catheter mitral valve repair in October 2013, the present study shows that only seven economic evaluation studies have been conducted to evaluate the cost-effectiveness of this method, so it seems that more economic evaluation studies are needed to draw robust conclusions.
- Due to the novelty of this surgical method, its long-term outcomes such as reoperation and long-term mortality such as 20 years in the real world are unclear.
- Given that all cost-effectiveness studies are conducted in developed countries, due to lower WTP thresholds in middle- and low-income countries, as well as differences in intervention costs, results cannot be generalized and we cannot comment on the possibility of cost-effectiveness in these countries.

Conclusion

To conclude, evidence from this systematic review suggests that MitraClip strategy improved both life expectancy and quality-adjusted life years compared with medical treatment in patients at high surgical risk and it was also a cost-effective treatment option; results show that in all six selected countries (UK, Canada, France, Italy, USA, and Japan), WTP threshold is upper than the cost per QALY from a different perspective and in different health care systems.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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