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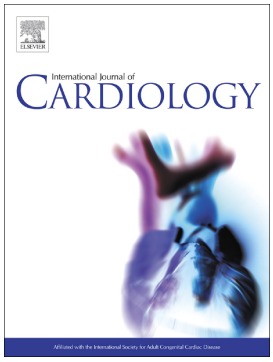

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Prognostic Impact of MitraClip In Patients with Left Ventricular Dysfunction and Functional Mitral Valve Regurgitation: A Comprehensive Meta-analysis of RCTs and Adjusted Observational Studies

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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*= both authors gave the same contribution.

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Abstract

The real prognostic impact of MitraClip in patients with significant functional mitral regurgitation (FMR) and left ventricular (LV) dysfunction remains to be elucidated. Two randomized controlled trials (RCTs) with conflicting results have been recently published.

We conducted a comprehensive meta-analysis of all RCTs and adjusted observational studies to evaluate the clinical impact of percutaneous mitral valve repair when compared with optimal medical therapy (OMT) alone, in patients with symptomatic FMR and LV dysfunction. Death from any cause and heart failure rehospitalizations at the longest available follow-up were the primary endpoints. Cardiac death, one year and short-term death were the secondary ones. 2255 patients (1207 for MitraClip and 1048 for OMT-only) from 8 studies (2 RCTs and 6 observational studies) were included. At a median (mid-term) follow-up of 438 days (IQR 360-625) MitraClip was associated with a significant reduction of all-cause death (odds Ratio [OR] 0.55, 95%CI 0.41-0.73, p<0.001; [ORadj] 0.66, 95%CI 0.49-0.90, p=0.009) and rehospitalization (OR 0.49, 95%CI 0.24-1.00, p=0.05 and ORadj 0.63, 95%CI 0.43-0.94, p=0.02). At one year, adjusted analysis demonstrated a trend favoring the experimental cohort (ORadj 0.73, 95%CI 0.53-1.02, p=0.07). Meta-regression suggested that benefit of MitraClip on mid-term survival persists even after accounting for the prevalence of implanted CRT, burden of comorbidities, NYHA class, cardiomyopathy etiology and LV function and dimensions. In conclusion, MitraClip for FMR in patients with LV dysfunction is associated with a considerable reduction of death and HF hospitalization at mid-term follow-up. Further ongoing RCTs are needed to strengthen present results.

Keywords MitraClip; FMR; HFrEF; OMT

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Introduction

Functional mitral regurgitation (FMR), resulting from left ventricular enlargement and remodeling in otherwise structurally normal mitral leaflets, is the most frequent valvular disease in heart failure with reduced ejection fraction (HFrEF). Its severe forms affect up to 24% of this population (1). Although the presence of FMR has shown to predict lower survival, it is not clear if it represents a negative prognostic determinant independently or whether it is only a marker of the disease (2). While controversies exist concerning mitral valve repair in addition to CABG in the context of heart failure (3), the role of isolated mitral valve surgery in HFrEF patients with severe FMR without an indication for revascularization is even more disputed (4). Percutaneous mitral valve repair (PMVR) with the Mitraclip system has been shown to be safer, even if not equally effective, than the surgical approach in high-risk patients with primary MR (5). Furthermore, several observational registries showed good performance of this approach in FMR (6,7), suggesting potential survival benefit when compared to optimal medical therapy (OMT) alone (8-12). Two RCTs evaluating the impact of MitraClip on top of medical therapy in FMR secondary to left ventricle (LV) dysfunction have been recently published, showing conflicting results (13,14). We therefore performed a meta-analysis of all RCTs and adjusted observational studies to evaluate the presence of a real independent prognostic effect of PMVR when compared with medical therapy alone.

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Methods

This analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, respecting recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (15-17). Pubmed, Cochrane and Google Scholar were systematically screened using the terms “medical therapy” or "OMT" and "mitraclip" or “percutaneous repair” and “functional” or “secondary” and “mitral regurgitation”. Moreover, abstract presentations at national and international congresses of last 10 years were screened.

All studies identified were screened by two independent reviewers (MB and AG) at abstract level. Potentially eligible studies were then appraised as full text. Divergences were solved by consensus with the opinion of a third reviewer (FC). The most relevant papers quoted in selected articles, in other meta-analysis, in recent guidelines or consensus papers on this topic were screened too.

Included articles were randomized controlled trials or observational studies with multivariate analysis comparing optimal medical therapy alone and percutaneous mitral repair through MitraClip system in FMR. Exclusion criteria were: non-human studies, articles not written in English, duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected), studies with less than 40 patients in each subgroup and those enrolling more than 30% of primary mitral regurgitation (PMR). In case of mixed etiologies, outcome referring to FMR were considered when available. Three independent reviewers (MB, AG, FC) abstracted the data on outcome of included articles as well as baseline characteristics of enrolled populations. MB and AG independently evaluated the quality of the selected studies using modified MOOSE criteria to take into account the specific features of included studies (15). MB and AG

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separately appraised study design, geographical area, data source and statistical methods for multivariable analysis, as well as risk of analytical, selection, adjudication, detection, and attrition bias. Death and heart failure hospitalization occurring at the longest available follow-up period were the primary endpoints. Twelve-month death, short term death (defined as events occurring within 30 days from interventions) and cardiac death were the secondary ones. All outcomes were evaluated only at study level and initially analyzed pooling together univariate analysis results, followed by pooling results after adjustment by multivariate analysis and logarithmic transformation of results of randomized controlled trial or adjusted multivariate analysis. Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). A random-effect meta-regression was performed to assess the impact of age, NYHA class, comorbidities (Chronic Kidney Disease [CKD], Atrial Fibrillation [AF] and Diabetes Mellitus [DM]), cardiomyopathy etiology and echocardiographic data (Ejection Fraction [EF] and left ventricle end-systolic diameter [LVESD]) on association between MitraClip and primary endpoint. Standard hypothesis testing was set at the two-tailed 0.05 level.

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Results

A flowchart summarizing the literature search flow is shown in Figure 1. 130 studies were initially screened. 122 citations were excluded, as they were judged non-pertinent or not fitting of the inclusion criteria. Eventually, 7 articles were selected in the present meta-analysis and appraised as full text. Full text for the paper by Adamo et al. was not available (18). Therefore, data were derived from the abstract as in the meta-analysis by Giannini et al. (19). Finally, 6 adjusted observational studies (8-12,18) and two RCTs (13-14) were included in the analysis. All observational studies except for one used propensity score matching to limit selection biases in result interpretation. Accuracy of propensity score was good along all of the included studies. Swaans et al. and Velazquez et al. (8,9) also included degenerative mitral regurgitation (DMR). While the first provided data of outcomes in patients with FMR only, the second did not. We therefore performed a sensitivity analysis excluding results from Velazquez et al. An additional analysis excluding data from Adamo et al was performed since their data have not been published in a journal (and thus had no peer-review). Ultimately, 2255 patients in 8 studies were included in the present analysis. Table 1 summarizes the general characteristics of the enrolled population weighted for each study, while table 2 shows patients' characteristics in each of the studies that were included. Inclusion/exclusion criteria for each study are summarized in the Appendix (see **Table S1)**. Overall, 1207 patients were treated with MitraClip and 1048 with conservative therapy. Included patients were predominantly males (75%), with a mean age of 71 years and a high surgical risk profile (mean STS 10.4%, mean Euroscore- 21). They also suffered from a significant burden of comorbidities and were highly symptomatic (85% were described as NYHA class III-IV). The most frequent etiology was ischemic cardiomyopathy (65%), with a severely reduced ejection fraction (mean value of 26%). Procedural results and in-hospital adverse events are depicted in **Table S2**. A minority of the studies provided

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complete data but, overall, technical and clinical success rates were high. The rate of technical success is similar between the two RCTs, while in the COAPT a slightly higher percentage of the procedures resulted in mild MR after the implantation and more patients were implanted with 2 clips.

Over a median follow-up of 438 days [IQR 360-625] (mid-term follow-up), MitraClip was associated with a significant reduction in all-cause death when compared with OMT alone [Odds Ratio [OR] 0.55, 95%CI 0.41-0.73, p<0.001; Adjusted Odds Ratio [ORadj] 0.66, 95%CI 0.49-0.90, p=0.009, **Figure 2**]. A significant reduction was also demonstrated in the unadjusted analysis for mid-term cardiovascular death [OR 0.44, 95%CI 0.22-0.89, p=0.020, **Figure S1a**], albeit not in the adjusted analysis [ORadj 0.59, 95%CI 0.32-1.10, p=0.100, **Figure S1b**]. When using data limited to 1 year of follow-up, only a non-significant trend favoring MitraClip over medical therapy remained following adjustment for confounders [OR 0.56, 95%CI 0.38-0.83, p=0.003; ORadj 0.73, 95%CI 0.53-1.02, p=0.07, see **Figure S2a-S2b**].

Short-term death was reported in 4 of the studies (9,10,13,14). No significant association between treatment arm and 1-month death had emerged in either unadjusted [OR 0.88, 95% CI 0.50-1.57, p=0.67, **Figure S3a**] or adjusted analyses [ORadj 1.04, 95% CI 0.44-2.51, p=0.92, **Figure S3b**].

Five studies provided adjusted data on rehospitalizations for heart failure (10,12,13,14). Patients in the device group had a reduced risk of rehospitalizations after adjustment [OR 0.49, 95%CI 0.24-1.00, p=0.05 and ORadj 0.63, 95%CI 0.43-0.94, p=0.02, **Figure 3**].

Meta-regression analysis showed no evidence of effect modification of many clinical and echocardiographic variables. In particular, age (ß -0.064, 95% CI from -0.214 to 0.085; p 0.400), ischemic versus non-ischemic cardiomyopathy (ß -0.034, 95% CI from -0.106 to 0.038; p 0.350), LVEF (ß -0.004, 95% CI from -0.087 to 0.078; p 0.916),

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prevalence of implanted CRT (ß 0.019, 95% CI from -0.031 to 0.068; p 0.463) and NYHA IV (ß 0.016, 95% CI from -0.063 to 0.096, p 0.686) did not modify the benefit of MitraClip on mid-term survival (see **Table 3**).

As Velazquez et al (9) included both FMR and primary MR, in order to assess the consistency of the main results in selected FMR patients, we performed a sensitivity analysis for the primary endpoint of all-cause mid-term death. We also excluded unpublished data from Adamo et al, that have not been peer-reviewed. The association between the percutaneous repair and reduction of death was confirmed by both sensitivity analyses [see **Figure S6**].

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Discussion

To the best of our knowledge, this is the largest and most comprehensive meta-analysis, pooling data from all RCTs and adjusted observational studies, comparing MitraClip and OMT in patients with FMR and HFrEF. Our main findings are: MitraClip in addition to OMT is associated with a reduction in death and rehospitalizations for heart failure at mid-term follow-up; The reduction in death seems to emerge after the first year from the procedure and is mainly driven by observational adjusted studies; Metaregression analysis suggests that benefit of MitraClip persists irrespective of age, prevalence of implanted CRT, NYHA class and burden of comorbidities.

Despite its high prevalence in HFrEF, FMR seems to be highly undertreated in these patients (1,20). This fact probably results from the scientific community's perception that FMR is more a consequence of ventricular failure than a real contributor to the disease. However, it has been clearly demonstrated that, particularly in earlier phases, FMR represents an independent prognostic determinant, such that a dedicated therapeutic approach beyond medical therapy is needed in this setting (21). Surgical repair or replacement are often limited by the high peri-procedural mortality rate in a such frail patients, and has shown unconvincing results in terms of long-term improvement in survival (3). Consequently, the MitraClip percutaneous approach has emerged as an important therapeutic strategy in this setting, also considering the low procedural mortality risk and high feasibility rate. The EVEREST II pivotal RCT was mainly focused on degenerative MR, with less than one third of the patients diagnosed as FMR prior to the procedure. The study demonstrated good safety and durability of this approach, including at long term follow-up (22). However, worse early efficacy outcomes were exhibited, when compared with the surgical strategy (5). Subsequent experience from European registries showed that interventional cardiologists seemed to prefer the MitraClip solution for patients with secondary regurgitation, confirming and

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even demonstrating improved results than the approval trial (6,7,23,24). For this reason, the European Society of Cardiology guidelines state that PMVR may be considered for patients with left ventricular dysfunction and FMR who are symptomatic despite optimized medical and device therapy (e.g. CRT when indicated) (4,25). On the contrary, the American society guidelines did not make any recommendations for PMVR for FMR, considering the lack of randomized evidence since their last publication (26). Our analysis collects all published data on the prognostic impact of MitraClip repair, as compared with conventional treatment, including all adjusted observational studies as well as the two recently published RCTs, showing significant reduction in death at long term follow-up. This benefit seems to emerge only after the first year from the intervention and reaches significance only following the addition of observational studies to the randomized ones. Until now, only one other meta-analysis, which has preceded the publication of the two RCTs, has been published on this issue, confirming our conclusions also at a patient level analysis (19). Among real-world observational studies, the one by Adamo et al. (18) was the only one which did not demonstrate a reduction in death, after adjustment for baseline confounders. The inclusion of an advanced heart failure population could justify this report. Among this subgroup of HFrEF patients, in fact, selecting those that could benefit from PMVR still poses a significant challenge. Highly compromised left ventricle function, scarcely reversible pulmonary hypertension and out-of-proportion right heart dysfunction should be accounted as red flags. Nevertheless, even in a such arduous context, some multicenter experience showed good survival (around 94%) 6 months after clipping, confirming furthermore a clear reduction in re-hospitalization rates and improvement in functional capacity (27). From a pathophysiological point of view, an elegant haemodynamic study by Gaemperli et al. demonstrated how, after MitraClip implantation, the acute increase in left ventricle afterload is overcome by the reduction in end-diastolic wall stress, leading

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to a significant increase in cardiac index (CI) and a reduction in left atrial and pulmonary artery pressures. Importantly, these latter consequences correlate with outcome on follow-up (28). Moreover, the slight increase in CI could contribute to an improvement in prognosis of these patients, delaying multiorgan failure by hypoperfusion, reducing hospitalizations for acute decompensations. They may also allow for titration or introduction of new heart failure medications, such as Angiotensin Receptor-Neprilisin Inhibitors (ARNI), which have shown a dramatic improvement in survival (29). When a successful procedure is performed and a 2+ or less MR is achieved thereafter, these beneficial haemodynamic effects tend to persist for a long period of time (22), contributing to a certain degree of LV remodeling and probably explaining the observed survival benefit when compared with medical therapy alone (30).

After years of relying on observational studies, two RCTs have been recently published. Surprisingly, their conclusions were conflicting. While the MITRA-FR (by Obadia and Colleagues) found no significant benefit, in terms of survival or rehospitalizations after one year, the COAPT trial (Stone and Colleagues) demonstrated an impressive reduction in death and rehospitalizations due to heart failure at 2 years of follow-up with a convincing NNT (5.9 and 3.1, respectively) (13,14). Many reasons have been suggested to justify this discrepancy. First of all, Obadia et al. enrolled around 300 patients while Stone et al., with more than 600 patients enrolled, had enough power to show superiority in terms of death at a longer follow-up. Furthermore, different echocardiographic criteria for MR severity were used: the first study included patients with an effective regurgitant orifice area (EROA) over 20 mm^2 while the second used 30 mm^2 as the cutoff. However, patients enrolled in the French trial seemed to be “sicker” than those in the North-American one. Mean death and hospitalization rates at one year, in fact, were significantly higher than those in all real-world observational registries published since then (6,7,23). This data suggests that HF patients enrolled by Obadia et

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al. may be beyond their “window of opportunity” to benefit from such an interventional approach. Moreover, the technical and clinical success of the interventional procedure in the European trial was inferior to that in Stone et al., perhaps because of the inclusion of centers with little former experience with the procedure. Finally, the significant lack of data, particularly related to right heart function and the medical therapy optimization in the two groups during the follow-up period, strongly limits further interpretations. Our meta-analysis did not show a significant reduction in rates of death, as well as HF rehospitalizations, at mid-term follow-up pooling only RCT evidence, probably because of the limited sample size, underscoring the need for further adequately designed and powered RCTs to strengthen our conclusions.

Finally, the benefit of PMVR in terms of mid-term death reduction in our analysis seems to persist irrespective of the presence of CRT, burden of comorbidities, type of cardiomyopathy and LV function or dimensions. Our findings are consistent with those derived by Giannini et al., using patient level analysis (19), and those by the Sentinel registry on FMR, concerning the impact of ischaemic etiology on outcomes (23). Nevertheless, severe LV dysfunction and dilatation have been clearly shown as poor prognostic predictors (31). Along with right heart reserve, these factors have to be the main determinants of assessment when selecting patients for MitraClip.

Our work bears several limitations. First, a small number of studies and patients were evaluated. However, after pooling data of more than 2200 patients with rEF and severe MR, our study represents, to the best of our knowledge, one of the largest in this field. A minority of the studies provided complete data and even if technical and clinical success rates were high among several studies, incompleteness of echo data and lack of independent echo lab in observational works partly weakens interpretation of results. The primary endpoint analysis, moreover, resulted in a high level of heterogeneity not related to differences in clinical variables among the studies which were similar: we tried

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to manage it by performing a subgroup analysis (RCT vs. not RCT) and by using random effect method. The reduction of death using MitraClip reaches significance only after adding observational studies, partly limiting our main conclusions. Even if solid statistical adjustment methods have been performed, a certain degree of selection as well as adjudication biases may persist. Furthermore, lack of control of performance of propensity score in 3 observational studies represents a limitation in this sense. On the other hand, observational studies have the merit of providing a “real life” view, maybe with more generalizability than some not optimally designed RCTs. As with any meta-analysis, particularly those with a non-patient level design, inter-study heterogeneity in inclusion and exclusion criteria, as well as outcome definitions, complicates our result generalizability. The possible bias of mixed functional and degenerative MR population in Velazquez et al. paper (9) was tested by a sensitivity analysis that confirmed our results. The lack of full text availability for Adamo et al. (18) could represent another major issue, but the recently published meta-analysis by Giannini et al. was used to obtain needed data (19) and our results were confirmed using a sensitivity analysis.

In conclusion, the present meta-analysis shows that MitraClip correction of FMR is associated with a considerable reduction in death and heart failure rehospitalizations at mid-term follow-up in patients with LV dysfunction. Benefit seems to persist irrespective of comorbidities, prevalence of implanted CRT, cardiomyopathy etiology and left ventricle function and dimensions. Further ongoing RCTs are needed to confirm present results.

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Figure legends

Figure 1: PRISMA flow diagram

Figure 2: Adjusted all-cause mid-term death

Figure 3: Adjusted mid-term hospitalization for HF

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Table 1. General patients' characteristics	
	Mean value or percentage
Age	71,3
Male sex	74,8
BMI°	23,9
Log Euroscore*	21
STS score°	10,4
Hypertension°	46,0
Hyperlipedemia°	40,8
Diabetes mellitus	41,8
Atrial fibrillation	45,9
COPD°	40,1
CKD	47,7
Ischemic heart disease	65,0
FMR	95,1
NYHA III-IV	85,3
EF	26

° data not available for MITRA-FR
* data not available for MITRA-FR and COAPT

BMI: body mass index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; FMR: functional mitral regurgitation; EF: ejection fraction

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Table 2. Baseline characteristics in Mitraclip vs OMT groups

	Number of pts		Functional MR		Age		Male gender		Prior MI		DM		CKD[#]		AF		EF		LVESD (mm)		LVEDV (ml/m2)		EUROSCORE		STS		NYHA III-IV	
	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT	Mitraclip	OMT
Observational studies																												
Swaans et al	139	59	107 (77)	48 (81)	75 ± 9	72 ± 10	94 (68)	32 (54)	72 (51)	25 (42)	32 (23)	17 (29)	55 (40)	18 (31)	74 (53)	24 (41)	37 ± 15	35 ± 17	-	-	-	-	24 ± 16	19 ± 13	13.5 ± 9[§]	4.3 ± 4[§]	123 (89)	51 (86)
Velazquez et al*	239	239	198 (83)	217 (91)	74 ± 11	74 ± 11	143 (60)	130 (54)	124 (52)	109 (46)	94 (40)	105 (44)	64 (27)	62 (26)	137 (65)	139 (58)	42 ± 12	42 ± 11	47 ± 10	39 ± 10	-	-	-	-	9.9 ± 7	13.8 ± 10.9	187 (78)	190 (80)
Adamo et al[§]	33	33	33 (100)	33 (100)	71 ± 9	71 ± 12	23 (70)	22 (67)	14 (42)°	12 (36)°	-	-	20 (61)	19 (58)	16 (48)	18 (55)	30 ± 9	30 ± 8	-	-	-	-	-	-	-	-	-	-
Giannini et al	60	60	60 (100)	60 (100)	74 ± 8	76 ± 8	42 (70)	38 (63)	22 (37)	23 (38)	17 (28)	18 (30)	29 (48)	20 (33)	21 (35)	26 (43)	37 ± 15[§]	35 ± 11[§]	50 ± 13	49 ± 10	187 ± 70	178 ± 54	21 ± 14[§]	21 ± 13[§]	4.9 ± 4.2[§]	3.8 ± 2.6[§]	44 (73)	45 (76)
Armeni et al	232	151	232 (100)	151 (100)	71 ± 10	71 ± 11	171 (73)	112 (74)	105 (45)	75 (50)	67 (30)	44 (29)	-	-	77 (33)	50 (33)	34 ± 13	32 ± 10	-	-	-	-	-	-	-	-	-	-
Asgar et al	50	42	50 (100)	42 (100)	75 ± 9	68 ± 16	37 (74)	33 (77)	39 (78)°	30 (71)°	21 (42)	13 (31)	-	-	29 (58)	27 (64)	38 ± 16	32 ± 14	-	-	-	-	-	-	-	-	49 (98)	9 (21)
RCT																												
MITRA-FR	152	152	152 (100)	152 (100)	70 ± 10	71 ± 10	120 (79)	107 (70)	75 (49)	52 (34)	50 (33)	39 (26)	22 (15)	19 (13)	49 (35)	48 (33)	33 ± 6	33 ± 7	-	-	136 ± 37	134± 33	6,6 (3,5; 11,9)[√]	5,9 (3,4; 10,4)[√]	-	-	96 (63)	108 (71)
COAPT	302	312	302 (100)	312 (100)	72 ± 12	73 ± 11	201 (67)	192 (61)	156 (52)	160 (51)	106 (35)	123 (39)	214/299 (72)	227/302 (75)	173 (57)	166 (53)	31 ± 9	31 ± 10	53 ± 9	53 ± 9	194 ± 69[^]	191 ± 73[^]	-	-	7.8 ± 5.5	8.5 ± 6.2	172/302 (57)	201/311 (65)

Data are expressed as mean ± SD or absolute numbers (%)

* High-risk propensity-matched patients

[§] Data from Giannini et al, 2018

° Coronary artery disease

[#] CKD defined as eGFR < 45 ml/min by Swaans et al and Giannini et al. In COAPT number of patients with eGFR < 60 ml/min is specified. CKD definition not specified in other studies.

[√] Data for EUROSCORE II (IQR)

[^] Values not indexed for BSA

MR: mitral regurgitation; MI: myocardial infarction; DM: diabetes mellitus; CKD: chronic kidney disease; AF: atrial fibrillation; EF: ejection fraction; LVESD: left ventricular end systolic diameter

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Table 3. Meta-regression analysis

Covariate	β	Lower Bound	Upper Bound	Standard Error	p-value
EF	- 0,004	-0,087	0,078	0,042	0,916
Age	-0,064	-0,214	0,085	0,076	0,400
LVESD	-0,001	-0,013	0,010	0,006	0,808
CRT	0,019	-0,031	0,068	0,025	0,463
Ischemic CMP	-0,034	-0,106	0,038	0,037	0,350
NYHA class IV	0,016	-0,063	0,096	0,040	0,686
AF	0,001	-0,024	0,025	0,012	0,963
CKD	-0,008	-0,018	0,003	0,005	0,154
Diabetes mellitus	0,010	-0,013	0,034	0,012	0,388
Previous myocardial infarction	0,001	-0,032	0,034	0,017	0,939

EF: ejection fraction; LVESD: left ventricular end systolic diameter; CRT: cardiac resynchronization therapy; CMP: cardiomyopathy; AF: atrial fibrillation; CKD: chronic kidney disease

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Highlights

- MitraClip may reduce death and HF hospitalizations in functional mitral regurgitation;
- The reduction in death seems to emerge after the first year from Mitraclip;
- These benefits persist irrespective of age, CRT, functional class and comorbidities;

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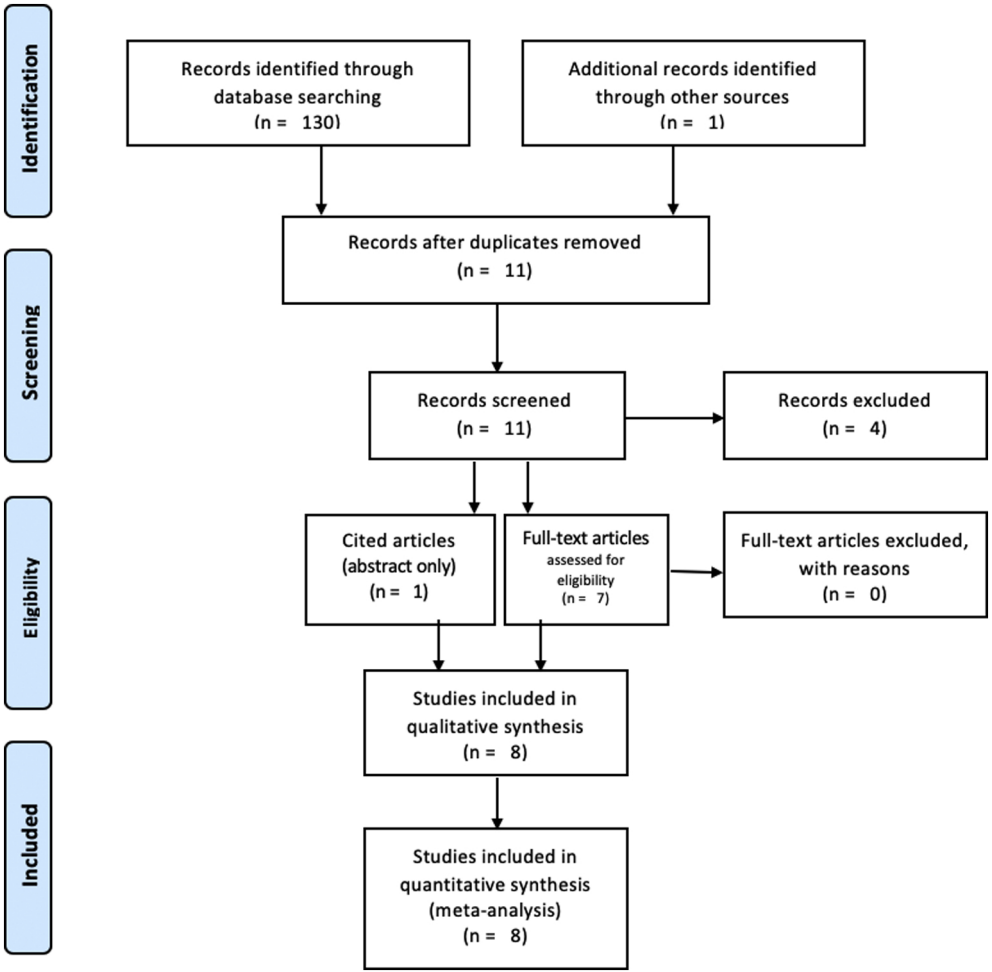
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Screening
Eligibility
Included
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Records after duplicates removed (n = 11)
Records screened (n = 11)
Records excluded (n = 4)
Cited articles (abstract only) (n = 1)
Full-text articles assessed for eligibility (n = 7)
Full-text articles excluded, with reasons (n = 0)
Studies included in qualitative synthesis (n = 8)
Studies included in quantitative synthesis (meta-analysis) (n = 8)

Figure 1

Adjusted long-term death

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
2.4.1 Adjusted observational studies				
Adamo 2017	0.11	0.039	16.7%	1.12 [1.03, 1.20]
Armeni 2016	−0.462	0.0422	16.7%	0.63 [0.58, 0.68]
Asgar 2017	−0.978	0.4624	6.8%	0.38 [0.15, 0.93]
Giannini 2016	−0.844	0.2975	10.5%	0.43 [0.24, 0.77]
Swaans 2014	−0.7765	0.3537	9.1%	0.46 [0.23, 0.92]
Velazquez 2015	−0.5108	0.182	13.7%	0.60 [0.42, 0.86]
Subtotal (95% CI)			**73.5%**	**0.61 [0.42, 0.89]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 114.02$, df = 5 (P < 0.00001); $I^2 = 96\%$				
Test for overall effect: Z = 2.58 (P = 0.010)				
2.4.2 RCT				
COAPT NEJM '18	−0.478	0.1523	14.5%	0.62 [0.46, 0.84]
MITRA–FR NEJM'18	0.1044	0.2426	12.0%	1.11 [0.69, 1.79]
Subtotal (95% CI)			**26.5%**	**0.80 [0.46, 1.42]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 4.13$, df = 1 (P = 0.04); $I^2 = 76\%$				
Test for overall effect: Z = 0.75 (P = 0.45)				
Total (95% CI)			**100.0%**	**0.66 [0.49, 0.90]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 119.26$, df = 7 (P < 0.00001); $I^2 = 94\%$				
Test for overall effect: Z = 2.63 (P = 0.009)				
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.43), $I^2 = 0\%$				

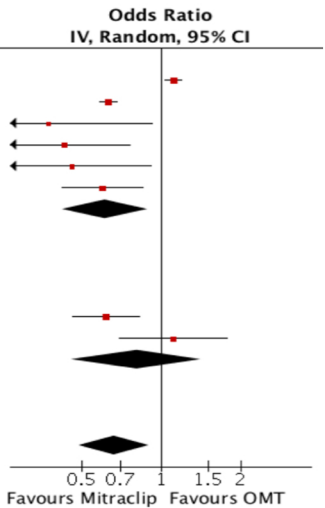


Figure 2

Adjusted long-term hospitalization for HF

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
2.3.1 Adjusted observational studies				
Adamo 2017	-0.1165	0.0481	26.6%	0.89 [0.81, 0.98]
Asgar 2017	-1.9459	0.496	10.2%	0.14 [0.05, 0.38]
Giannini 2016	-0.6162	0.2999	16.9%	0.54 [0.30, 0.97]
Subtotal (95% CI)			**53.7%**	**0.46 [0.20, 1.09]**
Heterogeneity: $Tau^2 = 0.47$; $Chi^2 = 16.00$, df = 2 (P = 0.0003); $I^2 = 88\%$				
Test for overall effect: Z = 1.76 (P = 0.08)				
2.3.2 RCT				
COAPT NEJM '18	-0.6349	0.1436	23.7%	0.53 [0.40, 0.70]
MITRA-FR NEJM'18	0.1222	0.1699	22.6%	1.13 [0.81, 1.58]
Subtotal (95% CI)			**46.3%**	**0.77 [0.37, 1.62]**
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 11.58$, df = 1 (P = 0.0007); $I^2 = 91\%$				
Test for overall effect: Z = 0.69 (P = 0.49)				
Total (95% CI)			**100.0%**	**0.63 [0.43, 0.94]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 29.71$, df = 4 (P < 0.00001); $I^2 = 87\%$				
Test for overall effect: Z = 2.27 (P = 0.02)				
Test for subgroup differences: $Chi^2 = 0.77$, df = 1 (P = 0.38), $I^2 = 0\%$				

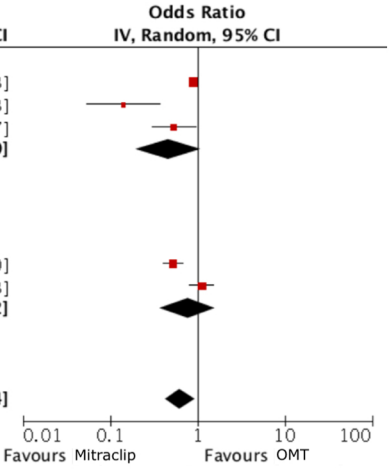
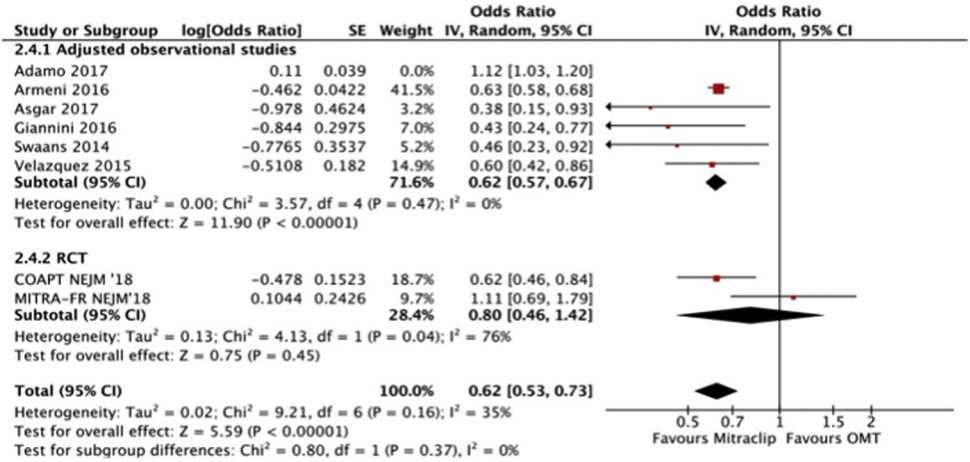
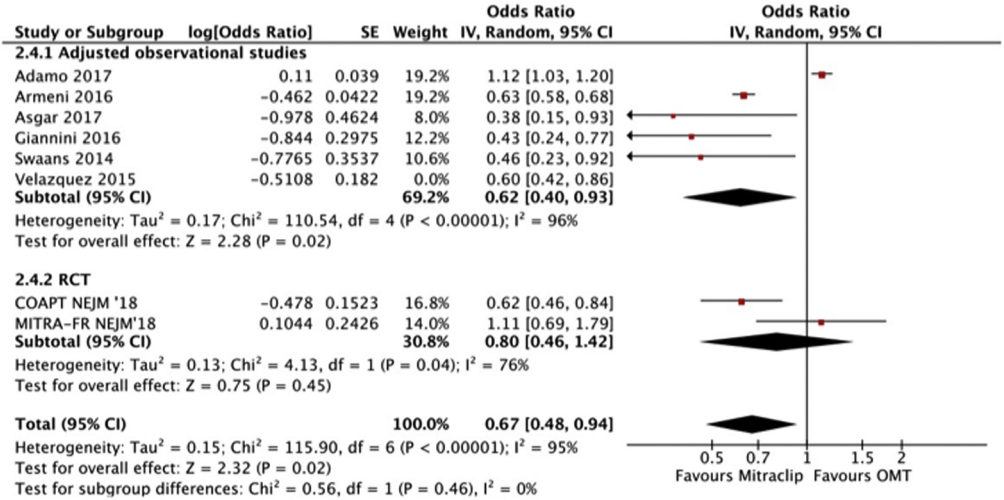
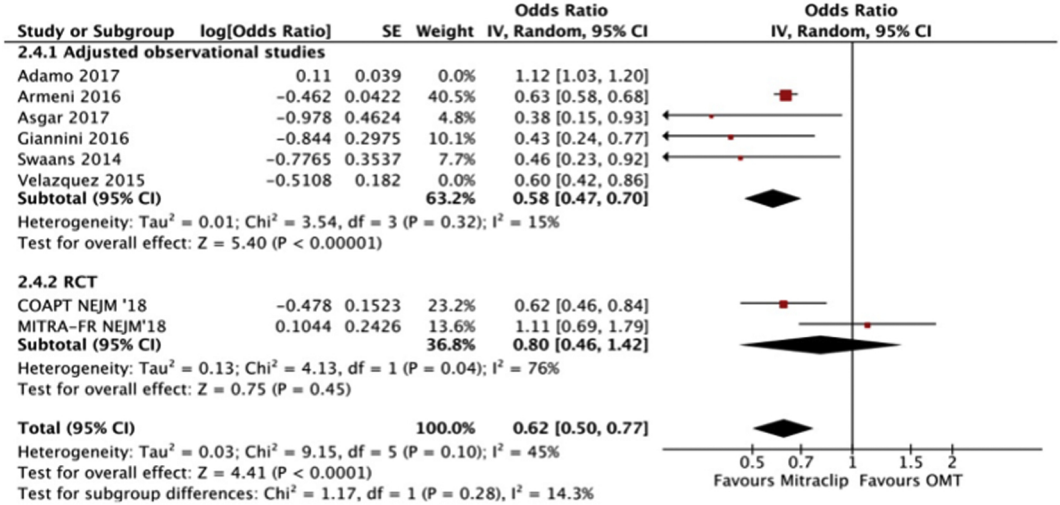


Figure 3


Study or Subgroup log[Odds Ratio] SE Weight Odds Ratio IV, Random, 95% CI
Odds Ratio IV, Random, 95% CI
2.4.1 Adjusted observational studies
Adamo 2017 0.11 0.039 0.0% 1.12 [1.03, 1.20]
Armeni 2016 −0.462 0.0422 41.5% 0.63 [0.58, 0.68]
Asgar 2017 −0.978 0.4624 3.2% 0.38 [0.15, 0.93]
Giannini 2016 −0.844 0.2975 7.0% 0.43 [0.24, 0.77]
Swaans 2014 −0.7765 0.3537 5.2% 0.46 [0.23, 0.92]
Velazquez 2015 −0.5108 0.182 14.9% 0.60 [0.42, 0.86]
Subtotal (95% CI) 71.6% 0.62 [0.57, 0.67]
Heterogeneity: Tau² = 0.00; Chi² = 3.57, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 11.90 (P < 0.00001)
2.4.2 RCT
COAPT NEJM '18 −0.478 0.1523 18.7% 0.62 [0.46, 0.84]
MITRA-FR NEJM'18 0.1044 0.2426 9.7% 1.11 [0.69, 1.79]
Subtotal (95% CI) 28.4% 0.80 [0.46, 1.42]
Heterogeneity: Tau² = 0.13; Chi² = 4.13, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 0.75 (P = 0.45)
Total (95% CI) 100.0% 0.62 [0.53, 0.73]
Heterogeneity: Tau² = 0.02; Chi² = 9.21, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 5.59 (P < 0.00001)
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%
0.5 0.7 1 1.5 2
Favours Mitraclip Favours OMT


Study or Subgroup log[Odds Ratio] SE Weight Odds Ratio IV, Random, 95% CI
Odds Ratio IV, Random, 95% CI
2.4.1 Adjusted observational studies
Adamo 2017 0.11 0.039 19.2% 1.12 [1.03, 1.20]
Armeni 2016 −0.462 0.0422 19.2% 0.63 [0.58, 0.68]
Asgar 2017 −0.978 0.4624 8.0% 0.38 [0.15, 0.93]
Giannini 2016 −0.844 0.2975 12.2% 0.43 [0.24, 0.77]
Swaans 2014 −0.7765 0.3537 10.6% 0.46 [0.23, 0.92]
Velazquez 2015 −0.5108 0.182 0.0% 0.60 [0.42, 0.86]
Subtotal (95% CI) 69.2% 0.62 [0.40, 0.93]
Heterogeneity: Tau² = 0.17; Chi² = 110.54, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.28 (P = 0.02)
2.4.2 RCT
COAPT NEJM '18 −0.478 0.1523 16.8% 0.62 [0.46, 0.84]
MITRA-FR NEJM'18 0.1044 0.2426 14.0% 1.11 [0.69, 1.79]
Subtotal (95% CI) 30.8% 0.80 [0.46, 1.42]
Heterogeneity: Tau² = 0.13; Chi² = 4.13, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 0.75 (P = 0.45)
Total (95% CI) 100.0% 0.67 [0.48, 0.94]
Heterogeneity: Tau² = 0.15; Chi² = 115.90, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.46), I² = 0%
0.5 0.7 1 1.5 2
Favours Mitraclip Favours OMT


Study or Subgroup log[Odds Ratio] SE Weight Odds Ratio IV, Random, 95% CI
Odds Ratio IV, Random, 95% CI
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Asgar 2017 −0.978 0.4624 4.8% 0.38 [0.15, 0.93]
Giannini 2016 −0.844 0.2975 10.1% 0.43 [0.24, 0.77]
Swaans 2014 −0.7765 0.3537 7.7% 0.46 [0.23, 0.92]
Velazquez 2015 −0.5108 0.182 0.0% 0.60 [0.42, 0.86]
Subtotal (95% CI) 63.2% 0.58 [0.47, 0.70]
Heterogeneity: Tau² = 0.01; Chi² = 3.54, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 5.40 (P < 0.00001)
2.4.2 RCT
COAPT NEJM '18 −0.478 0.1523 23.2% 0.62 [0.46, 0.84]
MITRA-FR NEJM'18 0.1044 0.2426 13.6% 1.11 [0.69, 1.79]
Subtotal (95% CI) 36.8% 0.80 [0.46, 1.42]
Heterogeneity: Tau² = 0.13; Chi² = 4.13, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 0.75 (P = 0.45)
Total (95% CI) 100.0% 0.62 [0.50, 0.77]
Heterogeneity: Tau² = 0.03; Chi² = 9.15, df = 5 (P = 0.10); I² = 45%
Test for overall effect: Z = 4.41 (P < 0.0001)
Test for subgroup differences: Chi² = 1.17, df = 1 (P = 0.28), I² = 14.3%
0.5 0.7 1 1.5 2
Favours Mitraclip Favours OMT

Figure 4