

Comparison of Men Versus Women Undergoing Transcatheter Mitral Valve Repair With Mitraclip

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ABSTRACT

AIMS: Transcatheter mitral valve repair (TMVR) with MitraClip is being used with increasing popularity for significant mitral regurgitation and suitable valve anatomy. Whether there are difference in baseline, procedural, or outcome data in men versus women undergoing this procedure is uncertain.

METHODS: We thus analyzed retrospectively collected data on patients undergoing TMVR at 3 tertiary care centers. Baseline, procedural, and outcome details were systematically sought. Patients were followed after discharge for clinical events and

echocardiographic changes.

RESULTS: A total of 84 subjects were included: 39 (46%) males and 45 (54%) females. Women and men had significant differences in age, height, body surface area, prevalence of coronary artery disease, chronic obstructive pulmonary disease, receipt of implantable cardioverter defibrillators, and systolic dysfunction. Despite this, procedural success was similarly high in both genders, with only one procedural failure in a man. Echocardiographic follow-up showed persistent improvement in mitral regurgitation in 38 (98%) males and 45 females (100%, $p=0.464$), with similarly significant reductions in vena contracta (within-subject $p<0.001$, between-subject $p=0.728$), effective regurgitant orifice area (within-subject $p<0.001$, between-subject $p=0.884$), and systolic pulmonary artery pressure (within-subject $p<0.001$, between-subject $p=0.282$). Clinical outcomes at 12-month follow-up were also not different in males versus females, with 4 (10%) deaths in men and 11 (24%) in women ($p=0.152$). Sensitivity analyses limited to propensity score matched pairs confirmed the similar procedural, echocardiographic and clinical outlook in men and women (all $p>0.05$).

CONCLUSION: Males and females with significant mitral regurgitation and established indications to TMVR with MitraClip appear to equally benefit from this procedure, despite obvious gender-related differences in baseline features.

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Key words: Gender; Heart failure; MitraClip; Mitral regurgitation; Mitral valve repair; Sex

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INTRODUCTION

Transcatheter mitral valve repair (TMVR) is an intense and promising field of research, with several interesting devices already available or under development^[1]. MitraClip (Abbott Vascular, Santa Rosa, CA) represents one of the most promising of these technologies. It is already approved for routine clinical use in several countries, with an extensive evidence base encompassing randomized trials as well as observational studies^[2]. Several studies have tried to identify baseline and procedural features which may impact on short- and long-term outcomes^[3-8]. Despite such breath of clinical data, there is limited evidence focusing explicitly on gender differences in subjects treated with MitraClip^[9].

Gender analyses represent an important topic in clinical practice and research, as they may inform clinical decision making, verify appropriateness and bias in treating men in comparison to women, as well as appraising the potential independent prognostic effect of gender on early or late clinical results^[10]. Indeed, gender issues are important and may impact significantly in the management of patients with acute myocardial infarction^[11], those undergoing percutaneous coronary intervention^[12], or subjects with heart failure^[13]. As the incidence and prevalence of conditions leading to significant mitral regurgitation are different in men and women^[14], differences in the procedural features and clinical outlook of MitraClip implantation may occur in males versus females, with important clinical implications. Indeed, we hypothesized that, among patients undergoing TMVR, men may have a higher prevalence of post-ischemic mitral regurgitation, with relevant consequences on the acute success and long-term outcome of MitraClip implantation.

METHODS

This was a retrospective registry exploiting prospectively-collected data entered into administrative database, as reported elsewhere^[15]. Patients provided written informed consent for data collection, and the competent ethics committee was notified of the use of administrative data for scientific purposes. Specifically, patients were included if undergoing elective MitraClip implantation for significant (at least moderate) mitral regurgitation, irrespective of the underlying etiology or morphology. Given the retrospective and all-comer design, no specific prospective inclusion or exclusion criteria were enforced. However, clinically established indications were used, and all patients were deemed at moderately high or high surgical risk at heart team evaluation and were considered suitable candidates for transcatheter mitral valve repair on the basis of acceptable (at least 1 year) life expectancy and lack of anatomic contraindications to MitraClip implantation^[16-17]. Typical features identifying moderately high or high risk included advanced (>80 years) age, chronic renal failure, or dilated cardiomyopathy.

Procedures were performed by experienced operators under general anesthesia and through fluoroscopic and trans-esophageal echocardiographic (TEE) guidance. MitraClip implantation was performed according to established protocols after having accessed the right femoral vein with a 24 French sheath and having completed trans-septal puncture. All MitraClip implantations were attempted with the standard central clip concept. After successful implantation of the first MitraClip, additional MitraClip implantations were attempted or envisioned only if TEE did not disclose a meaningful reduction ($\leq 2+$) in mitral regurgitation. At the end of the procedure patients were weaned and subsequently extubated and then monitored for at least 24 hours. Subjects without an indication for

oral anticoagulants continued aspirin plus clopidogrel for 1 month followed by aspirin alone for additional 2 months. Control transthoracic echocardiography (TTE) was performed before discharge, 1 month, 3 months, and 6 months after the indeed procedure, with subsequent follow-up exams every 6-12 months. Clinical follow-up was performed at the same time intervals by office visit or phone contact, if TTE had been performed elsewhere.

Outcomes of interest were procedural success (successful clip implantation with residual mitral regurgitation grade $\leq 2+$), total hospital stay, and in-hospital events (death, myocardial infarction, major bleeding or acute kidney injury). In addition, we appraised the occurrence during follow-up of death, myocardial infarction, stroke, mitral valve surgery, rehospitalizations after successful discharge, mitral regurgitation grade, and New York Heart Association class.

Descriptive analyses were based on counts (%) for categorical variables and median (1st-3rd quartile) for continuous variables. Inferential analysis was based on bivariate analyses using chi-squared tests for categorical variables belonging to a ≥ 2 by >2 contingency table, Fisher exact tests for categorical variables belonging to a 2 by 2 contingency table, and Mann-Whitney U tests for continuous variables. As a sensitivity analysis, we computed a non-parsimonious propensity score (including all variables reported in tables 1 and 2), which showed adequate discrimination (c statistic=0.73). Then, we matched men and women with 1:1 ratio and a 0.15 propensity caliper. Finally, survival analyses were carried out with unadjusted and adjusted Cox proportional hazard analysis. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA).

RESULTS

A total of 84 patients were included in whom MitraClip implantation was attempted, with 39 (46%) men and 45 (54%) women (Table 1). Several baseline differences were found between genders. In particular men were younger ($p=0.016$), taller ($p<0.001$), with larger body surface area (0.005), a higher prevalence of chronic obstructive pulmonary disease ($p=0.011$), prior myocardial infarction ($p=0.001$), prior percutaneous coronary intervention ($p=0.016$), prior coronary artery bypass grafting ($p=0.044$), prior receipt of arrhythmia devices ($p=0.026$), and, accordingly, an ischemic etiology for cardiomyopathy ($p=0.049$). However, EuroSCORE II and Society of Thoracic Surgery scores were similar in men and women (respectively $p=0.308$ and $p=0.440$). Echocardiographic features were largely similar in the two groups (Table 2), with the notable exclusion of left ventricular ejection fraction, which was significantly lower in men ($p<0.001$). In terms of etiology, analysis of the mitral valve morphology according to the established and detailed Carpentier classification, showed that type I (annular dilation) was present in 69% men and 62% women ($p=0.646$), type II (leaflet prolapsed) in 15% and 31% ($p=0.124$), type IIIa (restricted leaflet motion in both diastole and systole) in 31% and 22% ($p=0.458$), and type IIIb (restricted leaflet motion in systole only) in 0 and 4% ($p=0.501$).

Despite such disparities, procedural results and follow-up echocardiography findings were similar in males and females (Table 2). Specifically, improvement in mitral regurgitation occurred in 38 (97%) men versus 45 (100%) women ($p=0.464$), after implantation of a single MitraClip in, respectively, 28 (74%) and 29 (66%), and two MitraClips in 9 (24%) and 15 (34%). Indeed, in a 78-year-old man with extremely high surgical risk and severely depressed systolic function no clip could be implanted because of unsuitable septal anatomy.

Table 1 Baseline features.

| Feature | Men (N=39) | Women (N=45) | P value |
|--|-----------------|-----------------|---------|
| Age (years) | 73 (71; 78) | 78 (72; 81) | 0.016 |
| Height (cm) | 168 (163; 170) | 160 (155; 165) | <0.001 |
| Weight (kg) | 73 (65; 81) | 70 (64; 75) | 0.126 |
| Body mass index (kg/m ²) | 26 (24; 28) | 27 (25; 28) | 0.542 |
| Body surface area (m ²) | 1.8 (1.7; 1.9) | 1.7 (1.6; 1.8) | 0.005 |
| Hypertension | 33 (84.6%) | 32 (72.7%) | 0.286 |
| Diabetes mellitus | 16 (80.0%) | 10 (50.0%) | 0.096 |
| Prior myocardial infarction | 23 (60.5%) | 10 (22.7%) | 0.001 |
| Prior percutaneous coronary intervention | 17 (43.6%) | 8 (17.8%) | 0.016 |
| Prior coronary artery bypass grafting | 14 (35.9%) | 7 (15.6%) | 0.044 |
| Prior PM, ICD or CRT implantation | 14 (70.0%) | 6 (30.0%) | 0.026 |
| Ischemic cardiomyopathy | 15 (38.5%) | 8 (17.8%) | 0.049 |
| New York Heart Association class | | | 0.468 |
| III | 30 (76.9%) | 31 (68.9%) | |
| IV | 9 (23.1%) | 14 (31.1%) | |
| Atrial fibrillation | 17 (43.6%) | 24 (53.3%) | 0.391 |
| Renal failure | 15 (38.5%) | 14 (31.8%) | 0.645 |
| Chronic obstructive pulmonary disease | 15 (38.5%) | 6 (13.3%) | 0.011 |
| EuroSCORE II (%) | 3.7 (1.7; 14.3) | 2.5 (1.7; 7.9) | 0.308 |
| Society of Thoracic Surgery score (%) | 5.1 (3.0; 8.3) | 4.1 (2.6; 7.1) | 0.440 |

CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; PM: pace-maker.

Table 2 Procedural and echocardiographic features.

| | Men (N=39) | Women (N=45) | P value |
|--|-----------------|-----------------|---------|
| Baseline echocardiography | | | |
| MR degree | | | 0.796 |
| Moderate | 3 (7.7%) | 3 (7.7%) | |
| Moderate-severe | 12 (30.8%) | 17 (37.8%) | |
| Severe | 24 (61.5%) | 25 (55.6%) | |
| Type of MR (Carpentier classification) | | | |
| I | 27 (69.2%) | 28 (62.2%) | 0.646 |
| II | 6 (15.4%) | 14 (31.1%) | 0.124 |
| IIIa | 12 (30.8%) | 10 (22.2%) | 0.458 |
| IIIb | 0 | 2 (4.1%) | 0.501 |
| LVEF (%) | 33 (30; 40) | 44 (35; 55) | <0.001 |
| LVEDVI (mL) | 77 (39; 105) | 84 (62; 98) | 0.901 |
| LVESVI (mL) | 47 (27; 67) | 44 (28; 59) | 0.650 |
| Vena contracta (mm) | 7 (6; 12) | 9 (7; 12) | 0.406 |
| EROA (mm ²) | 11 (8; 13) | 9 (4; 12) | 0.223 |
| SPAP (mm Hg) | 46 (35; 55) | 50 (41; 60) | 0.091 |
| Clips implanted | | | 0.352 |
| None | 1 (2.6%) | 0 | |
| 1 | 28 (73.7%) | 29 (65.9%) | |
| 2 | 9 (23.7%) | 15 (34.1%) | |
| Procedural success | 38 (97.4%) | 45 (100%) | 0.464 |
| Procedural time (minutes) | 112 (59; 159) | 142 (91; 189) | 0.091 |
| Radiation dose (Gy cm ²) | 259 (165; 333) | 136 (60; 308) | 0.199 |
| Follow-up echocardiography | | | |
| MR degree | | | 0.466 |
| Less than moderate | 27 (69.2%) | 37 (82.2%) | |
| Moderate | 9 (23.1%) | 7 (15.6%) | |
| Moderate to severe | 2 (5.1%) | 1 (2.2%) | |
| Severe | 1 (2.6%) | 0 | |
| Improvement in MR degree | 38 (97.4%) | 45 (100%) | 0.464 |
| Improvement in LVEF (%) | 0 (-1.8; 2.0) | 0 (-1.3; 2.0) | 0.803 |
| Improvement in LVEDVI (mL) | 0.8 (-3.4; 6.5) | 3.4 (-2.0; 7.4) | 0.348 |
| Improvement in LVESVI (mL) | 0.4 (-7.4; 4.2) | 1.1 (-2.7; 6.8) | 0.291 |
| Improvement in vena contracta (mm) | 4.0 (1.5; 8.0) | 6.0 (3.0; 7.0) | 0.728 |
| Improvement in EROA (mm ²) | 5.0 (2.0; 6.0) | 4.0 (3.0; 6.8) | 0.884 |
| Improvement in SPAP (mm Hg) | 9 (0; 19) | 13 (5; 19) | 0.282 |

EROA: effective regurgitant orifice area; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index; LV: left ventricular; MR: mitral regurgitation; SPAP: systolic pulmonary artery pressure.

Clinical outcomes, in-hospital or at mid-term (12-month) follow-up, were similarly favorable despite the common presence of high risk features (Table 3). Specifically, in-hospital death occurred in 2 (5%) men versus 3 (7%) women ($p=0.538$), with cumulative death at follow-up in 4 (10%) and 11 (24%), respectively ($p=0.152$). Analysis of the rate of rehospitalizations for heart failure or the composite of death or rehospitalizations for heart failure also provided favorable results without gender-related differences [respectively 3 (8%) vs 3 (7%), $p=1.0$, and 6 (15%) vs 13 (29%), $p=0.192$]. Focusing on causes of death, all case fatalities were due to non-cardiac conditions.

Sensitivity analyses exploiting propensity score matching, which yielded 20 matched pairs, confirmed the above unadjusted analyses (Table 4), despite the caveat of residual disparities at standardized differences. Specifically, propensity matched males and females exhibited similar clinical and echocardiographic outcomes at follow-up, including risk of death at follow-up [1 (5%) vs 5 (25%), $p=0.182$] and improvement in mitral regurgitation [20 (100%) vs 20 (100%), $p=1.0$]. Even at Cox proportional hazard analysis no significant differences were found between men and women when focusing on the occurrence of death or rehospitalizations (Table 5).

DISCUSSION

The present work, originally reporting on the gender-related differences in patients undergoing TMVR with MitraClip, suggest that, despite obvious differences in baseline and procedural features, both men and women may equally benefit from this innovative therapy when appropriate indications and contraindications are followed.

The benefit of MitraClip for TMVR in high-risk patients has already been demonstrated in several clinical trials and observational registries^[2-7,16]. The available evidence base has suggested that procedural success, short-term prognosis, and long-term outlook can be rather accurately predicted using one or more of the following features: age, COPD, eGFR^[5], baseline NYHA^[8], STS score, MR type, EROA, mitral valve orifice area, mean transmitral pressure gradient, vena contracta, anterior leaflet pathology and thickness, regurgitant volume, and LVEF^[4-6,8,18-24]. Accordingly, limited or no emphasis at all has been given, to date, on gender comparisons

Table 3 Outcomes.

| | Men (N=39) | Women (N=45) | P value |
|---|---------------|-----------------|---------|
| In-hospital follow-up | | | |
| Total hospital stay (days) | 6 (5; 8) | 5 (5; 7) | 0.321 |
| Final disposition | | | 0.538 |
| Discharge home | 36 (92.3%) | 42 (93.3%) | |
| Transfer to other facility | 1 (2.6%) | 0 | |
| Death | 2 (5.1%) | 3 (6.7%) | |
| Acute kidney injury | 1 (2.6%) | 3 (6.7%) | 0.620 |
| Cumulative follow-up | | | |
| Follow-up duration (months)* | 11 (10; 15) | 12 (7; 16) | 0.804 |
| Death | 4 (10.3%) | 11 (24.4%) | 0.152 |
| Myocardial infarction | 0 | 0 | 1.0 |
| Stroke | 0 | 0 | 1.0 |
| Mitral valve replacement | 1 (2.6%) | 0 | 0.464 |
| Major bleeding | 0 | 0 | 1.0 |
| Rehospitalization after successful discharge | 3 (7.7%) | 3 (6.7%) | 1.0 |
| Rehospitalization or death after successful discharge | 6 (15.4%) | 13 (28.9%) | 0.192 |
| Improvement in New York Heart Association class | 16 (41.0%) | 20 (44.4%) | 0.827 |

* in those eligible for at least 6-month follow-up.

Table 4 Selected baseline features, procedural results and follow-up events in propensity matched pairs.

| | Men (N=20) | Women (N=20) | P value |
|---|-----------------|------------------|---------|
| Age (years) | 73 (71; 78) | 71 (68; 79) | 0.967 |
| Height (cm) | 168 (162; 170) | 160 (155; 165) | 0.004 |
| Body surface area (m ²) | 1.8 (1.7; 1.9) | 1.7 (1.6; 1.9) | 0.070 |
| Prior myocardial infarction | 9 (45.0%) | 9 (45.0%) | 1.0 |
| Prior percutaneous coronary intervention | 8 (40.0%) | 5 (25.0%) | 0.501 |
| Prior coronary artery bypass grafting | 5 (25.0%) | 8 (40.0%) | 0.501 |
| Prior PM, ICD, or CRT | 5 (25.0%) | 8 (40.0%) | 0.501 |
| Ischemic cardiomyopathy | 7 (35.0%) | 5 (25.0%) | 0.731 |
| Chronic obstructive pulmonary disease | 7 (35.0%) | 7 (35.0%) | 1.0 |
| LVEF (%) | 30 (29; 35) | 40 (30; 48) | 0.007 |
| Multiple clips implanted | 6 (30.0%) | 6 (30.0%) | 1.0 |
| Procedural success | 19 (95.0%) | 20 (100%) | 1.0 |
| Follow-up echocardiography | | | |
| Improvement in MR degree | 20 (100%) | 20 (100%) | 1.0 |
| Improvement in LVEF (%) | 0 (-4.0; 1.0) | 0 (-1.0; 1.8) | 0.683 |
| Improvement in LVEDVI (mL) | 0.7 (-2.6; 3.4) | 4.6 (-2.2; 16.9) | 0.292 |
| Improvement in LVESVI (mL) | 0.3 (-6.4; 2.7) | 2.2 (-3.5; 5.3) | 0.264 |
| Improvement in vena contracta (mm) | 4.5 (2.3; 8.3) | 3.0 (1.8; 7.3) | 0.447 |
| Improvement in EROA (mm ²) | 5.0 (2.0; 6.0) | 3.5 (0.5; 4.3) | 0.266 |
| Improvement in SPAP (mm Hg) | 5 (-5; 15) | 10 (0; 23) | 0.287 |
| In-hospital follow-up | | | |
| Total hospital stay (days) | 6 (5; 7) | 6 (5; 7) | 0.988 |
| Final disposition | | | 1.0 |
| Discharge home | 19 (95.0%) | 18 (90.0%) | |
| Transfer to other facility | 0 | 0 | |
| Death | 1 (5.0%) | 2 (10.0%) | |
| Acute kidney injury | 1 (5.0%) | 0 | 1.0 |
| Cumulative follow-up | | | |
| Follow-up duration (months) | 12 (9; 15) | 10 (7; 14) | 0.475 |
| Death | 1 (5.0%) | 5 (25.0%) | 0.182 |
| Mitral valve replacement | 1 (5.0%) | 0 | 1.0 |
| Rehospitalization after successful discharge | 1 (5.0%) | 2 (10.0%) | 1.0 |
| Rehospitalization or death after successful discharge | 2 (10.0%) | 6 (30.0%) | 0.235 |
| Improvement in New York Heart Association class | 10 (50.0%) | 10 (50.0%) | 1.0 |

EROA: effective regurgitant orifice area; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index; LV: left ventricular; MR: mitral regurgitation; SD: standardized difference; SPAP: systolic pulmonary artery pressure.

Table 5 Cox proportional hazard analysis.

| | Unadjusted analysis | Adjusted analysis* |
|---|---|--|
| Overall sample | | |
| Death | HR=0.51 (95%CI 0.16-1.64) p=0.259 | HR=0.732 (95%CI 0.17-3.52) p=0.732 |
| Rehospitalization or death after successful discharge | HR=0.61 (95%CI 0.23-1.64) p=0.331 | HR=0.56 (95%CI 0.09-3.52) p=0.533 |
| Propensity matched pairs | | |
| Death | HR=0.63 (95%CI 0.14-2.89) p=0.555 | HR=0.17 (95%CI 0.01-13.81) p=0.171 |
| Rehospitalization or death after successful discharge | HR=0.68 (95%CI 0.21-2.27) p=0.535 | HR=0.40 (95%CI 0.03-5.63) p=0.500 |

*adjusting for age, height, body surface area, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior arrhythmia device implantation, ischemic cardiomyopathy, chronic obstructive pulmonary disease, and left ventricular ejection fraction; HR=hazard ratio for male versus female gender; 95%CI=95% confidence interval

among patients undergoing MitraClip implantation^[9]. This is at odds with the fact that women have often been treated with MitraClip (e.g. they were 36% in the pivotal EVEREST II trial), including very publicly visible cases^[16,25]. In the present work, pooling on a multicenter registry including three Italian centers, we provide useful data on the baseline, procedural and outcome details of men vs women undergoing TMVR.

Specifically, we found that, despite several differences in baseline features and procedural details (including lower systolic function in males), short- and mid-term outcomes were similarly favorable in both genders. Accordingly, notwithstanding such baseline differences, it is clear that adjusting pre- and procedural strategies to the specific individual situation may lead to favorable results irrespective of gender. Our findings should be viewed in light of the recently reported results of the GRASP registry on 171 patients followed for at least 12 months after MitraClip implantation. In this study, men and women also fared similarly both acutely and after discharge, despite a non-significant trend toward worse outcomes in females^[9].

Gender-based comparisons are of crucial importance in clinical medicine, as they may inform on incidence and prevalence of disease, on treatment patterns and potential gender bias, as well as, occasionally, on the pathophysiologic differences between men and women. Several studies have shown that women with symptomatic coronary artery disease are typically older, sicker, and at higher risk of adverse events, yet they are often treated less aggressively^[11,12,26]. Similar findings have been reported for heart failure, hypertension, atrial fibrillation, aortic stenosis, and other important cardiovascular conditions. In most cases sex differences depend on baseline or procedural differences, rather than on an inherent pathophysiologic role of gender^[9]. However, exceptions do occur, and may be due to the protective effects of estrogen levels during fertile years as well as on specific difference in genetic patterns. For instance, men may be at risk of higher cardiomyocyte apoptosis after myocardial infarction^[27]. Specific gender based comparison are strongly recommended and supported internationally, by funding agencies (e.g. the HORIZON 2020 program

in the European Union) as well as journals and publishers.

Our work builds upon such premises and provides useful information despite its observational retrospective design and relatively small sample, with the underlying risk of residual confounding^[28]. In addition, the inclusion of patients with only moderately high surgical risk may be at odds with reports on other patients at higher surgical risk and may dilute our statistical precision. Other limitations of our work include the mid-term follow-up and lack of centralized core laboratory assessment of echocardiographic data. The fact that only a minority of patients could be matched with a similar propensity score and that despite such matching standardized differences after matching still highlighted some disparities are also other limitations underlying the fact that men and women undergoing TMVR have often starkly different features.

Nonetheless, awaiting for further and larger studies on this topic, this work provides useful and original data on gender differences (or the lack of thereof) among patients treated with MitraClip.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- Rylski B, Beyersdorf F. Current concepts for minimally invasive mitral valve repair. *Heart Lung Vessel* 2013;**5**:207-12
- Wan B, Rahnavardi M, Tian DH, Phan K, Munkholm-Larsen S, Bannon PG, Yan TD. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. *Ann Cardiothorac Surg* 2013;**2**:683-92.
- Di Mario C, Alfieri O, Iung B, Serruys PW. Transcatheter valves and interventional cardiology. *Euro Intervention* 2011;**6**:673-7.
- Paranskaya L, D'Ancona G, Bozdog-Turan I, Akin I, Kische S, Turan GR, Rehders T, Ortak J, Nienaber CA, Ince H. Residual mitral valve regurgitation after percutaneous mitral valve repair with the MitraClip system is a risk factor for adverse one-year outcome. *Catheter Cardiovasc Interv* 2013;**81**:609-17.
- Ledwoch J, Bertog S, Wunderlich N, Doss M, Fichtlscherer S, Teufel T, Herholz T, Vaskelyte L, Hofmann I, Sievert H. Predictors for prolonged hospital stay after transcatheter mitral valve repair with the MitraClip. *Catheter Cardiovasc Interv* 2014 Feb 26 doi: 10.1002/ccd.25460 [Epub ahead of print].
- Sürder D, Pedrazzini G, Gaemperli O, Biaggi P, Felix C, Rufibach K, der Maur CA, Jeger R, Buser P, Kaufmann BA, Moccetti M, Hürlimann D, Bühler I, Bettex D, Scherman J, Pasotti E, Faletta FF, Zuber M, Moccetti T, Lüscher TF, Erne P, Grünenfelder J, Corti R. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. *Heart* 2013;**99**:1034-40.
- Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, Colombo A, Giacomini A, Michev I, Mangiafico S, Cammalleri V, Barbanti M, Alfieri O. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010;**31**:1382-9.
- Puls M, Tichelbäcker T, Bleckmann A, Hünlich M, von der Ehe K, Beuthner BE, Rüter K, Reißbarth T, Seipelt R, Schöndube F, Hasenfuß G, Schillinger W. Failure of acute procedural success predicts adverse outcome after percutaneous edge-to-edge mitral valve repair with MitraClip. *Euro Intervention* 2014;**9**:1407-17.
- Attizzani GF, Ohno Y, Capodanno D, Cannata S, Dipasqua F, Immè S, Mangiafico S, Barbanti M, Ministeri M, Caggegi A, Pistrutto AM, Giaquinta S, Farruggio S, Chiarandà M, Ronsivalle G, Scandura S, Tamburino C, Capranzano P, Grasso C. Gender-related clinical and echocardiographic outcomes at 30-day and 12-month follow up after MitraClip implantation in the GRASP registry. *Catheter Cardiovasc Interv* 2014 Nov 4. Doi: 10.1002/ccd.25715 [Epub ahead of print].
- Wenger NK. Gender disparity in cardiovascular disease: bias or biology? *Expert Rev Cardiovasc Ther* 2012;**10**:1401-11.
- D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, Omedè P, Sciuto F, Gaita F, Sheiban I. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol* 2011;**107**:651-4.
- Sheiban I, La Spina C, Cavallero E, Biondi-Zoccai G, Colombo F, Palmerini T, Marzocchi A, Tamburino C, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli AL, Briguori C, Vignali L, di Pede F, Ramondo A, Fantoni C, de Carlo M, Falsini G, Benassi A, Palmieri C, Filippone V, Sangiorgi D, de Servi S. Sex-related differences in patients undergoing percutaneous unprotected left main stenting. *Euro Intervention* 2010;**5**:795-800.
- Stein GY, Ben-Gal T, Kremer A, Bental T, Alon D, Korenfeld R, Yedidia I, Porter A, Abramson E, Sagie A, Fuchs S. Gender-related differences in hospitalized heart failure patients. *Eur J Heart Fail* 2013;**15**:734-41.
- Abbate A, Arena R, Abouzaki N, Van Tassel BW, Canada J, Shah K, Biondi-Zoccai G, Voelkel NF. Heart failure with preserved ejection fraction: refocusing on diastole. *Int J Cardiol* 2015;**179**:430-40.
- Giordano A, Indolfi C, Ferraro P, Corcione N, Polimeno M, Messina S, Mongiardo A, Avellino R, Biondi-Zoccai G, Frati G, Mancone M, Sardella G. Implantation of more than one MitraClip in patients undergoing transcatheter mitral valve repair: friend or foe? *Journal of Cardiol Ther* 2014;**1**:133-37.
- Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, Hermiller J, Gray W, Wang A, Pedersen WR, Bajwa T, Lasala J, Low R, Grayburn P, Feldman T; EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol* 2013;**62**:317-28.
- Prifti E, Frati G, Bonacchi M, Vanini V, Chauvaud S. Accessory mitral valve tissue causing left ventricular outflow tract obstruction: case reports and literature review. *J Heart Valve Dis* 2001;**10**:774-8.
- Armstrong EJ, Rogers JH, Swan CH, Upadhyaya D, Vilorio E, McCulloch C, Slater J, Qureshi M, Williams J, Whisenant B, Feldman T, Foster E. Echocardiographic predictors of single versus dual MitraClip device implantation and long-term reduction of mitral regurgitation after percutaneous repair. *Catheter Cardiovasc Interv* 2013;**82**:673-9.
- Rudolph V, Lubos E, Schlüter M, Lubs D, Goldmann B, Knap M, de Vries T, Treede H, Schirmer J, Conradi L, Wegscheider K, Reichenspurner H, Blankenberg S, Baldus S. Aetiology of mitral regurgitation differentially affects 2-year adverse outcomes after MitraClip therapy in high-risk patients. *Eur J Heart Fail* 2013;**15**:796-807.
- Alegria-Barrero E, Chan PH, Foin N, Syrseloudis D, Tavazzi G, Price S, Lindsay AC, Duncan A, Moat N, Di Mario C, Franzen OW. Concept of the central clip: when to use one or two MitraClips®. *Euro Intervention* 2014;**9**:1217-24.
- Lubos E, Schlüter M, Vettorazzi E, Goldmann B, Lubs D, Schirmer J, Treede H, Reichenspurner H, Blankenberg S, Baldus S, Rudolph V. MitraClip Therapy in Surgical High-Risk Patients: Identification of Echocardiographic Variables Affecting Acute Procedural Outcome. *JACC Cardiovasc Interv* 2014;**7**:394-402.
- Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghini C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;**364**:1395-406.
- Glower D, Ailawadi G, Argenziano M, Mack M, Trento A, Wang A, Lim DS, Gray W, Grayburn P, Dent J, Gillam L, Sethuraman B, Feldman T, Foster E, Mauri L, Kron I; EVEREST II Investigators.

- EVEREST II randomized clinical trial: predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure. *J Thorac Cardiovasc Surg* 2012;**143**:S60-3.
24. Bozdog-Turan I, Paranskaya L, Birkemeyer R, Turan RG, Kische S, Akin I, Ortak J, Stoeckicht Y, Schubert J, Westphal B, Nienaber CA, Ince H. Percutaneous mitral repair with the MitraClip system in patients with mild-to-moderate and severe heart failure: a single-centre experience. *Cardiovasc Ther* 2014;**32**:66-73
 25. Actress Elizabeth Taylor, Early Recipient of MitraClip, Dies. March 24, 2011. Heartwire. Available from: <http://www.medscape.com/viewarticle/739635> (last accessed on July 31, 2014).
 26. Fineschi M, Guerrieri G, Orphal D, Palmerini E, Münzel T, Warnholtz A, Pierli C, Gori T. The impact of gender on fractional flow reserve measurements. *Euro Intervention* 2013;**9**:360-6.
 27. Biondi-Zoccai GG, Abate A, Bussani R, Camilot D, Giorgio FD, Marino MP, Silvestri F, Baldi F, Biasucci LM, Baldi A. Reduced post-infarction myocardial apoptosis in women: a clue to their different clinical course? *Heart* 2005;**91**:99-101.
 28. Biondi-Zoccai G, Romagnoli E, Agostoni P, Capodanno D, Castagno D, D'Ascenzo F, Sangiorgi G, Modena MG. Are propensity scores really superior to standard multivariable analysis? *Contemp Clin Trials* 2011;**32**:731-40.

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