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Role of the tricuspid regurgitation after mitraclip and transcatheter aortic valve implantation: a systematic review and meta-analysis

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Aims Treatment of tricuspid regurgitation (TR) is common after surgery for mitral and/or aortic valves. The prognostic role of moderate to severe TR in patients undergoing mitraclip or transcatheter aortic valve implantation (TAVI) is not well-defined. Thus, the aim of this article is to perform a systematic review and meta-analysis of articles valuing the prognostic role of TR for patients undergoing mitraclip and TAVI.

Methods and results Articles were searched in Pubmed, Cochrane Library, Google Scholar and Biomed Central in September 2016. Inclusion criteria: observational or randomized clinical trials with data on the prognostic role of TR in patients undergoing mitraclip or TAVI. Primary outcome was all-cause mortality expressed as hazard ratio (HR). Six articles fulfilled inclusion criteria, three were on mitraclip and three on TAVI. A total of 2329 patients were analysed (mean age was 78.38 (3.09), 63% male): 1328 treated with TAVI and 1001 with mitraclip. The HR for all-cause mortality of moderate to severe TR was 2.0 (95% CI 1.57–2.55, $I^2 = 0\%$). Data were confirmed also after subgroup analysis for mitraclip vs. TAVI. None of the factor considered in meta-regression analyses was affecting the primary outcome.

Conclusions The current meta-analysis suggests that the presence of moderate to severe TR in patients undergoing mitraclip or TAVI might be a major determinant of all-cause mortality. New studies are needed to confirm it and to plan possible intervention in order to reduce its impact.

Keywords tricuspid regurgitation • TAVI • transcatheter aortic valve implantation • mitraclip • mortality

Introduction

Left heart valve disease is the most common cause of tricuspid regurgitation (TR).[1] The prevalence of TR in patients undergoing left heart valve surgery is ranging between 25 and 30%,[2] and the loss of coaptation due to annular or right ventricle dilatation the most usual cause of TR.[3] A recent meta-analysis on 2488 patients showed that the absence of treatment on tricuspid valve during mitral valve operations is related to a higher risk of developing moderate to severe TR, even when the valve defect is mild to moderate.[4] For this reason, current guidelines suggest the treatment of tricuspid valve in case of (i) severe primary or secondary TR (Class I LoE C); (ii) moderate primary TR (Class II LoE C); (iii) right annular dilatation (Class II LoE C).[5] In the last 10 years, the approach to the treatment of left heart valve disease has changed, and for high risk patients, the percutaneous approach is substituting the more conventional surgery.[6–7] The selection criteria for both patients treated with transcatheter aortic valve implantation (TAVI) or with mitraclip do not take into account the presence of

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moderate to severe TR,[6–7] despite the suggestion of an increased risk of mortality in patients with moderate to severe TR.[8–14] Considering these data, we have performed a systematic review and meta-analysis on all the available evidences in the literature regarding the predictive role TR on all-cause mortality or on cardiovascular death for patients undergoing TAVI or mitraclip.

Methods

Search strategy

We performed a systematic review and meta-analysis following preferred reporting items for systematic reviews and meta-analyses (PRISMA) amendment to the quality of reporting of meta-analyses (QUOROM) statement.[15–18] The search strategy was elaborated in September 2016. The terms searched were (((mitraclip) OR ((transcatheter) OR (percutaneous) AND (mitral valve repair)) OR ((TAVI) OR (transcatheter aortic valve implantation))) AND ((outcome) OR (mortality) OR (cardiac death) OR (hospitalization) OR (heart failure) OR (reintervention)). The databases analysed were Google Scholar, Pubmed, Biomed Central, and Cochrane library. Only articles published in English and in peer-reviewed journal were selected. Two independent reviewers analysed the records and decided the ones deserving a full-text analysis.

Selection criteria

The inclusion criteria for the studies were: (i) observational or randomized clinical trials (RCTs) in patients treated with mitraclip or TAVI; (ii) evaluation of the TR degree; (iii) data on the predictive role of TR on all-cause mortality or cardiovascular mortality expressed as adjusted odds ratio (OR) or hazard ratio (HR); (iv) inclusion of at least 50 patients. Exclusion criteria were: (i) duplicate reports; (ii) duplicate of the sample size; (iii) case reports/series. The same reviewers (RP, SR) independently analysed references of all the evaluated articles for avoiding the eventual exclusion of additional studies. All the authors agreed on the final number of studies included.

Data abstraction, endpoints, and subgroup analyses

The reviewers completed a database with data regarding: the journal, year of publication, the hospital centre, population characteristics, echocardiographic data (degree of TR, ejection fraction (EF), systolic pulmonary arterial pressure (sPAP), valve implanted, variables analysed at multivariate analysis). The primary endpoint of the analysis was the HR of moderate to severe TR in patients undergoing TAVI or mitraclip procedures. A subgroup analysis according the kind of procedure done (mitraclip vs. TAVI) and the length of the follow-up (≤ 1 year vs. >1 year) was also performed. The secondary endpoint was cardiovascular mortality. The definition of the severity of TR for analysis differed between articles: Ohno *et al.*,[9] Hutter *et al.*,[12] and Barbanti *et al.*[13] and considered moderate/severe TR vs. mild/none; Giannini considered a TR grade > 2;[10] Puls *et al.*[8] considered severe TR; Lindman considered mild vs. moderate vs. severe and we decided to use the HR of all-cause mortality for severe TR.[11]

Internal validity and quality appraisal

Two unblinded reviewers evaluated the quality of included studies using pre-specified electronic forms that were piloted over the first three cases and using a modified version of the Newcastle-Ottawa Scale for cohort studies (*Table 2*).[19] The divergences were resolved by consensus. No studies were excluded on the basis of this analysis.

Data analysis and synthesis

Continuous variables were reported as mean [±standard deviation (SD)] or median [interquartile range (IQR)]. To convert median (IQR) to mean (SD) we used formula accepted in the literature.[20] Categorical variables were expressed as number and percentage (%). Continuous variables were reported as mean (±SD) or median (IQR). The endpoints were expressed as HR. Point estimates and standard errors were calculated and combined by the generic inverse variance method,[21] computing risk estimates with 95% confidence intervals (CIs) according to logarithmic transformation of the hazard measures. Considering the high likelihood of between-study variance, we used a random effect model. Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistic with a value of I^2 of 0–25% considered insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and >75% high heterogeneity.[22] To test the difference between sub-group analyses the χ^2 test has been used. Finally, random effect meta-regression analysis was performed to assess the effect of some potential confounding factors (sex, previous myocardial infarction, diabetes, hypertension, and severe kidney disease) on results. Publication bias was appraised by graphical valuation of funnel plots and through Begg and Mazumdar rank correlation, Egger's regression intercept, and Duval and Tweedie trim and fill.[23] Prometa software 3 (Internovi, Cesena, Itay) and RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) were the software used for statistical analysis.

Results

Search strategy

A total of 815 records were analysed: 687 about mitraclip and 128 about TAVI (*Figure 1*). After a first evaluation of titles and abstracts 86 records were screened and 77 of these were excluded because they failed to report on TR. Nine studies were analysed as full-article (*Figure 1*). Three articles were excluded: one was a review, one was not reporting data about TR and all-cause mortality and one[14] (*Figure 1*) was a possible sample duplicate of the population of Puls *et al.*[8] Six studies were included in qualitative and quantitative analysis.[8–14] Of these only the study of Lindman *et al.*[11] was a RCT, all the others were observational studies.[8–10,12,13]

Population characteristics

A total of 2329 patients were analysed: 1328 treated with TAVI and 1001 with mitraclip. The mean age was 78.38 (3.09), 63% of patients were male. Hypertension was present in 39% of the population, diabetes in 25%, a previous myocardial infarction affected the 16% of the patients (*Table 1*) and atrial fibrillation 37% of the population. Mean EF pre procedure was 41% (14%); mean pre procedure sPAP was 50(7) mmHg and mean EuroSCORE was 20(06).

Primary outcome and secondary outcomes

The HR for all-cause mortality of moderate to severe TR in patients undergoing TAVI or mitraclip was 2.0 (95% CI 1.57–2.55) (*Figure 2*). The HR just for patients undergoing TAVI was 2.10 (95% CI 1.52–2.91) and for those receiving mitraclip was 1.87 (95% CI 1.30–2.71) (*Figure 2*). Subgroup analysis according the length of the follow-up disclosed the absence of statistical significance (HR 2, $P < 0.00001$ for follow-up ≤ 1 year versus HR 1.89, $P = 0.04$ for follow-up <1 year,

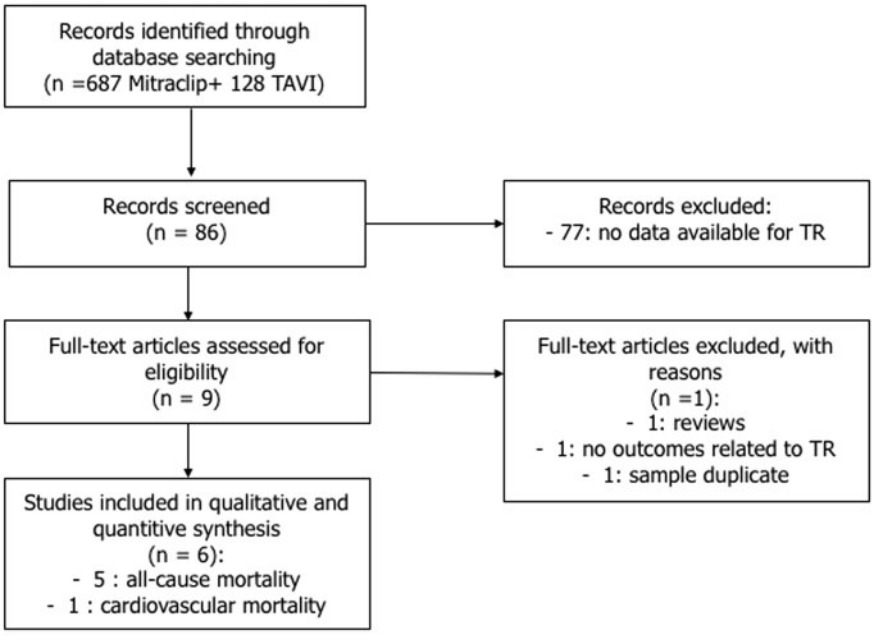

Figure 1 Outline of the search strategy.

Table 1 Sample characteristics

References	Study	T/M	N°	Male (%)	HPT (%)	Diabetes (%)	Previous MI (%)	GFR<30 mL/min	AF	Follow-up (year)	Factors valued at multivariate analysis
Barbanti 2015	OBS P	T	518	55	78	30	NA	38	38	2	PM, AF, mean trans-aortic gradient, renal failure.
Giannini 2015	OBS R	M	169	78	68	33	64	26	40	3	age, logistic EuroSCORE, GFR < 30, AF, LVEDD, LVEDV, LVESV, LVEF, LA area, TAPSE, RV PVS TDI
Hutter 2013	OBS P	T	268	38	NA	NA	53	19	23*	1	only data available for univariate analysis
Lindman 2015	RCT	T	542	75	51	15	25	6	30	1	age, sex, BMI, STS score, prior MI, prior CABG, frailty, PM, atrial arrhythmia, aortic valve mean gradient, LVEF, and MR
Ohno 2014	OBS P	M	146	64	75	39	NA	51	38	1	chronic kidney disease and AF
Puls 2016	OBS P	M	749	61	78	30	NA	62	44	1	age, sex, NYHA; anaemia, previous aortic valve implantation, creatinine > 1.5, PAD, LVEF < 30, procedural failure

OBS, observational; P, prospective; R, retrospective; HPT, hypertension; GFR, glomerular filtration rate; PM, pacemaker, AF, atrial fibrillation; LVEDD, left ventricle end diastolic diameter; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; BMI, body mass index; MI, myocardial infarction; CABG, coronary artery bypass graft; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; PAD, peripheral artery disease; NYHA, New York Heart Association; NA, not assessed; RCT, randomized clinical trials; T/M: TAVI or Mitraclip; RV PVS TDI: right ventricle pulse velocity systolic tissue doppler imaging; STS: The Society of Toracic Surgeons; *, atrial arrhythmia.

$\chi^2 = 0.03$, $P = 0.87$) (Supplementary data online, e*Figure S1*). Of note, data from Hutter *et al.* relates to the univariate analysis. After the exclusion of the study of Hutter *et al.*, the cumulative HR for all-cause death did not change (HR 2.03; 95% CI 1.52–2.71) (Supplementary data online, e*Figure S2*). The heterogeneity between study was insignificant ($I^2 = 0\%$). None of the factor considered in meta-regression analyses was affecting the primary outcome. The analyses disclosed the absence of publication bias (*P* for Egger's linear regression test = 0.213, *P* for Begg and Mazumdar's rank correlation test = 0.142; 0 trimmed studies) (*Figure 3*).

Finally, only the study of Giannini *et al.* reported the HR of TR > 2 for cardiovascular death, showing the absence of predictive value at

Table 2 New Castle Ottawa scale for quality assessment

References	Score (max 6)	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Outcome 1	Outcome 2	Outcome 3
Barbanti	4	a*	NA	a*	a*	NA	d	a*	d
Giannini	5	a*	NA	a*	a*	NA	b*	a*	d
Hutter	6	a*	NA	a*	a*	NA	b*	a*	b*
Lindman	6	a*	NA	a*	a*	NA	b*	a*	b*
Ohno	6	a*	NA	a*	a*	NA	b*	a*	a*
Puls	6	a*	NA	a*	a*	NA	b*	a*	b*

Only letter with * give points; NA, not assessed.

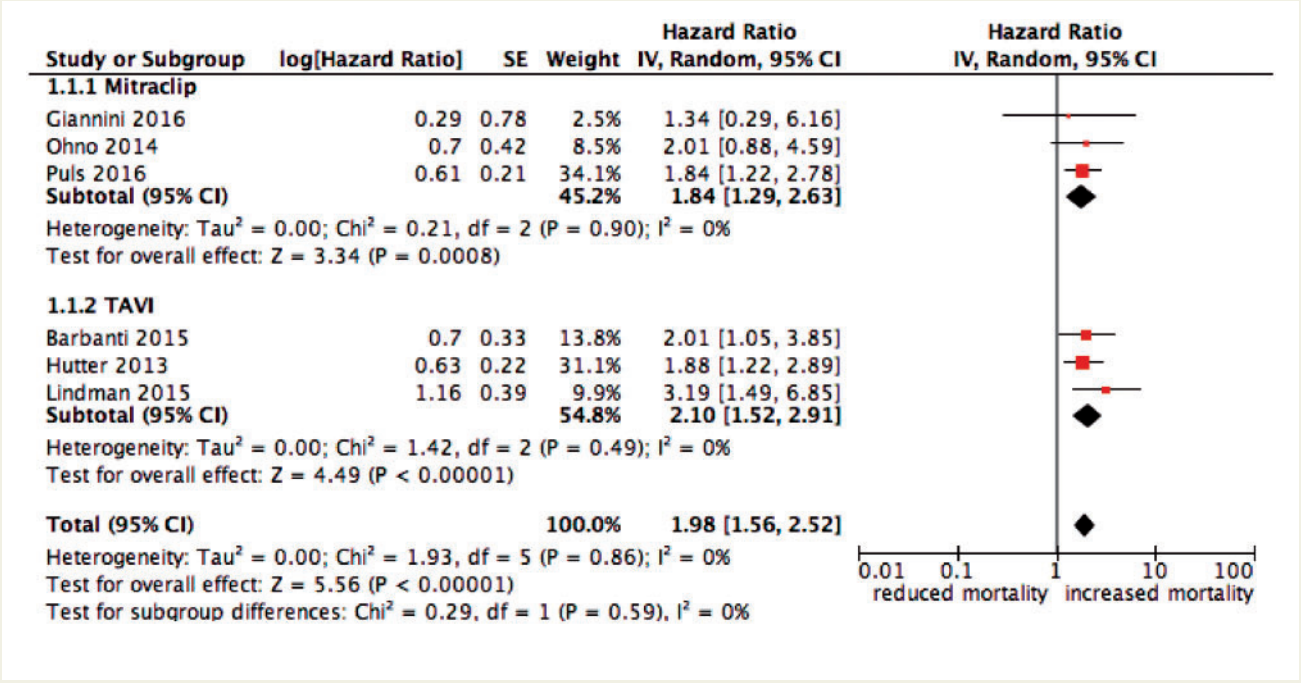

Figure 2 Forest plot of the studies valuing the relation between the presence of moderate to severe TR and all-cause mortality in patients undergoing mitraclip or TAVI procedure. Data are displayed as HR (95% CI).

the multivariate analysis (HR 1.33, 95% CI 0.29–6.10) for patients undergoing mitraclip.

Discussion

At the state of the art, this is the first systematic review on the predictive role of TR on all-cause mortality in patients undergoing mitraclip or TAVI procedure. The data are confirmed for both procedures and no-one of the factors valued at the meta-regression analysis affected the outcome. Interestingly, even if the studies were conducted on patients with mixed diseases (mitral regurgitation vs. aortic stenosis), the heterogeneity expressed as I^2 was insignificant, even more corroborating the data obtained. Unfortunately, it was not possible to draw any conclusion on cardiovascular death since only the study by Giannini *et al.*[10] was focused on this outcome and enrolled a small number of patients undergoing mitraclip. The population analysed in our meta-analysis was a high risk one as showed by the mean age, EF, PAPs, and EuroSCORE. Our results represent the first step in the understanding of the relationship between TR and outcome in patients undergoing percutaneous repair of left heart valve disease. However, there are several questions still unsolved.

First of all, does TR play a primary role in determining the outcome of these patients or is it just a marker of patients' risk and complexity? In this regard, current available data are scanty and conflicting. On one side, the study of Barbanti *et al.*[13] showed that, in patients treated with TAVI, the risk for all-cause mortality was higher in those with moderate to severe TR, only in case of EF > 40%. Authors suggested that comorbidities are the real responsible of the adverse outcome in the presence of severe TR, and that severe TR could be considered as a surrogate marker of other concomitant risk factors. On the other side, in patients treated with mitraclip, the presence of

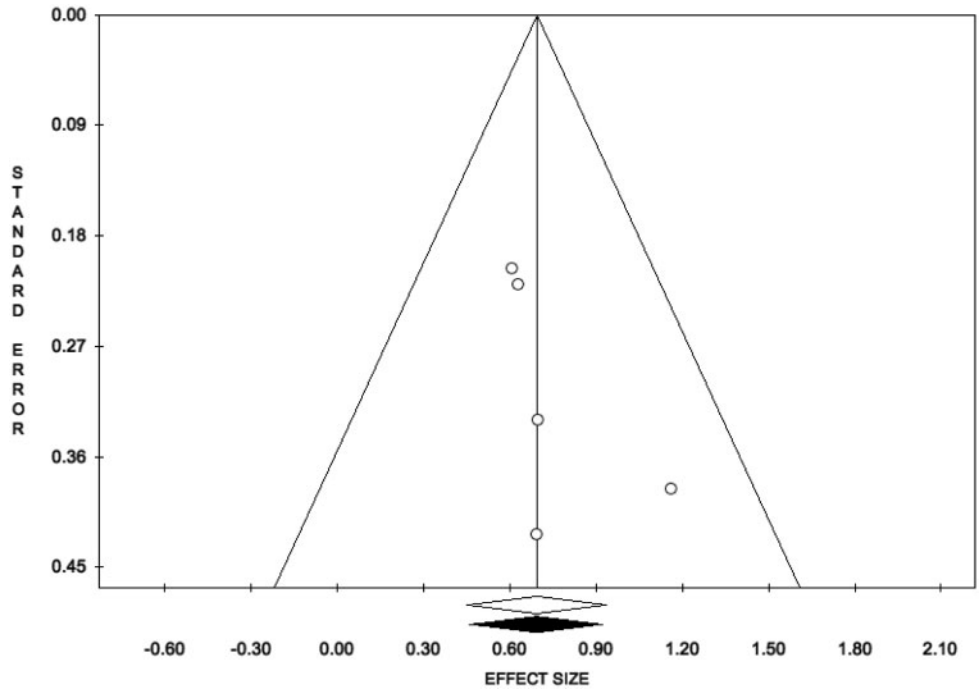

Figure 3 Funnel plot and trim and fill analysis for publication bias detection.

moderate to severe TR is predictive of a composite outcome of death and hospital readmission for HF ($P = 0.015$) but only in patients with EF < 35%.[9] In this case, authors suggested that this particular finding could be related to the high risk of these patients to develop biventricular failure. Our meta-analysis did not give an answer to this dilemma, even if it underlines once again the necessity to improve the definition of the risk in patients affected by TR and left heart valve disease undergoing percutaneous procedures. Secondly, a more defined approach to the quantification of the severity of the TR is needed. Currently, in clinical practice, the quantification of TR is less standardized than it is for mitral valve. The same semi quantitative and quantitative methods used for mitral valve should be systematically employed to quantify TR.

Thirdly, does TR improve as a result of the correction of the left heart valve disease or is it necessary a combined approach involving tricuspid valve? After the correction of the left heart valve disease there is an improvement of the TR,[9,12] even if this phenomenon seems to be extremely variable[13] and related also to other comorbidities and heart disease. Thus, new tailored randomized trials are needed to determine whether the presence of moderate to severe TR, with or without right ventricular or annular dilatation, is a new potential target for a combined percutaneous approach in patients undergoing percutaneous left heart valve procedure. This could be particularly important since several and new percutaneous techniques are now available to treat also tricuspid valve. The cardioband device (ValtechCardio, OrYehuda, Israel) is an already successfully used transcatheter annuloplasty system consisting in a Dacron band implantable under echocardiographic and fluoroscopic guidance;[24] the Trialign is another sutarable annuloplasty system device, which is under evaluation in the Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System (PTVAS) Also Known as Trialign (SCOUT) (NCT02574650) trial;[25] mitraclip system has already been used to successfully treat patients with TR[26] and finally also The TriCinch (4Tech Inc., Galway, Ireland) device is another potential option for the percutaneous treatment of TR.[27]

All these unsolved issues suggest that a 'mentality shift' in the percutaneous approach to heart valve is needed. Nowadays, the use of echocardiography is crucial to guide the selection of the patients and correct apposition of the mitraclip.[28] As for TAVI, the whole procedure is planned on a combined approach made by echocardiography, multislice computed tomography, angiography, and cardiovascular magnetic resonance.[29] Along with this 'procedure-centred' approach, a more detailed and shared evaluation of the tricuspid valve disease severity would be necessary to understand its impact and the possible need of a standardized combined approach involving also the treatment of tricuspid valve in patients undergoing TAVI or mitraclip.

Study limitation

This is a study level meta-analysis and for this reason it has several limitations. First of all, we compared data of patients treated for mitral regurgitation with those treated for aortic stenosis. However, subgroup analysis confirmed the same data also for every single category of patients. Secondly, factors analysed at the multivariate analysis are widely different among studies and in particular we considered data at the univariate analysis for the study of Hutter *et al.*

Nevertheless, heterogeneity expressed as I^2 was insignificant. Moreover, including only data from univariate analysis from the studies of Ohno, Barbanti, Hutter, and Lindman the cumulative HR of severe TR for all-cause death was 2.61 (95% CI 1.73–3.96, $I^2 = 52\%$) (Supplementary data online, e*Figure* S3), showing a higher degree of heterogeneity, but the same increased HR for all-cause death. Thirdly, only one study showed data about cardiovascular death. Finally, there are no data to clearly define the pathophysiologic mechanism behind the TR (e.g. annular dilatation, right ventricle dysfunction, and degenerative disease) and how other factors like systolic PAP or EF change in the follow-up. For all these limitations and because this meta-analysis is based on data coming from observational study and one RCT, data obtained should be considered only hypothesis generating and a background to plan future trial to define the criteria for the percutaneous treatment of TR in patients with concomitant left heart valve disease undergoing TAVI or mitraclip.

Conclusions

The current meta-analysis suggests that the presence of moderate to severe TR in patients undergoing mitraclip or TAVI might be a major determinant of all-cause mortality. New studies are needed to confirm it and to plan possible intervention in order to reduce its impact.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

Conflict of interest: none declared.

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