International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Tricuspid annuloplasty versus a conservative approach in patients with functional tricuspid regurgitation undergoing left-sided heart valve surgery: A study-level meta-analysis

Matteo Pagnesi [a], Claudio Montalto [a], Antonio Mangieri [a], Eustachio Agricola [b], Rishi Puri [c], Mauro Chiarito [d], Marco B. Ancona [a], Damiano Regazzoli [a], Luca Testa [e], Michele De Bonis [f], Neil E. Moat [g], Josep Rodés-Cabau [c], Antonio Colombo [a,h,i], Azeem Latib [a,i,*]

[a] Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy
[b] Echocardiography Laboratory, San Raffaele Scientific Institute, Milan, Italy
[c] Quebec Heart & Lung Institute, Laval University, Québec City, Canada
[d] Division of Clinical and Interventional Cardiology, Humanitas Research Hospital, Milan, Italy
[e] Department of Cardiology, IRCCS Policlinico San Donato, Milan, Italy
[f] Department of Cardiovascular and Thoracic Surgery, San Raffaele Scientific Institute, Milan, Italy
[g] Department of Cardiothoracic Surgery, Royal Brompton Hospital, London, United Kingdom
[h] Vita-Salute San Raffaele University, Milan, Italy
[i] Interventional Cardiology Unit, EMO-GVM Centro Cuore Columbus, Milan, Italy

ARTICLE INFO

Article history:
Received 4 April 2017
Received in revised form 29 April 2017
Accepted 4 May 2017
Available online xxxx

Keywords:
Tricuspid regurgitation
Tricuspid valve repair
Tricuspid annuloplasty
Cardiac surgery
Valvular heart disease
Meta-analysis

ABSTRACT

Background: Tricuspid valve (TV) repair at the time of left-sided valve surgery is indicated in patients with either severe functional tricuspid regurgitation (TR) or mild-to-moderate TR with coexistent tricuspid annular dilation or right heart failure. We assessed the benefits of a concomitant TV repair strategy during left-sided surgical valve interventions, focusing on mortality and echocardiographic TR-related outcomes.
Methods: A meta-analysis was performed of studies reporting outcomes of patients who underwent left-sided (mitral and/or aortic) valve surgery with or without concomitant TV repair. Primary endpoints were all-cause and cardiac-related mortality; secondary endpoints were the presence of more-than-moderate TR, TR progression, and TR severity grade. All endpoints were evaluated at the longest available follow-up.
Results: Fifteen studies were included for a total of 2840 patients. TV repair at the time of left-sided valve surgery was associated with a significantly lower risk of cardiac-related mortality (odds ratio [OR] 0.38; 95% confidence interval [CI]: 0.25–0.58; $p < 0.001$), with a trend towards a lower risk of all-cause mortality (OR 0.57; 95% CI: 0.32–1.05; $p = 0.07$) at a mean weighted follow-up of 6 years. The presence of more-than-moderate TR (OR 0.19; 95% CI: 0.12–0.30; $p < 0.001$), TR progression (OR 0.03; 95% CI: 0.01–0.05; $p < 0.001$), and TR grade (standardized mean difference −1.11; 95% CI: −1.57 to −0.65; $p < 0.001$) were significantly lower in the TV repair group at a mean weighted follow-up of 4.7 years.
Conclusions: A concomitant TV repair strategy during left-sided valve surgery is associated with a reduction in cardiac-related mortality and improved echocardiographic TR outcomes at follow-up.

1. Introduction

In the majority of cases, tricuspid regurgitation (TR) results from a range of pathologies promoting tricuspid annular dilation, typically within the context of left-sided heart disease [1]. Commonly referred to as functional (or secondary) TR, its early stages are generally well tolerated; when left untreated, disease progression results in progressive right ventricular (RV) dilatation, dysfunction, and subsequent poor clinical outcomes [2]. Following successful left-sided heart valve surgery, late significant functional TR develops in approximately 25–30% of patients and its incidence increases with time [3–6]. Current European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend concomitant tricuspid valve (TV) surgery in patients with severe TR undergoing left-sided valve surgery (class I recommendation) [7,8]. In patients with mild-to-moderate TR, there is a class IIa indication for concomitant TV surgery in the setting of tricuspid annular dilation [7,8] or prior evidence of

* Corresponding author at: Interventional Cardiology Unit, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: alatib@gmail.com (A. Latib).

http://dx.doi.org/10.1016/j.ijcard.2017.05.014
0167-5273/

right heart failure [7]. Concomitant TV repair during mitral valve surgery seems not to increase operative mortality, regardless of TR severity [9], and associates with improved long-term right ventricular remodelling [10]. However, a long-term survival benefit of this approach has yet to be definitively established [1].

A prior meta-analysis of studies comparing TV annuloplasty versus no TV intervention at the time of mitral valve surgery in patients with mild-to-moderate TR did not investigate cardiac-related mortality, reporting similar all-cause mortality in patients irrespective of whether they underwent TV repair [11]. With the inclusion of more recent clinical data in addition to studies evaluating patients with any baseline TR grade, as well as studies including patients undergoing mitral or aortic valve interventions, the present meta-analysis was undertaken to more systematically assess the benefits of a concomitant TV repair strategy at the time of left-sided valve intervention versus a conservative approach, focusing on mortality (both overall and cardiac-related) and echocardiographic TR-related outcomes.

2. Methods

2.1. Search strategy and study selection

All prospective or retrospective studies evaluating patients with functional TR undergoing left-sided heart valve surgical interventions and comparing a prophylactic tricuspid annuloplasty during the surgical procedure with a conservative approach (no tricuspid annuloplasty) were evaluated for inclusion in this meta-analysis. Two authors (CM, AM) independently searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials for articles published between Jan 1, 2000, and April 15, 2016, using the following combinations of search keywords: "functional tricuspid regurgitation" or "secondary tricuspid regurgitation" or "late tricuspid regurgitation" and "tricuspid annuloplasty" or "tricuspid valve repair". We included studies that reported outcomes at follow-up of adult patients undergoing left-sided valve surgery with versus without prophylactic tricuspid annuloplasty. In addition, we checked the reference lists from all eligible studies to identify additional citations. Excluded were studies that failed to clearly report the numbers and rates of all-cause or cardiac-related mortality, echocardiography-based TR outcomes at follow-up, and those reporting only operative (in-hospital or 30-day) outcomes.

2.2. Data extraction

Two investigators (MP, CM) independently assessed studies for possible inclusion. Non-relevant articles were excluded based on title and abstract. Two authors (CM, MP) independently extracted data on study design, patient characteristics, and outcomes. Conflicts about data extraction were discussed and resolved with another author (AM).

2.3. Outcomes

Primary endpoints were the rate of all-cause mortality and cardiac-related mortality. Secondary endpoints were more-than-moderate TR, TR progression (defined as the increase in at least one grade of TR), and TR grade severity. All endpoints were assessed at the longest follow-up available.

2.4. Statistical analysis

We performed a meta-analysis of studies comparing a tricuspid repair strategy with a conservative approach during left-sided valve surgical operations. When available, numbers of events were derived from propensity score matched patients. We compared the pooled baseline characteristics of both groups, presenting continuous variables as pooled weighted means and composite standard deviations. When data was available only as median and interquartile range or range, mean and standard deviation were calculated according to Wan et al. [12]. Pooled odds ratios (ORs) and standardized mean differences with 95% confidence intervals (CIs) were used as summary statistics for outcomes of interest and were calculated using a binary and continuous random-effects model, respectively, according to DerSimonian and Laird [13]. To assess heterogeneity across studies, we used Cochrane Q statistic to compute I^2 values: <25%, 25–50%, or >50% indicated low, moderate, or high heterogeneity, respectively [14]. Statistical significance was set at p-value <0.05 (two-sided). Publication bias and small study effect were assessed for primary endpoints by visual inspection of funnel plots and Egger's and Begg's tests [15]. Sensitivity analyses were performed for primary endpoints by assessing the effect of removing individual studies on the pooled OR. Analysis for primary endpoints was stratified by inclusion of patients with more-than-moderate TR (studies including vs. studies not including patients with more-than-moderate TR) and by type of left-sided heart valve procedure (studies including vs. studies not including only patients undergoing mitral valve interventions). A weighted meta-regression with a random-effects model was performed to evaluate the effect of follow-up length and baseline TR grade, age, left ventricular ejection fraction (LVEF), and pulmonary artery systolic pressure (PASP) in the TV repair group on primary endpoints [16].

Statistical analyses were conducted by using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, 2014) and Stata version 13.0 (Stata Corp., College Station, Texas). Search strategy, study selection, data extraction, and data analysis were performed in accordance with The Cochrane Collaboration and the PRISMA guidelines [17].

3. Results

Of 825 potentially relevant studies, 15 studies were included in the meta-analysis (Fig. 1) for a total of 2840 patients who underwent left-sided valve surgery with (n = 1356) or without (n = 1484) concomitant tricuspid annuloplasty [3,18–31]. Only 2 studies had a randomized design [18,28], while the other studies were observational in nature (1 prospective [20] and 12 retrospective) [3,19,21–27,29–31]. Patients evaluated in these studies had differing degrees of functional TR as assessed by pre-operative echocardiography (Table 1): 329 patients (11.6%) had more-than-moderate TR, 2376 patients (83.7%) had none-to-moderate TR, while the exact number of subjects in these two TR categories was not specified for 135 patients (4.7%).

TV repair was performed either with a ring or with a suture technique (De Vega or Kay methods). The proportion of women was higher among patients who underwent tricuspid annuloplasty compared with those who did not (57.0 vs. 51.3%; p = 0.04). Patients who underwent concomitant tricuspid repair were older (57.4 ± 13.8 vs. 55.6 ± 13.9 years; p < 0.001), had higher TR grades (1.51 ± 0.79 vs. 1.11 ± 0.60; p < 0.001), tricuspid annular diameters (36.6 ± 8.1 vs. 34.2 ± 8.2 mm; p < 0.001), and PASP (45.4 ± 15.4 vs. 40.3 ± 14.7 mm Hg; p < 0.001), but had similar LVEF (53.3 ± 11.9 vs. 53.3 ± 13.2%; p = 0.94).

The follow-up time was reported in all studies, ranging from 3 months [29] to 7 years [26]. All-cause mortality was clearly reported by 11 studies [18,20–29], while cardiac-related mortality was described in 9 studies [18–25,28]; the mean weighted clinical follow-up time among studies reporting survival outcomes was 6.0 years. Tricuspid annuloplasty at the moment of left-sided valve surgery was associated with a non-significant trend towards a lower risk of all-cause mortality (OR 0.57; 95% CI: 0.32–1.05; p = 0.07), with significant inter-study heterogeneity ($Q = 40.8$; $p_{heterogeneity} < 0.0001$; $I^2 = 75\%$) (Fig. 2A). Cardiac mortality was significantly lower in patients treated with TV repair than in those who underwent a conservative strategy (OR 0.38; 95% CI: 0.25–0.58; p < 0.001), without significant inter-study heterogeneity ($Q = 5.2$; $p_{heterogeneity} = 0.73$; $I^2 = 0\%$) (Fig. 2B).

Echocardiographic data regarding TR at follow-up was reported in 12 studies [3,18–21,23–25,27–31] for a total of 1662 patients: 874 patients in the TV repair group vs. 788 patients in the control group.

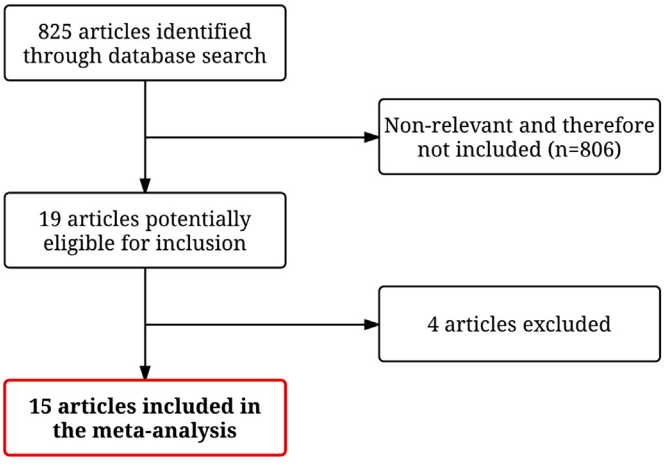

Fig. 1. Flow chart of the study selection process. After exclusion, 15 studies were included in the meta-analysis.