

The best approach for functional tricuspid regurgitation. A network meta-analysis.

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November 28, 2020

Abstract

OBJECTIVE. For many years, functional tricuspid regurgitation (FTR) was considered negligible after treatment of left-sided heart valve surgery. The aim of the present network meta-analysis is to summarize the results of four approaches in order to establish the possible gold standard. **METHODS** A systematic search was performed to identify all publications reporting the outcomes of four approach for FTR, not tricuspid annuloplasty (no TA), suture annuloplasty (SA), flexible (FRA), rigid rings (RRA). All studies reporting at least one the four endpoints (early and late mortality, early and late moderate or more TFR) were included in a Bayesian network meta-analysis. **RESULTS** There were 31 included studies with 9,663 patients. Aggregate early mortality was 5.3% no TA, 7.2% SA, 6.6% FRA and 6.4% RRA; Early TR moderate-or-more was 9.6%, 4.8%, 4.6% and 3.8%; Late mortality was 22.5%, 18.2%, 11.9% and 11.9%; Late TR moderate-or-more was 27.9%, 18.3%, 14.3% and 6.4%. Rigid or semirigid ring annuloplasty was the most effective approach for decreasing the risk of late moderate or more FTR (−85% vs. no TA; −64% vs. SA; −32% vs. FRA). Concerning late mortality, no significant differences were found among different surgical approaches, however, flexible or rigid rings reduced significantly the risk of late mortality (78% and 47%, respectively) compared with not performing TA mortality. No differences were found for early outcomes. **CONCLUSIONS.** Ring annuloplasty seems to offer better late outcomes compare to either suture annuloplasty or not performing TA. In particular rigid or semirigid rings provides more stable FTR across time.

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The best approach for functional tricuspid regurgitation.

Word count: 5508

data availability statement: the data associated with the paper are not publicly available but are available from the corresponding author on reasonable request

funding statement: no fund used

conflict of interest disclosure: none to disclose

Institutional Review Board approval or waiver: N/A

patient consent statement: N/A

clinical trial registration: N/A

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ABSTRACTOBJECTIVE. For many years, functional tricuspid regurgitation (FTR) was considered negligible after treatment of left-sided heart valve surgery. The aim of the present network meta-analysis is to summarize the results of four approaches in order to establish the possible gold standard. METHODS A systematic search was performed to identify all publications reporting the outcomes of four approach for FTR, not tricuspid annuloplasty (no TA), suture annuloplasty (SA), flexible (FRA), rigid rings (RRA). All studies reporting at least one the four endpoints (early and late mortality, early and late moderate or more TFR) were included in a Bayesian network meta-analysis. RESULTS There were 31 included studies with 9,663 patients. Aggregate early mortality was 5.3% no TA, 7.2% SA, 6.6% FRA and 6.4% RRA; Early TR moderate-or-more was 9.6%, 4.8%, 4.6% and 3.8%; Late mortality was 22.5%, 18.2%, 11.9% and 11.9%; Late TR moderate-or-more was 27.9%, 18.3%, 14.3% and 6.4%. Rigid or semirigid ring annuloplasty was the most effective approach for decreasing the risk of late moderate or more FTR (−85% vs. no TA; −64% vs. SA; −32% vs. FRA). Concerning late mortality, no significant differences were found among different surgical approaches, however, flexible or rigid rings reduced significantly the risk of late mortality (78% and 47%, respectively) compared with not performing TA mortality. No differences were found for early outcomes. CONCLUSIONS. Ring annuloplasty seems to offer better late outcomes compare to either suture annuloplasty or not performing TA. In particular rigid or semirigid rings provides more stable FTR across time. Keywords. Tricuspid regurgitation; tricuspid annuloplasty; tricuspid valve repair; suture annuloplasty; rigid ring; flexible ring. **Abbreviation list** Functional tricuspid regurgitation (FTR) Tricuspid valve (TV) disease Tricuspid annular dilatation (TAD) Pulmonary hypertension (PHT) No tricuspid annuloplasty (no TA) Suture annuloplasty (SA) Flexible ring annuloplasty (FRA) Semirigid/rigid ring annuloplasty (RRA) Odds ratios (ORs) Incidence rate ratios (IRRs) Surface under the cumulative ranking curve (SUCRA) Tricuspid annuloplasty (TA) **INTRODUCTION** Functional tricuspid regurgitation (FTR) is the most frequent

picture among tricuspid valve (TV) disease; it is mainly due to TV annular dilatation alongside with leaflets tethering, and is commonly associated with left-sided heart valve disease [1,2]. For many years, FTR was considered negligible after treatment of left-sided heart valve surgery [3,4]. Since the mid of two-thousands, Dreyfus et al. [5] emphasized the need to treat FTR, even less than severe, otherwise it could worsen at 5 years. This concept has also been confirmed by some recent meta-analytic studies [6,7]. So, guidelines for the management of heart valve disease [8,9] as well as surgical consensus [10], updated the indications for treatment of FTR, suggesting to treat not only severe TR, but also FTR graded less than severe, in presence of tricuspid annular dilatation (TAD), right ventricular dysfunction or pulmonary hypertension (PHT). On the other hand, the results of different surgical strategies, suture annuloplasty versus flexible rings or rigid rings are still controversial¹¹⁻¹⁶. Some meta-analyses report pairwise comparison¹⁴⁻¹⁶, however a global description of four most common approaches for functional tricuspid regurgitation (no tricuspid annuloplasty, suture annuloplasty, flexible and rigid ring annuloplasty) is still missing. Hence, the aim of the present network meta-analysis is to summarize the results of these four approaches in order to establish the possible gold standard.

METHODS LITERATURE SEARCH STRATEGY. Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Network Meta-analysis¹⁷, electronic searches were performed by 3 authors (JMR, FR, GB). Details of the literature search strategy are provided in the Appendix.

SELECTION CRITERIA. Eligible studies for the present systematic review and network meta-analysis were those published in English that compared two or more strategies in case of functional tricuspid regurgitation: no tricuspid annuloplasty (no TA), suture annuloplasty (SA), flexible annuloplasty (FRA) and semirigid/rigid ring (RRA). Studies that did not contain comparison were excluded. Detailed selection criteria are provided in the Appendix.

DATA EXTRACTION AND CRITICAL APPRAISAL. All data were extracted from article texts, tables and figures. Two investigators (MDM and FR) independently reviewed each included article. Details of study appraisal and quality scoring are provided in the Appendix. Discrepancies between the 2 investigators were resolved by discussion and consensus with the senior authors (AMC, RL, AP and UB).

STATISTICAL ANALYSIS. In the present network meta-analysis, dichotomous outcome variables were compared with odds ratios (ORs) and 95% confidence intervals (CIs) for early (within postoperative 30 days) mortality and FTR moderate or more. For long-term outcomes with potentially different follow-up durations between groups, we derived the log incidence and corresponding standard error from numbers of reported events and accumulated person-years of follow-up. For each eligible study, if the associated information was present merely in figures, Engauge Digitizer was used to collect data from the statistical graphs. Then log IRR and standard error were extracted using an excel calculator sheet based on previous reported literature¹⁸. Finally, IRR with 95% confidence interval (95%CI) were reported for late mortality or late TR moderate or more. Outcome variables were compared with incidence rate ratios (IRRs) and 95% confidence intervals (CIs). Analyses were performed using Bayesian Markov chain Monte Carlo modeling¹⁹. To provide a comparative hierarchy of procedural efficacy and safety, “Rankograms” with surface under the cumulative ranking curve (SUCRA) probabilities were reported. A SUCRA of 90% means that the treatment of interest achieves 90% of effectiveness or safety relative to other interventions. Thus, the larger the SUCRA value, the higher the rank of the treatment, indicating a safer or more effective treatment. The analyses were performed with NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada), R-studio version 1.1.463 (2009-2018) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). Detailed statistical methods are provided in the Appendix.

RESULTS LITERATURE SEARCH. A total of 7517 studies were initially identified (Figure 1 supplementary). After exclusion of duplicate or irrelevant references, 114 potentially relevant articles were retrieved. After application of the inclusion and exclusion criteria, 31 relevant articles were included in the study^{5,12,20-48}: randomized trials (n=3)^{23,41,44}, propensity score-adjusted (n=4)^{12,25,30,45} and observational non-adjusted (n=24)^{5,20-22,24,26-29,31-43,45-48}. A total of 9663 patients were included for analysis. Among them 1371 did not receive concomitant TA (no TA), 1931 received suture annuloplasty, 3248 got a flexible and 3104 where a semirigid or rigid ring were used. Study characteristics are summarized in Table 1. Study quality assessment is summarized in Table 1 supplementary. Inspection of the funnel plots did not show significant asymmetry to suggest publication bias with outcomes selected (Figure 2 supplementary). Network diagrams were reported in the figure 1. Network characteristics are summarized in

the table 2 supplementary. **Early mortality.** Estimates of early mortality were extracted from 25 studies (7383) with 469 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate early mortality of 5.3% (0.9-13.1), 7.2% (1.4-20.6) for SA, 6.6% (0.8-14.2) for FRA and 6.4% (0.7-13.5) for RRA (Table 2). No significant differences were found among the 4 different approaches (Figure 2A). Inconsistency was low (Figure 3A suppl.). Heterogeneity was very low ($I^2=0\%$). **Early TR moderate or more.** Estimates of FTR moderate or more were extracted from 16 studies (3543) with 173 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate early rate of FTR moderate or more of 9.6% (5.6-45.7), 4.8% (1.4-15.4) for SA, 4.6% (1.7-13.6) for FRA and 3.8% (2.8-9.2) for RRA (Table 2). No significant differences were found among the 4 different approaches (Figure 2B). Inconsistency was low (Figure 3B suppl.). Heterogeneity was very low ($I^2=0\%$). **Late mortality** Estimates of late mortality were extracted from 21 studies (4600) with 636 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate late mortality of 22.5% (5.3-55.6), 18.2% (4.1-32.0), for SA, 11.9% (2.6-13.6) for FRA and 11.9% (1.2-22.6) for RRA (Table 2). No significant differences were found among different surgical approaches FRA vs SA (IRR 1.52, 0.99-2.34), RRA vs SA (IRR 1.10, 0.68-1.77), and RRA vs FRA (IRR 0.72, 0.45-1.15) (Figure 2C). Conversely, prosthesis TA, either with flexible rings or rigid rings reduced significantly the risk of late mortality (78% and 47%, respectively) compared with not performing TA. Bayesian Markov chain Monte Carlo modeling demonstrated that FRA had the highest probability of having the lowest rate of late mortality (SUCRA 90%), followed by RRA (70%), SA (20%), and no TA (19%) (Figure 3A). Inconsistency was low (Figure 3C suppl.). Heterogeneity was moderate ($I^2=40\%$). **Late TR moderate or more** Estimates of late FTR moderate or more were extracted from 26 studies (7373) with 636 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate late rate of FTR moderate or more of 27.9% (3.1-77.1), 18.3% (4.1-45.2) for SA, 14.3% (13.3-55.6) for FRA and 6.4% (0.25-37.3) for RRA (Table 2). Different risks among the 4 approaches are summarized in the league table (Figure 2D). Bayesian Markov chain Monte Carlo modeling demonstrated that RRA had the highest probability of having the lowest rate of late FTR moderate or more (SUCRA 99%), followed by FRA (67%), SA (34%), and no TA (0%) (Figure 3B). Hence, RRA provides a significant risk reduction of 85%, 64%, 32% with respect to no TA, SA and FRA, respectively (Figure 4). FRA provides a risk reduction of 78% and 47% with respect to no TA and SA, respectively. Even SA is able to provide a risk reduction of 59% with respect to no TA. Inconsistency was low (Figure 3D suppl.). Heterogeneity was mild ($I^2=18\%$). **DISCUSSION** The present network meta-analysis confirms that treating FTR at the time of left-sided heart valve surgery is absolutely crucial to achieve both lower mortality and tricuspid regurgitation at follow up. In almost all the studies, TA was performed according to Guidelines⁸⁻¹⁰, even in presence of moderate or mild FTR with tricuspid annulus dilatation or right ventricular dysfunction or PHT. In contrast with the study by David et al.³, FTR recurrence is not so uncommon, accounting for 27.9% (3.1-77.1%) without any TA. The rate decreased to 18.3% with suture annuloplasty, to 14.3 with flexible rings and even to 6.4% with rigid ring implant (Table 2). The role of TA for FTR is summarized in recent meta-analyses^{6,7}. Tam et al⁶ reported the results of 56,027 patients where tricuspid valve was repaired at time of left-sided heart valve surgery compared with 11,787 patients where an observational approach was adopted, leaving untreated FTR. The pooled effect evidenced a significant protective effect of TV repair (IRR 0.28, 0.17-0.47) with respect to late FTR. Paganesi⁷ analyzed the pooled effect of 15 studies, confirming that surgery for FTR at the time of the left-sided heart valve surgery provides a significant risk reduction (-81%) rather than observational approach. In those studies^{5,23,30,41} where TA was performed prophylactically, the rate of late FTR moderate or more was very low (2.8%) when compared to the rate collected in patients without TA (48.7%). However, the main finding of the present network meta-analysis is the significant risk reduction for late FTR, implanting rigid rather than flexible rings (-49%), or performing suture annuloplasty, mainly DeVega, but also Kay or bicuspidalization, (-64%) and mostly with respect to leaving untreated FTR when performing left-sided heart valve surgery (-84%). Electing this procedure could be the best approach for the stabilization of FTR over time. Veen KM et al¹⁴ pooled the results of 14 studies comparing suture vs ring annuloplasty, even if only 4 studies reported data for a pairwise comparison between suture and ring annuloplasty, failing to found out any significant differences between these two procedures in terms of late moderate or more TR (RR 0.98, 0.72-1.32). Contrariwise, Parolari et al¹⁵, in a meta-analysis of 9 studies, reported a significant

reduction of risk for TA failure performing ring rather than suture annuloplasty (RR=0.76, 0.60-0.95). The introduction of the flexible rings was driven by some features such as the advantage for annular contraction during cardiac cycle due to their flexibility, the simple design and implantation procedure. Moreover, right coronary occlusion or damage due to flexible ring were anecdotal⁴⁹⁻⁵¹. Less device dehiscence rate may be another possible benefit of flexible with respect to rigid rings⁴². Nevertheless, the stability of tricuspid annulus offered by rigid ring seems to be greater than the one by flexible rings. In fact, if results of comparison between suture and ring annuloplasty are still controversial, the literature seems to be more concordant to recognize the superiority of rigid over flexible ring^{14,16}. In fact, both meta-analyses by Veen¹⁴ (RR flexible versus rigid: 1.84, 1.24-2.74) and by Wang¹⁶ (RR rigid versus flexible: 0.44, 0.20-0.99) confirm a more stable FTR over time after rigid versus flexible ring TA. The former pairwise comparison was performed with data from 4 studies, but rigid ring was demonstrated to be more effective than flexible rings (RR 1.84, 1.24-2.74). The main argument invoked by the detractors of TA at the time of left-sided heart valve surgery has been for years the possible increase in the risk of postoperative mortality. This fear has been disproved by many studies⁵² that have clearly reported similar mortality rate either with or without TA. In the present network meta-analysis, no differences were found among the four different approaches. No differences were found even in terms of FTR at discharge, inducing us to some speculations. It is very likely that in the short-term, performing only left-sided heart valve surgery can lead to a temporary reduction in pulmonary pressure and right ventricular overload, which can be an apparently satisfying result. Actually, this finding can be the result of high dosages of diuretics in postoperative stay and so be independent from TA or no TA. Although any surgical treatment showed more stable FTR over time than leaving untreated FTR, only ring implant guarantees lower risk of death at follow-up. In particular, risk reduction was higher in case of flexible rings than rigid rings, even if not statically significant. This is very likely to be explained considering that late mortality is not only driven by late FTR, but also by possible right ventricular positive remodeling which can happen regardless the type of surgery²⁵.

Study Limitations Among the enrolled studies, there are only three randomized trials with small sample size. Unadjusted summary estimates were used for meta-analysis and confounders could not be ruled out. However, the network meta-analysis offers greater power and precision for rare events while controlling for publication bias and small-study effects. The network model was tested for consistency and heterogeneity. There was a moderate amount of heterogeneity for late mortality, so these results should be interpreted with caution.

Conclusions. To our knowledge, this is the first network meta-analysis comparing early and late outcomes following four different approaches in case of FTR. The results suggest that more stable FTR over time can be achieved only with ring TA, and in particular with rigid ring implant. Performing or not TA at the time of left-sided heart valve surgery does not add any early risk, but can provide better long-term survival.

Author contributions statement

Michele Di Mauro: conception of the study, analysis of data and drafting of the work Roberto Lorusso: revising critically the work, analysis of data Alessandro Parolari: revising critically the work, drafting work Justine M Ravoux: acquisition of data, analysis of data Giorgia Bonalumi: acquisition of data, analysis of data Stefano Guarracini: acquisition of data, drafting work Fabrizio Ricci: acquisition of data, analysis of data Umberto Benedetto: revising critically the work, drafting work Antonio M Calafiore: revising critically the work, drafting work

Sources of Funding: none

Disclosures: none

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Table 1. Study characteristics

Author	Year	Cohort size	Arms	type of study	Age (year)	Female (%)	TR (%)	[?]moderation: only severe	surgical indication: also less than severe with TAD or RV dysfunction or PH [8-10]	Prophylactic TR	AE (%)	EF	NYH III-IV (%)
Roshanal	2010	105	2	RCT	55	36%	100%	YES	NO	NO		0,42	
Benedetto	2012	44	2		66	45%	25%	NO	YES	YES	48%	0,53	70%
Pettinari	2019	106	2		63	35%	N/A	NO	YES	YES	20%	0,58	
Calafiore	2009	110	2	Propensity score	65	25%	100%	NO	YES	NO	25%	0,3	
Shinn ¹²	2016	296	2		71	43%	64%	NO	YES	NO	59%	0,6	76%
Choi ³⁰	2018	144	2		55	62%	0%	NO	YES	YES	82%		41%
Sohon ⁴⁵	2019	218	2		60	67%	44%	NO	YES	NO	83%	0,57	54%
Carrier ²⁸	2004	463	3	Retrospective non-adjusted	60	79%	100%	YES	NO	NO			88%
Dreyfus ⁵	2005	311	2		60	39%	8%	NO	YES	YES	29%	0,6	
Ghanta ³²	2007	237	3		67	53%	96%	NO	YES	NO		0,48	53%
Izutani ³⁵	2010	117	2		72	39%	95%	NO	YES	NO	76%	0,57	
Navia ⁴⁰	2010	2013	3		68	60%	96%	NO	YES	NO	68%	0,47	49%
Calafiore ²⁶	2011	432	3		64	43%	41%	NO	YES	NO	32%	0,47	
Pfannmüller ^{10,42}	2012	820	2		69	54%	83%	NO	YES	NO	61%	0,57	
Ariyoshi ²³	2013	99	3		66	62%	100%	YES	NO	NO			65%
Guenther ³⁸	2013	688	2		65	61%	99%	NO	YES	NO	64%	0,55	60%
Koppers ³⁵	2013	175	2		69	57%	100%	NO	YES	NO		0,56	
Bertrand ²⁴	2014	78	2		68	50%	17%	NO	YES	NO		0,52	
Lin ³⁸	2014	399	3		47	53%	98%	NO	YES	NO	41%	0,54	64%
Murashita ³⁹	2014	162	2		63	48%	61%	NO	YES	NO	64%	0,64	38%
Chikwe ²⁹	2015	645	2		59	37%	11%	NO	YES	NO	19%	0,61	
Ren ⁴³	2015	74	2		49	85%	70%	NO	YES	NO		0,61	96%
Gatti ³¹	2016	527	3		70	53%		NO	YES	NO		0,55	64%
Jouan ³⁶	2016	201	2		60	45%	17%	NO	YES	NO			
Wang ⁴⁷	2016	106	2		57	54%	100%	NO	YES	NO		0,51	
Abdelgawad ^{20,29}	2017	40	2		37	45%	100%	YES	NO	NO	45%	0,53	80%
Ito ³⁴	2017	98	2		68	53%	42%	NO	YES	NO	78%		43%
Verdonk ⁴⁶	2018	287	2		62	56%	34%	NO	YES	NO	40%		
Adas ²¹	2019	200	3		34	59%	100%	NO	YES	NO	48%		
Calafiore ²⁷	2019	298	3		52	61%	83%	NO	YES	NO	28%	0,48	80%
Zhong ⁴⁸	2019	170	3		53	77%	54%	NO	YES	NO	67%	0,59	67%

Legend. TR = tricuspid regurgitation; TAD = tricuspid annular dilatation; RV = right ventricular; PH = pulmonary hypertension; AF = atrial fibrillation; EF = ejection fraction; NYHA = New York Heart Association.

Table 2. Intervention characteristics.

Treatment	Studies	Events	Patients	Aggregate Rate	Min. Rate	Max. Rate
Early Mortality	Early Mortality	Early Mortality	Early Mortality	Early Mortality	Early Mortality	Early Mortality
<i>No TA</i>	10	45	850	5.3	0.9	13.1
<i>SA</i>	12	113	1580	7.2	1.4	20.6
<i>FRA</i>	13	154	2340	6.6	0.8	14.2
<i>RRA</i>	17	167	2613	6.4	0.7	13.5
Early TR\geq2+	Early TR\geq2+	Early TR\geq2+	Early TR\geq2+	Early TR\geq2+	Early TR\geq2+	Early TR\geq2+
<i>No TA</i>	6	33	344	9.6	5.6	45.7
<i>SA</i>	9	32	668	4.8	1.4	15.4
<i>FRA</i>	10	68	1488	4.6	1.7	13.6
<i>RRA</i>	10	40	1043	3.8	2.8	9.2
Late Mortality	Late Mortality	Late Mortality	Late Mortality	Late Mortality	Late Mortality	Late Mortality
<i>No TA</i>	8	73	654	22.5	5.3	55.6
<i>SA</i>	10	197	874	18.2	4.1	32.0
<i>FRA</i>	12	168	1414	11.9	2.6	23.0
<i>RRA</i>	13	198	1658	11.9	1.2	22.6
Late TR\geq2+	Late TR\geq2+	Late TR\geq2+	Late TR\geq2+	Late TR\geq2+	Late TR\geq2+	Late TR\geq2+
<i>No TA</i>	10	229	819	27.9	3.1	77.1
<i>SA</i>	17	323	1.762	18.3	4.1	45.2
<i>FRA</i>	16	353	2.464	14.3	13.3	55.6
<i>RRA</i>	18	149	2328	6.4	0.25	37.3

Legend. TR = tricuspid regurgitation; TA = tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid ring annuloplasty.

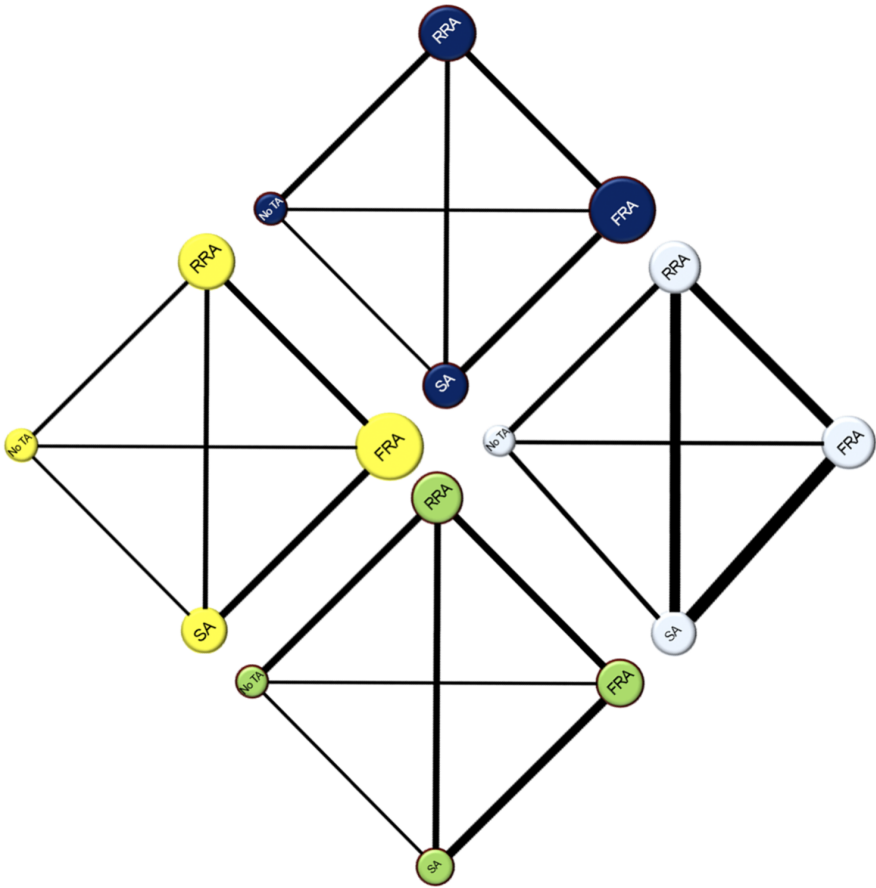
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Figure 1. Network diagram for early mortality (yellow), early moderate or more FTR (dark blue), late mortality (green) and late moderate or more FTR (light blue). No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty.

Figure 2. League tables for early mortality (A), early moderate or more FTR (B), late mortality (C) and late moderate or more FTR (D). No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty.

Figure 3. Rankogram with area under curve for late mortality (A) and late moderate or more FTR (B). Not tricuspid annuloplasty (black line); suture annuloplasty (red line); flexible ring annuloplasty (green line); rigid or semirigid ring annuloplasty (dark blue line).

Figure 4. Risk reduction late moderate or more. TV = tricuspid valve.



No TA			
0.95 (0.54-1.53)	SA		
1.06 (0.62-1.64)	1.12 (0.81-1.59)	FRA	
1.12 (0.62-1.78)	1.18 (0.85-1.65)	1.06 (0.71-1.62)	RRA

No TA			
1.35 (0.72-2.41)	SA		
1.45 (0.68-2.85)	1.07 (0.58-1.84)	FRA	
1.56 (0.55-3.32)	1.16 (0.56-2.64)	1.08 (0.54-2.15)	RRA

No TA			
1.20 (0.70-2.06)	SA		
1.84 (1.01-3.38)	1.52 (0.99-2.34)	FRA	
1.33 (1.01-2.31)	1.10 (0.68-1.77)	0.72 (0.45-1.15)	RRA

No TA			
2.44 (1.65-3.61)	SA		
4.58 (3.05-6.88)	1.87 (1.47-2.39)	FRA	
6.69 (4.41-10.15)	2.74 (2.04-3.68)	1.46 (1.11-1.91)	RRA

