Surgical Management of Tricuspid Valve Infective Endocarditis: A Systematic Review and Meta-Analysis

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Surgical Management of Tricuspid Valve Infective Endocarditis: A Systematic Review and Meta-Analysis

Running Head: Repair vs Replacement for Tricuspid Endocarditis

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Key Words: infective endocarditis, tricuspid repair, tricuspid replacement, valvectomy

Word Count: 4144
List of Abbreviations

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Abstract

Background: This meta-analysis compares the early and late outcomes of valve repair versus replacement, the primary surgical strategies for tricuspid valve infective endocarditis (IE).

Methods: We searched MEDLINE and EMBASE databases until 2016 for studies comparing tricuspid valve repair and replacement.

Results: The main outcomes were mortality, recurrent IE and need for reoperation. There were 12 unmatched retrospective observational studies with 1165 patients (median follow up 3.8 [inter-quartile range: 2.1-5.0] years). The most common indications for surgery were septic pulmonary embolism, left-sided IE, right heart failure and persistent bacteremia. Median repair proportion was 59% and replacement 41% among studies. The primary repair strategies are vegetectomy, De Vega procedure, annuloplasty ring, bicuspidization and leaflet patch augmentation. Of valve replacements, 83% were bioprosthetic and 17% mechanical prostheses. There were no differences in perioperative mortality between tricuspid valve repair vs replacement (RR 0.62, 95%CI:0.26-1.46, p=0.3). Long-term all-cause mortality was not different (RR 0.61, 95% CI:0.22-1.72, p=0.4). Valve repair was associated with lower recurrent IE (RR 0.17, 95% CI:0.05-0.57, p=0.004) and need for reoperation (RR 0.26, 95% CI:0.07-0.92, p=0.04) but a trend towards greater risk of moderate to severe tricuspid regurgitation (RR 4.14, 95%CI: 0.80-21.34, p=0.09). Furthermore, tricuspid valve repair is associated with lower need for permanent pacemaker (RR 0.20, 95%CI: 0.11-0.35, p<0.001).

Conclusions: Tricuspid valve repair and replacement offer similar long term survival. Valve repair may offer greater freedom from recurrent IE and reoperation as well as need for pacemaker and should be the preferred approach for patients with tricuspid valve IE.
Abstract Word Count: 250
Despite improvements in the diagnosis and management, infective endocarditis (IE) remains a high-risk condition [1]. The incidence of tricuspid valve IE has been steadily increasing over the last two decades [2, 3]. The primary causes are intravenous drug use, right-sided cardiac device implantation, central venous catheterization and repaired congenital defects, all of which are increasing in prevalence [2]. Most patients with tricuspid valve IE can be treated successfully with antibiotic therapy but in approximately 20% of cases, persistent infection, symptomatic valvular regurgitation, concomitant left-sided infection, or recurrent septic pulmonary embolic complications necessitate surgical intervention [4].

The principles of surgery for IE are complete removal of all infected tissues and reconstruction of cardiac structures. In tricuspid valve IE, valve repair is preferred to valve replacement to avoid the risk of prosthetic valve deterioration and to reduce the risk of recurrent IE, particularly in patients with a history of intravenous drug use. The 2015 Guidelines for the Management of Infective Endocarditis state that “valve repair is favoured whenever possible, particularly when IE affects the mitral or tricuspid valve without significant destruction.” [5]. The 2015 American Heart Association Guidelines on Infective Endocarditis in Adults recommends valve repair rather than replacement when feasible (Class I; Level of Evidence C) [6] and the Society of Thoracic Surgery Guidelines also recommend tricuspid valve repair for IE (Class I, Level of evidence B) [7]. The tricuspid valve is amenable to repair with a combination of vegetectomy, bicuspidization, leaflet patch, sliding or prosthetic ring annuloplasty, as well as chordal replacement, most of which have been described for functional TR [8-10]. However, surgeon and institutional experience for complex valve reconstruction is usually small and as such there is a low threshold for replacement, particularly for IE.
A rarely considered third surgical option is tricuspid valvectomy, which has been proposed to completely avoid any foreign material in cases of high recidivism in the intravenous drug use population, intractable infection or poor compliance to antibiotic therapy [11]. This may be offered as a staged or palliative procedure. This is poorly tolerated in patients with moderate-severe pulmonary hypertension and approximately 20% of patients experience acute right-sided hemodynamic compromise [11].

Here, we performed a systematic review and meta-analysis to determine the outcomes of mortality as well as freedom from recurrent tricuspid regurgitation, infective endocarditis and reoperation in patients with tricuspid valve IE undergoing valve repair versus replacement.

Material and Methods

Data sources

We systematically searched OVID versions of MEDLINE and EMBASE (1996 to 2017 February week 2 [performed on February 16th, 2017]) for all studies using the following: text words “tricuspid valve” AND “endocarditis” in the title or abstract, OR articles listed under the MeSH term “endocarditis”, AND all variations of text words “surgery”, “repair”, and “replace” in the title or abstract. We excluded non-English, non-human studies, and results with text word “case report” in the title.

Study Selection
We included all studies examining adults with tricuspid valve IE undergoing surgery with stratification based on repair versus replacement (Figure 1). Studies were required to report mortality. Those with concomitant left-sided IE or concomitant surgical procedures were included as long as the primary indication for surgery was tricuspid valve IE. Studies where the primary indication for surgery was not IE, and studies that reported on repair, replacement, or valvectomy only (without comparison) were excluded.

**Data extraction and quality assessment**

Two reviewers independently abstracted data including details of the publication, inclusion/exclusion criteria, patient demographics and cardiac risk factors, description of the interventions used, and outcome definitions and events (ME, SH). Study quality was assessed looking at the following indicators: retrospective versus prospective data collection, concurrent controls, comparable baseline characteristics, completeness of follow-up, and internal consistency of data presented. Disagreements on article inclusion were resolved by consensus.

**Statistical analysis**

All analyses were performed using Review Manager (RevMan version 5.2; Cochrane Collaboration, Oxford, UK) and random effects models, which incorporate between-trial heterogeneity and give wider and more conservative confidence intervals (CI) when heterogeneity is present [13]. We assessed statistical heterogeneity among trials using $I^2$, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and used published guidelines for low ($I^2=25\%$ to 49\%), moderate ($I^2=50\%$ to 74\%) and high ($I^2>75\%$) heterogeneity [14]. For peri-operative outcomes with similar follow up between
groups, relative risks (RR) were used to pool binary outcomes. For long-term outcomes with potentially different follow up between groups, we pooled incidence rate ratios (IRR) on the logarithmic scale using the generic inverse variance method. When hazard ratios (assumed to be equivalent to incidence rate ratios) were not provided, incidence rate ratios for each study were calculated where possible either 1) using Kaplan-Meier survival curve estimates for each group, and the log-rank survival curve p-value to estimate the standard error of the logarithm-transformed incidence rate ratio, or 2) numbers of reported events and accumulated group-specific person-years of follow-up. Individual trial and pooled summary results are reported with 95% CIs. When differential follow up durations by group were not provided, RR were used to pool studies reporting only mortality, recurrent infection, or need for reoperation event rates.

**Results**

*Description of Included Studies and Patients*

The initial search resulted in 1266 citations from MEDLINE and EMBASE and 13 observational studies were retrieved for full text review. One was a conference abstract, and was excluded [12]. Thus the final number of included articles was 12, enrolling 1165 patients (median follow up 3.8 [inter-quartile range: 2.1-5.0] years; Figure 1; Supplementary Table 1) [15–26].

*Study Quality Assessment (see Supplementary Table 1)*

All included studies were retrospective observational studies. All were single-centre except for Gaca et al [15], which derived data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. All studies compared concurrent tricuspid repair versus replacement patients (except for Capoun et al [17] where the 2 repair patients were the last in the series) with the
chosen technique based on surgeon discretion. In most studies it was not possible to compare baseline characteristics due to presentation of pooled data. Half the studies [18-22,25] specifically stated that tricuspid valve replacement was only performed if repair failed, though this may have been the case in the other studies as well, implying that the replacement patients had more severe disease. Some baseline differences were noted in Gaca et al [15], where preoperative tricuspid regurgitation was significantly higher in the replacement and valvectomy groups compared to the repair group (84% and 82% vs 69% respectively, p=0.001). In Renzulli et al [18], the replacement group had higher New York Heart Association (NYHA) class (3.4 vs 2.6, p=0.01) and a trend to younger age (36 vs 48 years, p=0.07). No study attempted to correct for baseline differences either through matching or adjustment. For studies reporting on all cases of right-sided infective endocarditis, we included only the data on tricuspid valve IE, when possible. All of the patients in Turley et al [25] had tricuspid valve IE involvement and Musci et al [22] analyzed tricuspid repair versus replacement separately. Jiang et al [24] included two patients (out of 35) with exclusively pulmonic IE and these were not separable from the rest of the cohort. Four studies analyzed patients with isolated tricuspid valve IE surgery only [16,17,20,23] and three [16,19,21] studied only actively infected patients.

**Patient Characteristics**

Mean or median age ranged from 38 to 60 years (Supplementary Table 2). In most studies it was not possible to compare baseline characteristics due to presentation of pooled data. Some baseline differences were noted in Gaca et al [15], where preoperative tricuspid regurgitation was significantly higher in the replacement and valvectomy groups compared to the repair group (83.67% and 81.82% vs 68.93% respectively, p=0.001). In Renzulli et al [18], the replacement
group had higher NYHA class (3.4 vs 2.6, p=0.01) and a trend to younger age (36 vs 48 years, p=0.07).

Tricuspid valve IE was most commonly associated with a history of intravenous drug use (41%), infected pacemaker leads (19%), and congenital defects (17%), (Supplementary Table 3). The majority of congenital defects reported were atrial and ventricular septal defects (86%). In Dawood et al [26], an unusually large percentage of patients had concurrent left-sided infective endocarditis (36%). As expected, Staphylococcus species were the most commonly isolated microorganism (median 54% among included studies), followed by streptococci (median 13%), enterococcus (median 5%), and culture negative IE (median 10%) (Supplementary Table 4) [15-26]. Indications for operation included persistent bacteremia, septic pulmonary embolism, systemic embolism, right-sided heart failure and shock, but this was incompletely reported.

Operative Details
The choice of procedure was at the surgeon’s discretion in all publications. Median repair proportion was 59% and replacement 41% among studies. The largest and only multi-centre study following patients only to hospital discharge reported a majority of replacements versus repairs (58% vs 42%)[15]. The indication for valve replacement was extensive valvular damage, which was based on the surgeon’s discretion but in 2 studies was objectively defined; Renzulli et al [18] performed valve repair for infection limited to a single leaflet or the posterior and part of the anterior leaflet. Gottardi et al [21] performed valve replacement for sub-valvular involvement. The primary repair strategies were vegetectomy, De Vega procedure, annuloplasty ring, bicuspidization and leaflet patch augmentation (Supplementary Table 5). Of valve
replacements, 83% were bioprosthetic and 17% mechanical prostheses among studies that reported this data (Supplementary Table 6).

**Surgical Outcomes**

There were no differences in early (30-day or hospital) mortality (RR 0.62, 95% CI: 0.26-1.46, p=0.27, I²=31%; 9 studies, 1042 patients, 31 vs 37 deaths) comparing tricuspid valve repair versus replacement (Supplementary Figure 1). Repair exhibited a trend to greater risk of postoperative moderate to severe tricuspid regurgitation (RR 4.17, 95% CI: 0.99-17.59, p=0.051, I²=0%; 6 studies, 154 patients, 12 vs 0 patients) (Figure 2). These outcome comparisons were not adjusted for baseline differences.

**Long-term Outcomes**

Only three studies reported survival curves allowing calculation of incidence rate ratios and these showed no difference in all-cause long-term mortality rates (IRR 0.98, 95% CI 0.92-1.05, p=0.64; 3 studies, 144 patients) with no heterogeneity (I²=0%) but this was primarily based on a single study [26] (Figure 3). Other studies only reported mortality, recurrent infection, and reoperation event rates without group-specific follow up durations allowing only calculation of RR. Using event rates, long-term all-cause mortality was also not different (RR 0.61, 95% CI:0.22-1.72, p=0.35, I²=22%; 4 studies, 87 patients, 7 vs 9 deaths) (Figure 4). Valve repair was associated with lower recurrent IE (RR 0.17, 95% CI:0.05-0.57, p=0.004; 7 studies, 210 patients, 3 vs 11 reinfections) and need for reoperation (RR 0.26, 95% CI:0.07-0.92, p=0.04; 7 studies, 229 patients, 3 vs 12 reoperations) but a continued trend towards greater risk of moderate-to-severe tricuspid regurgitation at follow up (RR 4.14, 95% CI: 0.80-21.34, p=0.09; 3 studies, 62
patients, 7 vs 0 patients) (Figure 4). Furthermore, tricuspid valve repair is associated with lower need for permanent pacemaker (RR 0.20, 95%CI: 0.11-0.35, p<0.001; 3 studies, 921 patients, 12 vs 84) but this was based primarily on a single study [15] (Supplementary Figure 2). None of these latter pooled analyses exhibited heterogeneity ($I^2=0\%$).

**Comment**

This meta-analysis suggests that valve replacement and repair for tricuspid valve IE is associated with acceptable short-term mortality. Patients with tricuspid valve IE undergoing valve repair tended to have more favourable freedom from re-intervention, less recurrence of infection, and lower need for pacemaker but a trend towards greater risk of moderate-to-severe recurrent TR. However, patients undergoing tricuspid valve replacement had a higher burden of disease and higher preoperative functional status, which may explain the tendency towards worse outcomes.

Patients with tricuspid valve IE usually present with extensive valve destruction requiring complex repair or replacement. Overall, more valve replacements were performed than repairs including in the multicenter study with the largest population [15]. The ratio of repairs to replacements performed varied widely across the study centres (1:6 to 6:1). In most centres, replacement was performed only when valves were irreparably damaged precluding repair but there were likely differing thresholds based on surgeon judgement and experience with complex valve reconstruction. The higher rate of valve replacement could also be attributed to the late referral to tertiary care centres at which time valves were beyond repair [16,21,22,24–26]. There are important differences to tricuspid valve repair techniques that deserve mention. Ring annuloplasty introduces greater prosthetic material than De Vega, but the latter has been
associated with TR recurrence [27]. Kay annuloplasty or bicuspidization can be considered if the vegetation is limited to the posterior leaflet. Vegetectomy may be associated with recurrent IE. Chordal replacement and leaflet patch augmentation is technically complex, particularly for surgeons not accustomed to tricuspid valve repair. For replacements, there are concerns that prosthetic tricuspid valves are prone to thrombosis or structural valve deterioration. However, Rizzoli et al [28] performed a meta-analysis comparing bioprosthetic versus mechanical tricuspid valves and did not find a difference in late survival or reoperations.

The primary advantage of tricuspid valve repair is limitation of foreign material to reduce the risk of reinfection, avoidance for the need for anticoagulation and lower risk of heart block necessitating permanent pacemaker. Given that a large proportion of patients had a history of intravenous drug use, the lower risk of recurrent infection is particularly important given the high risk for recidivism and recurrent IE as well as a shorter overall life expectancy. Furthermore, for TR secondary to intravenous drug use, surgeons may consider avoidance of an annuloplasty ring during valve repairs to further limit the amount of intracardiac foreign material. However, Dawood et al [26] suggests that an annuloplasty ring should be included to reduce the risk of recurrent TR as the only patient with severe post-operative TR in their study had not received a ring annuloplasty. In our study, valve repair was associated with greater recurrent TR but we could not determine the clinical sequelae, if any. Baraki et al [23] accepted residual grade II TR for repair as mild-to-moderate TR is reasonably well-tolerated especially with a normal left heart. The greater risk of heart block in patients with tricuspid valve replacement may be due to extension of infection into the region of the cardiac conduction system or as a complication of tricuspid valve replacement, which has been well-documented [29].
Once the decision to replace has been made, bioprosthetic valves were used more commonly than mechanical valves. This is not surprising given that several surgeons used biological prostheses exclusively in the intravenous drug use population despite the reduced durability citing the lower likelihood to adhere to anticoagulation regimens [20,24,26]. Bioprosthetic valves have shown good long-term freedom from structural valve deterioration and need for reoperation given the low transvalvular gradients in the tricuspid position [30].

As mentioned, the third and less commonly performed surgical option for tricuspid valve IE is valvectomy. The most common indication is intravenous drug use as a bridge to drug cessation. Such patients are usually young and otherwise healthy and more likely to tolerate the hemodynamic stress of complete tricuspid regurgitation. There were insufficient data to perform a comparison of this third surgical arm. The number of valvectomies performed were relatively few (n=69) and only in two of the included studies, Gaca et al [15] (n=66) and Lange et al [19] (n=3). Valvectomy was associated with the shortest cardiopulmonary bypass times and may be performed off-pump with inflow occlusion. It is associated with the lowest risk of post-operative heart block but carries a higher early mortality and a higher rate of reintervention as valvectomy is often performed as a staged procedure necessitating a second surgical procedure [11].

**Study Limitations**

Major limitations of this study are the exclusive availability of retrospective observational data, small sample sizes and very small numbers of outcome events in most studies. There are no prospective studies that randomized patients to tricuspid valve repair versus replacement. Some
studies had heterogeneity of disease characteristics, population size and follow-up length, which made comparison challenging. Several studies presented pooled data only for perioperative characteristics and for long term outcomes. As a result, baseline differences among the repair and replacement groups could not be adequately compared, including time to surgery and active versus healed infective status. Half of the studies [18-22,25] specifically stated that tricuspid valve replacement was only performed if repair failed, though this may have been the case in the other studies as well, implying that the replacement patients had more severe disease. All patients in Lange et al [19] had signs of active infection at the time of surgery, as evidenced by failed medical treatment or decision to early surgery. Gaca et al [15] had a high (68.5%) proportion of active cases at the time of surgery. Patients failing medical treatment tended to have a higher rate of replacement and more sequelae [26]. Overall, earlier time to surgery appeared to improve outcomes [16]. As expected, there is considerably higher morbidity and mortality when there is concurrent left-sided IE [22,26]. In Musci et al, concurrent left-sided IE patients had more complications such as abscess and fistula, neurological septic embolic complications, septic shock and renal insufficiency with reduced long term survival. Also, age, preoperative hemodynamic compromise and presenting NYHA class were also identified as additional independent predictors of outcome in some studies [15–17,21,22]. Unfortunately, no study adjusted for baseline differences. For the long-term outcomes, only a small number of studies reported group-specific follow up durations and then only for mortality to allow pooling of IRR rather than event rates using RR. Notably, it is possible that some patients in Dawood et al [26] may also be represented in the Society of Thoracic Surgeons Database study [15]. Also, three studies were from a prior era [18,19,25]. Valve repair techniques used in these studies are comparable to contemporary practices. Nevertheless, there have been changes infective agents
and incremental surgical advances which may limit the applicability of these results. Finally, surgeon bias is an important unmeasured confounder for all observational surgical studies and their meta-analyses [31,32]. As mentioned, most centres indicated that tricuspid valve repair was prioritized and valve replacement was performed after attempts to repair were unsuccessful suggesting that the replacement patients may have had more severe lesions or valve dysfunction. There were insufficient numbers to compare specific repair techniques and additionally reporting of these techniques was variable. A strength of this review is that it systematically summarizes all the limited published data in this field and highlights the need for more comprehensive comparative data.

Conclusions

Based on the results of this meta-analysis, there was no difference in short or long term mortality for tricuspid valve repair and replacement. However, valve repair may offer greater freedom from recurrent IE and reoperation as well as greater need for permanent pacemaker. Valve repair was associated with a trend towards greater risk of recurrent TR but this is generally well-tolerated. Overall, these results support the practice to attempt repair if possible and only replace the valve if repair is not feasible. A repair with residual tricuspid regurgitation may even be superior to replacement in patients at very high risk of recurrent infection such as those with history of injection drug use. However, there is a lack of high-quality or prospective data available on tricuspid valve IE. Better comparative data, and ideally long-term randomized trials are needed to determine the optimal surgical management.
References


2008;34:908–910.


[29] Sung K, Park PW, Park KH, et al. Is tricuspid valve replacement a catastrophic operation?


**Figure Legends**

Figure 1: MEDLINE and EMBASE were searched for all records until 2016. Abstracts were reviewed for 1072 citations. Thirteen studies were retrieved for full text review, and after excluding one study published only as an abstract, 12 studies met inclusion criteria following full article review.

Figure 2: Forest Plot for post-operative tricuspid regurgitation. Individual study and pooled risk ratios (RRs) in unadjusted observational studies comparing patients with tricuspid valve repair vs replacement. The pooled RRs with 95% CI were calculated using random-effects models.

Figure 3: Forest Plot for all-cause long-term mortality. Individual study and pooled incidence rate ratios (IRRs) in unadjusted observational studies comparing patients with tricuspid valve repair vs replacement. The pooled IRRs with 95% CI were calculated using random-effects models.

Figure 4: Forest Plot for all-cause follow up mortality, reinfection, reoperation and tricuspid regurgitation. Individual study and pooled risk ratios (RRs) in unadjusted observational studies comparing patients with tricuspid valve repair vs replacement. The pooled RRs with 95% CI were calculated using random-effects models.
1266 citations identified by initial search of MEDLINE and EMBASE databases (1946-2018 [Feb 16th, 2018])
Text words “tricuspid valve” and “endocarditis” in the title or abstract
OR
MeSH term “endocarditis”, and all variations of text words “surgery”, “repair”, and “replace” in the title or abstract

1253 ineligible on basis of title and abstract

13 retrieved for full text review

1 excluded (abstract only)

12 unmatched retrospective observational studies included
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<td></td>
</tr>
<tr>
<td>Eutsell 1997</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>10.0%</td>
<td>8.47 [10.13, 8.72]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiang 2011</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>1</td>
<td>15.0%</td>
<td>8.80 [0.02, 0.144]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bernstein 2013</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.80 [0.02, 0.144]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>1</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>85.0%</td>
<td>8.80 [0.02, 0.144]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 14
Interpretation: Test for overall effect: 2 = 1.21 (P = 0.26)

1.6.3 Randomized (Daily Events Does Not Account For Differential Follow-up)

<table>
<thead>
<tr>
<th>Study in Subgroup</th>
<th>Event</th>
<th>Total</th>
<th>Event</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tairol 1999</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.30 [0.03, 0.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large 1996</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.30 [0.03, 0.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eutsell 1997</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.30 [0.03, 0.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiang 2011</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.30 [0.03, 0.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernstein 2013</td>
<td>1</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>10.0%</td>
<td>8.30 [0.03, 0.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>85.0%</td>
<td>8.30 [0.03, 0.27]</td>
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</tr>
</tbody>
</table>

Total events: 12
Interpretation: Test for overall effect: 2 = 1.99 (P = 0.05)

1.6.4 Follow-Up (Daily Events Does Not Account For Differential Follow-up)

<table>
<thead>
<tr>
<th>Study in Subgroup</th>
<th>Event</th>
<th>Total</th>
<th>Event</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large 1996</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>2.0%</td>
<td>1.12 [0.06, 0.28]</td>
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</tr>
<tr>
<td>Eutsell 1997</td>
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<td>7</td>
<td>0</td>
<td>2</td>
<td>30.1%</td>
<td>1.90 [0.42, 0.06]</td>
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<td></td>
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</tr>
<tr>
<td>Bernstein 2013</td>
<td>2</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>22.6%</td>
<td>0.21 [0.04, 0.14]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>7</td>
<td>32</td>
<td>0</td>
<td>3</td>
<td>100.0%</td>
<td>0.21 [0.04, 0.14]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7
Interpretation: Test for overall effect: 2 = 1.17 (P = 0.28)