Original Article

Safety and Use of Anticoagulation After Aortic Valve Replacement With Bioprostheses
A Meta-Analysis

Haris Riaz, MD; Shehab Ahmad Redha Alansari, MD; Muhammad Shahzeb Khan, MD; Talha Riaz, MD; Sajjad Raza, MD; Faraz Khan Luni, MD; Abdur Rahman Khan, MD; Irbaz Bin Riaz, MD, MM; Richard A. Krasuski, MD

Background—The American College of Cardiology guidelines recommend 3 months of anticoagulation after replacement of the aortic valve with a bioprosthesis. However, there remains great variability in the current clinical practice and conflicting results from clinical studies. To assist clinical decision making, we pooled the existing evidence to assess whether anticoagulation in the setting of a new bioprosthesis was associated with improved outcomes or greater risk of bleeding.

Methods and Results—We searched the PubMed database from the inception of these databases until April 2015 to identify original studies (observational studies or clinical trials) that assessed anticoagulation with warfarin in comparison with either aspirin or no antiplatelet or anticoagulant therapy. We included the studies if their outcomes included thromboembolism or stroke/transient ischemic attacks and bleeding events. Quality assessment was performed in accordance with the Newland Ottawa Scale, and random effects analysis was used to pool the data from the available studies. P testing was done to assess the heterogeneity of the included studies. After screening through 170 articles, a total of 13 studies (cases=6431; controls=18210) were included in the final analyses. The use of warfarin was associated with a significantly increased risk of overall bleeding (odds ratio, 1.96; 95% confidence interval, 1.25–3.08; P<0.0001) or bleeding risk at 3 months (odds ratio, 1.92; 95% confidence interval, 1.10–3.34; P=0.0001) compared with aspirin or placebo. With regard to composite primary outcome variables (risk of venous thromboembolism, stroke, or transient ischemic attack) at 3 months, no significant difference was seen with warfarin (odds ratio, 1.13; 95% confidence interval, 0.82–1.56; P=0.67). Moreover, anticoagulation was also not shown to improve outcomes at time interval >3 months (odds ratio, 1.12; 95% confidence interval, 0.80–1.58; P=0.79).

Conclusions—Contrary to the current guidelines, a meta-analysis of previous studies suggests that anticoagulation in the setting of an aortic bioprosthesis significantly increases bleeding risk without a favorable effect on thromboembolic events. Larger, randomized controlled studies should be performed to further guide this clinical practice. (Circ Cardiovasc Qual Outcomes. 2016;9:294-302. DOI: 10.1161/CIRCOUTCOMES.115.002696.)

Key Words: anticoagulants • bioprosthesis • meta-analysis • platelet aggregation inhibitors • surgical aortic valve replacement • transcatheter aortic valve replacement

Thromboembolism, including systemic emboli and prosthetic valve thrombosis, is among the most dreaded complications after aortic valve replacement, with an annual incidence of major thromboembolism approaching 1.8 and 8 events per 100 patient-years on and off anticoagulation, respectively. Anticoagulation with warfarin is now routinely practiced with mechanical prosthetic heart valves to reduce this risk.1-3 In contrast to the lifelong necessity of anticoagulation with mechanical valves, the need for and optimal duration of anticoagulation after bioprosthetic valve implantation remains a contentious matter.4,4 Warfarin requires close monitoring, has many well-described food–drug and drug–drug interactions, and increases the risk of serious bleeding complications (approaching 1% annually). The risk of thromboembolism and bleeding seems highest in the first 3 months after either mechanical or bioprosthetic valve implantation.7 With bioprostheses, this is the presumed time it takes for adequate endothelialization of the valve cuff to occur.7 The current American Heart Association/American College of Cardiology guidelines recommend considering 3 months of...
WHAT IS KNOWN

- Lifelong anticoagulation is needed after the mechanical aortic valve replacement; however, the necessity and duration of anticoagulation after bioprosthesis aortic valve remain controversial.
- The current American College of Cardiology/American Heart Association guidelines for valvular heart disease recommend only short-term (3 months) anticoagulation after aortic valve replacement with a bioprosthesis in the absence of another indication for chronic anticoagulation.

WHAT THE STUDY ADDS

- The pooled analysis of existing studies indicates that chronic anticoagulation does not reduce the incidence of thromboembolic events and may increase the risk of major bleeding.
- All the studies included in the analysis were observational as randomized controlled trials are not available.
- This study supports the current American College of Cardiology/American Heart Association guideline recommendations. Randomized controlled trials would be needed to determine more definitively the efficacy and safety of long-term anticoagulation after bioprosthesis valve implantation.

anticoagulation (class IIb recommendation with B-level evidence) after bioprosthesis aortic valve implantation. However, many investigators have questioned this approach in the absence of other risk factors predisposing to thromboembolism, and anticoagulation for bioprostheses is not generally practiced.

Advances in cardiothoracic surgical techniques have greatly reduced operative risk and expanded the candidacy of older and higher risk patients for aortic valve replacement. Nowhere is this better evident than with transcatheter aortic valve replacement (TAVR), where survival benefit has been demonstrated in patients previously felt to be at prohibitive risk from traditional surgical techniques. Previous bioprostheses can also provide the scaffolding to facilitate future TAVR. As a result, more and more bioprosthetic valves are being implanted into the aortic position. The issue of routine anticoagulation in these patients has resurfaced with a recent publication linking the absence of postprocedural anticoagulation to reduced leaflet motion and subsequent stroke. In the present systematic review and meta-analysis, we have aimed to pool the existing published data to further assess the clinical efficacy and risks of anticoagulation in the setting of bioprosthetic aortic valve replacement.

Methods

The PubMed database was diligently searched to collect studies for the meta-analysis. Using the options of advanced search, the website was thoroughly filtered for warfarin, aspirin, bioprosthetic in aortic valve replacement, and mechanical in aortic valve replacement, and original research, including both observational studies and clinical trials, was selected.

Using the above search criteria, 13 studies were identified from the commencement of the database until April 2015, where anticoagulation with warfarin (case) was compared with either aspirin or no antiplatelet or anticoagulant therapy (control). Data extracted from each study included the primary outcome of clinical evidence for thromboembolism or stroke/transient ischemic attack and the secondary outcome of major bleeding. Outcomes were analyzed ≤3 months following surgery and >3 months after surgery for the primary outcome and at 3 months and the overall length of follow-up for the secondary outcome. Studies were included based on the assessment of anticoagulation in the setting of bioprosthetic aortic valve replacement regardless of whether concomitant coronary artery bypass grafting was performed. We excluded studies that did not specify bleeding rates, did not report hard clinical end points, or did not specify the duration of follow-up. Only English language articles were included.

Data were extracted from the studies based on the demographic and clinical attributes and were tabulated. Quality assessment was performed in accordance with the Newland Ottawa Scale, and random effects analysis was used to pool the data from the available studies, which was expressed in the form of forest plots. Data were pooled for the clinical end points, including major adverse cardiac and cerebrovascular events, as well as bleeding. Meta testing was done to assess the heterogeneity of the included studies. Publication bias was assessed and represented in the form of a funnel plot (Figure 1).

For the purpose of analysis, the 2 groups considered were warfarin as case and no warfarin as control. Data were analyzed through the Stata Statistical Software (StataCorp LP. College Station, TX). Comparison statistics were performed using Fisher exact tests and χ² test, as appropriate. For all tests, P<0.05 was considered statistically significant. Results were expressed as ranges in the form of 95% confidence intervals whenever possible.

Results

A total of 13 studies (cases, n=6431 and controls, n=18210) were included in the final analyses. The search strategy is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses sheet (Figure 2). The demographic and clinical characteristics along with the inclusion and exclusion criteria and the quality assessment (Data Supplement) as per the Newland Ottawa Scale are delineated in the Tables 1 and 2. As seen in the table, all the included studies were observational in nature, including 4 retrospective and 9 prospective cohort studies. Hence, no randomized controlled trials addressing the research question were identified.

Figure 1. Funnel plot representing publication bias.
The duration of anticoagulation used in 8 of 13 studies was 3 months, whereas it varied in other studies (1, 6, 12, and 24 months). Most of the studies were conducted in the United States. The mean age of patients enrolled in these studies was >70 years. Hypertension and heart failure were the most common comorbidities. All of the included studies assessed outcomes in terms of neurological complications, including transient ischemic attack, stroke, thromboembolism, and major bleeding complications, although the definitions of these outcomes differed between the studies.

The use of warfarin was associated with a significantly increased risk of overall bleeding ($P=0.013$; odds ratio, 1.38 [1.07–1.78]; Figure 3) with a trend toward increased bleeding at 3 months as well ($P=0.084$; odds ratio, 1.26 [0.97–1.64]; Figure 4) compared with either aspirin or no therapy/placebo. With regard to composite primary outcome variables (risk of venous thromboembolism, stroke, or transient ischemic attack) at 3 months, no significant difference was seen with warfarin ($P=0.967$; odds ratio, 1.01 [0.56–1.84]; Figure 5). Moreover, anticoagulation was also shown not to improve outcomes after 3 months ($P=0.780$; odds ratio, 1.08 [0.61–1.91]; Figure 6).

**Discussion**

Our pooled meta-analysis of published studies suggests that anticoagulation after aortic valve bioprosthesis implantation does not reduce the risk of clinical thromboembolic events and significantly increases the risk of bleeding. This is a critically important clinical finding that is contrary to current guideline recommendations. The rationale for anticoagulation stems from microthrombi that are occasionally observed on valves during early postoperative imaging.

Only recently, has this phenomenon been directly linked to neurological events. It remains uncertain, however, how commonly it occurs population wide. The perioperative period is a well-known hypercoagulable milieu, and the risk of thromboembolism in these patients rapidly declines over time. As such, any benefit from anticoagulation would likely be seen very early after surgery. It is further important to recognize that the highest risk for thrombi occurs during a period (within the first 24–48 hours) when anticoagulant use is generally prohibited because of the risk for incisional bleeding, an event that is strongly linked to perioperative morbidity and mortality.

Most patients who currently undergo AVR are older (>65 years of age) and at higher risk overall for both thrombotic and bleeding events. Weighing the risk-benefit profile for anticoagulation in these patients is extremely important. With increasing longevity, it is expected that greater numbers of elderly patients will receive AVR; data from observational studies confirm that bioprosthetic valve use has been progressively increasing. Because the decision to implant a bioprosthesis is often primarily driven by the desire to avoid anticoagulation, the lack of benefit from anticoagulation seen in our study is reassuring.

A meta-analysis is unfortunately only as strong as its individual components, and this is the main limiting factor...
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting/Center</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Study Design</th>
<th>Outcomes Measured</th>
<th>Follow-Up, mo</th>
<th>Quality Assessment, NOS</th>
</tr>
</thead>
</table>
| ElBardissi et al
8 | Brigham and Women's Hospital, United States | Isolated BAVR                                          | Concomitant operations, AC preoperatively, postoperative refractory AF               | Cohort         | TE including stroke, TIA or peripheral TE, and bleeding complications | 3             | 8/9                     |
| Sundt et al
9 | Mayo Clinic, United States     | BAVR±CABG                                             | Concomitant procedures                                                            | Retrospective analysis | Postoperative CVA, bleeding, and mortality             | 3             | 7/9                     |
| Moinudddeen et al
10 | Yale School of Medicine, United States | BAVR                                                  | N/A                                                                                 | Retrospective study | Cerebral ischemia, postoperative bleeding events, need for repeat operative AVR, and long-term survival | 3             | 7/9                     |
| Gherli et al
11 | Single Center, Italy           | BAVR in sinus rhythm before+after surgery             | Cerebral ischemia, coagulopathy, carotid atherosclerosis, peripheral vascular disease, double valve replacement, previous chronic AC, allergies to ASA or warfarin | Cohort         | Rate of cerebral ischemic events, bleeding, and survival | 3             | 7/9                     |
| Brennan et al
12 | Multicenter study, United States | ≥18 yr old; first-time BAVR Biocor, Biocor Supra, Epic, or Epic Supra valves | Active endocarditis, chronic hemodialysis, emergency surgery                      | Cohort         | Embolic events classified as neurological (eg, CVA and TIA) and nonneurological, overt bleeding events, valve thrombosis, and death | 6             | 8/9                     |
| Colli et al
13 | Hospital Clinic, Barcelona, Spain | ≥18 yr old; first-time isolated BAVR and in sinus rhythm before implantation | Previous prosthetic valve; double valve implant; concomitant CABG; IABP; ASA/VKA or other antithrombotic; IE; aortic dissection; history of TIA; history of GIB; coagulopathy; increased bleeding risk; vascular disease requiring medical/surgical treatment | Prospective pilot study | Postoperative CVA/TIA, rates of major bleeding, stroke-free survival, and overall survival | 3             | 8/9                     |
| Al-Atassi et al
14 | University of Ottawa Heart Institute, Canada | Planned BAVR and no indication for AC | Emergency/redo surgery; history of TIA or CVA; carotid artery stenosis >70%; previous documented TE; AF | Prospective cohort study | Cerebral microemboli and platelet function | 12            | 7/9                     |
| Colli et al
15 | Multicenter Study, Multinational | BAVR alone or with CABG                                | N/A                                                                                 | Prospective cohort study | TE, major bleed and other major cardiac adverse events (reoperation and death) | 6             | 8/9                     |
| Heras et al
16 | Mayo Clinic, United States     | BAVR                                                  | N/A                                                                                 | Retrospective study | Thromboembolic and bleeding events                     | 3             | 7/9                     |
| di Marco et al
17 | Single Center, Italy           | …                                                     | Concomitant surgery; comorbidities requiring chronic AC; concomitant mitral/tricuspid replacement | Prospective cohort study | Major neurological events, major bleeding, and mortality | 24±14        | 7/9                     |
| Mérie et al
18 | Multicenter, Denmark           | BAVR±CABG                                             | Previous cardiac surgery or other concomitant surgery, warfarin before surgery, diagnosis of AF within 30 d of surgery | Prospective cohort study | Stroke, TE complications (ie, ischemic CVA, myocardial infarction, and peripheral emboli), bleeding events (ie, gastrointestinal, intracranial, urinary tract, and airway), cardiovascular death | 3             | 7/9                     |

(Continued)
of our study. We found a surprising paucity of prospective data on this subject; the absence of any randomized controlled trials in this area is indeed disappointing, particularly given the number of decades that bioprostheses have regularly been used. Most of the studies included were observational cohorts subject to considerable selection bias.

Furthermore, the settings for each of these studies were conducted differed, as was the operative and postoperative management and follow-up. We identified significant heterogeneity among the included studies and analyzed our results through a random effects model to account for this. The studies provided little information on the international normalized ratio values, and as such little can be said about the degree of compliance and adherence to warfarin therapy. Some investigators have suggested that the valve morphology in terms of size and prosthesis-patient matching may be important

### Table 1. Baseline Demographic Variables of the Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Groups</th>
<th>n</th>
<th>Age, y</th>
<th>Men, %</th>
<th>DM, %</th>
<th>HTN, %</th>
<th>CHF, %</th>
<th>CABG, %</th>
<th>Smoking, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ElBardissi et al17</td>
<td>2 Warfarin/placebo</td>
<td>133/728</td>
<td>74.5±9.1/68.9±13.1</td>
<td>18/17</td>
<td>81/62</td>
<td>52/32</td>
<td>14/10</td>
<td>49/48</td>
<td></td>
</tr>
<tr>
<td>2 Sundt et al16</td>
<td>2 Warfarin+heparin/placebo</td>
<td>624/527</td>
<td>75.9±6.8/76.7±8.6</td>
<td>63.9/60.3</td>
<td>20.9/17.8</td>
<td>64.3/61.1</td>
<td>37.9/38.1</td>
<td>10.6/10.3</td>
<td>N/A</td>
</tr>
<tr>
<td>3 Mohr et al15</td>
<td>2 Heparin+warfarin/placebo</td>
<td>109/76</td>
<td>74±11/75±7</td>
<td>60.5/72.4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4 Gherli et al11</td>
<td>2 Aspirin/warfarin</td>
<td>141/108</td>
<td>70.0±8/72.9±7.1</td>
<td>38.3/40.8</td>
<td>15/12</td>
<td>48.9/51.4</td>
<td>74.5/79.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5 Brennan et al19</td>
<td>2 Warfarin/placebo</td>
<td>320/66</td>
<td>74/72</td>
<td>63.3/61.6</td>
<td>27.2/24.6</td>
<td>82.3/76.3</td>
<td>N/A</td>
<td>46.3/45.5</td>
<td>N/A</td>
</tr>
<tr>
<td>6 Colli et al13</td>
<td>2 Aspirin/warfarin+aspirin</td>
<td>35/34</td>
<td>70.7±3.7/69.5±3.3</td>
<td>74.3/97.1</td>
<td>25.7/38.2</td>
<td>51.4/55.9</td>
<td>71.4/82.4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7 Atassi et al18</td>
<td>2 Aspirin/warfarin</td>
<td>28/28</td>
<td>72±9/71±10</td>
<td>75/68</td>
<td>32/25</td>
<td>75/61</td>
<td>50/64</td>
<td>N/A</td>
<td>14/14</td>
</tr>
<tr>
<td>8 Colli et al13</td>
<td>2 VKA/ASA</td>
<td>500/618</td>
<td>74.6±7.0/74.8±7.0</td>
<td>57/57</td>
<td>23.4/19.3</td>
<td>66.0/62.9</td>
<td>59.4/63.4</td>
<td>N/A</td>
<td>20.6/26.8</td>
</tr>
<tr>
<td>9 Heras et al16</td>
<td>3 Aortic valve/mitral valve/aortic+mitral valve</td>
<td>424/326/66</td>
<td>64±16/61±14/61±13</td>
<td>79/38/45</td>
<td>N/A</td>
<td>N/A</td>
<td>77/84/89</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10 di Marco et al17</td>
<td>2 Aspirin/warfarin</td>
<td>125/125</td>
<td>75±6/75±5</td>
<td>53/52</td>
<td>22/22</td>
<td>52/46</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11 Mérie et al14</td>
<td>2 Warfarin/placebo</td>
<td>982/681</td>
<td>27/45/45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Brennan et al19</td>
<td>3 Aspirin/warfarin/aspirin+warfarin</td>
<td>12457/2999/5972</td>
<td>76.4±6.2/77.0±6.0/76±5.8</td>
<td>59.5/58.6/62.9</td>
<td>22.1/20.7/23.6</td>
<td>N/A</td>
<td>34.1/36.5/34.9</td>
<td>N/A</td>
<td>8.2/6.7/9.7</td>
</tr>
<tr>
<td>13 Jamieson et al20</td>
<td>3 Medtronic Mosaic/Carpentier-Edwards SAV/Carpentier-Edwards PERIMOUNT</td>
<td>415/462/495</td>
<td>70.4±10/77.2±8.3/74.4±8.8</td>
<td>74/74.9/46.3</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>19/18/25</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CACG indicates coronary artery bypass grafting; CHF, chronic heart failure; DM, diabetes mellitus; HTN, hypertension; and N/A, not available.
attributes in determining long-term prognosis. Not all the studies included these data and any subgroup analysis would, therefore, be of limited power.

Further discussion of some of the contributing studies to our analysis is certainly warranted. We excluded trials using the herbicide triflural and the antiplatelet agent ticlopidine because neither is currently used in the postoperative setting. In one of the largest studies comprising our analysis, the act of withholding anticoagulation <6 months after initiation was associated with a greater likelihood of cardiovascular death. Interestingly, the risk of bleeding was greater in nonanticoagulated patients compared with those who were receiving warfarin. This brings up possible confounding, including whether patients in the control arm may have experienced a bleeding incident that resulted in the discontinuation of warfarin or whether nonanticoagulated patients were simply too sick to ever receive any anticoagulation.

In our analysis, some patients in the control arm received aspirin; it is reasonable to wonder whether aspirin’s effect could have masked the potential benefit of anticoagulation. A recent study that may provide insight into this question assigned patients to either 100 mg of aspirin or no antiplatelet therapy after AVR based on surgeon preference. Interestingly, no significant change in clinical events was seen in patients who received aspirin.24,25 Another of these studies used propensity-matched analysis in an attempt to overcome the limitations of observational study design and also found a similar lack of benefit for aspirin.

The results of a randomized controlled trial suggested increased risk of major adverse cardiovascular events with dabigatran compared with the warfarin in the setting of mechanical valves.26 This has limited the use of direct acting oral anticoagulants in the setting of bioprosthetic valves, and to the best of the authors knowledge, there is no study of the direct acting agents in the setting of aortic valve bioprosthesis.

Whether our findings are applicable to patients who undergo TAVR is currently unknown. Several recent observational studies have suggested that the antithrombotic therapies used after the TAVR vary greatly.27 The meta-analysis on the use of single versus dual antiplatelet therapies after TAVR suggested increased bleeding at 30 days when dual antiplatelet therapies were used.28 Moreover, a small study suggested the incidence of valve thrombosis in post-TAVR patients found via autopsy.29 Most investigators think that transcatheter valves are comparable favorably with surgically implanted valve and that potential mechanisms of thrombosis should be similar. It is important to recognize that the inflammatory milieu differs between and surgical AVR. For the former, antiplatelet therapy has been aggressively used although recent studies question whether anticoagulation should also be considered. The best manner in which to determine the value of anticoagulation in these patients and patient with surgical AVR would be with a randomized controlled trial that would ideally be triple armed (antiplatelet versus anticoagulant versus placebo). Until that
time, our analysis suggests that anticoagulation of bioprosthetic valves in the absence of other indications for thrombosis prevention seems to be a dangerous practice.

Disclosures

None.

References


Safety and Use of Anticoagulation After Aortic Valve Replacement With Bioprostheses: A Meta-Analysis

Haris Riaz, Shehab Ahmad Redha Alansari, Muhammad Shahzeb Khan, Talha Riaz, Sajjad Raza, Faraz Khan Luni, Abdur Rahman Khan, Irbaz Bin Riaz and Richard A. Krasuski

*Circ Cardiovasc Qual Outcomes*. 2016;9:294-302; originally published online May 10, 2016;
doi: 10.1161/CIRCOUTCOMES.115.002696

*Circulation: Cardiovascular Quality and Outcomes* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/9/3/294

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2016/05/10/CIRCOUTCOMES.115.002696.DC1

**Permissions**: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Quality and Outcomes* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints**: Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions**: Information about subscribing to *Circulation: Cardiovascular Quality and Outcomes* is online at:
http://circoutcomes.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Supplemental Table. Quality assessment of the included studies in the meta-analysis

<table>
<thead>
<tr>
<th>Studies</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Outcome of interest not present at start of study</th>
<th>Comparability</th>
<th>Outcome of interest not present at start of study</th>
<th>Adequacy of follow up of cohorts</th>
<th>Adequacy of duration of follow up</th>
<th>Assessment of outcome</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ElBardissi, 2010(^1)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8/9</td>
</tr>
<tr>
<td>2 Sundt, 2005(^2)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7/9</td>
</tr>
<tr>
<td>3 Moinuddeen, 1998(^3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7/9</td>
</tr>
<tr>
<td>4 Gherli, 2014(^4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7/9</td>
</tr>
<tr>
<td>5 Brennan, 2012(^5)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8/9</td>
</tr>
<tr>
<td>6 Colli, 2007(^6)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8/9</td>
</tr>
<tr>
<td>7 Al-Atassi, 2011(^7)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7/9</td>
</tr>
<tr>
<td>8 Colli, 2012(^8)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8/9</td>
</tr>
<tr>
<td>9 Heras, 1995(^9)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7/9</td>
</tr>
<tr>
<td>10 Marco, 2006(^10)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7/9</td>
</tr>
<tr>
<td>11 Merie, 2012(^11)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7/9</td>
</tr>
<tr>
<td>12 Brennan, 2012(^12)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7/9</td>
</tr>
<tr>
<td>13 Jamieson, 2006(^13)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8/9</td>
</tr>
</tbody>
</table>
Supplemental References:


