*Review*

# Does Minimal-Access Aortic Valve Replacement Reduce the Incidence of Postoperative Atrial Fibrillation?

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*As the most common sequela of cardiac valvular surgery, atrial fibrillation (AF) has an important impact on postoperative morbidity. Minimal-access aortic valve replacement (AVR), with purported benefits on operative outcomes, has emerged as an alternative to conventional AVR. We used meta-analysis to determine whether minimal access influences the incidence of postoperative AF after AVR. Further, we sought first to evaluate via sensitivity analysis the impact of any differences and to identify the sources of possible heterogeneity between studies; second, we sought to evaluate any indirect effect of minimal-access AVR on other surrogate outcomes related to postoperative AF. We identified 10 studies from 26 comparative randomized and nonrandomized reports that documented the primary outcome of interest: new-onset AF. Overall meta-analysis showed no significant difference between minimal-access and conventional AVR in the incidence of postoperative AF (odds ratio, 0.85; 2,262 patients; P=0.24; 95% confidence interval, 0.66–1.11). Nor were there any apparent differences in surrogate outcome measures of intensive care unit stay, total length of stay, or stroke among studies that displayed a notable difference in AF incidence between groups. Sensitivity analysis that included only high-quality studies similarly showed no significant difference in the incidence of AF and further showed several intraoperative variables as potential sources of heterogeneity between studies. Therefore, minimal access may not have a significant effect on postoperative AF. Future randomized studies must take into account the potential sources of heterogeneity identified here to better demonstrate any differences between the 2 approaches in the onset of AF.* ***(Tex Heart Inst J 2008;35(4):428-38)***

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Atrial fibrillation (AF) is an important complication of valvular heart surgery: the reported incidence is as high as 60%.[1-3] Postoperative AF can result in hemodynamic compromise, thromboembolic phenomena, and anxiety. Other sequelae include prolonged length of stay (LoS) and increased cost. Controversy exists concerning the benefits of a minimal-access approach for aortic valve replacement (AVR); it is important, therefore, to evaluate whether the minimal-access approach carries a different incidence of AF than does the conventional approach.

Preoperative, intraoperative, and postoperative variables all affect the incidence of postoperative AF.[1,3-7] Therefore, the array of contributory pathophysiologic factors implicated in postoperative AF is diverse. It includes age- and hypertension-related structural changes in the atria, the effects of surgical manipulation of the heart or pericardium, the duration of myocardial ischemia, and the effects of systemic influences such as electrolyte imbalance, drug administration, and cardiopulmonary bypass (CPB)-related inflammatory effects.[8,9]

Minimal-access AVR (mAVR) offers apparent benefits in terms of postoperative morbidity, such as fewer respiratory complications and fewer patients transfused.[10-16] On the other hand, mAVR has been associated with longer CPB and aortic cross-clamp (CC) times and with a greater propensity for pleural and pericardial effusions.[14,15,17] We hypothesized that the incidence of AF after mAVR would relate to factors other than the technique of surgical access itself. To investigate this, we analyzed all studies in the surgical literature published in English that compared mAVR and conventional AVR (cAVR) with regard to the incidence of postoperative AF. We used a meta-analytical synthesis of data to examine the effects of minimal access on

the incidence of AF, and we focused on the variables associated with AF, including the established preoperative predictors of postoperative AF and predictors that are related to intraoperative manipulation of the heart.

## Methods

### Literature Search

As part of a larger analysis, we initially identified all studies of mAVR published up until July 2007. A MEDLINE literature search was performed using various permutations of the terms "minimal," "invasive," "access," and "aortic." For the purpose of this work, "minimal access" was defined as any surgical approach other than a complete median sternotomy or full thoracotomy. To ensure rigor, we also searched secondary sources cited in the reference lists of the 10 published studies that were used in the present overall meta-analysis.[10,13,17-24] In addition, we used the "related articles" function in PubMed as a further check. In cases of multiple studies by the same institution, we used only the largest, most recent, or most informative study. Of the studies so identified, we focused on those that reported the incidence of postoperative AF.

### Data Extraction

All data extraction from these 10 included studies[10,13,17-24] was performed by 2 members of our group (BM and TA), who independently extracted the following data: author, study design, geographic location, period of study, year of publication, exclusion and matching criteria, number of patients in each group, mean age, percentage of men, and native valvular disease. Certain intraoperative variables were also recorded: the type of incision, CC and CPB times, the techniques of cannulation, the method of myocardial protection, and the venting/de-airing strategy. Although the primary measurement of outcome was the incidence of postoperative AF, we also examined surrogate reported outcomes related to postoperative AF, such as intensive care unit (ICU) stay, total LoS, ventilation time, respiratory failure, cerebrovascular accident (CVA), incidence of chest infections, pleural or pericardial effusions, and percentage of patients transfused.

In performing the study, we followed guidelines for the reporting of meta-analysis of observational studies in epidemiology (MOOSE[25]); and in evaluating the quality of nonrandomized studies, we applied modified criteria of the Newcastle-Ottawa scale.[26] High-quality studies were defined as randomized controlled trials (RCTs) or as those matched for 4 or more criteria that have been identified as predictors of AF after cardiac surgery[4]: advanced age; male sex; impaired left ventricular (LV) function or congestive heart failure (CHF); chronic obstructive pulmonary disease (COPD); body mass index/body surface area or excessive weight; and hypertension or LV hypertrophy.

### Inclusion and Exclusion Criteria for Meta-Analysis

We included both randomized controlled trials and nonrandomized comparative studies in the analysis. The outcome of interest was postoperative AF, which gave rise to a previously unreported patient group. All noncomparative studies were excluded from this work, as were those in which the outcome of interest was not documented. Studies that reported only the incidence of supraventricular tachycardias (and not specifically AF) were also excluded.

### Statistical Analysis

Meta-analysis was performed using the odds ratio (OR) as the summary statistic for the presence or absence of AF. The analysis was performed according to recommendations of the Cochrane collaboration and guidelines from the Quality of Reporting of Meta-analyses.[27] An OR <1 favors mAVR. In this study, the random-effects model was used, because this model assumes variations between studies and is preferable for surgical data wherein selection criteria and risk profiles for patients differ among centers. We performed sensitivity analysis for quantitative evaluation of heterogeneity. For this, we considered high-quality studies, defined as RCTs or those matched for 4 or more preoperative predictors of AF. To further examine the effect of intraoperative variables on AF, we performed analyses that excluded studies of different strategies for myocardial protection, venting, and cannulation. We also examined the effect of excluding studies that showed notable differences in CPB or CC times. All data were analyzed by use of SPSS version 12.0 for Windows (SPSS Inc.; Chicago, Ill) and Review Manager version 4.2 (The Cochrane Collaboration, Software Update; Oxford, UK).

## Results

### Studies Included in the Meta-Analysis

Of 89 published reports that were identified, 26 were comparative and 10 reported the primary outcome of interest.[10,13,17-24] These comprised 2 RCTs and 8 nonrandomized retrospective or prospective studies. The total number of patients in these 10 studies was 2,262, with 854 in the mAVR group and 1,408 in the cAVR group. Characteristics of the 10 included studies are shown in Table I. Excluded were 10 studies that were larger, more informative, or more recent in their published data.[28-37] Studies that included mAVR reoperation were not excluded. One report contained data from an international registry, some of which had already been included in our present study; the pooled published data on mAVR

**TABLE I.** Characteristics of the Studies Included in the Meta-Analysis

| Study | Study Design | Geographic Location | Period of Study | Exclusion Criteria | Matching Criteria | Native Valve Disease: AS/AR/ Mixed mAVR | Native Valve Disease: AS/AR Mixed cAVR | Total | No. Patients: mAVR | No. Patients: cAVR | Mean Age (yr): mAVR | Mean Age (yr): cAVR | Sex (% male) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bonacchi M, et al.,[10] 2002 | 1 | Florence | 1/99–7/01 | A, B, C, D | a[P], b, c, d[P], e[P] | 8/12/20 | 10/7/23 | 80 | 40 | 40 | 62.6 ± 9.5 | 64 ± 12.4 | N/S |
| Doll N, et al.,[13] 2002 | 2 | Leipzig | 4/99–4/00 | A, B, E, F, G | a[P], b, e[P], f[P] | 41/45/90 | 99/61/97 | 434 | 176 | 258 | 59 ± 14 | 64 ± 15 | mAVR, 61.4%; cAVR, 62% |
| Szwerc MF, et al.,[17] 1999 | 3 | Pittsburgh | 3/97–9/98 | H | a[P], b, c, g[P], h | 25/15/10; bicuspid 6, endocarditis 1 | 31/10/9; bicuspid 2, endocarditis | 100 | 50 | 50 | 60 ± 2 | 63 ± 2 | mAVR, 61%; cAVR, 68% |
| Aris A, et al.,[18] 1999 | 1 | Barcelona | N/S | F | a[P], b, c, e[P] | 14/6/0 | 17/3/0 | 40 | 20 | 20 | 66.5 ± 10 | 62.2 ± 12 | N/S |
| Bakir I, et al.,[19] 2006 | 3 | Istanbul | 10/97–11/04 | B, F | a[P], b, d[P], e[P], f[P], h, i | 192/14/26 | 186/15/73 | 506 | 232 | 274 | 68.7 ± 9.2 | 71 ± 10.7 | mAVR, 51.7%; cAVR, 56.2% |
| Masiello P, et al.,[20] 2002 | 3 | Salerno | 11/97–11/99 | B | a[P], c, g[P] | 52/26/22 | 55/29/16 | 200 | 100 | 100 | 62 ± 12 | 63 ± 8 | mAVR, 58%; cAVR, 56% |
| Corbi P, et al.,[21] 2003 | 2 | Poitiers | 1/97–5/00 | A, B, C, D, G, I | e[P] | 21/4/5 | 54/6/10 | 100 | 30 | 70 | 64.2 ± 2.57 | 70.96 ± 1.17 | mAVR, 66.7%; cAVR, 62.9% |
| De Smet JM, et al.,[22] 2004 | 3 | Brussels | N/S | C, D | a[P], g[P] | N/S | N/S | 191 | 100 | 91 | 69.7 ± 12 | 68.3 ± 9 | mAVR, 47.9%; cAVR, 58.2% |
| Farhat F, et al.,[23] 2003 | 2 | Lyon | 1/00–12/00 | E | a[P], b, c, g[P] | 37/10/3 | 33/11/6 | 100 | 50 | 50 | 63 ± 14 | 67 ± 12 | mAVR, 60%; cAVR, 68% |
| Stamou SC, et al.,[24] 2003 | 3 | Washington | 1/97–12/01 | F | e[P], f[P], i, j, k[P] | N/S | N/S | 511 | 56 | 455 | 50–73 (median, 59) | 54–76 (median, 68) | mAVR, 73.2%; cAVR, 55.2% |

**Study Design:** 1 = randomized-control trial; 2 = nonrandomized prospective study; 3 = nonrandomized retrospective study

**Exclusion Criteria:** A = emergency, unstable, or cardiopulmonary resuscitation; B = plus another cardiac or aortic procedure; C = poor left ventricular ejection fraction; D = calcified aorta; E = coronary artery disease; F = reoperation; G = renal failure or dialysis; H = stentless aortic valve replacement or pulmonary autograft; I = left ventricular end-diastolic diameter >6 cm;

**Matching Criteria:** a = age; b = preoperative left ventricular ejection fraction; c = native valve pathology; d = chronic obstructive pulmonary disease/lung function; e = body mass index/body surface area/weight; f = hypertension or left ventricular hypertrophy; g = sex; h = diabetes mellitus; i = nonelective cases; j = renal impairment; k = congestive cardiac failure

[P] = preoperative predictor for atrial fibrillation

AR = aortic regurgitation; AS = aortic stenosis; cAVR = conventional aortic valve replacement; mAVR = minimal-access aortic valve replacement; Mixed = aortic regurgitation and stenosis; N/S = not specified

patients from this registry were therefore not included in the meta-analysis.[38]

In performing data extraction for the outcome of interest, there was 100% agreement between the 2 reviewers, in addition to complete agreement upon defining high-quality studies on the basis of matching criteria for independent predictors of AF (Table I). Aside from RCTs, only 3 studies were defined as high quality.[13,19,24] With respect to differences in clinical characteristics between the included studies, we should say that only 2 studies reported operative priority[19,24] and that 1 included a significant proportion of patients with CHF.[24] Intraoperative variables for the included studies are shown in Table II.

### Meta-Analysis of the Incidence of Atrial Fibrillation

All meta-analytical data were calculated using random-effects models. All included studies reported a nonzero incidence of AF in each of the mAVR and cAVR groups (Table III). The reported incidence of AF in the mAVR group ranged from 4% to 34%, and in the cAVR group it ranged from 4% to 42.6%. Only 3 studies reported a 10% or greater difference in the incidence of AF between groups[17,18,22]; of these, only that of DeSmet and colleagues[22] reported this difference to be significant ($P=0.02$). Using a random-effects model, our meta-analysis of the results in 2,262 patients showed an OR=0.85 and $P=0.24$ (95% confidence interval [CI], 0.66–1.11)

**TABLE II.** Intraoperative Variables of the Studies Included in the Meta-Analysis

| Study | Minimal-Access Incision | Cannulation Technique | Myocardial Protection | Venting/ De-Airing Approach | CBP Time (min) | | Cross-Clamp Time (min) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | mAVR | cAVR | mAVR | cAVR |
| Bonacchi M, et al.[10] | Reversed L(25) or C(15) | RA–Asc Ao | A/R CBCP; normothermia | No | N/S | N/S | 51.7 ± 12.2 | 52.4 ± 9.8 |
| Doll N, et al.[13] | J or inverted T | RA–Asc Ao; vac assistance | BCP mAVR, 34; BCP cAVR, 55; rest, CCrystCP; hypothermia | RtSPV or PA; $CO_2$ | 93 ± 38 | 88 ± 42 | 60 ± 22 | 55 ± 23 |
| Szwerc MF, et al.[17] | J | RA–Asc Ao | A/R CBCP; 32 °C | RtSPV | 101.2 ± 2.7 | 98.7 ± 3.1 | 72.1 ± 2.1 | 72.1 ± 2.3 |
| Aris A, et al.[18] | Reversed L(13) or C(7) | RA–Asc Ao | ACBCP | No | 95 ± 20 | 83 ± 19 | 70 ± 19 | 51 ± 13 |
| Bakir I, et al.[19] | Upper J | Ra/Fem ± IJ Vn– ; 24/152 ± 56 Asc Ao/Fem Art 155/77 | A/R CCrystCP; hypothermia | N/S | 88.8 ± 23.2 | 100.2 ± 22.6 | 61.8 ± 16.6 | 69.5 ± 16.6 |
| Masiello P, et al.[20] | L | RA–Asc Ao ± active suction | ACCrystCP; 32 °C | Root; $CO_2$ only in mAVR | 82.4 ± 22 | 66.8 ± 16 | 63.8 ± 17.2 | 50.2 ± 13 |
| Corbi P, et al.[21] | V | RA–Asc Ao | ACP | Root vent | 110.1 ± 4.86 | 102.3 ± 6.01 | 73.63 ± 3.35 | 68.3 ± 2.25 |
| De Smet JM, et al.[22] | J | RA–Asc Ao | ACCrystCP in mAVR ± RCCrystCP in cAVR; moderate hypothermia | RtSPV | 108 ± 25 | 104 ± 19 | 79 ± 16 | 79 ± 16 |
| Farhat F, et al.[23] | Reversed T | RA–Asc Ao, 34 mAVR and all cAVR; 16 in mAVR, Fem Vn | ACBCP; mild hypothermia | LV apical only in cAVR | 89 ± 18 | 70 ± 11 | 66 ± 15 | 49 ± 10 |
| Stamou SC, et al.[24] | Inverted L or T | RA–Asc Ao | A/R CBCP, normothermal | RtSPV | 102 median (78–119) | 75 median (61–96) | 69 median (60–90) | 55 median (45–71) |

ACBCP = anterograde cold-blood cardioplegia; ACCrystCP = anterograde cold crystalloid cardioplegia; ACP = anterograde cardioplegia; Art = artery; Asc Ao = ascending aorta; BCP = blood cardioplegia; cAVR = conventional aortic valve replacement; CBP = cardiopulmonary bypass; Fem = femoral; IJ = internal jugular; LV = left ventricular; mAVR = miminal-access aortic valve replacement; N/S = not specified; PA = pulmonary artery; RA = right atrium; RCBCP = retrograde cold-blood cardioplegia; RCCrystCP = retrograde cold crystalloid cardioplegia; RtSPV = right superior pulmonary vein; vac = vacuum; Vn = vein

**TABLE III.** Outcomes of the Studies Included in the Meta-Analysis

| Study | AF (%) | | ICU Stay (d) | | Length of Stay (d) | | Vent. Time (hr) | Resp. Failure (%) | CVA (n) | Chest Infection (%) | Pleural or Pericardial Effusion (%) | Patients Transfused (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mAVR | cAVR | mAVR | cAVR | mAVR | cAVR | | | | | | |
| Bonacchi M, et al.[10] | 10.0 | 7.5 | 1.1 ± 0.4 | 1.4 ± 0.8 | 7.2 ± 1.6 | 8.2 ± 2.3 | mAVR 4.4 ± 0.9; cAVR 5.3 ± 1.8 | mAVR 2.5<br>cAVR 5.0 | N/S | N/S | N/S | N/S |
| Doll N, et al.[13] | 34.1 | 42.6 | N/S | N/S | N/S | N/S | N/S | mAVR 2.8<br>cAVR 10.1 | mAVR 11<br>cAVR 13 | N/S | N/S | N/S |
| Szwerc MF, et al.[17] | 20.0 | 34.0 | 1.1 ± 0.1 | 1.1 ± 0.1 | 5.7 ± 0.3 | 6.4 ± 0.3 | mAVR 14.9 ± 0.9<br>cAVR 16.0 ± 1.1 | mAVR 4.0<br>cAVR 2.0 | mAVR 1<br>cAVR 1 | mAVR 2.0<br>cAVR 0 | mAVR 10.0<br>cAVR 0 (PL) | mAVR 50.0<br>cAVR 62.0 |
| Aris A, et al.[18] | 20.0 | 10.0 | 1.83 ± 0.7 | 1.94 ± 1 | 6.2 ± 2.3 | 6.3 ± 2.5 | mAVR 9.9 ± 8.0<br>cAVR 9.9 ± 4.5 | N/S | mAVR 0<br>cAVR 0 | N/S | mAVR 5.0<br>cAVR 0 (PC) | mAVR 25.0<br>cAVR 25.0 |
| Bakir I, et al.[19] | 31.0 | 27.4 | 2.1 ± 2.5 | 2.5 ± 5.3 | 10.8 ± 7.1 | 12.8 ± 10.6 | N/S | mAVR 3.9<br>cAVR 4.0 | mAVR 5<br>cAVR 2 | mAVR 4.3<br>cAVR 2.9 | mAVR 15.9<br>cAVR 11.7 (PL) | N/S |
| Masiello P, et al.[20] | 24.0 | 18.0 | 1.6 ± 0.9 | 1.6 ± 1.0 | 8.0 ± 3.0 | 7.5 ± 1.0 | mAVR 14 ± 2<br>cAVR 14 ± 6 | N/S | mAVR 1<br>cAVR 0 | N/S | mAVR 6.0<br>cAVR 5.0 (PL) | N/S |
| Corbi P, et al.[21] | 20.0 | 28.6 | 3.03 ± 0.26 | 4.06 ± 0.52 | N/S | N/S | mAVR 10.69 ± 1.86<br>cAVR 32.07 ± 11.99 | mAVR 3.3<br>cAVR 5.7 | mAVR 0<br>cAVR 1 | mAVR 3.3<br>cAVR 7.1 | N/S | mAVR 26.7<br>cAVR 30.0 |
| De Smet JM, et al.[22] | 26.0 | 41.8 | N/S | N/S | N/S | N/S | N/S | N/S | mAVR 1<br>cAVR 1 | mAVR 3.0<br>cAVR 5.5 | N/S | N/S |
| Farhat F, et al.[23] | 4.0 | 4.0 | 1.7 ± 1.6 | 2.6 ± 6 | 9.4 ± 3.8 | 10.0 ± 3.1 | mAVR 12 ± 7<br>cAVR 14 ± 9 | N/S | mAVR 1<br>cAVR 0 | mAVR 0<br>cAVR 2.0 | mAVR 2.0<br>cAVR 0 (PC) | N/S |
| Stamou SC, et al.[24] | 30.4 | 33.8 | N/S | N/S | N/S | N/S | N/S | mAVR 8.9<br>cAVR 7.9 | mAVR 2<br>cAVR 19 | N/S | N/S | mAVR 55.5<br>cAVR 73.8 |

AF = atrial fibrillation; cAVR = conventional aortic valve replacement; CVA = cerebrovascular accident; ICU = intensive care unit; mAVR = minimal-access aortic valve replacement; N/S = not specified; PC = pericardial; PL = pleural; Resp. = respiratory; Vent. = ventilation

Review: MINIMAL ACCESS AVR
Comparison 01 MINIMAL ACCESS AVR VERSUS CONVENTIONAL-OVERALL
Outcome: 14 MINIMAL ACCESS AVR VERSUS CONVENTIONAL FOR AF-OVERALL

| Study or Subcategory | mAVR n/N | cAVR n/N | OR (Random) 95% CI | Weight (%) | OR (random) 95% CI |
|---|---|---|---|---|---|
| Aris A[18] | 4/20 | 2/20 | | 1.99 | 2.25 (0.36, 13.97) |
| Szwerc M[17] | 10/50 | 16/50 | | 6.98 | 0.53 (0.21, 1.32) |
| Bonacci[10] | 4/40 | 3/40 | | 2.66 | 1.37 (0.29, 6.56) |
| Doll N[13] | 60/176 | 110/258 | | 21.59 | 0.70 (0.47, 1.04) |
| Masiello P[20] | 24/100 | 18/100 | | 10.97 | 1.44 (0.72, 2.86) |
| Corbi P[21] | 6/30 | 20/70 | | 5.65 | 0.63 (0.22, 1.76) |
| Farhat F[23] | 2/50 | 2/50 | | 1.67 | 1.00 (0.14, 7.39) |
| Stamou S[24] | 17/56 | 154/455 | | 13.23 | 0.85 (0.47, 1.56) |
| De Smet J[22] | 26/100 | 38/91 | | 12.96 | 0.49 (0.27, 0.90) |
| Bakir I[19] | 72/232 | 75/274 | | 22.29 | 1.19 (0.81, 1.75) |
| Total (95% CI) | 854 | 1,408 | | 100.00 | 0.85 (0.66, 1.11) |

Total events: 225 (mAVR), 438 (cAVR)
Test for heterogeneity: $Chi^2$ = 12.16, df = 9 ($P$ = 0.20), $I^2$ = 26.0%
Test for overall effect Z: = 1.18 ($P$ = 0.24)

0.1 0.2 0.5 1 2 5 10
Favors Treatment Favors control

***Fig. 1*** *Results of overall meta-analysis performed to compare the incidence of atrial fibrillation after minimal-access aortic valve replacement (mAVR) with the incidence after conventional aortic valve replacement (cAVR). The squares indicate point estimates of treatment effect (OR), with 95% confidence intervals (CI) indicated by horizontal bars. The size of the squares represents the weight attributed to each study, and the diamond represents the overall OR from the pooled studies listed with 95% CIs; the overall OR is significant (P ≤0.05) only if the diamond does not touch the central vertical line (outside the 95% CI). These data therefore indicate no significant difference between the mAVR group and the cAVR group in the incidence of atrial fibrillation.*

with a $\chi^2$ of heterogeneity of 12.16 ($P$=0.20; Fig. 1). This suggests that there is no significant effect of mAVR on incidence of AF, in comparison with cAVR.

### Sensitivity Analysis

When we considered only high-quality studies, there was still a lack of significant difference in the incidence of AF between groups. We defined high-quality studies as RCTs or those matched for 4 or more predictors of AF. Using these criteria (scenario 2, Table IV), sensitivity analysis of 5 studies comprising 1,571 patients yielded an OR=0.94 ($P$=0.67; 95% CI, 0.70–1.26) and $\chi^2$=4.88, $P$=0.30. The lack of a significant difference in the incidence of AF therefore persisted. Further subgroup analyses were performed, by use of various criteria to exclude patients on the basis of differences in reported intraoperative variables of CPB and CC times or in myocardial protection and venting approaches (Tables IV and V). Notably, the exclusion of studies that reported differences in CPB times[18-20,23] and of 1 study that did not report mean values[24] resulted in an OR=0.63 ($P$=0.002; 95% CI, 0.47–0.85) with very low heterogeneity ($\chi^2$=1.97, $P$=0.74; Table IV).

## Discussion

This study was designed to discover whether a minimal-access approach to AVR affects the incidence of AF. This is important, because the relative benefits of this approach, compared with a conventional approach in terms of clinical outcomes and cost-effectiveness, are not well defined. Overall meta-analysis did not show any significant differences between the mAVR and cAVR groups in the incidence of postoperative AF. Sensitivity analysis that took into consideration only the high-quality studies showed this finding to be robust. Further, the exclusion of studies with differences in cannulation techniques, CPB and CC times, myocardial protection, or venting approaches showed that intraoperative variables constitute an important source of heterogeneity and that any effect of minimal access on the incidence of postoperative AF is related to factors other than the technique of access itself—even when groups are matched for preoperative predictors of AF.

In a recent meta-analysis of all comparative studies of mAVR versus cAVR,[39] we did not find any significant differences in overall death or other primary outcomes of respiratory failure, renal failure, or incidence of CVA. This raises the following question: On what grounds can minimal-access AVR now be offered to patients? Because the most frequent complication of valvular surgery is AF, this is an important measure of outcome in evaluating the relative merits of a minimal-access approach—particularly because the incidence of AF has been related to ICU stay, total LoS, incidence of CVA, and, therefore, cost-related morbidity.[3,6,40,41]

The best available evidence for mAVR versus cAVR with respect to the incidence of AF comes from 2 ran-

**TABLE IV.** Sensitivity Analysis of 9 Various Subgroups

| Scenario | No. Patients | No. Studies | OR (95% CI) | *P* Value | Heterogeneity ($\chi^2$) | *P* Value ($\chi^2$) |
|---|---|---|---|---|---|---|
| S1 | 2,262 | 10 | 0.85 (0.66, 1.11) | 0.24 | 12.16 | 0.2 |
| S2 | 1,571 | 5 | 0.94 (0.70, 1.26) | 0.67 | 4.88 | 0.3 |
| S3 | 1,711 | 8 | 0.83 (0.61, 1.14) | 0.25 | 11.09 | 0.13 |
| S4 | 1,656 | 8 | 0.77 (0.58, 1.01) | 0.06 | 8.26 | 0.31 |
| S5 | 1,531 | 6 | 0.83 (0.57, 1.20) | 0.32 | 10.39 | 0.06 |
| S6 | 874 | 5 | 0.88 (0.60, 1.30) | 0.53 | 4.68 | 0.32 |
| S7 | 1,265 | 6 | 0.76 (0.56, 1.02) | 0.07 | 2.89 | 0.72 |
| S8 | 520 | 5 | 1.19 (0.72, 1.96) | 0.49 | 2.31 | 0.68 |
| S9 | 905 | 5 | 0.63 (0.47, 0.85) | 0.002 | 1.97 | 0.74 |

CI = confidence interval; OR = odds ratio

S1 = overall meta-analysis; S2 = includes only high-quality studies[13,19,24] or randomized controlled trials[10,18]; S3 = excludes study with significant difference in cross-clamp time[18] and study that did not report mean value[24]; S4 = excludes studies that reported femoral vein cannulations[19,23]; S5 = excludes studies that did not report the use of hypothermia during cardiopulmonary bypass[10,18,21,24]; S6 = excludes studies that used retrograde cardioplegia[10,17,19,22,24]; S7 = excludes studies that used cold crystalloid cardioplegia[13,19,20,22]; S8 = excludes studies that used a right superior pulmonary vein vent[13,17,22,24] or where this was not stated[19]; S9 = excludes studies with large differences in cardiopulmonary bypass times,[18,20,23] or where this was not stated,[10] or if means were not reported.[2]

**TABLE V.** Cross-Clamp and Cardiopulmonary Bypass Times Reported in the 10 Included Studies

| Study | Cross-Clamp Time (min) | | Cardiopulmonary Bypass Time (min) | |
|---|---|---|---|---|
| | mAVR | cAVR | mAVR | cAVR |
| Bonacchi M, et al.[10] | 51.7 ± 12.2 | 52.4 ± 9.8 | N/S | N/S |
| Doll N, et al.[13] | 60 ± 22 | 55 ± 23 | 93 ± 38 | 88 ± 42 |
| Swerc MF, et al.[17] | 72.1 ± 2.1 | 72.1 ± 2.3 | 101.2 ± 2.7 | 98.7 ± 3.1 |
| Aris A, et al.[18] | 70 ± 19 | 51 ± 13 | 95 ± 20 | 83 ± 19 |
| Bakir I, et al.[19] | 61.8 ± 16.6 | 69.5 ± 16.6 | 88.8 ± 23.2 | 100.2 ± 22.6 |
| Masiello P, et al.[20] | 63.8 ± 17.2 | 50.2 ± 13 | 82.4 ± 22 | 66.8 ± 16 |
| Corbi P, et al.[21] | 73.63 ± 3.35 | 68.3 ± 2.25 | 110.1 ± 4.86 | 102.3 ± 6.01 |
| De Smet JM, et al.[22] | 79 ± 16 | 79 ± 16 | 108 ± 25 | 104 ± 19 |
| Farhat F, et al.[23] | 66 ± 15 | 49 ± 10 | 89 ± 18 | 70 ± 11 |
| Stamou SC, et al.[24] | 69 median (range, 60–90) | 55 median (range, 45–71) | 102 median (range, 78–119) | 75 median (range, 61–96) |

cAVR = conventional aortic valve replacement; mAVR = minimal-access aortic valve replacement; N/S = not specified

domized studies[10,18] that did not show a significant difference in the incidence of AF; however, both studies had fewer than 50 patients in each group. Our meta-analysis reveals similar findings. One must therefore consider what pre-, intra-, and postoperative factors result in this lack of apparent difference, and what the implications of this finding are in terms of associated postoperative morbidity and cost-effectiveness.

The electrophysiologic phenomena that underlie the occurrence of AF include possible automatic foci in the pulmonary veins, superior vena cava, and coronary sinus, in addition to fractionation of wavefronts that propagate across the atria (the multiple-wavelets hypothesis[8]). The induction and maintenance of these phenomena, however, require appropriate anatomic and physiologic substrates, and the currently known preop-

erative predictors of AF after cardiac surgery relate to these potential substrates.[1-3,4,6,40] We found heterogeneity between studies, which was less marked in considering only the high-quality studies: RCTs or studies matched for 4 or more of these predictors for AF (Table IV). However, only 2 randomized and 3 nonrandomized studies could be considered high quality; therefore, larger, better-matched studies are needed in the future.

In addition to preoperative factors relevant to AF, we found various intraoperative factors that were important sources of heterogeneity. These data are in agreement with previous published work and include the following considerations: type of venous cannulation and the use of superior pulmonary vein vents,[40] cardioplegia technique,[42] and duration of CPB and CC time[3,7,40] (Tables II, IV, and V). Manipulation of the atria has been reported to increase the probability of postoperative AF. We found only 2 studies that reported a substantial number of peripheral venous cannulations.[19,23] Several of the studies included here[10,17,19,22,24] used retrograde administration of cardioplegic solution, which has also been reported as a risk factor for AF,[42] as have the use of superior pulmonary vein vents or bicaval venous cannulation.[40] The influence of CPB and CC times on the incidence of AF in our sensitivity analysis can perhaps be attributed to inflammation and ischemia, respectively, which are thought to be important physiologic substrates for AF.

Several studies of AF after coronary artery bypass grafting (CABG) have been performed to compare the incidence of AF after off-CPB procedures with the incidence of AF after on-CPB procedures. Results from these studies enable us to examine whether CPB-related effects really influence the incidence of AF. In meta-analyses of these data, Athanasiou and colleagues[4,5] have shown that the incidence of AF was reduced with off-CPB techniques only in an elderly (>70 years old) population. This suggests that elderly patients at higher risk of AF would be the most informative group for comparison of the effects of mAVR with those of cAVR—particularly because CPB times are often longer in cAVR.[39] Interestingly, a study that compared off-pump CABG via conventional median sternotomy versus mini-thoracotomy[43] showed no significant difference in the incidence of AF. This uncouples the effects of CPB from our present considerations and suggests, further, that the size of the portal of access in itself does not influence the rate of postoperative AF—a conclusion that appears to agree with that of our present study. In the only comparative study specifically designed to examine the incidence of AF after AVR by minimal-access (limited) sternotomy compared with complete sternotomy, Asher and co-authors[44] similarly found no significant difference between mAVR and cAVR in the incidence of AF.

Postoperative factors associated with AF include respiratory failure, pleural or pericardial effusions,[45] transfusions, prolonged ventilation time,[46] and use of inotropic solutions or an intra-aortic balloon pump or both.[2] Only 3 studies included in the present analysis reported a difference in the incidence of postoperative AF of 10% or greater between minimal-access and control groups,[17,18,22] and, of these, only DeSmet and his group[22] reported this difference to be significant ($P=0.02$; Table III). Consideration of associated outcomes in these 3 studies shows that none of them reported differences in ICU stay, total LoS, ventilation times, incidence of chest infections, or CVA. It can be noted, however, that Aris and colleagues[18] found a 10% higher incidence of AF in association with mAVR and a 5% incidence of pericardial effusions in the mAVR group, versus 0 in the cAVR group. They did not, however, find a difference in the numbers of patients transfused. Interestingly, in contrast, Szwerc and colleagues[17] found a 10% incidence of pleural effusion in their mAVR group, versus 0 in their cAVR group. The incidence of AF was 14% higher in Szwerc's cAVR group; however, it might be added that the incidence of transfusion was 12% greater in that group as well. Stamou and co-authors[24] found that the incidence of AF was similar in association with mAVR or with cAVR ($P=0.60$), although their cAVR group had an almost 20% higher number of transfused patients. Finally, Corbi and associates[21] found a similar incidence of AF in the 2 groups, despite marked differences (favoring mAVR) in ventilation times and incidence of chest infections. Therefore, no consistent conclusions can be drawn from these limited data.

Concerning the cost-effectiveness of mAVR versus cAVR with respect to their influence upon postoperative AF, there are no randomized studies to date. In post-CABG patients, the adjusted increase in total LoS attributable to AF alone is 4.9 days, and the associated increase in costs is approximately $10,000.[46] In their recent meta-analysis of the effectiveness of different strategies for the prevention of AF after cardiac surgery, Burgess and colleagues[47] found that a reduction in the occurrence of AF was associated with a significant reduction in the incidence of CVA and in total LoS. In a detailed report, Mahoney and co-investigators[48] examined the relative cost-effectiveness of amiodarone for the prevention of post-cardiac-surgery AF in different groups of patients. These authors suggested that the cost-effectiveness was greatest in elderly patients with COPD who were undergoing valve surgery. In the present context, one might therefore suggest that evaluating the cost-effectiveness of mAVR versus cAVR requires considering not only periprocedural costs—such as those related to surgical instrumentation and equipment, total operating room time, and length of ICU and hospital stays—but also patient cohorts. Because elderly patients with COPD are a

high-risk cohort for development of AF, that group may more readily manifest any relative clinical and cost benefits of minimal access in future randomized trials.

### Study Limitations

It is important to note that the studies included in our survey were not designed to measure the incidence of AF as a primary outcome, so differences in the definitions of AF and in the mode or intensity of perioperative electrocardiographic monitoring are important limitations. Only 2 of the studies included in our meta-analysis had random assignment of patients,[10,18] and the small numbers of patients in these 2 studies further limit the robustness of our overall findings. Indeed, while statistical techniques such as those used in the present work permit analysis of data obtained from both randomized and nonrandomized studies, the clinical implications of the results obtained may be limited first by the small number of available RCTs and second by the fact that these studies were not designed specifically to evaluate atrial fibrillation as a primary outcome of interest. Selection bias due to differences in operative strategy, number of centers and surgeons, and the effects of learning curves means that one cannot completely eliminate confounding factors; and the mAVR and cAVR groups were certainly not comparable for all factors that could alter the outcome of interest. Indeed, in analyzing data from the Port Access registry of minimal-access valve operations, Glower and colleagues[38] found that being a medium- or low-volume center was a risk factor for postoperative AF. In addition, the studies included in our meta-analysis do not report details concerning perioperative drug regimens (administration of β-blockers, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and steroids), electrolyte levels, inotropic requirements, or inflammatory markers, all of which appear to influence the pathogenesis of postoperative AF.[49,50] Finally, publication bias is inherent in meta-analysis, because studies that report positive findings are more readily published than are those that report negative findings.

## Conclusion

We did not find a significant difference between the incidence of AF after minimal-access AVR and the incidence of AF after conventional AVR. This conclusion persisted after sensitivity analysis, when we used only the highest quality studies available, matched for predictors of AF. Further, we were able to identify several intraoperative variables as important sources of heterogeneity among studies. Those studies that reported large (although insufficient for meta-analysis) absolute-percentage differences in AF incidence between groups did not show consistent associations between costs—such as costs associated with ICU stay, total LoS, or CVA—and outcomes of interest. Although at present mAVR does not appear to offer overall clinical benefits, cost-related morbidities associated with the technique itself, such as the occurrence of postoperative AF, should be investigated more rigorously through randomized studies. Prospective studies designed to measure the incidence of AF should be matched carefully for all known predictors of AF, for other intraoperative variables, and for perioperative drug regimens.

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