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Review

# Surgical treatment of atrial fibrillation; a systematic review☆

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**Summary**

In this review the efficacies of the alternative sources of energy (radiofrequency-microwave and cryo ablation; group I) and the classical 'cut and sew' Cox-Maze III (group II), which claims a 97–99% sinus rhythm (SR) success rate, were evaluated in the surgical treatment of atrial fibrillation (AF). A computerized search in the PubMed and Medline database was conducted. Only original, English written, clinical manuscripts on the surgical treatment of atrial fibrillation using an alternative source of energy or the classical 'cut and sew' Cox-Maze III technique, citing the clinical outcome, including the postoperative sinus rhythm, were included. The data included in this review were the number and percentage of treated patients, gender distribution, the type of arrhythmia and surgery, postoperative morbidity, pacemaker implantation rate, 30-day mortality, survival- and sinus rhythm conversion rates. Mean values for age, left atrial diameter, preoperative duration of AF and left ventricular ejection fraction were also recorded. Forty-eight studies were included comprising 3832 patients; 2279 in group I and 1553 in group II. The mean duration of AF, left atrial diameter and LVEF were 5.4 vs. 5.5 years ($p=0.90$), 55.5 vs. 57.8 mm ($p=0.23$) and 57 vs. 58% ($p=0.63$). The postoperative SR rates for group I and II were 78.3 vs. 84.9% ($p=0.03$). However, the "cut and sew" Cox-Maze III was conducted in younger patients (55.0 vs. 61.2 years; $p=0.005$), more often to treat paroxysmal (22.9 vs. 8.0%; $p=0.05$) and lone AF (19.3 vs. 1.6%). Alternative sources of energy were predominantly used to treat permanent AF (92.0%), almost always as a concomitant surgical procedure (98.4%) and increasingly in combination with non-mitral valve surgery (18.5%). After correction for these variations, the postoperative SR conversion rates for group I and II did not differ significantly anymore ($p=0.260$). **Conclusions**: We could not identify any significant difference in the postoperative SR conversion rates between the classical 'cut and sew' and the alternative sources of energy, which were used to treat atrial fibrillation.
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*Keywords:* Atrial fibrillation; Radiofrequency; Microwave; Cryoablation; Maze; Electrophysiology

## 1. Introduction

The Cox Maze III procedure is a precisely defined pattern of bi-atrial incisions, in order to eliminate atrial fibrillation (AF). This procedure aims to interrupt the multiple wavelet macro reentry circuits, which perpetuate AF. The reported sinus rhythm SR conversion rate after the Cox-Maze III procedure is 97–99% and is therefore, considered the golden standard [1,2]. The major indication for the "cut and sew" Cox-Maze III surgery, as published by Cox and associates, was intolerance for anti-arrhythmic medication and medically refractory arrhythmia. Main symptoms in this series were dyspneu on exertion, easy fatigability, lethargy and malaise. In addition to that, 17% (60/346) of the operated patients had at least one episode of cerebral thromboembolism. Contraindication in this series was the presence of significant left ventricular function dysfunction and a concomitant cardiac or non-cardiac disease. The postoperative pacemaker implantation rate was 15%. Postoperative AF occurred in 11% (38/346) patients during the first 3 postoperative months [1,2]. The complexity of the 'cut and sew' Cox-Maze III technique is considered a major drawback. Therefore, this procedure is not universally accepted as a standard practice in the surgical treatment of AF. As a consequence, alternative sources of energy, such as radiofrequency, microwave and cryoablation, have emerged to surgically treat AF. But, the efficacy of the alternative energy sources is debated, because the creation of continuous linear

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transmural atrial lesions, which act as an electrophysiological conduction block, is considered to be doubtful. In this review the efficacy of the alternative sources of energy (radiofrequency-microwave and cryoablation; (group I) and the classical 'cut and sew' Cox-Maze III (group II), which claims a 97–99% sinus rhythm (SR) success rate, were evaluated in the surgical treatment of atrial fibrillation (AF).

## 2. Methods

### 2.1. Selection of studies

A computerized search in the PubMed and Medline database was conducted over the period 1980 and March 2004. Keywords, used in the title heading, were maze, radiofrequency or microwave or cryo-, ultrasound- or laser ablation and atrial fibrillation and surgery. Only original, english written, clinical articles on the surgical treatment of atrial fibrillation, citing their outcome including the postoperative sinus rhythm conversion rates, were included. Publications reporting on the 'cut and sew' technique of the left atrium only, e.g. the so called 'mini maze' operation, were excluded because this surgical technique did not meet the definition of a classical Cox-Maze III procedure nor of an alternative source of energy. Animal or in vitro experimental studies, case reports and review manuscripts were excluded. Papers which contained previously reported patients' groups from the same surgical group were also excluded, to avoid double patients counting. Cardiological papers reporting on percutaneous performed procedures were also excluded. Publications reporting on cryoablation were only considered in our analysis when linear continuous atrial lesions were conducted.

### 2.2. Data extraction

The most recent publication using the last postoperative results was extracted if multiple publications were available from the same surgical institute. The following data were extracted form each included study: numbers and percentages of treated patients, gender (male vs. female) distribution, the type of arrhythmia (permanent- or paroxysmal AF), type of surgery (mitral valve, non-mitral valve or a lone AF surgery), postoperative morbidity (bleedings, intra-aortic balloon pumps, cerebral vascular events), postoperative pacemaker implantations, 30-day mortality, survival- and sinus rhythm conversion rates. The mean values for age (years), left atrial diameter (millimeters), preoperative duration of AF (years) and left ventricular ejection fraction (%) were also recorded. We have assessed the SR conversion rates and not the 'out of AF' rates. The ECG was the examination of choice in all assessed publications to establish the postoperative rhythm.

### 2.3. Statistical analysis

For dichotomous parameters (gender, sinus rhythm conversion, bleeding, cerebral vascular accidents, intra-aortic balloon pump, 30-day mortality) a percentage per study was calculated by dividing the absolute number of events by the total number of patients. Heterogeneity in outcome events was tested using the $\chi^2$ test. Since the $\chi^2$ test indicated significant heterogeneity between the studies, the calculated percentages were averaged by adding the percentages of all studies divided by the number of studies. This approaches a random effect method, which was also applied for the computation of means of continuous parameters. The means and mean percentages were compared between the two intervention groups (group I: alternative, group II: cut and sew) using the independent *t*-test or a Mann–Whitney test in case of a skewed distribution. The relation between sinus rhythm conversion and the intervention method was also evaluated with meta-regression. In this model adjustments were made for potential confounders. An arcsine transformation was used for the outcome sinus rhythm conversion to stabilize the variance.

## 3. Results

### 3.1. Description of studies

Only publications after 1995 were found. The number of original clinical publications containing the words Maze and atrial fibrillation in the title heading was 90. The numbers of publications concerning the treatment of AF using RF, microwave, cryo, ultrasound and laser were 484, 22, 85, 4 and 6. The total number of articles, which were eligible for our analysis was 48; 19 for RF, 5 for microwave, 6 for cryo, 0 for ultrasound, 0 for laser 3–32 and 16 for the 'cut and sew' classical Cox-Maze III 33–49 (Tables 1 and 2). Two publications reported both on cryo, respectively, RF, and the "cut and sew" technique (Table 2; Lee et al. and Chiappini et al.). The total number of patients with alternative sources was 2279 (59%) and for the cut and sew 1553 (41%). Subdivided for the alternative sources the total number of RF patients was 1652 (73%), 281 (12%) microwave, 346 (15%) cryo. Irrigated RF was used in 465 patients (28%) whereas 1187 (72%) used temperature controlled RF. The patients' characteristics, type of arrhythmia and surgery are shown in Table 3.

### 3.2. Main outcome

The mean duration of AF, left atrial diameter and LVEF were 5.4 vs. 5.5 years ($p=0.90$), 55.5 vs. 57.8 mm ($p=0.23$) and 57 vs. 58% ($p=0.63$). The postoperative SR rates for group I and II were 78.3% vs. 84.9% ($p=0.03$). However, the 'cut and sew' Cox-Maze III was conducted in younger patients (55.0 vs. 61.2 years; $p=0.005$), more often to treat paroxysmal (22.9% vs. 8.0%; $p=0.05$) and lone AF (19.3% vs. 1.6%) and the SR conversion rate was below the expected 97–99%. Alternative sources of energy were predominantly used to treat permanent AF (92.0%), almost always as a concomitant surgical procedure (98.4%) and increasingly in combination with non-mitral valve surgery (18.5%). Meta regression showed that the occurrence of postoperative SR was related to the type of arrhythmia (permanent vs. paroxysmal; $p=0.004$) and type of surgery (lone AF vs. non-lone AF; $p=0.001$) if these parameters were

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Table 1
Extracted data

| Author | Year | AS/CS | n= | age (yr) | Male (%) | Chron (%) | Dur (ys) | LA (mm) | EF (%) | MV (%) | NMV (%) | Lone (%) | BP (%) | Ble (%) | IABP (%) | CVA (%) | 30-d (%) | SR (n) | SR av (n=) | SR (%) | PM (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mohr, Doll | 2002 | RF | 234 | 62.8 | 61.1 | 100 | 7.8 | 58.0 | 53.7 | 40.6 | 27.8 | 31.6 | 0 | 7.7 | 3.4 | 1.3 | 6.4 | 58 | 80 | 73 | 9.8 |
| Sie | 2004 | Irr RF | 200 | 68.0 | 46.0 | 100 | 5.6 | 50.0 | . | 81.0 | 19.0 | 0.0 | 100 | 8.0 | 4.0 | 0.5 | 3.5 | 116 | 158 | 73 | 3.5 |
| Güden | 2001 | Irr RF | 62 | 52.0 | 33.9 | 100 | . | . | 50 | 85.5 | 14.5 | 0.0 | 63 | 4.8 | | | 3.2 | 51 | 58 | 88 | 1.6 |
| Williams | 2001 | RF | 48 | 65.0 | | 100 | 4.8 | 60.0 | . | 81.3 | 18.7 | 0.0 | 0 | | | | 13.0 | 34 | 42 | 81 | 0 |
| Pasic | 2001 | RF | 48 | 64.0 | 41.7 | 100 | 7.0 | 47.0 | 55 | 79.2 | 20.8 | 0.0 | 0 | 0.0 | | | 4.2 | 12 | 13 | 92 | 10 |
| Melo | 2000 | RF | 65 | 60.0 | 16.9 | 79 | 4.9 | . | . | 89.2 | 7.7 | 3.1 | 0 | | | | 0.0 | 13 | 31 | 42 | . |
| Ruchat | 2002 | RF | 40 | 65.2 | 65.0 | 100 | 3.7 | 59.0 | 58 | 92.5 | 7.5 | 0.0 | 0 | | | | 7.5 | 27 | 40 | 68 | 2.5 |
| Kress | 2002 | RF | 23 | . | | 83 | 3.7 | 54.0 | . | 100.0 | 0.0 | 0.0 | 0 | | | 4.3 | 4.3 | 19 | 22 | 86 | . |
| Benussi | 2002 | RF | 132 | 58.5 | 48.5 | 92 | 3.5 | 57.2 | 59 | 97.7 | 2.3 | 0.0 | 0 | 2.3 | | | 2.3 | 87 | 108 | 81 | 0 |
| Geidel | 2003 | RF | 29 | 73.1 | 37.9 | 100 | 4.5 | 55.9 | 59 | 79.3 | 20.7 | 0.0 | 0 | | | | 0.0 | 14 | 16 | 88 | 0 |
| Hornero | 2003 | RF | 55 | 58.0 | 38.2 | 100 | 5.6 | 54.8 | . | 92.7 | 7.3 | 0.0 | 0 | 5.5 | 1.0 | 1.8 | 1.8 | 46 | 54 | 85 | 0 |
| Starck | 2003 | RF | 100 | 65.7 | 53.0 | 38 | . | 51.0 | . | 43.0 | 57.0 | 0.0 | 0 | | | | 5.0 | 72 | 90 | 80 | . |
| Khargi | 2003 | Irr RF | 203 | 67.9 | 49.8 | 77 | 4.5 | 48.9 | 58 | 55.2 | 44.8 | 0.0 | 46 | 3.9 | | 1.0 | 5.9 | 34 | 45 | 76 | 2.5 |
| Wellens | 2002 | RF | 30 | . | | . | . | . | . | 100.0 | 0.0 | 0.0 | 0 | | | 3.3 | . | 19 | 30 | 63 | 6.7 |
| Mantovan | 2003 | RF | 103 | 62.0 | 37.9 | 80 | 3.5 | 56.0 | 61 | 86.4 | 13.6 | 0.0 | 0 | | | 1.0 | 1.0 | 83 | 103 | 81 | 1 |
| Guang | 2002 | RF | 96 | 40.6 | 38.5 | 100 | 9.8 | 62.7 | . | 100.0 | 0.0 | 0.0 | 100 | 2.1 | | | 0.0 | 74 | 96 | 77 | 0 |
| Chen | 1998 | RF | 12 | 49.8 | 75.0 | 100 | 2.6 | 55.0 | . | 100.0 | 0.0 | 0.0 | 100 | | | | 17.0 | 4 | 5 | 80 | 0 |
| Raman | 2003 | RF | 132 | 66.0 | 68.9 | 75 | 3.0 | 51.3 | . | 78.8 | 21.2 | 0.0 | 100 | | | | 6.8 | 45 | 50 | 90 | 3 |
| Chiappini | 2003 | RF | 40 | 62.0 | 20.0 | 100 | 5.2 | 56.0 | 56.8 | 92.5 | 7.5 | 0.0 | 100 | | | 0.0 | 7.5 | 33 | 37 | 89 | 7.5 |
| Maessen | 2002 | MW | 24 | 67.4 | | 88 | 4.4 | . | . | 41.5 | 58.5 | 0.0 | 0 | 8.3 | | | 4.2 | 20 | 23 | 87 | 0 |
| Knaut | 2002 | MW | 181 | 68.6 | | 100 | 8.3 | 52.9 | 50.8 | 50.8 | 49.2 | 0.0 | 0 | | | | 1.7 | 132 | 181 | 73 | 8.3 |
| Chiappini | 2003 | MW | 10 | 61.7 | 40.0 | 100 | 6.9 | 56.3 | . | 80.0 | 20.0 | 0.0 | 0 | | | | 10.0 | 7 | 9 | 78 | 0 |
| Zembala | 2003 | MW | 42 | . | | . | . | . | . | 100.0 | 0.0 | 0.0 | 0 | | | | . | . | . | . | . |
| Schuetz | 2003 | MW | 24 | 64.6 | 50.0 | 100 | 3.8 | 54.9 | 63 | 66.7 | 33.3 | 0.0 | 0 | | | 0.0 | 4.2 | 12 | 15 | 80 | 13 |
| Kondo | 2003 | Cryo | 31 | 59.8 | 38.7 | 100 | 6.4 | . | . | 93.5 | 0.0 | 6.5 | 0 | | | 0.0 | 6.5 | 21 | 29 | 72 | 16 |
| Doll | 2003 | Cryo | 28 | 60.0 | 67.9 | 82 | 6.8 | 56.0 | 59 | 46.4 | 50.0 | 3.6 | 0 | | | | 0.0 | 23 | 28 | 82 | 14 |
| Lee | 2001 | Cryo | 53 | 48.0 | 35.8 | 100 | 4.8 | 62.8 | 55 | 66.0 | 34.0 | 0.0 | 100 | | | | 0.0 | 44 | 53 | 83 | 0 |
| Fukada | 1998 | Cryo | 29 | 59.8 | 48.3 | . | 9.0 | 47.1 | . | 100.0 | 0.0 | 0.0 | 100 | | | | 0.0 | 17 | 29 | 59 | 21 |
| Manasse | 2003 | Cryo | 95 | 61.0 | 42.1 | 98 | 5.4 | 65.2 | . | 88.4 | 10.4 | 1.2 | 0 | 2.1 | 1.1 | 4.3 | 3.2 | 70 | 86 | 81 | 6.3 |
| Nakajima | 2002 | Cryo | 110 | 60.4 | 59.1 | . | 5.7 | 59.5 | . | 100.0 | 0.0 | 0.0 | 100 | 3.6 | | | 0.0 | 92 | 110 | 84 | 0.9 |
| Loennerholm | 2000 | CS | 49 | 52.0 | 79.6 | 53 | 8.0 | . | . | 2.0 | 12.4 | 85.6 | 100 | 6.7 | | | 0.0 | 30 | 30 | 100 | 4.1 |
| Cox /Damiano | 2002 | CS | 308 | 54.0 | 72.1 | 42 | 8.8 | . | . | 28.9 | 15.3 | 55.8 | 100 | 4.5 | 2.5 | 1.5 | 1.6 | 294 | 303 | 97 | 15 |
| McCarthy | 2000 | CS | 100 | 58.0 | 72.0 | 78 | 8.0 | 60.4 | . | 66.0 | 11.0 | 23.0 | 100 | | | | 1.0 | 85 | 94 | 90 | 6 |
| Schaff | 2000 | CS | 221 | 56.0 | 63.8 | 79 | 5.1 | . | . | 65.6 | 11.8 | 22.6 | 100 | 5.0 | 5.1 | | 1.4 | 32 | 39 | 82 | 3.2 |
| Millar | 2000 | CS | 99 | 59.6 | 54.5 | 78 | 8.5 | . | 60 | 62.6 | 16.2 | 21.2 | 100 | 3.0 | 1.0 | 2.0 | 0.0 | 83 | 95 | 87 | 10 |
| Bando | 2002 | CS | 258 | 59.1 | 48.4 | 96 | . | . | . | 100.0 | 0.0 | 0.0 | 100 | 2.7 | 1.2 | | 1.9 | 188 | 245 | 77 | 6.2 |
| Chiappini | 2004 | CS | 30 | 60.9 | 20.0 | 100 | 4.6 | 56.4 | 58 | 96.7 | 3.3 | 0.0 | 100 | | | 0.0 | 6.7 | 19 | 28 | 68 | 6.7 |
| Isobe | 1998 | CS | 31 | 57.4 | 45.2 | 97 | . | . | . | 100.0 | 0.0 | 0.0 | 100 | | | | 3.2 | 27 | 30 | 90 | 3.2 |
| Izumoto | 2000 | CS | 104 | 59.7 | 43.3 | 100 | . | . | . | 79.0 | 21.0 | 0.0 | 100 | | | | 1.0 | 52 | 72 | 72 | 5.8 |
| Khalil | 2002 | CS | 69 | 49.9 | 30.4 | 100 | . | . | . | 100.0 | 0.0 | 0.0 | 100 | | | | 7.2 | 50 | 68 | 74 | 12 |
| Kim | 1999 | CS | 75 | 48.0 | 33.3 | 100 | 5.6 | 58.0 | 52 | 100.0 | 0.0 | 0.0 | 100 | 5.3 | 5.3 | | 2.7 | 66 | 73 | 90 | 2.7 |
| Raanani | 2001 | CS | 47 | 68.0 | 55.3 | 89 | 1.4 | 57.4 | 51 | 100.0 | 0.0 | 0.0 | 100 | 6.4 | | 0.0 | 4.3 | 38 | 45 | 84 | 11 |
| Jatene | 1999 | CS | 20 | 50.5 | 15.0 | 50 | 2.7 | 53.5 | 69 | 100.0 | 0.0 | 0.0 | 100 | 10.0 | 5.0 | | 5.0 | 18 | 19 | 95 | 5 |
| Lee | 2001 | CS | 30 | 45.0 | 60.0 | 100 | 3.1 | 58.0 | 57 | 100.0 | 0.0 | 0.0 | 100 | | | | 0.0 | 25 | 30 | 83 | 0 |
| Jessurun | 2003 | CS | 25 | 64.0 | 56.0 | 48 | . | . | . | 100.0 | 0.0 | 0.0 | 100 | | 0.0 | 0.0 | 0.0 | 22 | 25 | 88 | 4 |
| Jessurun | 2000 | CS | 41 | 49.0 | 85.4 | 0 | 5.0 | . | . | 0.0 | 0.0 | 100.0 | 100 | 0.0 | 0.0 | 0.0 | 0.0 | 31 | 34 | 91 | 4.9 |
| Albage | 2000 | CS | 26 | 55.0 | 73.1 | . | . | . | . | | | | 100 | | | | . | 22 | 26 | 85 | . |
| Gregori | 1995 | CS | 20 | 43.0 | 30.0 | 100 | . | 61.0 | . | 100.0 | 0.0 | 0.0 | 100 | | | | 0.0 | 15 | 20 | 75 | 0 |

AS, alternative sources of energy; CS, Cut and Sew technique; yr, years; Chron, Chronic atrial fibrillation; Dur, duration of atrial fibrillation; LA, Left atrial diameter; mm, millimeters; EF, Left ventricular ejection fraction; MV, mitral valve surgery; NMV, non mitral valve surgery; Lone, lone Atrial fibrillation surgery; BP, bi-atrial lesion pattern; Ble, postoperative bleeding; IABP, intra aortic balloon pump; CVA, cerebral vascular event; 30-d, 30 day mortality; SR, sinus rhythm; av, number of available patients; PM, Postoperative pace maker implantation rate; irr RF, irrigated radiofrequency; MW, Microwave; Cryo, Cryo ablation.

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Table 2
Considered publications for this review

| Authors | Publication |
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| Chen MC, Guo BF, Chang JP, Yeh KH, Fu M. | Radiofrequency and cryoablation of atrial fibrillation in patients undergoing valvular operations. Ann Thorac Surg 1998; 65: 1666–72. |
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(*continued on next page*)

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Table 2 (*continued*)

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yrs, years, mm, millimeters, LVEF, left ventricular ejection fraction, AF, atrial fibrillation, LP, Lesion pattern, IABP, intra-aortic balloon pump, CVA, cerebral vascular accident, PM, postoperative pacemaker implantation, SR, postoperative sinus rhythm.

tested univariately. Therefore, we adjusted for type of arrhythmia and type surgery in a meta- regression analysis, which revealed a non-significant difference in the post-operative SR conversion rate ($p=0.260$). A clear relationship between postoperative SR and atrial lesion pattern could not be established. The SR conversion rates for the biatrial vs. the left atrial lesion pattern were 83.2% vs. 77.5%. Univariate analysis revealed a potential relationship ($p=0.05$) between the type of lesion pattern (left vs. biatrial) and the postoperative SR conversion rate, but this potential statistically significance disappeared in a multivariate analysis ($p=0.69$). The postoperative complication- and pacemaker implantation rates for group I and II are shown in Table 3. Thirty day- mortality was 4.2% vs. 2.1% ($p=0.09$).

## 4. Discussion

The hypothetic sequence of events, after the surgical treatment of AF, includes the abolition of AF, enabling the sinus node to regain its activity, permitting the restoration of the atrial contractility with associated atrial kick which will subsequently enhance the left and right ventricular filling during the late diastolic phase, optimizing the cardiac output and performance. As a consequence, an improved quality of life and survival and a decrease in cerebral vascular events can theoretically be anticipated. Each preceding element of the described sequence is a prerequisite for a successful next consecutive step. Obviously, any single study is unable to answer all these consecutive

Table 3
Patients' characteristics, operative procedures and outcome

| | | | | | | Alternative sources | CS | *P* value |
|---|---|---|---|---|---|---|---|---|
| *Age (yrs; mean)* | | | | | | 61.2 | 55.0 | 0.005 |
| *Duration AF (yrs; mean)* | | | | | | 5.4 | 5.5 | 0.90 |
| *Left atrial size (mm;mean)* | | | | | | 55.5 | 57.8 | 0.23 |
| *LVEF (%; mean)* | | | | | | 57 | 58 | 0.63 |
| | *Chronic AF (%)* | | | | | 92.0 | 77.1 | 0.05 |
| | *Lone AF (%)* | | | | | 1.6 | 19.3 | 0.06 |
| | *Biatrial LP (%)* | | | | | 30.3 | 100 | 0.00 |
| | | *Bleeding (%)* | | | | 4.4 | 4.9 | 0.65 |
| | | *IABP (%)* | | | | 2.4 | 2.5 | 0.87 |
| | | *CVA (%)* | | | | 1.6 | 0.5 | 0.21 |
| | | | *30-d Mortality (%)* | | | 4.2 | 2.1 | 0.09 |
| | | | *PM (%)* | | | 4.9 | 5.8 | 0.21 |
| | | | | *SR (%)* | | 78.3 | 84.9 | 0.03 |

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elementary questions at once. Therefore, the only endpoint of all the included studies was the restoration of SR, evaluating the efficacy of the surgical technique.

This systematic review was conducted to evaluate the English written literature concerning the surgical therapy of atrial fibrillation. All included studies were observational non-randomized studies lacking any control patients groups, although 2 studies compared cryo respectively, RF and the 'cut and sew' technique to each other (Table 2; Lee et al. and Chiappini et al.). Analysis revealed a heterogeneity of the recruited study patients and their treatment, mandating several statistically adjustments, as performed in this review, to enhance the interpretation of the outcome data.

In our opinion, this systematically review is valuable because the presented data will hopefully facilitate the process of sound clinical judgment of the various surgical techniques, which are used to treat AF.

### 4.1. Patients' characteristics

This study revealed a significant and unexpected difference in mean age of 6.2 years for the group I and II patients; 61.2 vs. 55.0 years ($p=0.005$). As a consequence, the anticipated postoperative morbidity and mortality for both groups will be different. The mean difference in Euro score was 1 point. The duration of AF and left atrial size were similar, which theoretically would provide a comparable base to evaluate the postoperative success rate.

### 4.2. Postoperative SR conversion rate

The primary endpoint in all studies was postoperative SR conversion. The mean postoperative SR rates for group I and II were 78.3% vs. 84.9% ($p=0.03$). Although the preoperative duration of AF and the size of the left atrium was similar for both groups, this difference in favor of the 'cut and sew' group can be potentially explained by the substantially higher incidence of paroxysmal AF in group II; 8.0% vs. 22.9%. In general, paroxysmal AF is better amendable for any therapy than permanent AF. In addition to that, the mere occurrence of SR on a standard surface ECG is an inappropriate definition of success, as was conducted in all, but one, of the evaluated studies. Only Loennerholm reported an improved quality of life appreciation in 18 patients with paroxysmal AF (Table 2). All other studies failed to provide any information on the postoperative 'burden of atrial fibrillation' which includes an evaluation of the number and duration of the AF episodes and its associated clinical symptoms, such as shortness of breath, perspiration, level anxiety. As consequences, this omission was a major drawback of all studies.

A second major difference between group I and II patients, potentially affecting the postoperative SR conversion rates, was the incidence of lone AF. Lone AF was the primary indication in 19.3% in group II, whereas in group I only 1.6% of the patients had a lone AF surgery. Lone AF treatment, especially in patients below 60 years of age, is associated with excellent results. So, in summary the 6.6% difference SR conversion rate in favor of the 'cut and sew' can not unequivocally be attributed to the superiority of the efficacy of 'cut and sew' surgical technique.

Experienced surgical groups including McCarthy, Schaff, Arcidi and Jessurun who precisely performed the 'cut and sew' Cox-Maze III procedure reported a SR success rate of 90.4, 85, 87.4 and 88%. These groups were unable to duplicate the 97–99% SR conversion rate (Table 2).

### 4.3. Postoperative mortality

The postoperative mortality in group I is twice as high as in group II; 4.2% (83/2207) vs. 2.1% ($p=0.09$). But the difference in mean euro score, due to the mean age difference, was at least 1 point. In addition to that, a concomitant cardiac procedure was performed more often in the group I patients; 98.4% vs. 80.7%. Clearly, a higher expected mortality can be anticipated for the group I patients.

### 4.4. Pacemaker implantation

This study revealed a small difference in postoperative pacemaker implantation in favor of the group I patients; 4.9% vs. 5.8% ($p=0.21$). But the interpretation of this finding is blurred due to the variable investigator and time-dependant indication of pacemaker implantation. Obviously, a sick sinus syndrome is a proper and absolute indication. But the various studies also reported an AV junctional, an atypical bradycardic arrhythmia or the lack of an exercise- induced SR tachycardia as a relative indication for pacemaker implantation. The postoperative time interval was variable and certain surgical groups were more aggressive in their indication for pacemaker implantation, while others adopted a more conservative approach. This certainly influenced the eventual postoperative pacemaker rate. Whether the 'cut and sew' technique is a risk factor for a sick sinus syndrome due to devascularisation and denervation of the sinus node remains a matter of debate.

### 4.5. Postoperative morbidity

The postoperative bleeding rates in both groups were similar although the'cut and sew' technique includes multiple atrial incisions which theoretically increased the risk of postoperative bleeding. Postoperative cerebral vascular accident rates in both groups were equal. So, the presumed advantage of negligible cerebral vascular event rate in the group II is not solitary confined to this subset of patients. Low cardiac output, expressed by the use of the intra aortic balloon pump was similar. But group II patients were younger and had a lone AF procedure more often. So, there tends to be an increased risk for the use of an IABP in the group II patients

### 4.6. Lesion transmurality and SR conversion rate

The main difference between the classical 'cut and sew' Cox-Maze III procedure and the alternative sources of energy is the uncertainty of the continuity and transmurality of the induced atrial wall linear lesions. The difference in

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postoperative SR conversion rate for the group I patients, who had a bi-atrial lesion pattern, and the 'cut and sew' group II patients was 6.6; 78.3 vs. 84.9% ($p=0.03$). A potential explanation for this small but distinct difference is the lack of continuous and transmural atrial lesions. However, the necessity of histologically proven transmural lesion as a prerequisite to achieve SR is still debated. Santiago and colleagues who correlated the intra-tissue temperature with the tissue thickness and with the histological appearance of lesions in 10 mitral valve patients, found in transmural lesions in only 20% (2/10), a variable myocardium damage in 30% (3/10) and only endocardial damage in 50% (5/10). At 6 months, 4 out 5 patients with a myocardial, but non-transmural lesions, were still in SR and even 2 of the 5 patients, who only had an endocardial lesion converted in SR [3]. This finding suggests that even non-transmural lesions are associated with SR conversion. Pappone, who conducted circumferential pulmonary vein orifices isolation in 589 patients, of whom 31% had a chronic AF, reported a SR conversion rate of 80% [4]. This finding corroborates the finding of Chen, who showed that the pulmonary veins itself can be a substrate for easier induction and maintenance of AF [5]. Jalife postulated that in some case, AF is organized by one or a small number of high-frequency sources localized in the left atrium, indicating that targeting these sources might prevent the formation of reentrant sources, eliminating AF [6].

### *4.7. Left versus bi-atrial lesion pattern in relationship to the SR conversion rate*

A clear relationship between postoperative SR and atrial lesion pattern could not be established. The SR conversion rates for the biatrial- versus the left atrial lesion pattern were 83.2% vs. 77.5%. Univariate analysis revealed a potential relationship ($p=0.05$) between the type of lesion pattern (left vs. biatrial) and the postoperative SR conversion rate, but this potential statistically significance disappeared in a multivariate analysis ($p=0.69$). This indicated that the left atrial lesion pattern appeared as efficacious as the bi-atrial lesion pattern. So, the concept of 'trigger and substrate' with left atrium as the predominate site for atrial fibrillation still remains valid [7], although Konings and associates, suggested that both atria as a whole participate, although not equally, in the perpetuation of the fibrillatory process [8]. Nair observed that the induced AF in patients with rheumatic heart valve disease show a rapid organized arrhythmia with earliest atrial activity in the coronary sinus orifice and isthmus. Targeting these regions of the coronary sinus orifice was associated with a successful suppressing of the arrhythmia [9]. Waldo postulated that there is a major interaction between fibrillation and flutter, indicating that atrial fibrillation is usual required for the devolvement of a line of functional block between the vena cavae, which in turn is required for the development of an atrial flutter, which in itself can provoke a fibrillatory conduction and therefore maintaining AF [10]. Nevertheless, it appeared that the left atrial lesion pattern was effective in the abolition of AF.

### *4.8. Limitations of the study*

A couple of confounding factors, which potentially can affect the interpretation of the data, can be identified. The unavailability of prospective randomized studies on the surgical treatment of atrial fibrillation was a drawback of this systemic review. Each of the various energy sources, radiofrequency, microwave and cryo ablation, has its own specific ablative characteristics on the atrial tissue, which barely can be quantified and were therefore not considered in this review. The performed ablation pattern in the various studies using alternative sources of energy could only be distinguished between a left vs. bi-atrial lesion pattern. A bi-atrial lesion pattern was conducted in 815 group I patients, whereas 1422 group I patients had a left atrial lesion pattern. Patients who had a solitary left atrial lesion pattern showed a broad variety of ablation lines within the left atrium, which might had an impact on the outcome of this review. Nevertheless, we felt it was still worthwhile and appropriate to classify and categorize the patients, as we have done in this review. The heterogeneity of the various included studies was addressed using a statistical regression correction in order to enhance the comparison of the data of the various studies. It was our opinion that this approach was considered the best alternative to review the international literature.

In conclusion, we could not identify any significant difference in the postoperative SR conversion rates between the classical 'cut and sew' and the alternative sources of energy, which were used to treat atrial fibrillation.

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## Appendix A. Conference discussion

***Dr F. Casselman*** (*Aalst, Belgium*): You did not mention at what time interval you pointed out the sinus rhythm rate. And did you see any difference between the two groups over time, 3 months, 6 months, and further on in follow-up?

***Dr Khargi***: I took the sinus rhythm rate from the most recent publication if I had a choice. I used the SR incidence after 6 months.The reason for that is that we do know that before 6 months you have an instability of arrhythmia, so I felt that after 6 months you could use this value as the most stable situation.

***Dr Casselman***: And any evolution throughout time later on between the two groups?

***Dr Khargi***: Because of the differentiation in the published time intervals in the various publications, it was very difficult to establish a 3-month, 6-month, and 12-month subdivision, so, as a consequence, I cannot answer that question.

***Dr Z. Al-Halees*** (*Riyadh, Saudi Arabia*): In your review did you see any difference the size of the left atrium makes in relation to the conversion rate? Are like larger atria less likely to be converted back into sinus rhythm, and, if so, what is the upper limit or what is the atrial size after which you would say it probably will not work?

***Dr Khargi***: Well, we do know from other publications that there is a relation between the size of the left atrium and the conversion into sinus rhythm. So the larger the atrium, the lower the conversion. But there is one exception. If you are looking to the size of the atrium for mitral versus non-mitral valve pathology, then you will see that, generally speaking, the atrial size in the mitral valves is larger than for the non-mitral, but even those large atria in mitral patients might convert as good as well. But, to answer your question, the size relationship cannot be answered from this Meta-Analysis, but we do know that the upper limit size of 7 mm is poorly related to a successful sinus conversion rate and especially atrial contraction. And atrial contraction is what we are looking for.

***Dr A. Boening*** (*Kiel, Germany*): I have a question regarding the differences in the alternative techniques. Are there differences between radiofrequency and cryoablation? Were you able to find something out?

***Dr Khargi***: I tried to distinguish between the various sources in themselves, but due to the small numbers, especially for the cryo and microwave, and the overwhelming number of radiofrequency, I would skew the data, so, as a consequence, I omitted this analysis.

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