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## Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

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**Background**—We tested the hypothesis that patients with untreated obstructive sleep apnea (OSA) would be at increased risk for recurrence of atrial fibrillation (AF) after cardioversion.

**Methods and Results**—We prospectively obtained data on history, echocardiogram, ECG, body mass index, hypertension, diabetes, NYHA functional class, ejection fraction, left atrial appendage velocity, and medications in patients with AF/atrial flutter referred for DC cardioversion. Forty-three individuals were identified as having OSA on the basis of a previous sleep study. Data regarding the use of continuous positive airway pressure (CPAP) and recurrence of AF were obtained for 39 of these patients. Follow-up data were also obtained in 79 randomly selected postcardioversion patients (controls) who did not have any previous sleep study. Twenty-seven of the 39 OSA patients either were not receiving any CPAP therapy (n=25) or were using CPAP inappropriately (n=2). Recurrence of AF at 12 months in these 27 patients was 82%, higher than the 42% recurrence in the treated OSA group (n=12,  $P=0.013$ ) and the 53% recurrence (n=79,  $P=0.009$ ) in the 79 control patients. Of the 25 OSA patients who had not been treated at all, the nocturnal fall in oxygen saturation was greater ( $P=0.034$ ) in those who had recurrence of AF (n=20) than in those without recurrence (n=5).

**Conclusions**—Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a polysomnographic diagnosis of sleep apnea. Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF. (*Circulation*. 2003;107:2589-2594.)

**Key Words:** fibrillation ■ sleep ■ apnea ■ cardioversion

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting more than 2 million Americans.<sup>1</sup> It is associated with significant morbidity and mortality.<sup>2</sup> Factors implicated in the pathogenesis of AF include hypertension, thyroid disorders, and structural heart disease.<sup>3</sup> Recent cross-sectional studies have suggested that the prevalence of AF may be increased in patients with sleep disordered breathing and coexisting heart failure or recent coronary artery bypass surgery, suggesting that sleep apnea may contribute to arrhythmogenesis.<sup>4-6</sup>

There has been an alarming increase in obesity in North America and other countries.<sup>7</sup> The prevalence of obstructive sleep apnea (OSA) increases with obesity.<sup>8</sup> This raises the intriguing possibility that sleep apnea may contribute to the dramatic increase in the incidence of AF during the past 2 to 3 decades.

OSA induces intermittent hypoxemia, carbon dioxide retention, sympathetic activation, and abrupt surges in arterial pressure.<sup>9</sup> Thus, there is reason to suppose that in a heart susceptible to AF, the presence of OSA would predispose to the subsequent development of AF. However, there are no

prospective data addressing a potential pathogenetic role for OSA in AF.

We tested the hypothesis that OSA increases the risk of AF recurrence after successful cardioversion and that treatment of OSA would be associated with lower recurrence. Any demonstrable relationship between sleep apnea and recurrence of AF might provide evidence suggesting a link between sleep apnea and the initial development of AF.

### Methods

We prospectively recorded data on history, echocardiogram, ECG, body mass index (BMI), hypertension, diabetes, NYHA functional class, ejection fraction, left atrial appendage velocity, and the use of medications in patients with AF/atrial flutter referred to the Mayo Clinic Cardioversion Center for electrical cardioversion. Forty-three individuals were identified as having had a formal sleep study resulting in the diagnosis of OSA.

Data regarding the use of continuous positive airway pressure (CPAP) and the recurrence of AF were obtained by a questionnaire sent to each patient through the mail, from hospital records from subsequent visits to the Mayo Clinic, or from follow-up phone interviews. Both the questionnaire and phone interviews were performed at 12 months (range, 11–13 months) after successful cardioversion. In the phone interviews, patients were considered to

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**TABLE 1. Patient Characteristics**

| Variable   | OSA<br>(n=39) | Control<br>(n=79) | P      |
|--|---------------|-------------------|--------|
| Male, n (%)                                      | 30 (81)       | 51 (65)           | 0.071  |
| Age, y   |               |                   |        |
| Mean±SD  | 65±10         | 67±13             | 0.131  |
| Median, IQR                                      | 67 (60, 73)   | 70 (62, 75)       |        |
| BMI, kg/m <sup>2</sup>                           |               |                   |        |
| Mean±SD  | 37±11         | 30±8              | <0.001 |
| Median, IQR                                      | 35 (29, 44)   | 27 (24, 32)       |        |
| NYHA class II/III/IV, n (%)                      | 21 (58)       | 32 (42)           | 0.108  |
| History of hypertension, n (%)                   | 29 (78)       | 37 (48)           | 0.002  |
| History of DM, n (%)                             | 8 (22)        | 9 (12)            | 0.155  |
| Current heart rate, bpm                          |               |                   |        |
| Mean±SD  | 89±28         | 82±25             | 0.233  |
| Median, IQR                                      | 80 (66, 115)  | 76 (62, 94)       |        |
| Ejection fraction, %                             |               |                   |        |
| Mean±SD  | 52±13         | 48±17             | 0.820  |
| Median, IQR                                      | 55 (45, 60)   | 55 (35, 63)       |        |
| LAA average emptying velocity, cm/s <sup>2</sup> |               |                   |        |
| Mean±SD  | 32±16         | 38±19             | 0.269  |
| Median, IQR                                      | 28 (18, 46)   | 32 (24, 55)       |        |
| Medications at dismissal, n (%)                  |               |                   |        |
| Amiodarone                                       | 5 (13)        | 4 (5)             | 0.999  |
| β-Blockers                                       | 11 (28)       | 11 (14)           | 0.239  |
| Dihydropyridines                                 | 5 (13)        | 1 (5)             | 0.404  |
| Nondihydropyridines                              | 9 (23)        | 6 (7)             | 0.715  |
| Disopyramide                                     | 0             | 0                 | ...    |
| Dofetilide                                       | 0             | 0                 | ...    |
| Flecainide                                       | 0             | 1 (4)             | 0.400  |
| Digoxin  | 10 (26)       | 7 (7)             | 0.908  |
| Procainamide                                     | 0             | 1 (4)             | 0.391  |
| Propafenone                                      | 10 (26)       | 9 (35)            | 0.436  |
| Quinidine  | 0             | 0                 | ...    |
| Sotalol  | 4 (10)        | 0                 | 0.144  |
| ACE inhibitors                                   | 17 (44)       | 12 (46)           | 0.839  |
| A2 blockers                                      | 3 (8)         | 2 (8)             | 0.999  |
| Diuretic   | 17 (44)       | 10 (39)           | 0.681  |

IQR indicates interquartile range, which lies between the 25th and 75th percentiles; DM, diabetes mellitus; and LAA, left atrial appendage.

have recurrence of AF only if a physician had documented them to be in AF by either clinical examination or ECG. Follow-up was complete in 39 of 43 patients. One patient was excluded because of an initial unsuccessful cardioversion, and the other 3 patients were excluded because of a lack of recurrence data. Follow-up recurrence data were also obtained on 79 randomly selected postcardioversion patients in whom the same data variables as described above were obtained prospectively but who did not have any previous history of a formal sleep study. These patients underwent treatment during the same time period and served as a control group. This study was approved by the Institutional Human Subjects Review Board of the Mayo Clinic.

Comparisons of continuous variables between groups were made with a 2-sample *t* test where appropriate and otherwise with the Wilcoxon rank-sum test. Categorical variables were compared by

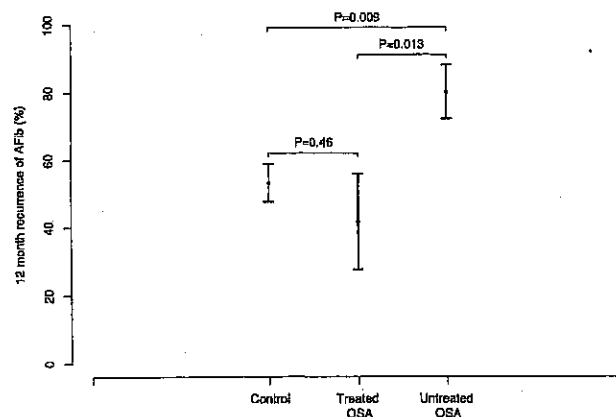
Fisher's exact test or the  $\chi^2$  test, depending on which was more appropriate. The 1-year AF/atrial flutter recurrence rate for each group was the number of patients who had at least 1 recurrence within 1 year of their initial successful cardioversion divided by the total number of patients within the group.

## Results

Characteristics of the OSA and control groups are shown in Table 1. Twenty-seven of the 39 patients with OSA were not receiving any CPAP therapy (n=25) or were noncompliant with CPAP (n=2). Of the 2 noncompliant patients, 1 was using CPAP only once or twice a week; the other was using CPAP <5 times a week and taking the mask off frequently during the night because of discomfort. These 27 patients composed the untreated OSA group, and the remaining 12 patients who used CPAP appropriately composed the treated OSA group. A comparison of the patient characteristics of these 2 groups is summarized in Table 2.

The recurrence rate of AF at 12 months in the 27 untreated or inappropriately treated subjects with OSA was 82%, versus 42% in the treated OSA group ( $P=0.013$ ) and 53% in the control group without known OSA ( $P=0.009$ ) (Figure 1). This higher rate of recurrence in the untreated OSA group was evident even though the untreated OSA patients tended to have a lower BMI ( $P=0.39$ ), less history of hypertension ( $P=0.07$ ), and better functional capacity as defined by NYHA class ( $P=0.11$ ) than treated OSA patients (Table 2). In addition, if the 2 patients who were noncompliant with CPAP were considered as part of the treated group on an intention-to-treat analysis, there would have been a recurrence in 7 of the 14 "treated" patients (50%) and a recurrence in 20 of the 25 patients who did not receive any CPAP whatsoever (80%). The difference between the recurrence rate in the 2 groups would still remain significant at a value of  $P=0.05$ .

To further determine the relationship between OSA therapy and AF recurrence, we compared the OSA patients with no recurrence (n=12) with those with recurrence (n=27). Only 19% of patients with recurrence were treated appropriately with CPAP versus 58% with appropriate OSA treatment in patients without recurrence ( $P=0.013$ ) (Table 3). Further-



**Figure 1.** Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean±SD).

**TABLE 2. Comparison of Treated and Untreated OSA**

| Variable                                   | Treated OSA<br>(n=12) | Untreated OSA<br>(n=27) | P     |
|--|-----------------------|-------------------------|-------|
| Male, n (%)                                | 9 (82)                | 21 (81)                 | 0.941 |
| Age, y                                     |                       |                         |       |
| Mean±SD                                    | 66±12                 | 65±10                   | 0.680 |
| Median, IQR                                | 68 (54, 74)           | 67 (60, 72)             |       |
| BMI, kg/m <sup>2</sup>                     |                       |                         |       |
| Mean±SD                                    | 42±15                 | 36±8                    | 0.391 |
| Median, IQR                                | 36 (33, 44)           | 35 (28, 42)             |       |
| NYHA class II/III/IV, n (%)                | 7 (70)                | 14 (54)                 | 0.468 |
| History of DM, n (%)                       | 2 (18)                | 6 (23)                  | 0.999 |
| History of hypertension, n (%)             | 11 (100)              | 18 (69)                 | 0.076 |
| Apnea-hypopnea Index, events/h             |                       |                         |       |
| Mean±SD                                    | 45±38                 | 34±29                   | 0.966 |
| Median, IQR                                | 43 (12, 63)           | 25 (8, 59)              |       |
| Arousal index, events/h                    |                       |                         |       |
| Mean±SD                                    | 56±43                 | 41±29                   | 0.594 |
| Median, IQR                                | 39 (31, 73)           | 31 (21, 55)             |       |
| Mean nocturnal oxygen, %                   |                       |                         |       |
| Mean±SD                                    | 92±4                  | 92±3                    | 0.655 |
| Median, IQR                                | 93 (91, 94)           | 92 (91, 94)             |       |
| Lowest nocturnal oxygen, %                 |                       |                         |       |
| Mean±SD                                    | 78±10                 | 80±9                    | 0.625 |
| Median, IQR                                | 81 (69, 87)           | 84 (76, 86)             |       |
| Change in nocturnal oxygen saturation, %   |                       |                         |       |
| Mean±SD                                    | 4±3                   | 4±2                     | 0.464 |
| Median, IQR                                | 3 (2, 5)              | 4 (2, 5)                |       |
| Percent Sa <sub>o</sub> <sub>2</sub> < 90% |                       |                         |       |
| Mean±SD                                    | 23±37                 | 18±23                   | 0.232 |
| Median, IQR                                | 9 (1, 17)             | 7 (4, 22)               |       |
| Recurred, n (%)                            | 5 (42)                | 22 (82)                 | 0.023 |

Abbreviations as in Table 1.

more, in those with arrhythmia recurrence, there was a trend toward lower nocturnal oxygen saturation (78% versus 83%; *P*=0.092) (Table 3). No significant difference was noted for BMI, age, diabetes, hypertension, or male predominance between the recurrence and nonrecurrence groups.

We then focused specifically on the 25 untreated OSA patients to compare those without arrhythmia recurrence (*n*=5) with those with recurrence (*n*=20). The mean nocturnal fall in oxygen saturation during the sleep study was 8% in untreated patients without recurrence versus 18% in those with recurrence (*P*=0.034) (Figure 2). Also, untreated patients without recurrence spent 4% of the night with an oxygen saturation of <90% versus 23% in patients with recurrence (*P*=0.063) (Figure 2). BMI, age, history of diabetes, and history of hypertension were not greater in untreated OSA patients who had a recurrence compared with those without recurrence, suggesting that these variables may not be responsible for the recurrences of AF (Table 4).

### Discussion

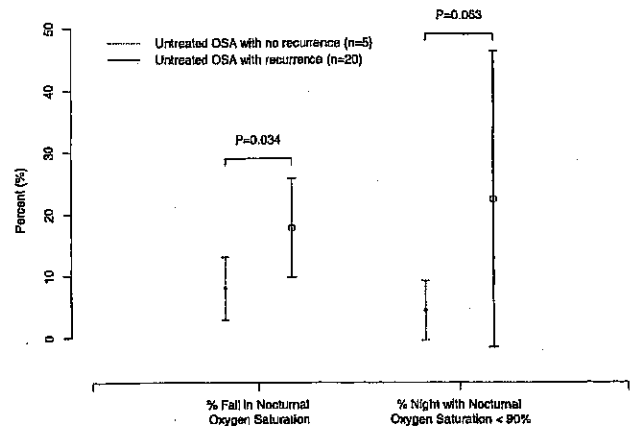
The novel findings of this study are, first, that patients with untreated OSA have a higher risk of recurrence of AF after successful cardioversion than patients without known sleep apnea. Second, appropriate treatment of OSA with CPAP was associated with a significant reduction in arrhythmia recurrence, which appears to be independent of age, BMI, hypertension, or diabetes. Third, the high rate of recurrence is not secondary to differences in age, sex, antiarrhythmic therapy, BMI, functional status, echocardiographic measures, or co-existing diabetes or hypertension. Our data also suggest that the major determinant of recurrence seems to be whether or not patients are treated appropriately for OSA. In those who are untreated, recurrence is higher in those patients with lower nocturnal oxygen saturation. These findings underscore the importance of hypoxemia and insufficient CPAP use during the night and point toward a new and potentially rewarding therapeutic strategy in patients with AF.

Several mechanisms may account for the relationship between recurrent AF and OSA. The autonomic and hemo-

**TABLE 3. Comparison of All OSA Patients Without and With Recurrence**

| Variable                                 | Did Not Recur<br>(n=12) | Recurred<br>(n=27) | P     |
|--|-------------------------|--------------------|-------|
| Male, n (%)                              | 11 (92)                 | 19 (76)            | 0.389 |
| Age, y                                   |                         |                    |       |
| Mean±SD                                  | 67±11                   | 64±10              | 0.531 |
| Median, IQR                              | 69 (58, 74)             | 67 (60, 72)        |       |
| BMI, kg/m <sup>2</sup>                   |                         |                    |       |
| Mean±SD                                  | 39±12                   | 37±11              | 0.662 |
| Median, IQR                              | 35 (33, 44)             | 37 (28, 42)        |       |
| NYHA class I/III/IV, n (%)               | 8 (67)                  | 13 (54)            | 0.721 |
| History of DM, n (%)                     | 3 (25)                  | 5 (20)             | 0.999 |
| History of hypertension, n (%)           | 11 (92)                 | 18 (72)            | 0.232 |
| Medications at dismissal, n (%)          |                         |                    |       |
| Amlodarone                               | 1 (8)                   | 4 (15)             | 0.999 |
| β-Blockers                               | 2 (17)                  | 9 (33)             | 0.446 |
| Dihydropyridines                         | 1 (8)                   | 4 (15)             | 0.999 |
| Nondihydropyridines                      | 3 (25)                  | 6 (22)             | 0.999 |
| Disopyramide                             | 0                       | 0                  | ...   |
| Dofetilide                               | 0                       | 0                  | ...   |
| Flecainide                               | 0                       | 0                  | ...   |
| Digoxin                                  | 5 (42)                  | 5 (19)             | 0.127 |
| Procainamide                             | 0                       | 0                  | ...   |
| Propafenone                              | 2 (17)                  | 8 (30)             | 0.693 |
| Quinidine                                | 0                       | 0                  | ...   |
| Sotalol                                  | 1 (8)                   | 3 (11)             | 0.999 |
| ACE inhibitors                           | 7 (58)                  | 10 (37)            | 0.216 |
| A2 blockers                              | 0                       | 3 (11)             | 0.539 |
| Diuretic                                 | 5 (42)                  | 12 (44)            | 0.872 |
| Apnea-hypopnea index, events/h           |                         |                    |       |
| Mean±SD                                  | 39±35                   | 37±39              | 0.868 |
| Median, IQR                              | 32 (9, 78)              | 33 (11, 52)        |       |
| Arousal index, events/h                  |                         |                    |       |
| Mean±SD                                  | 53±39                   | 42±31              | 0.587 |
| Median, IQR                              | 39 (18, 86)             | 32 (24, 45)        |       |
| Mean nocturnal oxygen, %                 |                         |                    |       |
| Mean±SD                                  | 92±4                    | 92±3               | 0.354 |
| Median, IQR                              | 93 (91, 95)             | 92 (91, 93)        |       |
| Lowest nocturnal oxygen, %               |                         |                    |       |
| Mean±SD                                  | 83±8                    | 78±9               | 0.092 |
| Median, IQR                              | 86 (81, 87)             | 79 (70, 85)        |       |
| Change in nocturnal oxygen saturation, % |                         |                    |       |
| Mean±SD                                  | 4±3                     | 4±3                | 0.943 |
| Median, IQR                              | 4 (2, 5)                | 4 (2, 5)           |       |
| Percent SaO <sub>2</sub> < 90%           |                         |                    |       |
| Mean±SD                                  | 21±38                   | 19±22              | 0.176 |
| Median, IQR                              | 4 (0, 12)               | 9 (4, 22)          |       |
| Treated at all                           | 7 (58)                  | 7 (26)             | 0.052 |
| Treated appropriately                    | 7 (58)                  | 5 (19)             | 0.013 |

Abbreviations as in Table 1.

**Figure 2.** Relationship between oxygen saturation and recurrence of AF in OSA patients. A box-plot comparison of percent fall in nocturnal O<sub>2</sub> saturation (left) and percent of night with O<sub>2</sub> saturations <90% (right) between the untreated OSA patients with recurrence of AF and those without (mean±SD).

dynamic responses to intermittent nocturnal obstructive apneas may be arrhythmogenic. Hypoxemia and hypercapnia have direct adverse effects on cardiac electrical stability<sup>10,11</sup> and also activate the chemoreflexes, resulting in sympathetic vasoconstriction and increased blood pressure.<sup>12</sup> Furthermore, the marked increases in intrathoracic pressure associated with inspiration against an obstructed airway result in abrupt and substantial increases in transmural pressure gradient<sup>13–15</sup> and distortion of cardiac configuration.<sup>16,17</sup> Increases in transmural pressure gradient coupled with the increased afterload resulting from sleep apnea-induced vasoconstriction may contribute to an increase in left atrial dimension. Stimulation of atrial stretch-responsive channels could in turn predispose to AF through a variety of mechanisms.<sup>18,19</sup> There is also evidence linking the intermittent hypoxemia of OSA to pulmonary vasoconstriction and increased pulmonary artery pressures.<sup>20,21</sup> These hemodynamic, neurohumoral, and metabolic stresses, together with increases in circulating catecholamines and inflammatory mediators, may act synergistically to heighten the risk for AF in these patients.

The clearest data implicating the severity of hypoxemia in the recurrence of AF is evident in the 25 OSA patients who had not been treated at all. In these patients, the recurrence rate was in excess of 80%. Of the 25 untreated patients, the 20 patients who experienced a recurrence of AF had a lower nocturnal oxygen saturation nadir, and the duration of the night spent with an oxygen saturation of <90% was 5-fold greater than in those with untreated OSA who remained in normal sinus rhythm at 1 year after cardioversion. Because BMI, age, diabetes, and hypertension could each predispose to recurrence of AF, it is very important that these measures were not greater in the untreated OSA patients in whom AF recurred than in those who remained in normal sinus rhythm. It is also important to note that it is not possible to evaluate the influence of all potentially relevant factors on recurrence of AF, including extent of therapeutic compliance with CPAP.

**TABLE 4. Comparison of Untreated OSA Patients Without and With Recurrence**

| Variable                                    | Did Not Recur (n=5) | Recurred (n=20) | P     |
|---|---------------------|-----------------|-------|
| Male, n (%)                                 | 4 (80)              | 15 (79)         | 0.999 |
| Age, y                                      |                     |                 |       |
| Mean±SD                                     | 69±11               | 63±10           | 0.297 |
| Median, IQR                                 | 71 (64, 73)         | 64 (57, 71)     |       |
| BMI, kg/m <sup>2</sup>                      |                     |                 |       |
| Mean±SD                                     | 37±10               | 36±8            | 0.973 |
| Median, IQR                                 | 35 (29, 44)         | 36 (29, 41)     |       |
| NYHA class II/III/IV, n (%)                 | 2 (40)              | 10 (53)         | 0.999 |
| History of DM, n (%)                        | 2 (40)              | 3 (16)          | 0.271 |
| History of hypertension, n (%)              | 4 (80.0)            | 13 (68)         | 0.999 |
| Medications at dismissal, n (%)             |                     |                 |       |
| Amlodarone                                  | 0                   | 3 (15)          | 0.999 |
| β-Blockers                                  | 1 (20)              | 8 (40)          | 0.621 |
| Dihydropyridines                            | 0                   | 1 (5)           | 0.999 |
| Nondihydropyridines                         | 1 (20)              | 4 (20)          | 0.999 |
| Disopyramide                                | 0                   | 0               | ...   |
| Dofetilide                                  | 0                   | 0               | ...   |
| Flecainide                                  | 0                   | 0               | ...   |
| Digoxin                                     | 2 (40)              | 3 (15)          | 0.252 |
| Procaïnamide                                | 0                   | 0               | ...   |
| Propafenone                                 | 1 (20)              | 6 (30)          | 0.999 |
| Quinidine                                   | 0                   | 0               | ...   |
| Sotalol                                     | 1 (20)              | 1 (5)           | 0.367 |
| ACE inhibitors                              | 2 (40)              | 9 (45)          | 0.999 |
| A2 blockers                                 | 0                   | 3 (15)          | 0.999 |
| Diuretic                                    | 1 (20)              | 10 (50)         | 0.341 |
| Apnea-hypopnea index, events/h              |                     |                 |       |
| Mean±SD                                     | 39±42               | 36±25           | 0.840 |
| Median, IQR                                 | 10 (8, 82)          | 31 (15, 55)     |       |
| Arousal index, events/h                     |                     |                 |       |
| Mean±SD                                     | 51±46               | 41±25           | 0.944 |
| Median, IQR                                 | 30 (18, 86)         | 32 (24, 55)     |       |
| Percent Sao <sub>2</sub> < 90%              |                     |                 |       |
| Mean±SD                                     | 4±5                 | 23±24           | 0.063 |
| Median, IQR                                 | 4 (1, 6)            | 9 (5, 42)       |       |
| Nocturnal fall in O <sub>2</sub> saturation |                     |                 |       |
| Mean±SD                                     | 8±5                 | 18±8            | 0.034 |
| Median, IQR                                 | 9 (5, 12)           | 17 (12, 26)     |       |

Abbreviations as in Table 1.

It is relevant that in the 79 "non-OSA" patients who did not have a sleep study, BMI averaged 30 kg/m<sup>2</sup>, indicating a high prevalence of obesity. In the general population, the estimated prevalence of significant OSA is 24% in men and 9% in women 30 to 60 years old<sup>22</sup> and is even higher when associated with obesity or cardiovascular disease such as hypertension. Thus, it is quite likely that a very substantial percentage of the 79 "non-OSA" postcardioversion control

patients actually had sleep apnea. Given the high recurrence rate in the patients with known untreated OSA, it would be reasonable to assume that the difference in the recurrence at 12 months would be even more striking if recurrence were estimated exclusively in those patients confirmed on polysomnography to be free of significant OSA, in whom a lower recurrence would be expected.

**Clinical Implications**

The prevalence of AF is high and rising.<sup>23</sup> This increasing prevalence may be linked in part to the increasing obesity and consequent high prevalence of OSA in the general population. OSA affects ≈10 to 15 million people, and a large proportion of sleep apnea patients remain undiagnosed.<sup>24</sup> Given the high prevalence of sleep apnea and the emerging epidemics of obesity and AF, any pathogenetic relationship between OSA and AF will have profound implications for both diseases. Our data identify an increased risk of AF in untreated sleep apnea.

We propose that patients with AF, particularly those who are obese, should be screened for OSA, because OSA is treatable and successful treatment may reduce the risk for arrhythmia. Similarly, patients with OSA may benefit from screening for AF, because both OSA and AF predispose to stroke and heart failure.

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