Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery

The PRESAGE Trial

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Objective: We performed a prospective, randomized clinical study to assess whether prophylactic treatment with metoprolol or losartan, initiated soon after lung cancer surgery in patients with elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, reduces the incidence of postoperative atrial fibrillation.

Background: Postoperative atrial fibrillation is a well recognized complication after lung cancer surgery, with an incidence as high as 30%. Perioperative increase of NT-proBNP has been demonstrated to be a strong independent predictor of postoperative atrial fibrillation in this setting.

Methods: NT-proBNP concentration was measured 24 hours before surgery and soon after surgery in 1116 patients. Three hundred twenty (29%) patients showed a high NT-proBNP value and were enrolled: 108 were assigned to the metoprolol group, 102 to the losartan group, and 110 to the control group.

Results: Overall, the incidence of postoperative atrial fibrillation was 20% (n = 64); it was significantly lower in the metoprolol and losartan groups compared with the control group [6%, 12%, and 40%, respectively; relative risk 0.19, 95% confidence intervals (CIs), 0.09–0.37; $P < 0.001$ in the metoprolol group; and 0.29, 95% CI, 0.16–0.52; $P < 0.001$ in the losartan group). No significant difference was found when the metoprolol and losartan groups were directly compared ($P = 0.21$).

Conclusions: A prophylactic treatment with metoprolol or losartan, initiated soon after lung cancer surgery in patients with high NT-proBNP levels, significantly reduced the occurrence of postoperative atrial fibrillation.

Keywords: losartan, lung cancer surgery, metoprolol, NT-proBNP, postoperative atrial fibrillation

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Postoperative atrial fibrillation (PAF) is a well recognized complication of lung cancer surgery, with an incidence ranging from 2% to 4% after wedge resection, to 10% to 15% after lobectomy, and to 20% to 30% after pneumonectomy.[1] Postoperative atrial fibrillation has been associated with increased intensive care unit and hospital length of stay, morbidity, mortality, hospital readmission, and long-term risk of stroke.[2–4] Hence, prediction and prevention of PAF represent very important goals from a clinical point of view.[5] Several pharmacologic strategies have been proposed for the prevention of PAF with varying degrees of success.[1–3,6–10] However, their use involves some risk related to untoward effects, and increase of costs, particularly when applied indiscriminately to all patients scheduled for lung cancer surgery.[1,2,6–10] Therefore, a targeted prophylactic therapy for selected high-risk patients only remains a challenging goal.

In a previous study, we demonstrated that an increase of N-terminal pro-brain natriuretic peptide (NT-proBNP) before or soon after surgery for lung cancer was a strong independent predictor of PAF.[11] Its accuracy to identify patients at risk of developing PAF in this clinical setting was then confirmed by the following studies.[5,12–14] These results strongly indicate that NT-proBNP may help to select patients at risk who may benefit the most from a preventive strategy.

Beta-blockers may reduce PAF incidence after cardiac surgery and after lung resection, most likely, thanks to the decrease of beta-adrenergic overactivity involved in the genesis of post-operative arrhythmias.[7,8,15,16] It has also been demonstrated that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) may prevent atrial fibrillation in patients with heart failure and hypertension, and after myocardial infarction and electrical cardioversion.[17–22]

Moreover, both beta-blockers and ACEI/ARBs have been shown to rapidly decrease natriuretic peptide levels in heart failure patients.[23–29]

On these bases, we performed a prospective, single-center, randomized clinical trial to assess whether prophylactic treatment with either metoprolol or losartan reduces the incidence of PAF in high-risk patients undergoing lung cancer surgery, selected according to elevated NT-proBNP plasma levels in the perioperative period. Moreover, we investigated whether their possible prophylactic effect might be associated with changes in NT-proBNP levels in the days following the beginning of the treatment.

METHODS

Study Population

Between January 1, 2009 and June 30, 2013, we screened all patients consecutively scheduled for lung cancer surgery at our institution. Age at least 18 years and evidence of elevated NT-proBNP value, either before or soon after surgery, were the only

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inclusion criteria. Known hypersensitivity and/or intolerance to metoprolol or losartan, history of heart failure, left ventricular ejection fraction less than 50% echocardiography (ECHO), permanent atrial fibrillation, current therapy with antiarrhythmics, beta-blockers, ARBs and ACEI, and systolic blood pressure below 95 mm Hg in the first 12 hours after surgery were considered as the exclusion criteria. Additional exclusion criteria were history of sick sinus syndrome, atrioventricular block grade II or greater, heart rate below 65 beats/min in the first 12 hours after surgery, history of bronchial asthma, severe bronchopneumopathy, evidence of bronchospasm, or prolonged (>12 hours) mechanical ventilation after surgery. All patients included were in stable clinical condition and in good performance status. The investigation conformed with the principles of the Declaration of Helsinki.[30] The local Ethics Committee approved the protocol, and informed written consent was obtained from all patients. The study has been registered (ClinicalTrial.gov number NCT01281787). No extramural funding was used to support this work.

Study Protocol

Clinical evaluation, electrocardiogram, echocardiogram, chest x-ray, and pulmonary function tests were part of the preoperative assessment. Plasma NT-proBNP concentration was measured in all patients 24 hours before and within 1 hour after surgery. Additional daily samples were taken in the following 2 days. Patients showing high NT-proBNP levels at baseline or soon after surgery were randomly assigned in a 1:1:1 ratio to receive metoprolol (starting dose 25 mg bid; target dose 100 mg bid; metoprolol group), losartan (starting dose 12.5 mg bid; target dose 50 mg/d; losartan group), and no therapy (control group). Randomization was based on computer-generated random numbers. The therapy was started within 12 hours after surgery and was continued for the duration of hospital stay. All patients remained under continuous electrocardiographic monitoring for at least 72 hours after surgery; then, they underwent daily clinical and electrocardiographic evaluation until discharge. Treatment of PAF was left to the discretion of the referring cardiologist, as directed by the international guidelines.[31]

NT-proBNP Measurement

For determination of the serum NT-proBNP levels, blood samples were centrifuged at 1000*g* for 10 minutes and stored at −30°C until analysis was performed. NT-proBNP was measured using a radial partition immunoassay (Stratus CS; Siemens

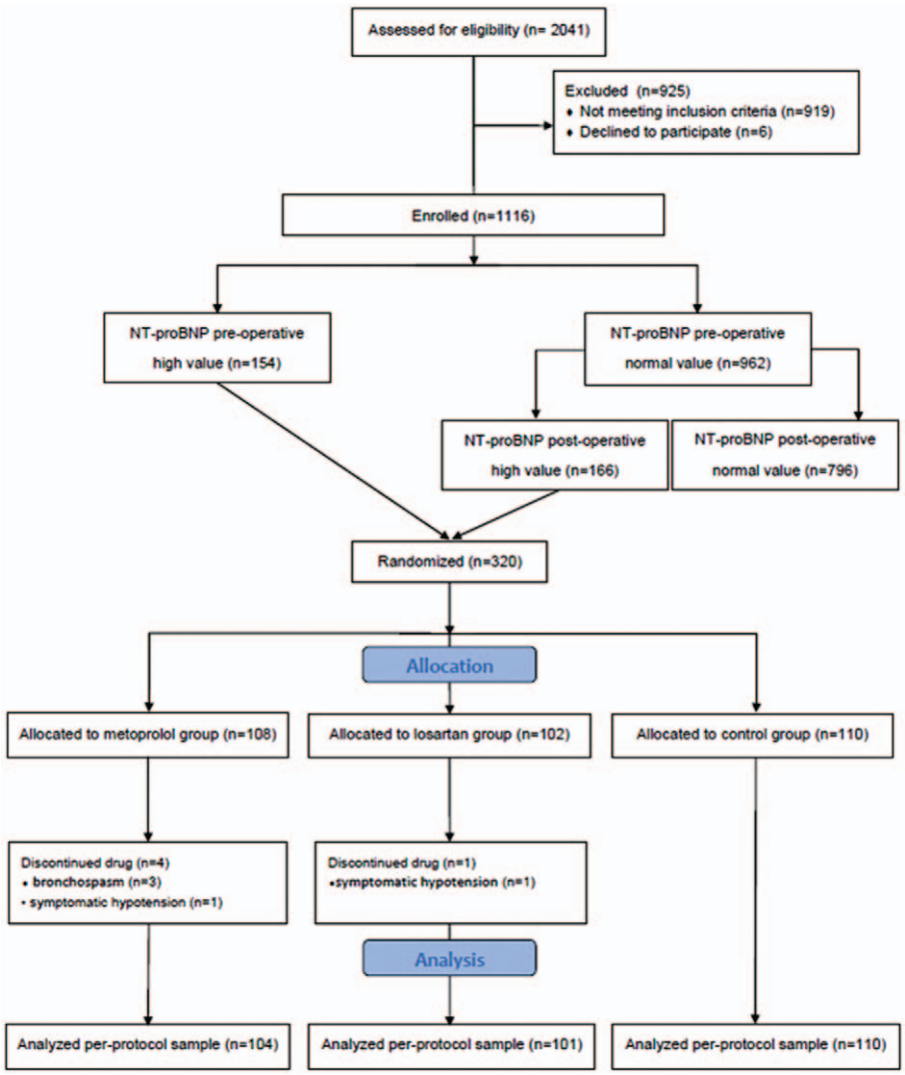

FIGURE 1. Consort flow diagram of the PRESAGE study.

Healthcare Diagnostic, Deerfield, IL). We used different cut-off levels according to sex and age: 63.9 ng/L for men and 125 ng/L for women aged 49 years or less, 125 ng/L for men and 186 ng/L for women aged from 50 to 59 years, and 194 and 204 ng/L for men and women aged at least 60 years, as shown by the previous study.[11]

Study Endpoints

The primary endpoint of the study was the occurrence of PAF during hospitalization. Any documented episode of PAF lasting at least for 30 seconds or for the duration of the ECG recording (if <30 s) were considered.[2] The occurrence of PAF in patients showing high baseline NT-proBNP value, and in those patients in whom it increased soon after surgery was also evaluated separately as a secondary endpoint.

Statistical Analysis

We based calculation of the sample size on a power analysis that assumed an expected PAF incidence of 60% in the control group, similar to that previously reported for patients with elevated NT-proBNP in the operative period.[11] The inclusion of 100 patients in each group allowed for an 85% power to deem as significant, with a type I error of 0.025 and an incidence reduction to 40% [20% absolute and 33% relative risk (RR) reduction] in at least one of the treated groups. Continuous data are reported as mean ± SD and were compared by *t* test or analysis of variance (ANOVA), as appropriate. Variables not normally distributed are presented as the median and interquartile range (IQR). Categorical data are presented as absolute values and percentages. The clinical characteristics of the 3 groups were compared by using the ANOVA for continuous variables and the chi-square test for categorical variables. Fisher exact test was employed when the number of expected frequencies in 1 cell was below 5. The analysis of covariance for repeated measures was used to compare the time course of NT-proBNP values in the 3 groups. Unadjusted RR of PAF in the treated groups were estimated by Log-binomial models, instead of logistic regression, because event occurrence was relatively high (>10%), and therefore the odds ratio (OR) might have resulted in an overestimation of RR.[32] To determine the benefits of therapy with metoprolol or losartan, we calculated the number of patients needed to be treated (NNT) to prevent 1 patient from developing PAF. To determine the risk of side effects associated with the therapy, we calculated the number of patients needed to be treated for every additional patient to be harmed (NNH). All calculations were computed with the aid of the SAS software package (Version 9.02; SAS Institute Inc, Cary, NC).

RESULTS

A total of 2041 patients were initially screened and 1116 patients were enrolled. Of them, 154 (14%) patients showed a presurgery high NT-proBNP value and were considered eligible for randomization. Of the remaining 962 patients with a presurgery-negative NT-proBNP value, 166 (15%) patients increased NT-proBNP soon after surgery and were considered eligible for randomization. Therefore, a total of 320 patients were randomized: 108 patients were assigned to the metoprolol group, 102 to the losartan group, and 110 to the control group. In 4 patients in the metoprolol group and in 1 patient in the losartan group, intervention was withdrawn for adverse effects; thus, 315 patients completed the study. A detailed flow diagram of the study is given in Figure 1.

Clinical and demographic characteristics of patients with normal (n = 796) and increased (n = 320) NT-proBNP value are reported in Table 1. Notably, patients with increased NT-proBNP had worse pulmonary function tests at presurgery evaluation.

TABLE 1. Clinical and Demographic Characteristics of Enrolled Population

	NT-proBNP		
	Normal (n = 796)	High (n = 320)	*P*
Age (y)	60 ± 11	63 ± 10	0.091
Male sex, n (%)	443 (56)	176 (55)	0.895
Hypertension, n (%)	159 (20)	43 (13)	0.013
CAD, n (%)	18 (2)	13 (4)	0.146
Diabetes, n (%)	84 (10)	27 (8)	0.338
Hypercolesterolemia, n (%)	103 (13)	34 (11)	0.335
Current or past smokers, n (%)	494 (62)	185 (58)	0.388
History of paroxysmal AF, n (%)	16 (2)	2 (1)	0.055*
Previous chemotherapy, n (%)	226 (28)	37 (12)	<0.001
Previous chest radiotherapy, n (%)	52 (6)	16 (5)	0.407
Creatinine clearance,† (mL/min)	100 ± 25	100 ± 28	0.722
LVEF (%)	64 ± 7	64 ± 5	0.091
FEV1 (% predicted)	96 ± 22	89 ± 21	<0.001
FVC (% predicted)	93 ± 18	88 ± 19	<0.001
DLCO (% predicted)	80 ± 20	73 ± 24	<0.001
Type of operation			
Pneumonectomy, n (%)	66 (8)	43 (13)	0.012
Lobectomy, n (%)	334 (42)	146 (46)	0.293
Bilobectomy, n (%)	22 (3)	12 (4)	0.500
Single wedge resection, n (%)	279 (35)	95 (30)	0.100
Multiple wedge resections, n (%)	95 (12)	24 (7)	0.039

Data are expressed as numbers (%) or mean ± SD.
*By Fisher exact test.
†Calculated by Cockcroft-Gault formula.
CAD indicates coronary artery disease; DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory ventilation in 1 second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction.

Baseline characteristics of the 320 patients randomized to the 3 study groups are shown in Table 2. No significant differences were identified among the groups.

Overall, PAF occurred in 95/1116 (9%) patients, with 78% of events occurring during the first 3 days [median time 2 (IQR 1–3) d]. In NT-proBNP-negative patients, PAF occurred in 31 (4%) cases; it occurred in 64 (20%) cases in NT-proBNP-positive patients (Fig. 2, upper panel). In the latter group, PAF incidence was significantly higher in patients with elevated presurgery NT-proBNP than in those with only postsurgery elevated NT-proBNP value (Fig. 2, lower panel).

Medications were well tolerated by almost all patients. Only 5 patients withdrew from treatment: 4 patients in the metoprolol group (due to bronchospasm in 3 and to symptomatic hypotension in 1; NNH = 27), and 1 in the losartan group (due to symptomatic hypotension; NNH = 102). Two patients who withdrew metoprolol subsequently experienced anemia requiring blood transfusion, and 1 experienced acute respiratory failure.

The incidence of PAF was significantly lower in the 2 treated groups than in the control group, with the lowest incidence observed in metoprolol-treated patients (Fig. 3, upper panel). Again, in each group, PAF incidence was higher in patients showing a presurgery high NT-proBNP than in those who increased NT-proBNP after surgery (Fig. 3, lower panel). When the incidence of PAF was evaluated by intention-to-treat analysis, similar results were obtained (7%, 12%, and 40% in metoprolol, losartan, and control groups, respectively; $P < 0.001$). Unadjusted RR in the metoprolol group was 0.19 (95% CI, 0.09–0.37; $P < 0.001$; NNT = 3.0) when compared with the control group. It was 0.29 (95% CI, 0.16–0.52; $P < 0.001$; NNT = 3.5) in the losartan group. No significant difference was found when losartan group was compared with the metoprolol group (RR 1.59; 95% CI, 0.68, 3.73; $P = 0.21$).

TABLE 2. Clinical and Demographic Characteristics of the 3 Study Groups

	Metoprolol (n = 104)	Losartan (n = 101)	Control (n = 110)	*P*
Age (y)	62 ± 11	62 ± 10	62 ± 10	0.80
Male sex, n (%)	55 (54)	59 (58)	59 (54)	0.68
Hypertension, n (%)	16 (15)	15 (15)	13 (12)	0.73
Coronary artery disease, n (%)	6 (6)	3 (3)	4 (4)	0.60∗
Diabetes, n (%)	6 (6)	8 (8)	11 (10)	0.52
Hypercolesterolemia, n (%)	6 (6)	13 (13)	14 (13)	0.16
Current or past smokers, n (%)	51 (49)	65 (64)	67 (61)	0.06
History of paroxysmal AF, n (%)	2 (2)	1 (1)	0 (0)	0.35*
Previous chemotherapy, n (%)	15 (14)	11 (11)	11 (10)	0.57
Previous chest radiotherapy, n (%)	2 (2)	7 (7)	7 (6)	0.19*
Creatinine clearance,† (mL/min)	80 ± 25	84 ± 37	84 ± 62	0.80
LVEF (%)	61 ± 6	62 ± 5	62 ± 4	0.51
Left atrial diameter (mm)	37 ± 4	37 ± 6	37 ± 4	0.85
TAPSE (mm)	24 ± 2	23 ± 2	24 ± 3	0.78
FEV1 (% predicted)	91 ± 22	89 ± 21	88 ± 22	0.60
FVC (% predicted)	88 ± 21	88 ± 19	87 ± 18	0.92
DLCO (% predicted)	76 ± 27	74 ± 23	69 ± 22	0.38
Type of operation				
Pneumonectomy, n (%)	15 (14)	12 (12)	16 (15)	0.82
Lobectomy, n (%)	49 (47)	44 (43)	50 (45)	0.87
Bilobectomy, n (%)	4 (4)	4 (4)	4 (4)	0.99*
Single wedge resection, n (%)	24 (23)	35 (35)	34 (31)	0.17
Multiple wedge resections, n (%)	6 (6)	12 (12)	6 (5)	0.18
Laterality (right), n (%)	60 (58)	66 (65)	61 (55)	0.31
High NT-proBNP, n (%)				
Before surgery	51 (49)	53 (52)	48 (44)	0.43
After surgery	104 (100)	101 (100)	110 (100)	1.00
Drug mean dose (mg/d)	148±55	45±14	–	–
Drug dose range (mg/d)	50-200	12.5-100	–	–

Data are expressed as numbers (%) or mean ± SD.
*By Fisher exact test.
†Calculated by Cockcroft-Gault formula.
CAD indicates coronary artery disease; DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory ventilation in 1 second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

Patients of the control group showed a longer postoperative length of stay and experienced a more complicated in-hospital clinical course than those of the 2 treated groups (Table 3).

Figure 4 shows NT-proBNP levels during the perioperative course in the 3 study groups. A similar progressive increase from baseline to 48 hours after surgery was observed in treated and not treated patients (P for trend < 0.001). No difference in NT-proBNP levels was found among the 3 groups at each timing of sampling.

DISCUSSION

The main finding of our study was that a prophylactic treatment with either metoprolol or losartan, initiated soon after lung surgery in high-risk patients, significantly reduced the occurrence of PAF. Moreover, we confirmed that increased levels of NT-proBNP are strong predictors of PAF, and can be useful for selection of high-risk patients who may benefit from a preventive therapy.

Postoperative atrial fibrillation is a frequent arrhythmia after thoracic surgery for lung cancer, with a reported incidence of up to 30%, and with occurrence in most cases in the first 4 postoperative days. Its onset has been associated with an increased risk of in-hospital stroke, heart failure, myocardial infarction, thromboembolism, and death.[1–3] More recently, a significant association between PAF and long-term risk of ischemic stroke has been documented in a large cohort of patients, after both cardiac and noncardiac surgery.[4]

Although prophylaxis against PAF after cardiac surgery has been extensively studied, data pertaining to its prevention after lung cancer surgery are more limited. To date, evidence from prospective, randomized controlled studies refers to the use of beta-blockers, diltiazem, verapamil, amiodarone, statins, and intravenous magnesium.[2] These pharmacologic strategies have shown to reduce the incidence of PAF after pulmonary resection with varying degrees of success.[2,10] However, these treatments have been frequently associated with a substantial incidence of adverse effects. As a result, recently published guidelines highlight that there is inadequate evidence to recommend routine prophylaxis against PAF in all patients undergoing lung cancer surgery, and that the kind of preventive strategy should be evaluated on a case-by-case basis.[2] Moreover, a preventive approach extended to all patients referred for surgery may have an unfavorable risk/benefit profile, with possible exposure to side effects of patients less prone to develop PAF. Therefore, there is a strong need for the identification of high-risk patients who require a close postoperative monitoring and who may benefit from a preventive antiarrhythmic therapy. Although several studies have been performed to determine independent predictors of PAF, the only widely validated risk factor thus far is advanced age.[14,33]

We previously demonstrated that high perioperative NT-proBNP levels are strong independent predictors of PAF in patients undergoing lung cancer surgery.[11] The present study confirms that NT-proBNP accurately identifies patients more prone to develop PAF (20% of our overall population), allowing us to exclude the majority (80%) of patients from a prophylactic treatment. Indeed, the incidence of PAF in NT-proBNP-negative patients, who were excluded from the present study, was significantly lower when compared with the control group (4% vs 40%; $P < 0.001$).

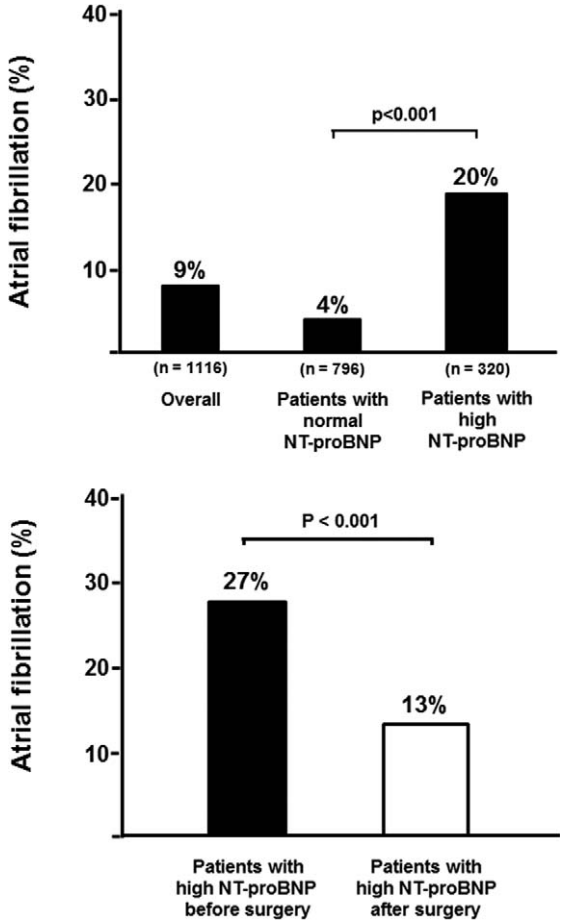

FIGURE 2. Upper panel: incidence of postoperative atrial fibrillation in the overall study population, and in patients with normal and high NT-proBNP value. Lower panel: incidence of postoperative atrial fibrillation in patients with high NT-proBNP stratified according to its positivity before or after surgery.

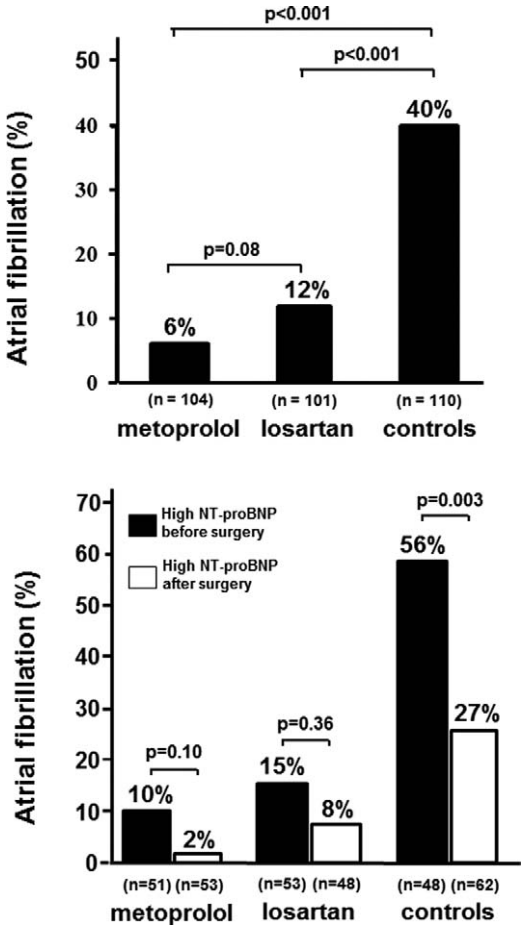

FIGURE 3. Upper panel: incidence of postoperative atrial fibrillation in the 3 study groups. Lower panel: incidence of postoperative atrial fibrillation in the 3 study groups stratified according to NT-proBNP high level before or after surgery.

In our study, both metoprolol and losartan significantly reduced the incidence of PAF (absolute risk reduction of 32% and 28%, respectively), with a low NNT. Notably, the lower incidence of PAF was associated with a shorter postoperative length of stay and a lower incidence of postoperative adverse events. Both drugs were well tolerated; indeed, only 1.5% of patients discontinued the drugs for symptomatic hypotension or bronchospasm.

The results of our study also confirm that PAF is closely associated with high NT-proBNP levels, both when preoperative and postoperative values are considered, with a stronger association for preoperative values. For this reason, NT-proBNP was measured at these two time points and patients with at least 1 high value were included in the study. Although we did not stratify our randomization process for the different timing of NT-proBNP positivity detection, the distribution was well matched in the 3 groups (Table 2) and the response to metoprolol and losartan, in terms of PAF incidence reduction, was similar (Fig. 3).

Beta-blockers have been reported to prevent PAF after general thoracic surgery. In the cardiac surgery setting, they have been recommended for the prevention and treatment of PAF after coronary artery bypass graft surgery (class 1 recommendation; level of evidence: A).[31,34,35] However, their use is more limited by side effects than other drugs, and thus they are less broadly applicable to a general thoracic surgery population.[2,7] Indeed, many patients undergoing lung cancer surgery have a history of smoking and some respiratory disease such as emphysema and chronic obstructive pulmonary disease. Therefore, when we use beta-blockers in patients after lung surgery, the presence of respiratory tract disorders (eg, bronchospasm, atelectasis), in addition to the general risk of inducing severe bradycardia and hypotension, is of concern,[1,8,36] and unselective administration of such medications seems to not be justified. Only 2 studies, involving small populations, have evaluated the efficacy of beta-blockers for prophylaxis of PAF after lung cancer surgery. In a prospective, randomized, double-blind study, involving 30 patients the incidence of PAF was significantly lower in metoprolol-treated patients than in controls.[15] In another randomized, placebo-controlled study including 99 patients undergoing lobectomy (46%), pneumonectomy (22%), or esophagectomy (31%), the incidence of postoperative tachyarrhythmias (including PAF, atrial flutter, sinus tachycardia, supraventricular tachycardia, and ventricular tachycardia) requiring treatment was lower in the propranolol group, compared with the placebo group. However, this study showed only a trend towards significance ($P = 0.07$) and the propranolol group suffered a 50% rate of hypotension.[8]

Angiotensin-converting enzyme inhibitors and ARBs display many actions which could mitigate the causes of PAF including

TABLE 3. Postoperative Complications in the 3 Study Groups

	Metoprolol (n = 104)	Losartan (n = 101)	Control (n = 110)	*P*
Acute pulmonary edema, n (%)	0 (0)	0 (0)	1 (1)	0.82*
Anemia requiring blood transfusion, n (%)	16 (16)	13 (13)	23 (21)	0.30
In-Hospital death, n (%)	0 (0)	0 (0)	0 (0)	0.50*
TIA or stroke, n (%)	0 (0)	1 (1)	2 (2)	0.26*
Acute coronary syndrome, n (%)	1 (1)	0 (0)	2 (1)	0.71*
Cardiac arrest, n (%)	0 (0)	1 (1)	0 (0)	0.16*
Reintervention, n (%)	2 (2)	2 (2)	5 (5)	0.50*
Sepsis, n (%)	4 (4)	6 (6)	7 (7)	0.65*
Need for CPAP, n (%)	4 (4)	6 (6)	8 (8)	0.55*
Acute kidney injury (stage ≥2–3 AKIN), n (%)†	1 (1)	1 (1)	4 (4)	0.35*
Postoperative length of stay (d)	6.8 ± 4	7.2 ± 5	8.6 ± 5	0.019
Cumulative events, n (%)	28 (27)	30 (30)	52 (47)	0.002

Data are mean ± SD.
*By Fisher exact test.
†According to AKIN classification.
AKIN indicates Acute Kidney Injury Network; CPAP, continuous positive airway pressure; TIA, transient ischemic attack.

modification of sympathetic tone and inflammation cascade in addition to having direct antiarrhythmic properties.[17,37] They have been found to reduce the risk of atrial fibrillation in various clinical settings including postmyocardial infarction and after direct current cardioversion.[22] In the only randomized trial that has evaluated ACEI for this indication, their use, either alone or in combination with an ARB, was significantly associated with a lower risk of PAF in patients undergoing cardiac surgery.[38] In a retrospective study including a large cohort of patients undergoing major noncardiac surgery, perioperative administration of ACEI and ARBs was associated with a lower risk of PAF.[39] However, data on the efficacy of ACEI/ARBs for preventing PAF have been scant thus far, particularly after lung resection.[16] Our study further supports the efficacy of both metoprolol and losartan in this particular clinical setting.

The electrophysiological mechanisms involved in PAF are not fully disclosed. After cardiac surgery, PAF may be a result of sympathetic nervous system activation, enhanced activity of the renin-angiotensin-aldosterone system, or postoperative inflammation.[7,40–43] Fewer data exist regarding mechanisms of PAF after pulmonary resection; it may be associated with various surgical stresses, such as excitation of sympathetic nerve activity, right ventricular overload, hypoxia, and systemic inflammatory responses.[2,44]

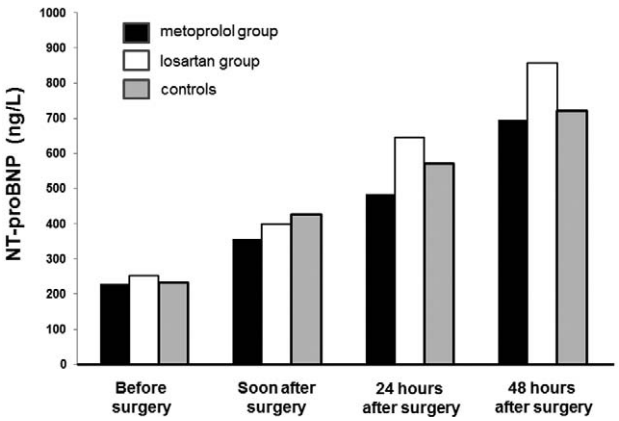

FIGURE 4. The NT-proBNP levels during the perioperative course in the 3 study groups. *P* for trend less than 0.001 for all groups.

The NT-proBNP level increases have been found in several clinical conditions, such as left ventricular hypertrophy, hypertension, left atrial enlargement, and heart failure.[45] In 2004, Wazni et al reported that increased BNP levels may predict PAF in patients undergoing cardiac surgery.[46] More recently, we demonstrated that NT-proBNP is a strong independent predictor of PAF in more than 400 patients undergoing thoracic surgery for lung cancer.[11] Thus far, an accumulating body of published data has illustrated that increased levels of natriuretic peptides predict postoperative major adverse clinical events, in general, and specifically PAF, both in cardiac and noncardiac surgery. [5,13,14,46–50] The mechanisms underlying the link between high NT-proBNP values and increased PAF risk remain unclear. Natriuretic peptides may increase with chronic conditions that include aging, atrial fibrosis, and inflammation—factors also known to contribute to PAF occurrence.[13,51] Elevated preoperative natriuretic peptide levels may be caused by right ventricular overload and right ventricular diastolic dysfunction in patients with COPD and other chronic respiratory diseases.[48] Notably, in our population, patients with a high NT-proBNP value showed a worse pulmonary function test at preoperative assessment. Thus, the high NT-proBNP levels before surgery may reflect a baseline electrophysiological substrate predisposing to PAF. In addition, several intraoperative factors are able to trigger PAF. Indeed, 50% of our study population increased NT-proBNP levels early after surgery. This rise was possibly due to the procedure itself.

A postoperative increase in NT-proBNP may be caused by an abrupt increase of right ventricular overload due to a decreased volume of the pulmonary vascular bed caused by pulmonary resection, particularly after extensive lung resection. However, as an increase in the marker was also observed in patients undergoing less extensive surgery, other mechanisms are possibly involved.

We hypothesized that drugs that may lower high baseline NT-proBNP levels after surgery could protect against PAF. However, despite the fact that both metoprolol and losartan have been shown to rapidly reduce natriuretic peptide levels in several clinical conditions,[23–29] we did not observe any significant reduction in NT-proBNP in the first 2 days of treatment when compared to the control group. Conversely, NT-proBNP levels increased in parallel after surgery in all the 3 study groups, suggesting that the prevention of PAF by metoprolol and losartan is not mediated by an acute reduction in NT-proBNP levels. Hence, high perioperative NT-proBNP value in this setting seems to represent a risk marker, rather than a risk factor of PAF.

Our study has some limitations. First, although our trial was designed as a prospective, randomized controlled study, it included a population admitted to a single center. The lack of placebo administration was a potential second limitation. Although patients' allocation to metoprolol, losartan, and control group was randomized, treatment was not blinded, for need of drug titration. However, it is unlikely that a placebo effect could have influenced an objective endpoint such as the occurrence of PAF. Third, despite the fact that we have chosen metoprolol and losartan because they are the agents more extensively investigated in this setting among beta-blockers and ACEI/ARBs, we cannot extrapolate a possible class effect from our results. Moreover, as metoprolol and losartan were studied separately, we cannot exclude that a combination of lower doses of these 2 drugs could have resulted in a synergistic preventive effect. Fourth, our study was not powered to directly compare the 2 drugs, and we cannot establish which of them has the highest preventive effect. However, the availability of the 2 effective drugs allows us to customize therapy according to patients' characteristics. Fifth, given that our population comprised only patients undergoing lung cancer surgery, the generalizability of these findings to other surgical settings remains uncertain.

CONCLUSIONS

In patients with elevated NT-proBNP levels, a prophylactic treatment with metoprolol or losartan, initiated soon after lung cancer surgery, was well tolerated and significantly reduced the occurrence of PAF.

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