Clinical Investigations

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# Oxidative Status, Inflammation, and Postoperative Atrial Fibrillation With Metoprolol vs Carvedilol or Carvedilol Plus N-Acetyl Cysteine Treatment

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ABSTRACT

*Background:* Atrial fibrillation is associated with inflammation and oxidative stress.

*Hypothesis:* Carvedilol and N-acetyl cysteine (NAC) combination decreases inflammation, oxidative stress, and postoperative atrial fibrillation (POAF) rates more than metoprolol or carvedilol.

*Methods:* Preoperative and postoperative total oxidative stress (TOS), total antioxidant capacity (TAC), and white blood cells (WBC) were measured in metoprolol, carvedilol, or carvedilol plus NAC groups, and association with POAF was evaluated.

*Results:* Preoperative TAC, TOS, and WBC levels were similar among the groups. Postoperative TAC levels were lower in the metoprolol group compared with the carvedilol group (1.0 vs 1.4) or the carvedilol plus NAC group (1.0 vs 1.9) and were also lower in the carvedilol group compared with the carvedilol plus NAC group (all $P < 0.0001$). Postoperative TOS levels were higher in the metoprolol group as compared with the carvedilol (29.6 vs 24.2; $P < 0.0001$) or the carvedilol plus NAC groups ($P < 0.0001$), and were also higher in the carvedilol group as compared with the carvedilol plus NAC group (24.2 vs 19.3; $P < 0.0001$). Postoperative WBC counts were lower in the carvedilol plus NAC group compared with the metoprolol group (12.9 vs 14.8; $P = 0.004$), were similar between the carvedilol and the metoprolol groups (13 vs 14.8) and between the carvedilol plus NAC group and the carvedilol group (both $P > 0.05$). Postoperative TAC, TOS, and WBC were associated with POAF.

*Conclusions:* Carvedilol plus NAC reduced oxidative stress and inflammation compared with metoprolol and decreased oxidative stress compared with carvedilol. Postoperative TAC, TOS, and WBC were associated with POAF.

## Introduction

Cardiopulmonary bypass may cause oxidative stress and inflammation[1] processes that have been shown to be associated with atrial fibrillation.[2–5] Carvedilol is a nonselective β-blocker and N-acetyl cysteine (NAC) is a mucolytic agent. These agents have anti-inflammatory and antioxidant properties,[6–16] and they decreased postoperative atrial fibrillation (POAF) rates in previous studies.[2,17–22] In a randomized study, we have shown that carvedilol plus NAC decreased POAF incidence compared with metoprolol or carvedilol.[23] However, it is not known whether the effect of carvedilol and NAC is associated with changes in the levels of oxidative markers or whether there is a correlation between these markers and the development of POAF.

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Therefore, this study was designed to compare the effects of metoprolol, a β-blocker without antioxidant and anti-inflammatory action, vs carvedilol or carvedilol plus NAC on the markers of oxidative status and inflammation, and to evaluate the relationship between these markers and POAF. This is a prespecified substudy of our randomized study.[23]

## Methods

This was a single-center, prospective, double-blind, randomized study.[23] The overall study population included 311 patients undergoing coronary artery bypass graft (CABG) or combined CABG and valve surgery. Patients undergoing their first cardiothoracic surgery without contraindications to β-blockers or NAC were included. Exclusion criteria were hyperthyroidism, age <18 years, prior cardiac surgery, class III or IV heart failure, previous atrial fibrillation, left atrial diameter >55 mm, left ventricular ejection fraction <0.25,


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Table 1. Preoperative, Postoperative, and Procedural Characteristics

| | Metoprolol (n = 87) | Carvedilol (n = 87) | Carvedilol + NAC (n = 85) | Carv + NAC vs Met, *P* Value | Carv + NAC vs Carv, *P* Value | Carv vs Met, *P* Value |
|---|---|---|---|---|---|---|
| Preoperative characteristics | | | | | | |
| Age, y | 63 ± 10.5 | 63 ± 9.4 | 62 ± 9.2 | 0.83 | 0.98 | 0.90 |
| Male gender (%) | 67 (77) | 63 (72.4) | 65 (76.5) | 1.00 | 0.6 | 0.6 |
| Heart failure (%) | 12 (13.8) | 16 (18.4) | 14 (16.5) | 0.67 | 0.84 | 0.54 |
| Hypertension, (%) | 54 (62.1) | 55 (63.2) | 53 (62.4) | 1.00 | 1.00 | 1.00 |
| Diabetes mellitus, (%) | 35 (40.2) | 37 (42.5) | 35 (41.2) | 1.00 | 0.87 | 0.87 |
| COPD, (%) | 6 (6.9) | 12 (13.8) | 9 (10.6) | 0.42 | 0.64 | 0.21 |
| Clinical presentation | | | | | | |
| Stable angina pectoris (%) | 40 (46) | 41 (47.1) | 31 (36.5) | 1.00 | 0.17 | 1.00 |
| Unstable angina pectoris/ myocardial infarction (%) | 47 (54) | 46 (52.9) | 54 (63.5) | | | |
| Body mass index, kg/m$^2$ | 26 ± 3.9 | 27 ± 3.9 | 26 ± 4.2 | 0.99 | 0.79 | 0.73 |
| Ejection fraction, % | 50 ± 10.3 | 49 ± 12.3 | 49 ± 11.9 | 0.85 | 0.94 | 0.66 |
| Left atrial diameters, mm | 40.4 ± 4 | 40.7 ± 3.8 | 40.9 ± 4.8 | 0.76 | 0.93 | 0.93 |
| Preoperative systolic BP | 119 ± 13 | 120 ± 12 | 118 ± 13 | 0.88 | 0.74 | 0.96 |
| Preoperative diastolic BP | 73 ± 9 | 75 ± 9 | 73 ± 10 | 0.98 | 0.36 | 0.45 |
| Prerandomization heart rate | 73 ± 7 | 71 ± 5 | 72 ± 7 | 0.37 | 0.73 | 0.10 |
| Preoperative heart rate | 70 ± 7 | 69 ± 5 | 69 ± 6 | 0.43 | 0.97 | 0.56 |
| Preoperative medications | | | | | | |
| β-Blocker (before randomization) | 78 (89.7) | 74 (85.1) | 67 (78.8) | 0.06 | 0.32 | 0.49 |
| ACEI and/or ARB | 35 (40.2) | 35 (40.2) | 38 (44.7) | 0.64 | 0.64 | 1.00 |
| Spironolactone | 7 (8) | 13 (14.9) | 14 (16.5) | 1.00 | 0.83 | 0.23 |
| Statin | 20 (23) | 32 (36.8) | 24 (28.2) | 0.48 | 0.25 | 0.07 |
| Procedural and postoperative characteristics | | | | | | |
| Procedure (%) | | | | | | |
| CABG | 80 (92) | 79 (90.8) | 81 (95.3) | 0.53 | 0.37 | 1.00 |
| CABG + MVR | 4 (4.6) | 4 (4.6) | 3 (3.5) | | | |
| CABG + AVR | 3 (3.4) | 4 (4.6) | 1 (1.2) | | | |
| Beating heart surgery (%) | 26 (29.9) | 34 (39.1) | 23 (27.1) | 0.73 | 0.10 | 0.26 |
| Cross-clamp duration, min | 58 ± 21 | 65 ± 27 | 59 ± 23 | 0.98 | 0.33 | 0.24 |
| Bypass duration, min | 109 ± 39 | 109 ± 35 | 104 ± 24 | 0.70 | 0.61 | 0.98 |
| Postoperative systolic BP (48th hour) | 112 ± 17 | 114 ± 14 | 112 ± 13 | 0.97 | 0.54 | 0.67 |
| Postoperative diastolic BP (48th hour) | 64 ± 10 | 63 ± 11 | 61 ± 9 | 0.20 | 0.31 | 0.96 |
| Postoperative heart rate | 93 ± 5 | 87 ± 2 | 86 ± 10 | 0.001 | 0.96 | 0.02 |


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Table 1. *Continued*

| | Metoprolol (n = 87) | Carvedilol (n = 87) | Carvedilol + NAC (n = 85) | Carv + NAC vs Met, *P* Value | Carv + NAC vs Carv, *P* Value | Carv vs Met, *P* Value |
|---|---|---|---|---|---|---|
| Postoperative medications (%) | | | | | | |
| ACEI and/or ARB | 11 (12.6) | 10 (11.5) | 10 (11.8) | 1.00 | 1.00 | 0.81 |
| Spironolactone | 3 (3.4) | 3 (3.4) | 4 (4.7) | 1.00 | 0.71 | 1.00 |
| Statin | 16 (18.4) | 12 (13.8) | 12 (14.1) | 0.53 | 1.00 | 0.41 |
| β-Blocker | 77 (88.5) | 82 (94.3) | 81 (95.5) | 0.32 | 0.72 | 0.56 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVR, aortic valve replacement; BP, blood pressure; CABG, coronary artery bypass graft; Carv, carvedilol; COPD, chronic obstructive pulmonary disease; Met, metoprolol; MVR, mitral valve replacement; NAC, N-acetyl cysteine.
Data are presented as mean ± standard deviation or number (%) of patients.

sepsis, heart rate <60 bpm, systolic blood pressure <90 mm Hg, inflammatory disease, and being already on antiarrhythmic or NAC treatment. According to these criteria, 36 patients were excluded due to previous atrial fibrillation (n = 12), heart rate <60 bpm (n = 10), previous NAC use (n = 10), and hyperthyroidism (n = 4). Measurement of preoperative and postoperative serum oxidative status and inflammation markers were not available in 16 patients. Therefore, 259 patients were included for this substudy.

In brief, patients were randomized to metoprolol succinate plus saline (n = 103), carvedilol plus saline (n = 104), and carvedilol plus NAC (n = 104). Metoprolol and carvedilol were started at doses of 50 mg once daily and 6.25 mg twice daily, respectively. The doses were up-titrated to maximum tolerated doses. The target doses for metoprolol and carvedilol were 200 mg once daily and 25 mg twice daily, respectively. N-acetyl cysteine (Asist, Husnu Arsan, Turkey) was administered intravenously at a dose of 50 mg/kg for 1 hour before surgery and at the same dose for 48 hours after the procedure. In the metoprolol and the carvedilol groups, normal saline solution was infused as placebo. The infusion rate and duration were similar for saline and NAC. Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The detailed information about the study design is given elsewhere.[23] Similar operative techniques were used in all of the patients.

## End Points

The end points were to compare the effects of treatment groups on the change in serum preoperative to postoperative markers of oxidative status and inflammation and to evaluate the relationship between these markers and POAF. Therefore, serum total oxidative stress (TOS), total antioxidant capacity (TAC) levels, and white blood cell (WBC) counts were measured preoperatively and at postoperative 48th hour. Decreased TAC and increased TOS were used as markers of oxidative stress, and WBCs were used as markers of inflammation. TAC and TOS levels were determined with new methods using a spectrophotometric kit (Rel Assay Diagnostics, Gaziantep, Turkey) and were assayed in an autoanalyzer (Olympus AU2700; Olympus, Tokyo, Japan). The results of TAC and TOS were expressed as mmol Trolox equivalent/L and mmol $H_2O_2$ equivalent/L, respectively.[24,25]

## Rhythm Follow-up

The rhythms were followed by continuous electrocardiogram monitoring during intensive care unit stay and by all-day Holter during the rest of hospitalization. A 12-lead electrocardiogram was recorded every morning routinely and whenever the patients had symptoms suggestive of dysrhythmia. Atrial fibrillation was defined as an irregular rhythm with the absence of discrete P waves in the 12-lead electrocardiogram. An atrial fibrillation episode lasting 5 minutes during hospitalization was defined as POAF.[23]

## Statistical Analysis

Categorical variables were expressed as frequency (%) and compared with the $\chi^2$ test. A Kolmogorov-Smirnov test was used to test the distribution of numeric variables, and those with normal distribution were expressed as mean ± standard deviation and were compared with the Student *t* test or analysis of variance as appropriate. Scheffe correction test was used for post hoc pairwise comparison of variables showing normal distribution (postoperative heart rates). On the other hand, those without normal distribution were expressed as median (minimum–maximum) and were compared with the Mann–Whitney *U* test or Kruskal-Wallis test as appropriate. Preoperative to postoperative differences in paired observations in each group were compared with the Wilcoxon rank test (Table 1, Figure 1). A 2-sided *P* value <0.05 was considered significant. SPSS version 11.0 (SPSS, Inc., Chicago, IL) was used for the analysis. Predictors of POAF were determined by logistic regression analysis. The strength of association between variables and the occurrence of POAF were represented by odds ratios and their accompanying 95% confidence intervals. Factors with $P < 0.10$ with univariate regression were entered in the multivariate model. Preoperative and postoperative TAC, TOS, and WBC counts; age; left-atrial diameter; ejection fraction; hypertension; diabetes mellitus; bypass duration; the carvedilol plus NAC group vs the metoprolol group; the carvedilol plus NAC group vs the carvedilol group; the carvedilol group vs the metoprolol group; prerandomization,


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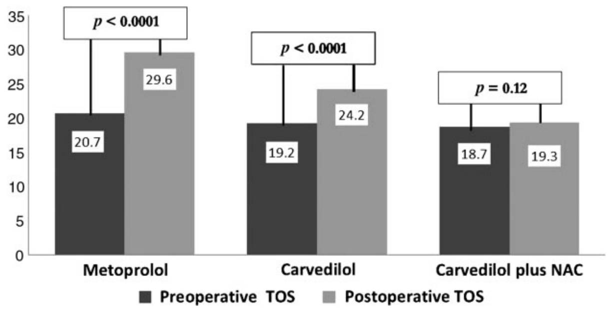


Figure 1. Preoperative to postoperative paired differences in the total oxidative stress (TOS) levels by intervention groups. Abbreviations: NAC, N-acetyl cysteine; TOS, total oxidative stress.

preoperative, and postoperative heart rates, postoperative spironolactone treatment; and CABG plus valve surgery or CABG had $P < 0.10$ with univariate comparison in terms of the end point of POAF.

## Results

### Patients

A total 259 patients (mean age, 63 ± 10 years; 231 male) constituted the study population. Postoperative heart rate was higher in the metoprolol group compared with the carvedilol group ($P = 0.02$) or the carvedilol plus NAC group ($P = 0.001$), but was similar between the carvedilol and the carvedilol plus NAC groups ($P = 0.9$). There were no statistically significant differences with respect to other preoperative, postoperative, and procedural characteristics (all $P$ values $>0.05$; Table 1).

### Oxidative Status and Inflammation

Preoperative TAC and TOS levels and WBC counts were similar among the 3 groups (all $P$ values $>0.05$) (Table 2). Compared with preoperative levels, postoperative TAC levels decreased in the metoprolol and the carvedilol groups, but increased in the carvedilol-plus NAC group (all $P$ values $<0.0001$). Compared with preoperative levels, postoperative TOS levels increased in the metoprolol ($P < 0.0001$) and the carvedilol groups ($P < 0.0001$), but no significant change occurred in the carvedilol plus NAC group ($P = 0.12$). Postoperative WBC counts increased significantly as compared with preoperative levels in all 3 groups (all $P$ values $< 0.0001$; Figure 1). Postoperative TAC levels were lower in the metoprolol group compared with the carvedilol group ($P < 0.0001$) or the carvedilol plus NAC group ($P < 0.0001$) and were also lower in the carvedilol group compared with the carvedilol plus NAC group ($P < 0.0001$). Postoperative TOS levels were higher in the metoprolol group as compared with the carvedilol group ($P < 0.0001$) or the carvedilol plus NAC group ($P < 0.0001$), and were also higher in the carvedilol group as compared with the carvedilol plus NAC group ($P < 0.0001$). Postoperative WBC counts were lower in the carvedilol plus NAC group compared with the metoprolol group ($P = 0.004$), and were similar between the carvedilol and the metoprolol groups and between the carvedilol plus NAC group and the carvedilol group (both $P$ values $> 0.05$).

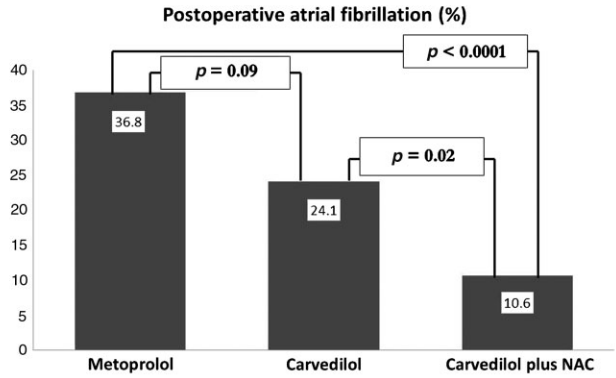


Figure 2. The incidence of postoperative atrial fibrillation according to intervention groups. Abbreviations: NAC, N-acetyl cysteine.

### Treatment Groups, POAF, and Markers of Oxidative Stress and Inflammation

Preoperative TOS levels were higher, and preoperative TAC levels were lower in patients with POAF as compared with those without POAF (both $P$ values $< 0.05$). There was no significant difference with respect to preoperative WBC counts in patients with POAF as compared with those without POAF ($P = 0.08$). Postoperative TAC and TOS levels and WBC counts were higher in patients with POAF as compared with those without POAF (all $P$ values $< 0.0001$).

Carvedilol plus NAC reduced the POAF rate as compared with carvedilol (10.6% vs 24.1%; $P = 0.02$) or metoprolol (10.6% vs 36.8%; $P < 0.0001$). There was a trend for lower POAF rates in the carvedilol group compared with the metoprolol group ($P = 0.09$; Figure 2). Postoperative TAC and TOS levels and WBC counts were independent predictors of POAF in multivariate regression analysis (all the multivariate predictors of POAF are given in Table 3).

## Discussion

The present study shows that carvedilol plus NAC reduced oxidative stress and inflammation as compared with metoprolol and reduced oxidative stress as compared with carvedilol. Similarly, the combination decreased POAF rates as compared with carvedilol or metoprolol. On the other hand, better antioxidant but similar anti-inflammatory actions and a trend for lower POAF rates were found in the carvedilol group as compared with the metoprolol group. Postoperative TAC and TOS levels and WBC counts were independent predictors of POAF. To the best of our knowledge, no previous study compared the antioxidant and anti-inflammatory actions of metoprolol vs carvedilol or carvedilol plus NAC using the present markers and evaluated their association with POAF.

NAC has been shown to reduce oxidative and inflammatory response[8–11] and ischemia/reperfusion injury after myocardial infarction[12] and after cardiac surgery.[13] Sucu et al[8] evaluated myeloperoxidase, malondialdehyde, interleukin-6, α1-acid glycoprotein, and C-reactive protein, and found that NAC decreased oxidoinflammatory response during surgery. Koramaz et al[9] compared cold-blood cardioplegia enriched with NAC and cold-blood cardioplegia alone, and found that postoperative troponin I levels were


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lower and malondialdehyde levels were higher in the control group compared with the NAC group. Vento et al have shown that myocardial glutathione content is better preserved, myeloperoxidase activity is lower, and leukocytes sequestered in the coronary circulation are lower in patients receiving NAC than in the control group.[10] In the study of Tossios et al,[11] left ventricular biopsy specimens collected before and at the end of cardiopulmonary bypass were subjected to immunocytochemical staining against 8-iso-prostaglandin F2-α as an indicator for reactive oxygen species-mediated lipid peroxidation and nitrotyrosine as a marker for peroxynitrite-mediated tissue injury. They found that the preoperative to postoperative change in ventricular cardiomyocyte staining for both 8-iso-prostaglandin F2-α and nitrotyrosine differed significantly in the NAC group compared with the placebo group.[11]

Carvedilol has been shown to have anti-inflammatory actions.[6,7,14–16] Arumanayagam et al showed that it has significant antioxidant effects as compared with metoprolol.[6] Similarly, it decreased interleukin-6 and tumor necrosis factor-α levels and increased tumor necrosis factor-α levels in patients with ischemic and nonischemic cardiomyopathy, respectively.[14,15] Alfieri et al showed that asymmetric

Table 2. Levels of the Markers of Oxidative Status and Inflammation

| | Metoprolol, n = 87 | Carvedilol, n = 87 | Carvedilol + NAC, n = 85 | Carv + NAC vs Met, *P* Value | Carv + NAC vs Carv, *P* Value | Carv vs Met, *P* Value |
|---|---|---|---|---|---|---|
| Marker | | | | | | |
| Preoperative TAC | 1.4 (0.7-2.9) | 1.6 (0.7-3.0) | 1.6 (0.7-2.9) | 0.08 | 0.89 | 0.12 |
| Preoperative TOS | 20.7 (4.8-39.3) | 19.2 (4.9-38.8) | 18.7 (3.0-65.0) | 0.1 | 0.81 | 0.11 |
| Preoperative WBC count | 8.5 (3.6-14.5) | 8.5 (4.9-12.3) | 8.5 (4.2-15.7) | 0.4 | 0.47 | 0.11 |
| Postoperative TAC | 1.0 (0.2-2.04) | 1.4 (0.6-3.2) | 1.9 (0.9-3.9) | <0.0001 | <0.0001 | <0.0001 |
| Postoperative TOS | 29.6 (5.3-76.9) | 24.2 (2.2-41.9) | 19.3 (4.0-41.0) | <0.0001 | <0.0001 | <0.0001 |
| Postoperative WBC count | 14.8 (5.7-22.7) | 13.0 (6.5-28) | 12.9 (6.4-19.6) | 0.004 | 0.28 | 0.09 |
| Group | Preoperative TAC | | Postoperative TAC | | *P* Value | |
| Metoprolol | 1.4 (0.7-2.9) | | 1.0 (0.2-2.0) | | <0.0001 | |
| Carvedilol | 1.6 (0.7-3.0) | | 1.4 (0.6-3.2) | | <0.0001 | |
| Carvedilol + NAC | 1.6 (0.7-2.9) | | 1.9 (0.9-3.9) | | <0.0001 | |
| Group | Preoperative TOS | | Postoperative TOS | | *P* Value | |
| Metoprolol | 20.7 (4.8-39.3) | | 29.6 (5.3-76.9) | | <0.0001 | |
| Carvedilol | 19.2 (4.9-38.8) | | 24.2 (2.2-41.9) | | <0.0001 | |
| Carvedilol + NAC | 18.7 (3.0-65.0) | | 19.3 (4.0-41.0) | | 0.12 | |
| Group | Preoperative WBC Count | | Postoperative WBC Count | | *P* Value | |
| Metoprolol | 8.0 (3.6-14.5) | | 14.8 (5.7-22.7) | | <0.0001 | |
| Carvedilol | 8.5 (4.9-12.3) | | 13.0 (6.5-28.0) | | <0.0001 | |
| Carvedilol + NAC | 8.5 (4.2-15.7) | | 12.9 (6.4-19.6) | | <0.0001 | |
| Marker | Patients Without POAF, n = 197 | | Patients With POAF, n = 62 | | *P* Value | |
| Preoperative TAC | 1.6 (0.7-3.0) | | 1.4 (0.7-2.9) | | 0.02 | |
| Preoperative TOS | 18 (3.0-65.0) | | 22.0 (5.7-38.8) | | <0.0001 | |
| Preoperative WBC count | 8.4 (4.2-15.7) | | 7.9 (3.6-14.5) | | 0.08 | |
| Postoperative TAC | 1.5 (0.3-3.9) | | 1.0 (0.2-2.1) | | <0.0001 | |
| Postoperative TOS | 21.4 (2.2-55.9) | | 32.1 (6.3-76.9) | | <0.0001 | |
| Postoperative WBC count | 12.5 (5.7-28.0) | | 17.1 (10.2-22.7) | | <0.0001 | |

Abbreviations: Carv, carvedilol; $H_2O_2$, hydrogen peroxide; Met, metoprolol; NAC, N-acetyl cysteine; POAF, postoperative atrial fibrillation; TAC, total antioxidant capacity; TOS, total oxidative stress; WBC, white blood cell.
The results of TAC TOS levels and WBC counts were expressed as mmol Trolox equivalent/L, mmol $H_2O_2$ equivalent/L and × 1000/$mm^3$, respectively. Data presented as median (maximum-minimum).


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Table 3. Multivariate Predictors of Postoperative Atrial Fibrillation

| Predictors | Odds Ratio | Confidence Interval | *P* Value |
|---|---|---|---|
| Postoperative WBC count | 1.94 | 1.47-2.55 | <0.0001 |
| Postoperative TAC | 0.18 | 0.04-0.69 | 0.01 |
| Postoperative TOS | 1.24 | 1.13-1.36 | <0.0001 |
| Carvedilol plus NAC vs carvedilol | 0.16 | 0.05-0.51 | 0.002 |
| Carvedilol plus NAC vs metoprolol | 0.18 | 0.03-0.92 | 0.04 |
| Hypertension | 10.93 | 2.41-49.45 | 0.002 |
| Diabetes mellitus | 3.87 | 1.20-12.47 | 0.02 |
| Left atrial diameter | 1.30 | 1.13-1.50 | <0.0001 |
| Bypass duration | 1.01 | 1.00-1.03 | 0.01 |
| Prerandomization heart rate | 1.22 | 1.10-1.34 | <0.0001 |
| Preoperative heart rate | 1.24 | 1.11-1.39 | <0.0001 |

Abbreviations: NAC, N-acetyl cysteine; TAC, total antioxidant capacity; TOS, total oxidative stress; WBC, white blood cell.

dimethylarginine and interleukin-18 levels decreased with carvedilol in heart failure.[16]

Bypass surgery may induce oxidative stress and inflammation, and these processes may be associated with complications after cardiac surgery including POAF.[4,26,27] Upregulated reactive oxygen species genes,[28] injured atrial myofibrils,[29] and increased reactive oxygen species and ratios of oxidized to reduced glutathione and cysteine[30] have been found in patients with atrial fibrillation. However, urinary F2-isoprostanes did not increase in these patients.[31] Leukocytes are inflammatory cells that may regulate oxidative stress by releasing reactive oxygen species.[32] They have been shown to be increased after cardiac surgery and may predict POAF.[33–35] In a very recent study, Rodrigo et al. randomized the patients undergoing cardiac surgery to n-3 polyunsaturated fatty acids, vitamin C, and vitamin E or placebo, and found that POAF rate and postoperative biomarkers of inflammation and oxidative stress were lower in the intervention group as compared with the placebo group.[36]

Carvedilol has been shown to be effective in preventing POAF.[20–22] However, conflicting results have been obtained with respect to the effects of NAC on POAF.[2,17–19,23,37] Postoperative TAC and TOS levels and WBC counts were independent predictors of POAF, suggesting that any treatment methods that effectively prevent postoperative oxidative stress and inflammation may markedly decrease POAF rates. Therefore, we speculated that either longer administration and/or a higher dose of carvedilol and NAC or the addition of other agents are needed to obtain better results.

## Limitations

This was a substudy. Patients without POAF had lower values of the markers of inflammation and oxidative stress. In the present study, new methods using a spectrophotometric kit have been used to measure oxidative capacity and total oxidative stress levels. There is a lack of data regarding specific oxidative stress and inflammatory markers, and this is the main deficiency of the present study. To confirm our data, it would be better if we had measured levels of other oxidative stress markers routinely used, such as malondialdehyde, nitrotyrosine, plasma lipid hydrogen peroxide levels, or paraoxonase and arylesterase activities. Also, instead of WBC count, it would be more reliable to use more sensitive markers of inflammation such as C-reactive protein. There was a trend of lower preoperative β-blocker use in the carvedilol plus NAC group as compared with the metoprolol group ($P = 0.06$). Therefore, if β-blocker use was higher in the carvedilol plus NAC group, the beneficial effects of carvediol plus NAC would be higher. To explore whether the effect of carvedilol plus NAC is due to the NAC alone or combination, a control group would have been interesting. Also, a metoprolol plus NAC group could be interesting to determine whether carvedilol is necessary for the antiarrhythmic effect. However, those groups are lacking.

## Conclusion

NAC plus carvedilol reduced oxidative stress and inflammation compared with metoprolol and decreased oxidative stress compared with carvedilol. Carvedilol showed better antioxidant effects than metoprolol, but their anti-inflammatory effects were similar. Postoperative TAC and TOS levels and WBC counts were independent predictors of POAF in multivariate regression analysis.


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