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## Antioxidant supplementation and atrial arrhythmias in critically ill trauma patients

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### ABSTRACT

**Background:** The purpose of this study is to determine if antioxidant supplementation influences the incidence of atrial arrhythmias in trauma intensive care unit (ICU) patients.

**Materials and methods:** In this retrospective pre-post study, critically ill injured patients aged  $\geq 18$  years, admitted to a single-center trauma ICU for  $\geq 48$  hours were eligible for inclusion. The control group consists of patients admitted from January 2000 to September 2005, before routine antioxidant supplementation in our ICU. The antioxidant group consists of patients admitted from October 2005 to June 2011 who received an antioxidant protocol for  $\geq 48$  hours. The primary outcome is the incidence of atrial arrhythmias in the first 2 weeks of hospitalization or before discharge.

**Results:** Of the 4699 patients, 1622 patients were in the antioxidant group and 2414 patients were in the control group. Adjusted for age, sex, year, injury severity, past medical history, and medication administration, the unadjusted incidence of atrial arrhythmias was 3.02% in the antioxidant group versus 3.31% in the control group, with no adjusted difference in atrial arrhythmias among those exposed to antioxidants (odds ratio: 1.31 [95% confidence interval: 0.46, 3.75],  $P = 0.62$ ). Although there was no change in overall mortality, the expected adjusted survival of patients in those without antioxidant therapy was lower (odds ratio: 0.65 [95% confidence interval: 0.43, 0.97],  $P = 0.04$ ).

**Conclusions:** ICU antioxidant supplementation did not decrease the incidence of atrial arrhythmias, nor alter the time from admission to development of arrhythmia. A longer

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expected survival time was observed in the antioxidant group compared with the control group but without a change in overall mortality between groups.

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## Introduction

Atrial fibrillation is the most common arrhythmia affecting the general population and can cause an increase in morbidity and mortality. The incidence of atrial fibrillation has been estimated from 15% to 50% of patients after cardiac surgery,<sup>1-3</sup> 4%-9% in general intensive care unit (ICU) patients,<sup>4</sup> and 6% in trauma ICU patients.<sup>5</sup> In trauma patients, atrial arrhythmias have been independently associated with higher mortality.<sup>5</sup> Supplementation with high-dose antioxidants including vitamin C, E, and selenium has shown possible improvements in mortality in critically ill trauma patients<sup>6</sup> but has not been studied in the setting of atrial arrhythmias. In cardiac surgery patients, antioxidants may reduce the rates of atrial fibrillation postoperatively.<sup>7</sup> One study documented the biochemical evidence of oxidative stress in atrial tissue of patients undergoing a maze procedure for treatment of permanent atrial fibrillation.<sup>8</sup> It is proposed that the uncontrolled inflammatory state from the decrease in natural circulating antioxidants seen in postsurgical patients may contribute to atrial fibrillation, which may be attenuated with antioxidant supplementation.<sup>8-10</sup>

Oxidative stress has been recognized as an important factor in the pathophysiology of critical illness. The production of reactive oxygen species can have detrimental effects and contribute to multiorgan dysfunction.<sup>11,12</sup> While the human body has defense mechanisms against these free radicals, such as superoxide dismutase, glutathione peroxidase (including one of its cofactors, selenium), and vitamins C and E, it has been shown that circulating plasma antioxidants are decreased during critical illness after surgery or trauma.<sup>13,14</sup> The degree of endogenous antioxidant depletion correlates with the severity of trauma or systemic inflammatory response syndrome.<sup>15,16</sup>

While the use of antioxidants has been suggested in the prevention of postoperative atrial fibrillation among cardiac surgery patients, there are limited data exploring the effects of antioxidant supplementation on the incidence of atrial arrhythmias in critically ill trauma patients, and there is general equipoise on antioxidant usage. We proposed that high-dose antioxidant supplementation consisting of ascorbic acid, selenium, and vitamin E may have an impact on the development of new atrial arrhythmias in critically ill injured patients by means of reducing oxidative stress.

## Methods

### Patient population

In this Institutional Review Board–approved, retrospective pre-post study, injured patients admitted to the Trauma ICU at Vanderbilt University Medical Center between January 1, 2000 and June 30, 2011 were eligible for enrollment in our

study. Patients aged  $\geq 18$  years and remaining in the ICU for at least 48 hours were included in this study. Patients were excluded if there was a history of cardiac arrhythmias, a baseline serum creatinine of 2.5 mg/dL or greater, or mortality occurred within 48 hours of admission. Subjects receiving high-dose ICU antioxidant supplementation were identified by antioxidant medication charges and excluded if treatment time was under 48 hours.

### Protocol

Eligible patients were assigned to one of the two groups based on the implementation of the antioxidant protocol. The control group consisted of patients admitted from January 1, 2000 through September 30, 2005, who did not receive ICU antioxidant supplementation. Any patients who received antioxidants before October 1, 2005 were excluded from the control group. The antioxidant group consisted of patients admitted from October 1, 2005 through June 30, 2011, who received the antioxidant protocol for at least 48 hours. The protocol was included in the admission order set but may have been ordered at any point in the hospitalization. The high-dose antioxidant protocol consisted of ascorbic acid 1000 mg by mouth (PO), per tube (PT), or intravenous (IV) every 8 hours, vitamin E 1000 units PO/PT every 8 hours, and selenium 200 mcg PO/PT/IV daily for a total of 7 days. Data on demographic and physiologic characteristics were collected from the electronic medical record and our trauma registry.

In addition to basic baseline demographic, such as age, sex, admission year, we gathered past medical history data regarding hypertension, myocardial infarction, coronary artery disease, prior cardiac surgery, and congestive heart failure. Injury severity score, predicted survival, abbreviated chest injury scale, and mechanism of trauma were also collected as baseline demographics.

The primary outcome of this study was the incidence of atrial arrhythmias during the first 2 weeks of hospitalization or before discharge, whichever occurred first. The primary outcome was identified through the use of International Classification of Diseases, Ninth Revision (ICD-9) codes, which is depicted in [Table 1](#). A manual chart review was performed

**Table 1 – ICD-9 Code list for atrial arrhythmias.**

427.0	Paroxysmal supraventricular tachycardia
427.1	Paroxysmal ventricular tachycardia
427.2	Paroxysmal tachycardia, unspecified
427.3	Atrial fibrillation and flutter
427.31	Atrial fibrillation
427.32	Atrial flutter
427.61	Supraventricular premature beats
427.8	Other specified cardiac dysrhythmias
427.89	Other specified cardiac dysrhythmias
427.9	Cardiac dysrhythmias unspecified

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