

COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Use of Amiodarone in Atrial Fibrillation Associated With Severe Sepsis or Septic Shock

NCT number: NCT02668432

IRB Approval Date: 02.01.16

Unique Protocol ID: HSC2016084H

Protocol Template Form

Item 1 UTHSCSA Tracking Number	HSC20150864H
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Item 2 Abstract / Project Summary

Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific.

DO NOT EXCEED THE SPACE PROVIDED.

Purpose/Objectives: Severe sepsis and septic shock are a common cause of new onset atrial fibrillation (NOAF) in the intensive care unit. Development of NOAF in this setting can prolong length of stay and increase mortality. Amiodarone is the most commonly used agent used in this setting to control rate and rhythm. However, limited data exist detailing appropriate dosing in this setting. The primary objective of this study is to evaluate two amiodarone dosing strategies, a full loading dose versus a partial loading dose, in patients with new-onset atrial fibrillation (AF) due to severe sepsis or septic shock to assess the mean heart rate every 6 hours after initiation of amiodarone infusion to day 7 or death.

Research Design/Plan: Consecutive patients admitted to the medical or cardiac intensive care unit at University Hospital with NOAF in the setting of severe sepsis or septic shock will be screened for study inclusion. Data will be collected and stored using Microsoft Excel or Access and analyzed with JMP 12.0 and SPSS.

Methods: Patients aged 18 years or older who develop new-onset atrial fibrillation in the setting of severe sepsis or septic shock and in whom the medical team deems appropriate to initiate amiodarone therapy in will be considered for study inclusion. Patients will be randomized to a full loading dose (≥ 5 g IV or ≥ 10 g PO \pm 20%) or a partial loading dose (<4 g IV or < 8 g PO).

Clinical Relevance: With ICU LOS and mortality being twice as high in NOAF with sepsis as compared to septic patients without NOAF, we ultimately aim to identify a management strategy that may minimize this morbidity and mortality while also minimizing exposure to a drug that may cause serious adverse effects.

Item 3

Background

Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving unapproved drugs, describe animal and human studies. For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.

Severe sepsis and septic shock, together, account for 2.9% and 10% of total hospital and intensive care unit (ICU) admissions in North America, respectively. An estimated 750,000 cases of sepsis occur annually in the United States, with a mortality rate of approximately 30%.¹ In the setting of new onset atrial fibrillation (NOAF), which affects between 7% and 30% of patients hospitalized with sepsis, the mortality rate is closer to 70-80% and the ICU length of stay is doubled.²⁻⁴ In sepsis, the causality has been widely disputed, and some even question whether atrial fibrillation (AF) may simply be a marker of illness severity, rather than an independent contributor to mortality.^{2,5,6}

AF is a multifactorial disease that can affect those with structural cardiac abnormalities and structurally normal hearts alike. The cascade of events that occur in the critically ill septic patient, including tissue hypoperfusion, organ dysfunction, inflammation, hypoxemia, electrolyte disturbances, hormonal dysregulation, fluctuations in autonomic tone, fluid imbalances, and catecholamine requirements, have each been implicated in the quest to identify the cause of NOAF.^{7,8}

To date, no studies have assessed what implications conversion back to NSR from NOAF may have on clinical outcomes. The approach to management of AF and conversion to NSR varies. Outside of sepsis, in patients with AF and hemodynamic instability, direct current cardioversion (DCC) is preferred because of its high acute efficacy of 67 to 94%.⁽⁷⁾ However, because the trigger for NOAF in the septic patient lies somewhere in the pathophysiology of sepsis, sustainable efficacy of DCC is debatable, especially without identification and removal of underlying triggers.^(6,8) Studies of NOAF in septic patients have shown that DCC with concomitant or subsequent pharmacologic therapy is often necessary; however, the best pharmacotherapeutic approach is a point of discussion. Rate control with beta blockers may exacerbate hypotension, and digoxin use is unsuccessful due to the absence of vagal tone.⁽⁹⁻¹¹⁾ Overall,

	<p>successful cardioversion with amiodarone in general is approximately 75% within the first 24 hours.(12</p> <p>Kanji and colleagues noted successful conversion to NSR was achieved in 50% of a mixed medical-surgical patient population that underwent DCC, though 73% reverted back to AF. Successful conversion to NSR was obtained in 87% of patients receiving amiodarone, some of whom also underwent DCC, though 42% reverted back to AF at some time during their ICU stay after maintaining normal sinus rhythm for at least 24 hours after conversion. The median duration of amiodarone therapy was 4 days (range 1-49) and a median cumulative intravenous dose of 2324 mg (range 150-20550 mg).(5) Clemo and colleagues found that in a mixed ICU population, within 2 hours of amiodarone initiation, aimed at an intravenous loading dose of 2-3 mg/kg, there were significant reductions in heart rate from 150 bpm to 104 bpm and increases in systolic blood pressure from 90 mmHg to 118 mmHg. Within 24 hours, 76% of patients had successfully converted to NSR, which was maintained in 52% of patients with an average cumulative intravenous dose of 2035 ± 1962 mg and an average duration of amiodarone treatment of 84 ± 79 hours.(13) Faneil and colleagues found that in a mixed ICU setting, patients refractory to DCC or other antiarrhythmic agents, amiodarone achieved successful conversion to NSR in 80.8% of patients in an average of 171 minutes. They noted that maintenance of NSR required an average amiodarone dose of 6.9 ± 2.3 mg/kg.(14) In a recent systematic review by Kanji and colleagues, they found that no study evaluated the maintenance of conversion to NSR(6).</p> <ol style="list-style-type: none"> 1. Rivers EP. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. <i>Can Med Assoc J.</i> 2005;173(9):1054–1065. 2. Christian S-A, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. <i>J Crit Care.</i> 2008;23(4):532–536. 3. Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: Epidemiologic study. <i>Crit Care Med.</i> 1990;18(12):1383–1388. 4. Seguin P, Signouret T, Laviolle B, Branger B, Mallédant Y. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit*: <i>Crit Care Med.</i> 2004;32(3):722–726. 5. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. <i>J Crit Care.</i> 2012;27(3):326.e1–326.e8; 6. Kanji S, Stewart R, Fergusson DA, McIntyre L, Turgeon AF, Hébert PC. Treatment of new-onset atrial fibrillation in noncardiac intensive care unit patients: A systematic review of randomized controlled trials*: <i>Crit Care Med.</i> 2008;36(5):1620–1624. 7. Crawford TC, Oral H. Cardiac Arrhythmias: Management of Atrial Fibrillation in the Critically Ill Patient. <i>Crit Care Clin.</i> 2007;23(4):855–872. doi:10.1016/j.ccc.2007.06.005. 8. Sleeswijk M, van Noord T, Ligtenberg JJM, Zijlstra JG. Response. <i>CHEST J.</i> 2009;136(2):650. doi:10.1378/chest.09-0928. 9. Heywood J, Graham B, Marais G, Jutzy K. Effects of intravenous diltiazem on rapid atrial fibrillation accompanied by congestive heart failure. <i>Am J Cardiol.</i> 1991;67:1150–1152. 10. Schwartz M, Michelson EL, Sawin HS, MacVaugh H. Esmolol: safety and efficacy in postoperative cardiothoracic patients with supraventricular tachyarrhythmias. <i>CHEST J.</i> 1988;93(4):705–711. 11. Goldman S, Probst P, Selzer A, Cohn K. Inefficacy of “therapeutic” serum levels of digoxin in controlling the ventricular rate in atrial fibrillation. <i>Am J Cardiol.</i> 1975;35(5):651–655. 12. Khan IA, Mehta NJ, Gowda RM. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. <i>Int J Cardiol.</i> 2003;89(2-3):239–248. doi:10.1016/S0167-5273(02)00477-1. 13. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous Amiodarone for Acute Heart Rate Control in the Critically Ill Patient with Atrial Tachyarrhythmias. <i>Am J Cardiol.</i> 1998;81:594–598. 14. Faniel R, Schoenfeld P. Efficacy of i.v. amiodarone in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. <i>Eur Heart J.</i> 1983;4(3):180–185.
<p>Item 4</p> <p>Purpose and rationale</p> <p><i>Insert purpose, objectives and research questions/hypotheses here.</i></p> <p><i>If you cut and paste from</i></p>	<p>Primary Outcome:</p> <p>Evaluate two amiodarone dosing strategies, a full loading dose versus a partial loading dose, in patients with new-onset atrial fibrillation (AF) due to severe sepsis or septic shock to assess the effect on:</p> <ul style="list-style-type: none"> • Mean heart rate every 6 hours within the first 7 days following initiation of amiodarone

<p><i>another document, make sure the excerpted material answers the question</i></p>	<p>Secondary Outcomes: Evaluate two amiodarone dosing strategies, a full loading dose versus a partial loading dose, in patients with new-onset AF due to severe sepsis or septic shock to assess the effect on:</p> <ul style="list-style-type: none"> Percentage of time spent hemodynamically unstable after initiation of amiodarone infusion to day 7 or death <ul style="list-style-type: none"> Hemodynamic instability: 1. SBP <90 mmHg OR MAP < 70 mmHg AND HR ≥ 120 bp for ≥ 2 hours OR 2. HR ≥ 120 for ≥ 2 hours OR 3. Fluid boluses ± vasopressors or dobutamine Percentage of patients with conversion from atrial fibrillation to normal sinus rhythm Proportion of time in atrial fibrillation vs normal sinus rhythm or other Mean arterial pressure (MAP) Systolic blood pressure (SBP) Heart rate (HR) Vasopressor use Dobutamine use Corticosteroid use Concomitant rate control medication use Concomitant rhythm control medication or intervention use 28-day mortality Intensive care unit length of stay (ICU LOS) Hospital LOS
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<p>Item 5 Study Population(s) Being Recruited</p> <p>In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number: 1</p>	<p>Identify the criteria for inclusion:</p>	<p>Identify the criteria for exclusion:</p>
<p><i>e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc.</i></p> <p>List each different population on a separate row and provide a short descriptive label: <i>(e.g., normal-healthy, diabetics, parents, children, etc.)</i></p> <p><i>To add rows use copy & paste</i></p>		
<p>Patients with severe sepsis or septic shock and new onset atrial fibrillation admitted to the medical or cardiac intensive care unit</p>	<ul style="list-style-type: none"> Age ≥ 18 years New onset atrial fibrillation Severe sepsis or septic shock (defined by ≥2 systemic inflammatory response syndrome criteria + infection) 	<ul style="list-style-type: none"> Age < 18 years History of atrial flutter History of atrial fibrillation QTc >500 msec at baseline 2nd or 3rd degree AV block Currently receiving anti-arrhythmic therapy Untreated thyroid dysfunction Acute or chronic hepatic failure Other indication for antiarrhythmic therapy

		<ul style="list-style-type: none"> • Recent cardiac surgery in last 30 days • Pregnancy • Known hypersensitivity to any of the components of amiodarone , including iodine • Cardiogenic shock • Marked sinus bradycardia
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Item 6

Research Plan / Description of the Research Methods *a. Provide a comprehensive narrative describing the research methods.*

Provide the plan for data analysis (include as applicable the sample size calculation).

Step-by-Step Methods:

Population: The study will be conducted at University Hospital, the 716-bed county hospital for Bexar County and serves a varied population, including patients from medically underserved areas. The patient population will come from the medical intensive care unit and the cardiac intensive care unit, a 20 and 26-bed unit, respectively, at University Hospital that is the clinical practice and teaching site for one study investigator.

Screening: Consecutive patients admitted to the medical or cardiac intensive care unit at University Hospital with new onset atrial fibrillation in the setting of severe sepsis or septic shock will be screened for study inclusion. Participants will be 18 years or older. Patients who develop new-onset atrial fibrillation in the setting of severe sepsis or septic shock will be considered for study inclusion. Exclusion criteria apply to those younger than 18 years of age, those with a history of atrial flutter, baseline QTc > 500 msec, atrial fibrillation during the index admission or in their past medical history, second or third degree AV block, those recovering from cardiac surgery done during the same hospital admission, those who have received amiodarone or other Vaughan Williams class I or III antiarrhythmic drugs in the last 6 months, untreated/poorly controlled hypothyroidism, hyperthyroidism, acute or chronic hepatic failure, other requirements of antiarrhythmic drug therapy, recent cardiac surgery in the preceding 30 days, and those who are pregnant.

Intervention: Patients aged 18 years or older who develop new-onset atrial fibrillation in the setting of severe sepsis or septic shock and in whom the medical team deems appropriate to initiate amiodarone therapy in will be considered for study inclusion. All patients will receive a 150 mg intravenous (IV) bolus dose of amiodarone, followed immediately by a continuous infusion of 1 mg/min for the first six hours, with a recommended reduction to 0.5 mg/min subsequently. Conversion from IV to oral (PO) amiodarone will occur based on patient hemodynamic stability and physician/pharmacist discretion. Patients will be randomized to receive amiodarone at a full loading dose ($\geq 5\text{g IV}$ or $\geq 10\text{g PO} \pm 20\%$) or a partial loading dose ($< 4\text{g IV}$ or $< 8\text{g PO}$). The assigned total loading dose will include all IV and PO amiodarone administered within 7 days from initiation of amiodarone. All doses will be compared in total PO amount (accounting for 50% bioavailability of PO versus IV amiodarone). The primary attending or fellow physician may over-ride randomization if the patient's amiodarone dose if the patient's severity of illness warrants a duration that differs from that assigned during randomization. In the full loading dose group, discontinuation of amiodarone will be at the discretion of the physician/pharmacists, after the pre-determined randomization loading dose has been provided.

Management Components: Facilities to be used throughout the project include the University Hospital and The University of Texas Health Science Center at San Antonio. Equipment use for direct patient care will be in keeping with standards-of-care, without any additional equipment being required for the clinical research study.

Data Collection: Data collection will include age, race, gender, BMI, data for calculating an APACHE II and SOFA scores, suspected source of infection, identified pathogens, pre-existing conditions that may predispose the patient to AF and the severity/classification of such illness (coronary artery disease, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus); vital signs at the onset of AF (mean arterial pressure, systolic blood pressure, heart rate), lactate, pH, and serum bicarbonate at the time of AF onset; fluid resuscitation volume for the 24 hours prior to AF, vasopressor use (including drug, dose, duration) in the preceding 24 hours; other medications used to stabilize hemodynamic status in AF (e.g. β -blockers, calcium channel blockers, digoxin), other attempted methods of cardioversion attempted prior to amiodarone use (e.g. direct current cardioversion, other antiarrhythmic drug therapy); amiodarone loading dose, cumulative study amiodarone dose; the duration of time spent in AF before conversion to NSR, the incidence of AF recurrence; and hemodynamic variables to be assessed at various time points after the initiation of amiodarone (-6 hours, at onset of AF, 2 hours, 6 hours, 12 hours, and every 6 hours thereafter until day 7 or death)

including mean arterial pressure, central venous pressure, systolic blood pressure, heart rate, pH, serum bicarbonate, and serum lactate.

Monitoring for Efficacy and Safety:

Efficacy: Patients will be stratified based on response to therapy into one of three groups: conversion to NSR, non-converting AF that is hemodynamically stable or non-converting AF that is hemodynamically unstable. The primary efficacy outcome is the mean heart rate every 6 hours after initiation of the amiodarone infusion to day 7 or death. Secondary efficacy endpoints will include the percentage of time spent hemodynamically unstable in the first 7 days following amiodarone initiation, intensive care unit length of stay (LOS), hospital LOS and 28-day mortality along with comparisons of the individual portions of the hemodynamic endpoints (MAP, HR, SBP), cumulative vasopressor doses of norepinephrine and vasopressin, CVP, conversion to NSR, maintenance of NSR, proportion of time spent in NSR after the start of the infusion to day 7 or death, pH, standard bicarbonate, serum lactate, and central venous oxygen saturation.

Safety: Safety outcomes include worsening of hypotension (largely related to the rate of infusion and the polysorbate 80 diluent), bradycardia, acute elevations of liver function tests ≥ 3 times the upper limit of normal, phlebitis, QTc prolongation, skin reactions, neuropathy, and pulmonary toxicity. We will also collect premature study discontinuation due to any adverse event. Because the experimental group of this study is a partial load of amiodarone, rather than a full load, it is likely that the experimental group will experience fewer amiodarone related adverse effects than those receiving the current practice. In the setting of worsening hemodynamic stability during amiodarone infusion (i.e. SBP < 90 mmHg OR MAP < 70 mmHg, despite HR control of < 120 bpm; need for fluid boluses \pm vasopressors or dobutamine), which the medical team believes to be caused by IV amiodarone therapy:

1. the amiodarone infusion rate should be decreased by 50%, with efforts to increase back to the standard infusion rate after the patient is hemodynamically stable, or
2. switch from IV amiodarone to PO amiodarone therapy at a dose of 400 mg PO TID, or
3. emergent electro-cardioversion at the discretion of the medical team (as is the standard of care)

Data Analysis Plan: Data will be collected and stored using Microsoft Excel or Access. After data organization and cleaning, data will be imported into JMP 12.0 or SPSS. Data will be analyzed using both descriptive and comparative statistics. The primary outcome will be analyzed using repeated measures ANOVA. Nominal and ordinal variables will be compared using Chi-square test or Fisher's Exact test, as appropriate. Continuous variables will be tested for normality using the Shapiro-Wilk W goodness of fit test. Continuous variables with normal distributions will be compared using the student's t-test, while non-parametric variables will be compared using the Wilcoxon rank sum test. Statistical significance will be defined as an alpha level less than 0.05.

All baseline demographics, including patient comorbidities, amount of fluid resuscitation, previous vasoactive therapies, and use of other interventions such as direct current cardioversion, will be entered into a multivariate regression model if the p value is less than 0.20 on univariate comparison between treatment groups. The multivariate regression model will be used to assess if baseline factors or previous treatment other than the intervention affected the study outcomes.

Based on extrapolation from available literature assessing HR control at 24 hours, we estimate that the full loading dose group will have a mean HR of 110 bpm over the course of 7 days, while the partial loading dose group will have a mean HR of 130 bpm over the course of 7 days. 7 day mean HR that is 20 bpm lower than the partial loading dose group. Therefore, we estimate that 250 patients will be necessary in each group to have an 85% power to detect a difference, assuming a 15% drop-out rate.

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures	Risks
<i>example:</i> <ul style="list-style-type: none">• History and physical• Questionnaire• Laboratory tests	List the reasonably expected risks under the following categories as appropriate:
<i>Add or delete rows as needed</i>	