The HOLIDAY (HOw ALcohol InDuces Atrial TachYarrhythmias) Study

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The HOLIDAY Study
(HOw ALcohol InDuces Atrial TachYarrhythmias)
Single-Center Randomized Controlled Trial

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Signature Page for Principal Investigators

Protocol name: The HOLIDAY Study

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Gregory M. Marcus, MD, MAS
(Principal Investigator) _____ Signature _____ Date

LIST OF ABBREVIATIONS

AUDIT	The Alcohol Use Disorders Identification Test
AERP	atrial effective refractory period
AF	atrial fibrillation
BAC	blood alcohol concentration
BrAC	breath alcohol concentration
$CHADS_2$	stroke risk index: Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]
CRF	case report form
CS	coronary sinus
CT	computed tomography
EC	Ethics Committee
ECG	electrocardiogram
PAC	premature atrial contraction
PV	pulmonary vein
TEE	transesophageal echocardiogram
TIA	transient ischemic attack
TTE	transthoracic echocardiogram
SAE	serious adverse event
UCSF	University of California, San Francisco

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ADMINISTRATIVE INFORMATION SUMMARY

Project Title:	The HOLIDAY (HOw ALcohol InDuces Atrial TachYarrhythmias) Study

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1.0 BACKGROUND

Atrial Fibrillation (AF), the most common sustained arrhythmia in the United States, has profound public health implications: the lifetime risk of AF is 1 in 4, the disease affects several million Americans, and it is the most common cause of embolic stroke.[1-3] Unfortunately, the pathogenesis of AF is still poorly understood and has multiple influences, with ethanol likely being one of particular importance. Ethanol is the most commonly consumed drug in the United States. In the 2001 US National Household Survey on Drug Abuse, 84% of people surveyed above the age of 12 admitted to having consumed ethanol in the past, with a quarter of men, and nearly a fifth of women, admitting to at least one episode of binge ethanol drinking (>5 drinks in a single sitting) during the previous month.[4] The mechanism(s) by which ethanol increases the risk for AF, or "triggers" AF in certain individuals are unknown.

The widest body of literature is epidemiological, and those studies have suggested an association between ethanol use and the risk for AF since the initial cases of "holiday heart" were described in the 1970s[5]. The patients in the initial case reports were generally male, middle-aged or younger chronic alcoholics who were without structural heart disease. The temporal association of acute onset paroxysmal AF with ethanol binges, in patients with otherwise normal hearts, led to the premise that AF paroxysms could be related to ethanol use. This premise was brought into question when large epidemiologic studies, such as the Framingham Heart Study, the Manitoba Follow-up Study, and the Renfrew/Paisley study, found no association between chronic ethanol use and AF[6-8]. Later studies, such as the Copenhagen Heart Study and a reanalysis of the Framingham cohort, demonstrated that when controlled for the quantity of ethanol consumed and sex, an association with chronic and paroxysmal AF was seen with moderate to heavy ethanol use (>3 drinks per day) in men[9-12]. From these studies it is apparent that the effect of ethanol is both multifactorial and complex. The case series and anecdotal evidence suggest that acute ethanol binging can induce temporary paroxysms of AF in younger patients without structural heart changes (consistent with acute electrophysiologic changes)[5, 13, 14], while the epidemiological evidence suggests that chronic moderate to heavy ethanol use in men is associated with more chronic AF (consistent with a structural effect on the atria)[9-12]. It is unclear if these two conditions are part of continuum of risk or if they represent the diverse effects that ethanol may have on different patient populations. In order to investigate the mechanistic relationship between acute ethanol use and AF, we will perform a study of the acute electrical effects of ethanol in a non-alcoholic patient population with baseline paroxysmal AF.

1.1 Previous Study Data

The prevailing theory is that a PAC triggers AF, representing multiple, partially-reentrant wavelets. As experiments have been limited to animal models, a few small comparative observational (not experimental) studies in humans, and mechanistic concepts inferred by the success of certain ablation procedures, there is no human experimental model for in vivo atrial EP changes in AF. The data suggest that three readily measurable EP properties are important in the initiation and perpetuation of AF: automaticity, the effective refractory period (ERP), also reflected in the action potential duration (APD), and conduction velocity.

The changing nature of ERP (or APD) relative to the previous diastolic interval, a property called restitution, may be critical to the initiation of fibrillation. There is some evidence that when the restitution curve becomes steep (>1), meaning that the ERP (or APD) shortens disproportionate to the diastolic interval, susceptibility to fibrillation is particularly enhanced. No human study has demonstrated a causal relationship wherein a change in restitution leads to a greater propensity to AF. In isolated animal myocardial tissue preparations, ethanol consistently reduces APD.

Intracoronary ethanol prolongs ventricular conduction times in canine models.

Small (n<15) case series describing invasive EP studies before and after oral ethanol in humans were performed decades ago. The following was observed: in 10 habitual drinkers, oral whiskey resulted in a decrease in the atrial ERP that did not reach statistical significance; atrial arrhythmias could be induced with atrial extra stimulus pacing in 5 after, but not before, drinking whiskey. In 14 patients, whiskey resulted in an increase in atrial conduction time and a decrease in the ventricular ERP. And in 14 patients, whiskey resulted in the His-Purkinje system delay, and sustained atrial arrhythmias could be induced in 4 of them. Our prior study of 48 consecutive patients undergoing a standard questionnaire and right atrial ERP measurements during invasive EP studies found that greater average ethanol intake was associated with a shorter right atrial ERP.

Utilizing the protocol detailed here, we have successfully obtained pilot data in 3 patients during AF ablation procedures. For the first patient, the PK model achieved a breath alcohol concentration (BrAC) of between 0.079-0.082% within 20 minutes, with successful clamping within that range for the duration of the experiments. No pacing maneuvers were performed in the first patient in order to focus on safety and feasibility of the ethanol infusion. With EP testing, patient 2 exhibited a 45 ms decrease in the proximal CS ERP; while no AF was observed with pacing prior to ethanol, AF was reproducibly observed during pacing from both upper pulmonary veins after ethanol. Patient 3 exhibited an 85 ms drop in the left upper pulmonary vein ERP after ethanol, with repeatedly induced AF after (but not before) the ethanol was administered. All 3 patients exhibited normal wound healing and recovery without complication. Thus, our experience with 3 patients receiving intravenous ethanol undergoing AF ablation procedures revealed no complications and normal recovery and wound healing.

This important preliminary data demonstrates: 1) The feasibility of delivering IV ethanol and serial EP assessments in patients undergoing invasive AF ablation procedures; 2) Our ability to utilize the BrAC method; 3) Dramatic changes in ERPs and AF inducibility in the two patients undergoing pacing maneuvers; 4) The safety of these experiments in patients undergoing AF ablation procedures.

2.0 INVESTIGATION PLAN

2.1 Study Design

This study is a randomized single-center single-blinded placebo controlled trial of patients age 21-90 with paroxysmal atrial fibrillation. This study will be conducted at University of California, San Francisco (UCSF) Medical Center. One hundred patients will be enrolled and will receive the study infusion (alcohol or placebo infusion).

2.2 Randomization and Treatment Groups

Participants will be allocated (1:1) to a study assignment, using alternating blocked randomization (in blocks of five). Participants will be assigned to either the Ethanol Infusion group or to the Placebo Infusion group.

2.3 Blinding

To preserve blinding to infusion assignment, as much as possible, the following individuals will be blinded, during the trial:

- Study participants

- UCSF Electrophysiology team, including the electrophysiologist, electrophysiology fellow, and nursing staff during the procedure* (not including the individuals noted below)

It will be necessary for the following individuals to be unblinded to individual participant randomization assignments only, during the trial:

- UCSF Study Coordinator(s) that administers the infusion, records the infusion assignment in the database, and oversees the infusion process during the procedure
- UCSF Anesthesia team
- UCSF Pharmacy team that prepares the study infusion

Only the following individuals will be unblinded to both individual and grouped participant randomization assignments, during the trial:

- UCSF Coordinating Center Epidemiologist that is the DSMB liasion
- UCSF Coordinating Center Analyst and Statistician that performs analyses for the DSMB reports and interim analysis

** NOTE: Breath alcohol readings will be taken during the study procedure for both the alcohol and placebo group participants, to help maintain blinding. Treatment group assignment will not be indicated on the infusion bags.*

2.4 Study Visits and Windows

After screening and eligibility has been determined, interested participants will be consented at either their pre-procedure, standard of care CT scan, or another pre-procedure appointment at UCSF Medical Center. At this point, questionnaires addressing alcohol consumption, triggers of AF, and medical history will be administered by the research team member performing the consent process. See Figure 1 for study flow.

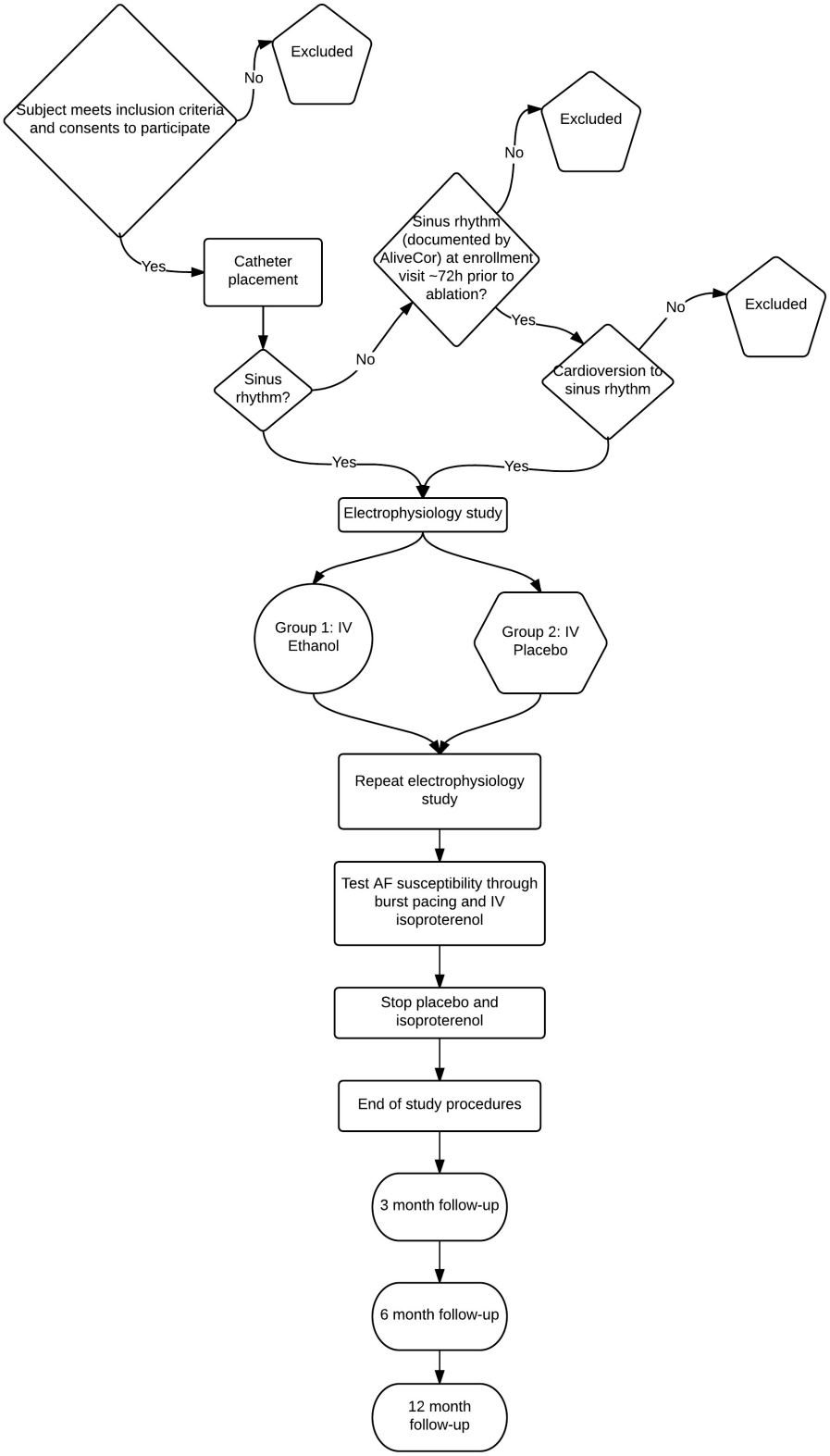
Safety follow-up will be performed by chart review at 3 months, 6 months, and 12 months post-procedure, when AF ablation patients normally return to clinic. If participants have no scheduled clinic appointment within the visit window (+/- 30 days for 3 and 6 months, + 6 months and - 30 days for 12 month), a member of the research team will attempt to contact the participant by phone to gather follow-up information. The clinical site will make every possible effort to ensure that each study visit is conducted within the specified window.

Table 1. Visit Windows

Study Visit	Scheduled Timepoint	Visit Window
Screening and Enrollment		
V0	Randomization and Procedure	
V1	Month 3*	+/- 30 days
V2	Month 6*	+/- 30 days
V3	Month 12*	+6 months/- 30 days

**Follow-up visits will be calculated from the date of ablation procedure (i.e., baseline).*

Figure 1. Study Flow Diagram



** The pharmacy that prepares the ethanol/placebo requires notification of the treatment assignment 1 business day prior to administration, therefore, participants must be consented and randomized at least 1 day prior to the scheduled procedure.*

2.5 Study Objective and Aims

The objective of this trial is to seek to reveal the mechanisms underlying the relationship between ethanol, the most commonly consumed drug in the world, and atrial fibrillation (AF), the most common arrhythmia. Specifically, we seek to determine the electrophysiological effects of acute ethanol exposure on atrial myocardium via a randomized trial of intravenous ethanol versus placebo in paroxysmal AF patients.

Study Aims:

1. To assess the acute effects of intravenous ethanol administration on the atrial effective refractory period (AERP) and atrial conduction velocity of *in vivo* human atrial myocardium.

   Hypothesis: Intravenous administration of ethanol decreases AERP and atrial conduction velocity.

2. To assess the acute effects of intravenous ethanol administration on the inducibility of AF of *in vivo* human atria.

   Hypothesis: Intravenous administration of ethanol increases in vivo susceptibility to AF.

2.6 Inclusion/Exclusion Criteria

2.6.1 Inclusion Criteria

1. Aged 21-90
2. History of paroxysmal or persistent atrial fibrillation (AF)
3. Planned procedure pulmonary vein isolation (PVI) or electrophysiology study (EPS)
4. Presenting in sinus rhythm or atrial fibrillation of recent onset (the latter confirmed by sinus rhythm documented no more than one week prior)

2.6.2 Exclusion Criteria

1. History of substance abuse or alcoholism (determined by history, Alcohol Use Disorders Identification Test (AUDIT) questionnaire, or chart review)
2. LVEF <50%
3. Liver dysfunction (AST, ALT, total bilirubin, or alkaline phosphatase level greater than two times the normal range)
4. Clinical evidence of liver disease (enlarged liver, caput medusa, spider angiomas, or other signs of liver disease on exam)
5. Pregnancy
6. Inability to give informed consent
7. Taking or have taken amiodarone within one month prior to procedure
8. Taking or have taken dofetilide within 24 hours prior to the procedure
9. General severe intolerance to alcohol

3.0 STUDY TREATMENT

Demographic and medical history information will be obtained by chart review and by questionnaire administered by a member of the research team. Prior to the procedure, patients will be instructed to abstain from alcohol for 48 hours and to stop antiarrhythmic drugs for at least 5 half-lives. Per the standard AF ablation procedure with a double transseptal puncture, catheters will be positioned. Study coordinators measure conduction times using electronic

calipers and custom software in regular use in the UCSF EP laboratory, and EP measurements are then reviewed offline by the PI blinded to treatment assignment.

3.1 Anesthesia Protocol

To minimize the effects of anesthestic agents on AERP and conduction time (see Operations Manual), the anesthesia team will follow a specific anesthesia protocol for HOLIDAY, devised in collaboration with the Anesthesia Department at UCSF, from induction to termination of the study protocol. Propofol, remifentanil and nitrous oxide may be used at induction, with cis-atracurium for paralysis. Prior to transseptal access, nitrous oxide and cis-atracurium should be turned off, though propofol and remifentanil infusions can continue. From transseptal access through the end of the experimental portion of the procedure, only a propofol infusion may be used. If remifentanil is necessary after transseptal access, the anesthesia team may also use remifentinal so long as remifentinal is also infused for the reminder of the experimental portion of the procedure to ensure consistency. Phenylephrine may be titrated throughout the procedure to maintain a mean arterial pressure above 70 mmHg.

The following medications may not be used until after completion of the experimental portion: benzodiazepines, fentanyl, rocuronium, succinylcholine, ketamine, scopolamine, and inhaled anesthetics other than nitrous oxide. Only in the case of an emergency, may anticholinergics be used.

3.2 Catheter Placement

Following the initiation of sedation, intra-cardiac multipolar electrocatheters will be placed in the following positions under fluoroscopic guidance: decapolar catheter in the coronary sinus (CS), decapolar catheter along the crista terminalis, quadripolar catheter along the medial tricuspid annulus at the position of the His bundle, duodecapolar circular catheter in the left upper pulmonary vein, and quadripolar ablation catheter in the right upper pulmonary vein. If the ablation procedure were a cryoballoon PVI, four, instead of five, catheters will be used: decapolar catheter in the coronary sinus (CS), decapolar catheter along the crista terminalis, quadripolar catheter along the medial tricuspid annulus at the position of the His bundle, and cryoballoon catheter in the left upper pulmonary vein. (See Operations Manual for details)

Catheter repositioning should be avoided to prevent disrupting post-procedure conduction time measurements. Prior to transseptal access, the alcohol or placebo solution will be connected to minimize left atrial time.

3.3 Pre-Infusion EP Study

Immediately following catheter placement, a one-minute premature atrial contraction (PAC) count will be conducted. AERP measurements will then be taken at the following bipoles: CS proximal, CS distal, high right atrium (crista terminalis catheter), left upper pulmonary vein, and right upper pulmonary vein. The AERP will be obtained by an incremental technique using a 600 ms drive cycle length for 8 beats (S1) at twice pacing threshold with incremental steps for the atrial extrastimuli (S2). The first drive train at each location should begin with an atrial extrastimuli (S2) of 140 ms, which is not expected to result in atrial capture. Once the first atrial capture is achieved, the S2 will be decreased by 5 ms. AERP will be defined as the longest S1-S2 interval that fails to result in atrial capture. (See Operations Manual for details)

3.4 Infusion

After the first EP study, the intravenous ethanol or placebo infusion will be initiated while the left atrial anatomic map is being constructed to reduce time added to the ablation procedure and minimize risk. The infusion is run by an iMED Gemini PC-2TX pump connected to and controlled by the CAIS 2.0 computer software. The ethanol infusion will consist of a 6% volume/volume ethanol solution in 0.45% saline titrated by the BrAC quick clamp method until a steady state is achieved at a blood alcohol concentration of 0.08%. The mean time to achieving this steady state is regulated by the CAIS 2.0 software to be approximately 20 minutes. Infusion rates are determined by the patient's height, weight, age, and sex, but are automatically adjusted depending on the patient's breath alcohol measurements, which are taken every three to four minutes until steady state is reached.

Patients assigned to the placebo group will receive 5% dextrose (D5) in 0.45% saline. BrAC measurements will be obtained at identical intervals for all participants; BrAC measurements will be randomly generated within two standard deviations of the predicted values calculated by the CAIS 2.0 software based on height, weight, age, and sex. The randomly generated BrAC values will be input into the CAIS 2.0 software, as for patients receiving an alcohol infusion, and the infusion rates will be automatically adjusted accordingly.

Once the BrAC reading is ±0.002% from 0.080% (steady state), BrAC measurements will be taken every 10 minutes and input into the CAIS 2.0 software. Breath alcohol measurements will be taken using the Intoximeters Alco Sensor IV fitted with a one-way valve adaptor for intubated patients. (See Operations Manual for details)

3.5 Post-Infusion EP Study

As soon as the blood alcohol content reaches a steady state of 0.080% ±0.002%, a one-minute premature atrial contraction (PAC) count will be conducted. AERP measurements will then be taken at the following bipoles: CS proximal, CS distal, high right atrium (crista terminalis catheter), left upper pulmonary vein, and right upper pulmonary vein. The AERP will be obtained by an incremental technique using a 600 ms drive cycle length for 8 beats (S1) at twice pacing threshold with incremental steps for the atrial extrastimuli (S2). The first drive train at each location should begin with an atrial extrastimuli (S2) of 140 ms, which is not expected to result in atrial capture. Once the first atrial capture is achieved, the S2 will be decreased by 5 ms. AERP will be defined as the longest S1-S2 interval that fails to result in atrial capture. (See Operations Manual for details)

Following the PAC count and AERP measurements, a phenylephrine infusion will be started prior to the initiation of the isoproterenol infusion to maintain a mean arterial pressure of >60 mmHg. Isoproterenol hydrochloride will then be infused at the following rates for 2 minutes each: 3 mcg/min, 6 mcg/min, 12 mcg/min, and 20 mcg/min. If AF or another arrhythmia initiates at any point during the isoproterenol infusion and is sustained over 30 seconds, the isoproterenol infusion will be stopped, the rhythm documented, and the study terminated.

If neither AF nor another arrhythmia lasting over 30 seconds occurs after 2 minutes of 20 mcg/min isoproterenol infusion, the isoproterenol infusion will be stopped. Once the heart rate falls below 100 bpm, up to 3 bursts of rapid atrial pacing will be performed from the CS proximal bipole. If AF or another arrhythmia initiates at any point during the burst pacing and is sustained over 30 seconds, the study will be terminated and the rhythm documented.

3.6 Assessment of Study Treatment Completion

At the Baseline Visit, upon completion of the study treatment, the Investigator will complete the Study Treatment CRF. The Investigator will record details from the study treatment procedure (e.g., pre-procedure medications, details regarding pericardial and transseptal access, and fluoroscopy time) and will indicate whether the study procedure was completed as intended.

4.0 PARTICIPANT EARLY TERMINATION

Full details regarding procedures for early termination will be outlined in the Operations Manual.

4.1 Untreated Randomized Participants

After randomization, if an exclusionary criterion is identified prior to or at the start of the study procedure, the participant will not undergo the study infusion procedure. Randomized participants may be early terminated, prior to commencing the study procedure, and will not receive the study infusion if any of the following study exclusions are identified:

- Participants who present in AF sustained >1 week
- If a participant does not present in sinus rhythm at the procedure, but he or she has proven to be in sinus rhythm at the enrollment visit, it is up to the attending whether or not to cardiovert the patient and proceed with study protocol. If the participant is to be cardioverted, the cardioversion should take place prior to transseptal puncture and following right catheter placement to minimize potential effects on AERP and conduction times. If a second AF episode initiates and is sustained over 2 minutes prior to initiation of study procedure, the study will be aborted.

These participants will be considered as “Untreated Participants”. Unrandomized participants who do not commence/receive the study infusion will not continue in follow-up and will not be included in analyses.

4.2 Unsuccessfully Treated Participants

After enrollment, if the study infusion commenced and was stopped and/or determined by the study Principal Investigator to be unsuccessful (i.e., immediately after the procedure, the investigator determines that the protocol was not completely executed) for any reason, the participant will continue in follow-up.

4.2.1 Early Stopping of Study Infusion Protocol ONLY

If the study infusion commenced and the participant develops AF that is sustained over 2 minutes during study procedure (excluding the AF susceptibility testing section), the patient should be cardioverted to sinus rhythm, at the discretion of his or her attending physician. If a second AF episode initiates and is sustained over 2 minutes, the study will be stopped. If a participant develops a non-AF tachyarrhythmia that persists over 2 minutes, it will be up to the attending physician to map and/or ablate the rhythms.

If the study infusion (ethanol or placebo) protocol commenced prior to AF development, the participant will not be early terminated and will continue in follow-up. These participants will be considered as “Unsuccessfully Treated Participants”.

4.3 Participant Withdrawals

Each participant will be informed that participation in the study is voluntary and that he or she may withdraw from the study at any time without effect on subsequent medical treatment or relationship with the treating physician. Participants who discontinue follow-up at any time after study treatment will be included in analyses.

4.4 Other Early Terminations

Participants who discontinue follow-up at any time after study treatment will be included in analyses.

Lost to Follow-Up: If a participant fails to return for at least one follow up visit (3, 6, and 12 months post-procedure) and cannot be reached by phone within the visit windows, the participant will be designated an early termination. The study personnel will show "due diligence" by documenting in the source documents, all steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. Vital status for participants lost to follow-up may be later obtained using outside records/death registries.

Principal Investigator Determination: Participants should also be early terminated at any time if the Principal Investigator concludes that it would be in the participant's best interest for any reason. Protocol deviations should not lead to early termination unless they indicate a significant risk to the participant's safety.

5.0 STUDY PROCEDURES

Table 2 provides an overview of the evaluations to be performed at each of the study visits. Full details regarding the all study measurements and timing of data collection will be outlined in the Operations Manual.

Table 2. Schedule of Evaluations and Visits

	Screening	Baseline	Follow-Up Visits		
		Study Infusion	Month 3	Month 6	Month 12/ Close-Out
Informed consent	x				
Inclusion/ Exclusion Evaluation	x				
Other laboratory evaluations	x				
Medical History	x				
Echo (TTE)*	x[1]				
Height	x				
Weight	x				
ECG	x	x			
Vital signs		x			
Concomitant Medications		x	x	x	x
Targeted Adverse Events		x	x	x	x
Serious Unexpected Adverse Events		x	x	x	x

Collection of materials for Targeted AEs/SAEs (if applicable)		x	x	x	x
Targeted medical care utilization (e.g., cardiac care during follow-up)			x	x	x

[1] *Must be performed ≥ 1 year prior to study procedure*

5.1 Screening for Inclusion/Exclusion Criteria & Randomization

Each potential participant's medical record will be reviewed for available inclusion and exclusion criteria data. After the participant provides informed consent, his or her medical history and additional demographic data will be obtained. Initial screening will occur at least 1 day prior to the patient's scheduled ablation procedure.

The pharmacy that prepares the ethanol/placebo infusion bags requires notification of the treatment assignment 1 business day prior to administration in order to prepare the infusion bag. Therefore, participants must be consented and randomized at least 1 day prior to the scheduled procedure.

Baseline measures will include:

- Inclusion/Exclusion criteria assessment
- Demographics and medical history
- World Health Organization AUDIT questionnaire
- CARDIA alcohol use questionnaire (shortened version)
- Vital signs
- Infusion, procedure, BrAC, and EP study measurements
- Arrhythmia episodes pre/during/post-procedure
- Adverse event assessment

5.2 Follow-up Visits (Months 3, 6, and 12)

Following an ablation, patients usually return to clinic at 3, 6, and 12 months post-procedure as per standard of care. HOLIDAY safety follow-up data will be collected by chart review. We will collect data on targeted AEs, serious, unexpected AEs, use of antiarrhythmic drugs, use of anticoagulation, incidence and burden of AF or atrial flutter, incidence of ablation or cardioversion, and emergency room visits since the last visit. Participants who do not return to clinic at 3, 6, and 12 months will be contacted by the Study Coordinator to conduct the visit by phone.

Follow-Up Visit measures will include:

- Medication use
- Arrhythmia episodes
- Cardioversions/ablations
- Adverse event assessment

5.3 Targeted Concomitant Medications

Current/regular use (since their last study visit) of a specific list of concomitant medications/therapies must be documented at Baseline (pre-study treatment) and at all follow-up visits. Medication data will be collected by chart review and will include type of medication,

frequency, and dosage. The list of targeted medications/therapies includes cardiovascular-related medications (e.g., anticoagulants and antiarrhythmics).

5.4 Targeted Adverse Event (AE) and Serious Unexpected Adverse Event (SAE) Evaluation and Reporting

An adverse event is any undesirable sign, symptom or medical condition occurring after initiation of the study treatment, even if the event is not considered to be related to study treatment. Medical conditions/diseases present before starting study treatment are only considered AEs if they worsen after starting study treatment (or any procedures specified in the study protocol).

A targeted adverse event (AE) is an event that may be reasonably anticipated to occur as a result of the study procedures or study participation or is part of the normal disease process or progression. Specific targeted AEs are documented in detail in the Operations Manual.

A serious unexpected adverse event (SAE) is defined as being unexpected if the event exceeds the nature, severity or frequency described in the current IRB Application, protocol, and consent form. An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation, or
- Due to a deviation from the IRB approved study protocol

After completion of the study treatment (at the Baseline Visit) and at all follow-up visits, safety evaluations will include monitoring for targeted adverse events and recording all serious adverse events for the assessment of the secondary exploratory study objective.

Information about targeted adverse events, whether volunteered by the subject, discovered by Principal Investigator questioning, or other means, will be collected and recorded and followed as appropriate.

As possible, each targeted adverse event will be described by:

- duration (start and end dates),
- severity grade (mild, moderate, severe),
- relationship to the study treatment and/or procedure (suspected/not suspected),
- action(s) taken and, as relevant, the outcome.

Even though planned/anticipated pregnancy is a study exclusion, pregnancy during follow-up may occur. If a female study participant should report pregnancy, this should be reported on a Protocol Deviation CRF. The pregnancy should be followed up to determine details of birth, outcome, including spontaneous or voluntary abortion, the presence or absence of any birth defects or congenital abnormalities, or any maternal/newborn hazards.

6.0 RISKS AND BENEFITS

6.1 Potential Risks

The primary risk to participants involves the receipt of IV ethanol. The procedure for IV ethanol infusion is well described and has previously been used for studies in the intoxication literature.[86-88] The target blood alcohol level of 0.08% that will be achieved is the legal limit for driving in California, and is equivalent to approximately 4 drinks of ethanol in a 180 pound man (equivalent to moderately heavy social drinking in one sitting). The use of IV ethanol in clinical settings is well established, with a long history of use in the treatment of such conditions as

methanol and ethylene glycol poisoning. The blood alcohol levels that have been used in such situations (0.1 to 0.2%) are higher than the level that we will use in our study (0.08%).[156, 157] Side effects from the ethanol infusion at our targeted dose may include mild headache, but it is unlikely to cause nausea and vomiting. Early studies with high dose IV ethanol infusions used for surgical anesthesia in the 1960s targeted to blood ethanol concentrations of 0.2 to 0.4% resulted in dizziness, nausea and/or vomiting.[158-160] Most of these symptoms resolved by 24 hours. In more recent experiments using the moderate levels of ethanol that we will target (0.08% blood alcohol concentration), only mild headache, with no nausea or vomiting, has been reported.[86-88] There have been no reports of serious adverse events with IV ethanol titrated by the BrAC quick clamp method. In addition, previous studies in which oral whiskey was administered to patients undergoing invasive electrophysiology (EP) studies (discussed above) did not result in any serious adverse events. While the total volume infused in either the ethanol group or the placebo (D5 half normal saline) group is not expected to exceed 500 cc, there is the theoretical possibility of causing volume overload; of note, patients with a history of heart failure or LVEF < 50% will be excluded. It is possible that ethanol may potentiate the side effects of other sedatives in patients undergoing AF ablation procedures, but this is unlikely. All of these cases are staffed by board certified anesthesiologists (with continuous 12 lead electrocardiograms, pulse oximetry, CO2 monitoring, and blood pressure monitoring per an arterial line per standard of care) as well as a cardiac EP attending, a cardiac EP fellow (board certified or board eligible in cardiology) and two nurses. All patients have several large sheaths in place for venous access, defibrillation pads already in place, and the intracardiac catheters can provide pacing if necessary. An echocardiography machine is immediately available in the EP laboratory and at least one on call interventional cardiologist and interventional cardiology fellow are available in the cardiac catheterization laboratory in the same suite

We observed no complications and no difficulties with recovery or wound healing in the 3 AF ablation patients receiving IV ethanol titrated to a blood ethanol concentration of 0.08% using the BrAC quick clamp method. We are not aware of any evidence to suggest that ethanol should adversely affect the efficacy of the AF ablation or the recovery or wound healing processes.

Additional risks include prolongation of the AF ablation procedure. We anticipate that the additional procedure time will average 40 minutes. The left atrial anatomic map will be created using the three dimensional mapping system per the standard clinical procedure while the ethanol or placebo infusion is started and titrated to steady state, helping to minimize any extra procedure time. This additional procedural time may minimally increase the patient's risk for stroke or sedation complications including pneumonia, deep vein thrombosis, or pulmonary embolism. Although the EP tests that will be performed and attempts to induce AF are consistent with standard of care during AF ablation procedures per the most recent expert consensus[10] (as well as standard of clinical practice in the UCSF cardiac EP laboratory), the potential induction of AF includes a risk of cardioversion, which may minimally increase the risk of skin burns and stroke. As per standard of care, all patients may undergo transesophageal echocardiograms immediately prior to the procedure to exclude the presence of a left atrial appendage thrombus and all will receive IV heparin with serial ACT monitoring to minimize the risk of stroke.

6.2 Potential Benefits

There are no direct benefits for participating in this study. However, the knowledge gained from this study may help to elucidate the mechanism underlying AF, which would be pertinent to the ~4 million Americans with the disease.[35, 54] In addition, understanding these particular cardiac

effects may ultimately benefit the greater than hundred million individuals that consume alcohol. This may be particularly important as the media often touts alcohol as being "heart healthy."[23-31]

7.0 Safety Monitoring

7.1 Data and Safety Monitoring Board (DSMB)

HOLIDAY has an independent DSMB that is responsible for safeguarding the interests of study participants, assessing the safety and validity of study procedures, and for monitoring the overall conduct of the study and outcomes data. The DSMB members are independent consultants to the PI at UCSF, and are required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the PI about:

- The effects of the HOLIDAY study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Adequacy of and amendments to consent forms
- Performance of the UCSF centers
- Participant safety
- Notification of and referral for abnormal findings

7.2 Safety monitoring for targeted adverse events

7.2.1 Intra procedure monitoring

During the procedure the patient will be monitored by a comprehensive care team. This will include the electrophysiology attending, the electrophysiology fellow (who is a board certified or board eligible cardiologist), the cardiac anesthesiologist attending (who will be unblinded), and 2 electrophysiology lab nurses. They will continually watch the patient for signs of distress, changes on the continual 12 lead electrocardiogram, hemodynamic changes on the arterial line blood pressure, continuous pulse oximetry and heart rate telemetry. If at any time there is a concern that the infusion is causing dangerous effects, it will be stopped immediately. Possible adverse events (AEs) include:

1. Hypotension: If hypotension occurs during the ethanol administration, intravenous fluids and presser medications will be administered as appropriate by the cardiac anesthesiologist. The anesthesiologist will have the prerogative to stop the infusion if he/she feels that the infusion is contributing to the hypotension and if it is not controlled with fluids or pressers.
2. Hypertension: If hypertension beyond a systolic blood pressure of 180 mmHg occurs during the ethanol administration, the cardiac anesthesiologist may administer intravenous blood pressure medications such as metoprolol, hydralazine, or nitroglycerin. The anesthesiologist will have the prerogative to stop the infusion if he/she feels that the infusion is contributing to the hypertension and if it is not controlled with blood pressure medications.
3. Atrial Fibrillation: This is to be expected and will be dealt with as appropriate. This may include electrical cardioversion or observation depending on what phase of the procedure the patient is in. It is important to emphasize that some of these procedures

are routinely performed while a patient is in atrial fibrillation for several hours or throughout the entire case.

4. Pulmonary compromise: The patients will be monitored by the anesthesia team throughout the procedure and the level of ethanol that we will target is not associated with respiratory depression. There is no evidence that ethanol (particularly at modest doses) affects oxygenation. The ethanol infusion can be stopped and the patient can be intubated if there are signs of pulmonary compromise.
5. Agitation: The patient will be monitored by the anesthesia team and agitation induced by ethanol will be dealt with appropriately with sedatives.

The PI will also monitor for AEs in all study participants. The research team will discuss the progress of the study and all AEs at weekly research and MMM conferences. At those meetings, feedback will be obtained from attendees. These meetings will also include the Chief of Cardiology, Chief of the EP service, head of quality assurance for electrophysiology, nurses, other EP faculty, fellows, and staff.

7.2.2 Post-Procedure Monitoring

We will monitor patients for up to 12 months via chart review and patient phone calls. Targeted adverse events will be recorded if reported/found at each study follow-up visit.

If three unexpected adverse events occur, then we will put the study on hold and discuss the circumstances associated with the adverse events with the EP group (including the Chief of Cardiology and Chief of Electrophysiology), the anesthesiologists that were present during those cases, and the DSMB. At that time, alternatives to the study design and the possibility of discontinuing the study will be discussed.

8.0 PROTOCOL DEVIATIONS

The Principal Investigator is required to adhere to the study protocol, the signed Principal Investigator's Agreement, applicable federal (national) or state/local, laws and regulations, and any conditions required by the IRB or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the clinical protocol was not followed. All deviations from the study protocol must be reported on the Protocol Deviation CRF to the UCSF CC, as soon as possible, but no later than 10 working days of notification of the event. In addition, all deviations must be reported to the local IRB per the IRB's reporting requirements. Protocol deviations will also be reported to the DSMB.

9.0 QUALITY ASSURANCE AND DATA MANAGEMENT

9.1 Clinical Site Investigator and Coordinator Training

Each investigator and coordinator will be trained on the study protocol and procedures to ensure accurate and consistent study methods are used study-wide and throughout the entire study duration. Trainings will include review of the protocol, operations manual, CRFs, event reporting, and data management procedures. If any protocol amendments occur during the study, research team trainings will be scheduled as needed.

9.2 Data Handling and Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the Principal Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study follow-up.

9.3 Source Documents

Study files will be kept in a secure location. Participant files should include archives of completed CRFs and source documents. The study case report forms (CRFs) are the primary data collection instrument for the study and are considered source documents. Source data also include original records of clinical findings, observations, or study measurement results (e.g., hospital records, clinical and office charts, laboratory notes, dispensing records, recorded data from automated instruments, and patient files).

9.4 Data Collection and Management

A member of the research team will enter data from each CRF into the study REDCap database. The study data is subjected to checks for completeness, consistency and validity. Upon completion of data collection and all data cleaning efforts have been performed, the database will be locked and analyses will commence.

10.0 STATISTICAL METHODS

Demographic and baseline characteristics will be described using mean with standard deviation, median and interquartile range, or proportions, where appropriate. The change in AERP and conduction times will be compared within cohorts using paired t-tests (if the outcome is not normally distributed, the Wilcoxon sign rank test will be used), and the changes in those values will be compared by treatment assignment (ethanol versus placebo) using t-tests or Wilcoxon rank sum tests as appropriate. The proportion with inducible AF will be compared by treatment assignment using the chi-squared test, and a logistic regression model will be utilized to adjust for potential confounders that are not addressed by randomization. Full details will be outlined in the Statistical Analysis Plan.

The Primary Analyses will be conducted in the “Analysis Population”, which includes all participants who are (1) randomized and (2) have received the study infusion. Secondary analyses will be conducted in the full “Randomized Population”, which includes all participants who have been randomized, whether or not they received the study infusion

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

11.1 Institutional Review Board (IRB) Approval

This protocol and any amendments will be submitted to a properly constituted IRB.

11.2 Informed Consent

Study personnel must explain to each participant (NOTE: consent by proxy is not allowed for this study) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. Patients will have to demonstrate adequate reasoning faculties and will have to demonstrate understanding of the implications, risks, benefits and alternatives to participating in the study before consent is obtained. This will include asking potential participants questions to assure they understand the ramifications of participation.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the participant cannot read or sign the document, oral presentation may be made or signature given by the participant's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the participant could not read or sign the documents. No participant will receive a study infusion before his/her informed consent has been obtained.

11.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the Declaration of Helsinki.

BIBLIOGRAPHY

1. Lauersen NH, Merkatz IR, Tejani N, Wilson KH, Roberson A, Mann LI, Fuchs F. Inhibition of premature labor: A multicenter comparison of ritodrine and ethanol. Am J Obstet Gynecol 1977;127:837-845
2. Bleicher SJ, Waltman R. Ethanol infusions. Lancet 1970;1:1404
3. Bourne HB, Ross RC, Philpott NW. Intravenous alcohol in obstetrical labour. Can Med Assoc J 1953;69:250-253
4. Fuchs F. Use of ethanol in prevention of premature delivery. Am J Obstet Gynecol 1971;110:1148-1149
5. Kesaniemi A, Kurpa K. Influence of ethanol on the rate of galactose elimination in women taking oral contraceptives and in pregnant women. Acta Obstet Gynecol Scand 1971;50:167-170
6. Lynn JM. Intravenous alcohol infusion for premature labor. J Am Osteopath Assoc 1970;70:167-170
7. Patel NB, Macnaughton MC. Premature labor--a new technique: The use of intravenous alcohol infusion in the prevention of premature labour. Nurs Times 1969;65:650-651
8. Watring WG, Benson WL, Wiebe RA, Vaughn DL. Intravenous alcohol -- a single blind study in the prevention of premature delivery: A preliminary report. J Reprod Med 1976;16:35-38
9. Zlatnik FJ, Fuchs F. A controlled study of ethanol in threatened premature labor. Am J Obstet Gynecol 1972;112:610-612
10. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, Dimarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D, Prystowsky EN, Damiano R, Jr., Jackman WM, Marchlinski F, McCarthy P. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the Heart Rhythm Society (HRS) task force on catheter and surgical ablation of atrial fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College Of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society Of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the heart Rhythm Society. Heart Rhythm 2012
11. Koyama T, Tada H, Sekiguchi Y, Arimoto T, Yamasaki H, Kuroki K, Machino T, Tajiri K, Zhu XD, Kanemoto-Igarashi M, Sugiyasu A, Kuga K, Nakata Y, Aonuma K. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation: A randomized controlled trial. J Am Coll Cardiol 2010;56:1463-1472
12. Substance abuse and mental health services administration, results from the 2010 national survey on drug use and health: Summary of national findings. NSDUH Series, H-41, HHS Publication No. (SMA) 11-4658. 2011
13. Malinski MK, Sesso HD, Lopez-Jimenez F, Buring JE, Gaziano JM. Alcohol consumption and cardiovascular disease mortality in hypertensive men. Arch Intern Med 2004;164:623-628

14. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW, Jr., Doll R. Alcohol consumption and mortality among middle-aged and elderly u.S. Adults. N Engl J Med 1997;337:1705-1714
15. Fuchs CS, Stampfer MJ, Colditz GA, Giovannucci EL, Manson JE, Kawachi I, Hunter DJ, Hankinson SE, Hennekens CH, Rosner B. Alcohol consumption and mortality among women. N Engl J Med 1995;332:1245-1250
16. Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among japanese men living in hawaii. N Engl J Med 1977;297:405-409
17. Berger K, Ajani UA, Kase CS, Gaziano JM, Buring JE, Glynn RJ, Hennekens CH. Light-to-moderate alcohol consumption and risk of stroke among u.S. Male physicians. N Engl J Med 1999;341:1557-1564
18. Abramson JL, Williams SA, Krumholz HM, Vaccarino V. Moderate alcohol consumption and risk of heart failure among older persons. JAMA 2001;285:1971-1977
19. Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rosner B, VanDenburgh M, Willett W, Hennekens CH. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829-1834
20. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Prior alcohol consumption and mortality following acute myocardial infarction. JAMA 2001;285:1965-1970
21. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319:267-273
22. Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA, Jr., Stampfer MJ, Willett WC, Rimm EB. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med 2003;348:109-118
23. Wikipedia. Alcohol and cardiovascular disease
24. Conley M. Alcohol may reduce death in men who survived heart attack ABC News. 2012
25. DeNoon D. Alcohol may lower risk of heart attack CBS News. 2007
26. Jaslow R. Men who drink two beers a day less likely to die after a heart attack CBS News. 2012
27. NewsCore. The health benefits of drinking red wine Fox News. 2012
28. Bakalar N. Study links alcohol to lower risk of coronaries New York Times. 2007
29. Bakalar N. Alcohol may help heart attack survivors New York Times. 2012
30. Parker-Pope T. Eating your way to a sturdy heart New York Times. 2008
31. Mann D. Moderate alcohol drinking may boost heart health WebMD. 2011
32. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, Writing Group for the Women's Health Initiative I. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. JAMA 2002;288:321-333
33. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, Women's Health Initiative I. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523-534
34. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (HERS) research group. JAMA 1998;280:605-613
35. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: Clinical implications. J Am Coll Cardiol 2001;37:371-378
36. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith

SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257-354-e257-354

37. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: A report from the American Heart Association. Circulation 2012;125:e2-e220
38. Chen J, Normand SL, Wang Y, Drye EE, Schreiner GC, Krumholz HM. Recent declines in hospitalizations for acute myocardial infarction for medicare fee-for-service beneficiaries: Progress and continuing challenges. Circulation 2010;121:1322-1328
39. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol 2009;53:13-20
40. Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom AR. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 us communities, 1987-2008. Circulation 2012;125:1848-1857
41. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155-2165
42. Koskinen P, Kupari M, Leinonen H, Luomanmaki K. Alcohol and new onset atrial fibrillation: A case-control study of a current series. Br Heart J 1987;57:468-473
43. Ettinger PO, Wu CF, De La Cruz C, Jr., Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": Alcohol-associated cardiac rhythm disorders. Am Heart J 1978;95:555-562
44. Lowenstein SR, Gabow PA, Cramer J, Oliva PB, Ratner K. The role of alcohol in new-onset atrial fibrillation. Arch Intern Med 1983;143:1882-1885
45. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840-844
46. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, Massaro JM, D'Agostino RB, Wolf PA, Ellison RC. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. Am J Cardiol 2004;93:710-713
47. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: A cohort study. Arch Intern Med 2004;164:1993-1998
48. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476-484
49. Mukamal KJ, Psaty BM, Rautaharju PM, Furberg CD, Kuller LH, Mittleman MA, Gottdiener JS, Siscovick DS. Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: The Cardiovascular Health Study. Am Heart J 2007;153:260-266
50. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: The Copenhagen City Heart Study. Circulation 2005;112:1736-1742

51. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley Study. Heart (British Cardiac Society) 2001;86:516-521
52. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, Anasako Y, Nishigaki Y, Yachi Y, Iida KT, Ohashi Y, Yamada N, Sone H. Alcohol consumption and risk of atrial fibrillation: A meta-analysis. J Am Coll Cardiol 2011;57:427-436
53. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation. Circulation 2004;110:1042-1046
54. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-125
55. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the united states. Value Health 2006;9:348-356
56. Kozak LJ, Lees KA, DeFrances CJ. National hospital discharge survey: 2003 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 2006:1-206
57. Engel TR, Luck JC. Effect of whiskey on atrial vulnerability and "holiday heart". J Am Coll Cardiol 1983;1:816-818
58. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J 1964;67:200-220
59. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230-246
60. Byrd GD, Prasad SM, Ripplinger CM, Cassilly TR, Schuessler RB, Boineau JP, Damiano RJ, Jr. Importance of geometry and refractory period in sustaining atrial fibrillation: Testing the critical mass hypothesis. Circulation 2005;112:I7-13
61. Chen PS, Chou CC, Tan AY, Zhou S, Fishbein MC, Hwang C, Karagueuzian HS, Lin SF. The mechanisms of atrial fibrillation. J Cardiovasc Electrophysiol 2006;17 Suppl 3:S2-7
62. Guerra JM, Everett THt, Lee KW, Wilson E, Olgin JE. Effects of the gap junction modifier rotigaptide (zp123) on atrial conduction and vulnerability to atrial fibrillation. Circulation 2006;114:110-118
63. Huang JL, Tai CT, Lin YJ, Ting CT, Chen YT, Chang MS, Lin FY, Lai WT, Chen SA. The mechanisms of an increased dominant frequency in the left atrial posterior wall during atrial fibrillation in acute atrial dilatation. J Cardiovasc Electrophysiol 2006;17:178-188
64. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. Circulation 1997;95:511-521
65. Nattel S, Shiroshita-Takeshita A, Brundel BJJM, Rivard Ln. Mechanisms of atrial fibrillation: Lessons from animal models. Prog Cardiovasc Dis;48:9-28
66. Tang M, Zhang S, Sun Q, Huang C. Alterations in electrophysiology and tissue structure of the left atrial posterior wall in a canine model of atrial fibrillation caused by chronic atrial dilatation. Circulation Journal: Official Journal of the Japanese Circulation Society 2007;71:1636-1642
67. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954-1968
68. Asano Y, Saito J, Matsumoto K, Kaneko K, Yamamoto T, Uchida M. On the mechanism of termination and perpetuation of atrial fibrillation. Am J Cardiol 1992;69:1033-1038
69. Buxton AE, Waxman HL, Marchlinski FE, Josephson ME. Atrial conduction: Effects of extrastimuli with and without atrial dysrhythmias. Am J Cardiol 1984;54:755-761

70. Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L. Electrophysiologic studies in atrial fibrillation. Slow conduction of premature impulses: A possible manifestation of the background for reentry. Am J Cardiol 1983;51:122-130
71. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666
72. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044-2053
73. Weiss JN, Garfinkel A, Karagueuzian HS, Qu Z, Chen PS. Chaos and the transition to ventricular fibrillation: A new approach to antiarrhythmic drug evaluation. Circulation 1999;99:2819-2826
74. Qu Z, Weiss JN, Garfinkel A. Cardiac electrical restitution properties and stability of reentrant spiral waves: A simulation study. Am J Physiol 1999;276:H269-283
75. Laurita KR. Role of action potential duration restitution in arrhythmogenesis. J Cardiovasc Electrophysiol 2004;15:464-465
76. Garfinkel A, Kim YH, Voroshilovsky O, Qu Z, Kil JR, Lee MH, Karagueuzian HS, Weiss JN, Chen PS. Preventing ventricular fibrillation by flattening cardiac restitution. Proc Natl Acad Sci U S A 2000;97:6061-6066
77. Narayan SM, Kazi D, Krummen DE, Rappel WJ. Repolarization and activation restitution near human pulmonary veins and atrial fibrillation initiation: A mechanism for the initiation of atrial fibrillation by premature beats. J Am Coll Cardiol 2008;52:1222-1230
78. Kim BS, Kim YH, Hwang GS, Pak HN, Lee SC, Shim WJ, Oh DJ, Ro YM. Action potential duration restitution kinetics in human atrial fibrillation. J Am Coll Cardiol 2002;39:1329-1336
79. Fisher VJ, Kavaler F. The action of ethanol upon the action potential and contraction of ventricular muscle. Recent Adv Stud Cardiac Struct Metab 1975;5:415-422
80. Gimeno AL, Gimeno MF, Webb JL. Effects of ethanol on cellular membrane potentials and contractility of isolated rat atrium. Am J Physiol 1962;203:194-196
81. Williams ES, Mirro MJ, Bailey JC. Electrophysiological effects of ethanol, acetaldehyde, and acetate on cardiac tissues from dog and guinea pig. Circ Res 1980;47:473-478
82. Gilmour RF, Jr., Ruffy R, Lovelace DE, Mueller TM, Zipes DP. Effect of ethanol on electrogram changes and regional myocardial blood flow during acute myocardial ischaemia. Cardiovasc Res 1981;15:47-58
83. Goodkind MJ, Gerber NH, Jr., Mellen JR, Kostis JB. Altered intracardiac conduction after acute administration of ethanol in the dog. J Pharmacol Exp Ther 1975;194:633-638
84. Gould L, Reddy CV, Becker W, Oh KC, Kim SG. Electrophysiologic properties of alcohol in man. J Electrocardiol 1978;11:219-226
85. Greenspon AJ, Schaal SF. The "holiday heart": Electrophysiologic studies of alcohol effects in alcoholics. Ann Intern Med 1983;98:135-139
86. Ramchandani VA, Bolane J, Li TK, O'Connor S. A physiologically-based pharmacokinetic (pbpk) model for alcohol facilitates rapid brac clamping. Alcohol Clin Exp Res 1999;23:617-623
87. Ramchandani VA, Plawecki M, Li T-K, O'Connor S. Intravenous ethanol infusions can mimic the time course of breath alcohol concentrations following oral alcohol administration in healthy volunteers. Alcohol Clin Exp Res 2009;33:938-944
88. O'Connor S, Morzorati S, Christian J, Li TK. Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. Alcohol Clin Exp Res 1998;22:202-210
89. Marcus GM, Smith LM, Whiteman D, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. Pacing Clin Electrophysiol 2008;31:266-272

90. Chen PS, Moser KM, Dembitsky WP, Auger WR, Daily PO, Calisi CM, Jamieson SW, Feld GK. Epicardial activation and repolarization patterns in patients with right ventricular hypertrophy. Circulation 1991;83:104-118
91. Haws CW, Lux RL. Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. Circulation 1990;81:281-288
92. Millar CK, Kralios FA, Lux RL. Correlation between refractory periods and activation-recovery intervals from electrograms: Effects of rate and adrenergic interventions. Circulation 1985;72:1372-1379
93. Yue AM, Franz MR, Roberts PR, Morgan JM. Global endocardial electrical restitution in human right and left ventricles determined by noncontact mapping. J Am Coll Cardiol 2005;46:1067-1075
94. Yue AM, Paisey JR, Robinson S, Betts TR, Roberts PR, Morgan JM. Determination of human ventricular repolarization by noncontact mapping: Validation with monophasic action potential recordings. Circulation 2004;110:1343-1350
95. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The audit alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory care quality improvement project (acquip). Alcohol use disorders identification test. Arch Intern Med 1998;158:1789-1795
96. Damato AN, Lau SH, Patton RD, Steiner C, Berkowitz WD. A study of atrioventricular conduction in man using premature atrial stimulation and his bundle recordings. Circulation 1969;40:61-69
97. Yu WC, Chen SA, Lee SH, Tai CT, Feng AN, Kuo BI, Ding YA, Chang MS. Tachycardia-induced change of atrial refractory period in humans: Rate dependency and effects of antiarrhythmic drugs. Circulation 1998;97:2331-2337
98. Narayan SM, Franz MR, Clopton P, Pruvot EJ, Krummen DE. Repolarization alternans reveals vulnerability to human atrial fibrillation. Circulation 2011;123:2922-2930
99. Krummen DE, Narayan SM. Mechanisms for the initiation of human atrial fibrillation. Heart Rhythm 2009;6:S12-16
100. Gerstenfeld EP, Callans DJ, Dixit S, Zado E, Marchlinski FE. Incidence and location of focal atrial fibrillation triggers in patients undergoing repeat pulmonary vein isolation: Implications for ablation strategies. J Cardiovasc Electrophysiol 2003;14:685-690
101. Oral H, Crawford T, Frederick M, Gadeela N, Wimmer A, Dey S, Sarrazin JF, Kuhne M, Chalfoun N, Wells D, Good E, Jongnarangsin K, Chugh A, Bogun F, Pelosi F, Jr., Morady F. Inducibility of paroxysmal atrial fibrillation by isoproterenol and its relation to the mode of onset of atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:466-470
102. Essebag V, Baldessin F, Reynolds MR, McClennen S, Shah J, Kwaku KF, Zimetbaum P, Josephson ME. Non-inducibility post-pulmonary vein isolation achieving exit block predicts freedom from atrial fibrillation. Eur Heart J 2005;26:2550-2555
103. Nguyen DT, Ding C, Wilson E, Marcus GM, Olgin JE. Pirfenidone mitigates left ventricular fibrosis and dysfunction after myocardial infarction and reduces arrhythmias. Heart Rhythm 2010;7:1438-1445
104. Gepstein L, Ding C, Rahmutula D, Wilson EE, Yankelson L, Caspi O, Gepstein A, Huber I, Olgin JE. In vivo assessment of the electrophysiological integration and arrhythmogenic risk of myocardial cell transplantation strategies. Stem Cells 2010;28:2151-2161
105. Ding C, Gepstein L, Nguyen DT, Wilson E, Hulley G, Beaser A, Lee RJ, Olgin J. High-resolution optical mapping of ventricular tachycardia in rats with chronic myocardial infarction. Pacing Clin Electrophysiol 2010;33:687-695
106. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, Vaz D, Olgin JE. Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. Circulation 2003;107:1816-1821

107. Everett THt, Verheule S, Wilson EE, Foreman S, Olgin JE. Left atrial dilatation resulting from chronic mitral regurgitation decreases spatiotemporal organization of atrial fibrillation in left atrium. Am J Physiol Heart Circ Physiol 2004;286:H2452-2460
108. Everett THt, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: A comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol 2006;291:H2911-2923
109. Lee KW, Everett THt, Rahmutula D, Guerra JM, Wilson E, Ding C, Olgin JE. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. Circulation 2006;114:1703-1712
110. Verheule S, Sato T, Everett Tt, Engle SK, Otten D, Rubart-von der Lohe M, Nakajima HO, Nakajima H, Field LJ, Olgin JE. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of tgf-beta1. Circ Res 2004;94:1458-1465
111. Verheule S, Wilson E, Banthia S, Everett THt, Shanbhag S, Sih HJ, Olgin J. Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. Am J Physiol Heart Circ Physiol 2004;287:H634-644
112. Verheule S, Wilson E, Everett Tt, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003;107:2615-2622
113. Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The cardiac arrhythmia suppression trial (CAST) investigators. N Engl J Med 1989;321:406-412
114. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: Morbidity and risk factors. J Intern Med 2001;250:382-389
115. George A, Figueredo VM. Alcoholic cardiomyopathy: A review. J Card Fail 2011;17:844-849
116. Piano MR. Alcoholic cardiomyopathy: Incidence, clinical characteristics, and pathophysiology. Chest 2002;121:1638-1650
117. Regan TJ. Alcoholic cardiomyopathy. Prog Cardiovasc Dis 1984;27:141-152
118. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscle. N Engl J Med 1989;320:409-415
119. Capasso JM, Li P, Guideri G, Malhotra A, Cortese R, Anversa P. Myocardial mechanical, biochemical, and structural alterations induced by chronic ethanol ingestion in rats. Circ Res 1992;71:346-356
120. Chan TC, Sutter MC. The effects of chronic ethanol consumption on cardiac function in rats. Can J Physiol Pharmacol 1982;60:777-782
121. Kim SD, Beck J, Bieniarz T, Schumacher A, Piano MR. A rodent model of alcoholic heart muscle disease and its evaluation by echocardiography. Alcohol Clin Exp Res 2001;25:457-463
122. Segel LD, Rendig SV, Mason DT. Left ventricular dysfunction of isolated working rat hearts after chronic alcohol consumption. Cardiovasc Res 1979;13:136-146
123. Vendemiale G, Grattagliano I, Altomare E, Serviddio G, Portincasa P, Prigigallo F, Palasciano G. Mitochondrial oxidative damage and myocardial fibrosis in rats chronically intoxicated with moderate doses of ethanol. Toxicol Lett 2001;123:209-216
124. Whitman V, Musselman J, Schuler HG, Fuller EO. Metabolic and functional consequences of chronic alcoholism on the rat heart. J Mol Cell Cardiol 1980;12:1249-1262
125. Zhang X, Li SY, Brown RA, Ren J. Ethanol and acetaldehyde in alcoholic cardiomyopathy: From bad to ugly en route to oxidative stress. Alcohol 2004;32:175-186
126. Burstein B, Libby E, Calderone A, Nattel S. Differential behaviors of atrial versus ventricular fibroblasts: A potential role for platelet-derived growth factor in atrial-ventricular remodeling differences. Circulation 2008;117:1630-1641

127. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: Mechanisms and implications. Circ Arrhythm Electrophysiol 2008;1:62-73
128. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The framingham heart study. Circulation 1994;89:724-730
129. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455-2461
130. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, Diamond PM, Marra MA, Gersh BJ, Wiebers DO, Petty GW, Seward JB. Left atrial volume: Important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001;76:467-475
131. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The framingham offspring study. Am J Epidemiol 1979;110:281-290
132. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: The framingham study. Am J Public Health Nations Health 1951;41:279-281
133. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, Weyman AE. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990;82:792-797
134. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997;96:3157-3163
135. McManus DD, Xanthakis V, Sullivan LM, Zachariah J, Aragam J, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left atrial diameter over the adult life course: Clinical correlates in the community. Circulation 2010;121:667-674
136. Becker HC. Animal models of excessive alcohol consumption in rodents. Curr Top Behav Neurosci 2013;13:355-377
137. Wang J, Carnicella S, Phamluong K, Jeanblanc J, Ronesi JA, Chaudhri N, Janak PH, Lovinger DM, Ron D. Ethanol induces long-term facilitation of NR2B-NMDA receptor activity in the dorsal striatum: Implications for alcohol drinking behavior. J Neurosci 2007;27:3593-3602
138. Wang J, Ben Hamida S, Darcq E, Zhu W, Gibb SL, Lanfranco MF, Carnicella S, Ron D. Ethanol-mediated facilitation of ampa receptor function in the dorsomedial striatum: Implications for alcohol drinking behavior. J Neurosci 2012;32:15124-15132
139. Rewal M, Donahue R, Gill TM, Nie H, Ron D, Janak PH. Alpha4 subunit-containing gabaa receptors in the accumbens shell contribute to the reinforcing effects of alcohol. Addiction biology 2012;17:309-321
140. Neasta J, Ben Hamida S, Yowell QV, Carnicella S, Ron D. Akt signaling pathway in the nucleus accumbens mediates excessive alcohol drinking behaviors. Biol Psychiatry 2011;70:575-582
141. Neasta J, Ben Hamida S, Yowell Q, Carnicella S, Ron D. Role for mammalian target of rapamycin complex 1 signaling in neuroadaptations underlying alcohol-related disorders. Proc Natl Acad Sci U S A 2010;107:20093-20098
142. Jeanblanc J, Logrip ML, Janak PH, Ron D. Bdnf-mediated regulation of ethanol consumption requires the activation of the map kinase pathway and protein synthesis. Eur J Neurosci 2012
143. Jeanblanc J, He DY, McGough NN, Logrip ML, Phamluong K, Janak PH, Ron D. The dopamine D3 receptor is part of a homeostatic pathway regulating ethanol consumption. J Neurosci 2006;26:1457-1464
144. Carnicella S, Yowell QV, Ron D. Regulation of operant oral ethanol self-administration: A dose-response curve study in rats. Alcohol Clin Exp Res 2011;35:116-125.

145. Carnicella S, Kharazia V, Jeanblanc J, Janak PH, Ron D. GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. Proc Natl Acad Sci U S A 2008;105:8114-8119
146. Carnicella S, He DY, Yowell QV, Glick SD, Ron D. Noribogaine, but not 18-MC, exhibits similar actions as ibogaine on GDNF expression and ethanol self-administration. Addict Biol 2010;15:424-433.
147. Carnicella S, Ahmadiantehrani S, He DY, Nielsen CK, Bartlett SE, Janak PH, Ron D. Cabergoline decreases alcohol drinking and seeking behaviors via glial cell line-derived neurotrophic factor. Biol Psychiatry 2009;66:146-153.
148. D'Souza El-Guindy NB, Kovacs EJ, De Witte P, Spies C, Littleton JM, de Villiers WJ, Lott AJ, Plackett TP, Lanzke N, Meadows GG. Laboratory models available to study alcohol-induced organ damage and immune variations: Choosing the appropriate model. Alcohol Clin Exp Res 2010;34:1489-1511.
149. Mandyam MC, Vedantham V, Scheinman MM, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Gerstenfeld EP, Olgin JE, Marcus GM. Alcohol and vagal tone as triggers for paroxysmal atrial fibrillation. Am J Cardiol 2012;110:364-368
150. Marques PR, McKnight AS. Field and laboratory alcohol detection with 2 types of transdermal devices. Alcohol Clin Exp Res 2009;33:703-711
151. Gnann H, Engelmann C, Skopp G, Winkler M, Auwarter V, Dresen S, Ferreiros N, Wurst FM, Weinmann W. Identification of 48 homologues of phosphatidylethanol in blood by LC-ESI-MS/MS. Anal Bioanal Chem 2010;396:2415-2423.
152. Hahn JA, Dobkin LM, Mayanja B, Emenyonu NI, Kigozi IM, Shiboski S, Bangsberg DR, Gnann H, Weinmann W, Wurst FM. Phosphatidylethanol (PETH) as a biomarker of alcohol consumption in HIV-positive patients in sub-saharan africa. Alcohol Clin Exp Res 2012 36(5):854-62.
153. Hougaard P. A class of multivariate failure time distributions. Biometrika 1986;73:671-678
154. Helping patients who drink too much: A clinician's guide, updated 2005 edition. NIH Publication No. 07–3769. 2007.
155. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): A community-based cohort study. Lancet 2009;373:739-745.
156. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA, American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol P. American academy of clinical toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol 2002;40:415-446.
157. Scalley RD, Ferguson DR, Piccaro JC, Smart ML, Archie TE. Treatment of ethylene glycol poisoning. Am Fam Physician 2002;66:807-812.
158. Isaac M, Pandit SK, Dundee JW, Galway JE. Intravenous ethanol anaesthesia. A study of sequelae and their implications. Acta Anaesthesiol Scand 1971;15:141-155
159. Dundee JW, Isaac M. Dosage studies with intravenous ethanol. Br J Anaesth 1969;41:554
160. Dundee JW. Intravenous ethanol anesthesia: A study of dosage and blood levels. Anesth Analg 1970;49:467-475.
161. Halonen J, Halonen P, Jarvinen O, Taskinen P, Auvinen T, Tarkka M, Hippelainen M, Juvonen T, Hartikainen J, Hakala T. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A randomized controlled trial. JAMA 2007;297:1562-1567.
162. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (atria) study. JAMA 2001;285:2370-2375.

163. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and african-americans: The atherosclerosis risk in communities (ARIC) study. Am Heart J 2009;158:111-117
164. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA, Fox ER, Levitzky YS, Mehra R, Kerr KF, Deo R, Sotoodehnia N, Akylbekova M, Ellinor PT, Paltoo DN, Soliman EZ, Benjamin EJ, Heckbert SR. European ancestry as a risk factor for atrial fibrillation in african americans. Circulation 2010;122:2009-2015
165. Marcus GM, Olgin JE, Whooley M, Vittinghoff E, Stone KL, Mehra R, Hulley SB, Schiller NB. Racial differences in atrial fibrillation prevalence and left atrial size. Am J Med 2010;123:375 e371-377