DECAF

Does Eliminating Coffee Avoid Fibrillation?

A randomized controlled trial to assess abstinence of coffee compared to continued consumption on recurrent atrial fibrillation following cardioversion

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ADMINISTRATIVE INFORMATION SUMMARY

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1.0 INTRODUCTION

1.1. Background and Significance

Atrial fibrillation (AF) is the most common, sustained heart rhythm disorder experienced by humans. It is anticipated that more than 10 million individuals in the United States will have AF by 2050.[1] This is concerning as AF is associated not only with complications including heart failure, stroke, and premature death, but also troubling symptoms such as palpitations, dyspnea, and fatigue.[2] As a result, the burden of AF-related symptoms and complications on affected individuals and society is growing, as represented by increasing hospitalizations and healthcare costs.[3] There is thus a pressing need to characterize modifiable factors that may reduce the incidence, prevalence, and overall impact of AF.

Coffee is one of the most ubiquitously consumed substances worldwide. In addition to caffeine, coffee contains a variety of other biologically active compounds.[4] Correspondingly, whether any effect of coffee on health outcomes exists is of considerable interest to physicians, scientists, and individual consumers. While significant data exist on the potential impact of coffee on many cardiometabolic parameters, [4] there is conflicting data on any role of coffee on AF.[5] Given both the increasing population impact of AF and the widespread use of coffee in society, determining even a modest associated benefit or risk would be of great clinical relevance.

1.2. Possible Mechanisms of Coffee and its Constituents

Amongst the constituent compounds in coffee, the majority of prior research has focused on caffeine. While the caffeine content of coffee varies significantly, an average cup is estimated to contain between 95 and 200mg of caffeine.[6] Caffeine is a methylxanthine alkaloid and a potent central nervous system stimulant. It also exerts a range of cardiovascular effects that may facilitate atrial arrhythmogenesis. This includes sympathetic stimulation, enhanced automaticity, and increased after depolarization-induced triggered activity.[5] Conversely, caffeine also has mechanisms that might reduce AF; for example, caffeine inhibits adenosine which can trigger AF, and it additionally has some antioxidant activity. Finally, it has been estimated that coffee contains over 1,000 compounds, including some with described biological effects such as diterpene alcohols and chlorogenic acid.[4] As a result, there are plausible mechanisms for coffee and its constituents to have both beneficial and harmful cardiovascular and arrhythmic effects.

1.3. Prior Observational Studies on Coffee, Caffeine, and AF

A number of prior observational studies have evaluated the role of chronic coffee consumption and incident AF with varied results. In the Multifactor Primary Prevention Study, moderate coffee consumption of 1-4 cups per day was associated with increased risk.[7] Similarly, intermittent coffee consumption of less than 0.5 cups/day appeared to be associated with greater AF risk in the Multi-Ethnic Study of Atherosclerosis.[8] In contrast, several reports have found no clear relationship between coffee or caffeine intake and incident AF. These include reports from the Danish Diet, Cancer, and Health Study,[9] the Framingham heart Study,[10] two Cohort of Swedish Men,[11] and the Swedish Mammography Cohort.[11] Conversely, other studies have described results potentially consistent with a linear benefit of increasing coffee consumption. These include reductions of risk in hospitalized Kaiser Permanente patients,[12] an updated analysis from the Danish Diet, Cancer, and Health Study,[13] an Italian cohort,[14] and the UK Biobank.[15] Finally, a few investigators have demonstrated J- or U-shaped associations with benefit at modest intakes no effect or harm at higher levels, such as that seen in the Women's Health Study,[16] Physicians' Health Study,[17] the Seguimiento Universidad de Navarra (SUN) cohort,[18] and the Prevencion con Dieta Mediterranea (PREDIMED) cohort.[18] Meta-analyses including the aforementioned studies have concluded either no effect or a reduced AF risk with coffee consumption.[11, 19, 20] Furthermore, Mendelian randomization techniques using alleles associated with caffeine metabolism and hence coffee consumption have also not provided supportive evidence for any significant effect on AF.[15, 21]

Comparatively fewer studies exist on the role of acute coffee or caffeine ingestion, or on AF and related outcomes in other settings. One study found that acute intravenous administration of caffeine did not alter invasive measures of cardiac conduction or refractoriness.[22] Two reports suggest that modest coffee consumption may

be associated with a greater likelihood for spontaneous cardioversion compared to higher consumption.[23, 24] Furthermore, no association between caffeine intake and atrial ectopy was found in another analysis from the Cardiovascular Health Study.[25]

1.4. Current Consumer and Physician Beliefs

Despite the varied evidence described above, established notions exist that coffee and caffeine contribute to AF and/or trigger AF episodes. In a large study of symptomatic patients with paroxysmal AF, caffeine was reported as the second most common triggering factor in almost one-third of individuals.[26] Prior surveys of physicians have also suggested reductions in caffeine to assist with arrhythmias.[27] Conversely, professional society guidelines either do not discuss coffee or caffeine [28] or suggest they are unlikely to contribute based on recent studies.[29]

1.4. Rationale for Current Study

A key limitation of existing data on the effects of coffee and caffeine on AF has been their observational nature. Even with careful study design methodology, including prospective data collection, comprehensive characterization of participants, and appropriate analytical techniques, it is challenging if at all feasible to eliminate the possibility of biases in observational studies such as residual confounding and reverse causality.[30] Instead, appropriate randomization of subjects to an exposure of interest is more likely to produce reliable, unbiased results where observational evidence is conflicting or requires confirmation.[31] To the best of our knowledge, no such assessment on the effect of coffee on AF outcomes has been undertaken to date.

While the general effect of coffee or caffeine on incident AF would be of significant interest, undertaking a randomized trial in this setting would be challenging and likely to require an extremely large number of otherwise healthy individuals to agree to consume or abstain. Many individuals may find this objectionable given the widely consumed nature of coffee and caffeine-containing substances.

An alternative and potentially more practical setting would be in patients with existing AF who are not only at higher risk for (recurrent) AF episodes but may be more likely to be interested in such a randomized evaluation given their personal situation.

Thus, this study proposes to evaluate the effect of random allocation to coffee abstinence compared to continued caffeinated coffee consumption in patients undergoing cardioversion for AF, with patients being followed up for recurrent episodes of AF.

This study will provide the first, randomized evaluation of coffee on AF outcomes. Given the conflicting evidence to date and widespread consumption of coffee, this study will be of significant interest to consumers and physicians alike.

2.0 INVESTIGATIONAL PLAN

2.1 Study Design

This study is an investigator-initiated, prospective, open-label, randomized (1:1) clinical trial of coffee abstinence compared to coffee continuation on recurrent AF in patients undergoing cardioversion.

This study will be conducted at the coordinating center in the United States (the University of California, San Francisco), in Australia (University of Adelaide), and in Canada (Sunnybrook Health Sciences Centre). Two-hundred (200) participants total will be enrolled and randomized.

2.1.1 Study Visits and Windows

After screening and eligibility has been determined, participants will be enrolled and randomized at the baseline visit (date of cardioversion).

No in-person follow-up visits will be required. Phone call follow-ups will be conducted at week 1, month 1, month 3, and month 6 until first recurrence of AF or study completion (whichever comes first). This will be supplemented with chart review, including scanned medical records if the patient does not return for medical care, and analyses of ECG strips obtained from AliveCor (San Francisco, CA) KardiaMobile devices and Apple Watch (Cupertino, CA) devices already owned and in use by patients.

Table 1 outlines the window for each of the study visits. Clinical sites should 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
V1a-V1b (Screening)		
V1c (Baseline)	Enrollment/Cardioversion	
V2	Month 1*	+/- 7 days
V3	Month 3*	+/- 7 days
V4	Month 6*	+/- 14 days

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

In the occasional event that routine clinical pre-operative care does not allow adequate time for study coordinators to approach potentially eligible patients for the baseline visit prior to their cardioversion procedure, study coordinators may call patients who were successfully cardioverted to normal sinus rhythm within a week after their cardioversion procedure to see if they are interested in participating. Visits V1a-V1c will be carried out remotely in this case. In this occasional remote situation, if a patient chooses to take part in the study, informed consent will be obtained through Docusign and they will be randomized to either continue or abstain from coffee. Phone call follow-ups Visits V2-V4 will accordingly be conducted at month 1, month 3, and month 6 until first recurrence of AF or study completion (whichever comes first).

Figure 1. Study Flow Diagram

Pre-Cardioversion Screening

- Initial inclusion/exclusion evaluation
- Screen for coffee consumption habits (≥ 1 cup of coffee per day)
- Screen for significant other caffeinated product consumption
- Informed consent

Baseline Visit (Cardioversion)

- Enrollment
- Demographics
- Height and weight
- Detailed history of coffee consumption habits
- Detailed history of alcohol consumption habits
- Detailed medical and medication history
- Cardioversion
- Assess pre- and post-cardioversion ECG
- Randomization to allocated treatment (coffee abstinence or continuation), provided as an instruction card and/or instruction letter they receive after cardioversion

Follow-Up Phone Calls at Month 1, 3, and 6

- Compliance with allocated treatment
- Consumption of coffee or other caffeinated products, if applicable
- Consumption of alcohol
- Symptomatic and/or known diagnosis of recurrent AF
- ECG strips from patient owned AliveCor KardiaMobile or Apple Watch (if required)
- AE/SAE evaluation
- Vital status

Recurrent AF Documentation from Physician/Healthcare Provider

- Documentation of ECG or any ambulatory ECG monitoring to confirm recurrent AF obtained from physician/healthcare provider if:
    - If patient reports diagnosis of recurrent AF
    - Patient not sure if has been diagnosed with recurrent AF
    - Patient declines further phone follow-up but still consents to access to physician/healthcare provider documentation
    - Patient unable to be contacted via phone

2.2 Study Objectives

The objectives of this clinical trial are to assess the effect of abstaining from coffee compared to continuation of coffee on the first recurrence of AF following cardioversion.

Primary objectives:

- To assess the number of people with first confirmed clinical recurrence of AF or atrial flutter, or device-detected recurrence lasting longer than 30 seconds, following cardioversion in the coffee abstinence group compared to the continued caffeinated coffee consumption group analyzed as a time-to-event outcome

Secondary exploratory objectives include assessment of the following:

- Adverse events before censorship, including myocardial infarction, stroke or transient ischaemic attack, heart failure exacerbation, syncope, emergency department visit, hospitalization, and death
- Atrial flutter and atrial fibrillation separately as incident outcomes

2.3 Inclusion/Exclusion Criteria

2.3.1 Inclusion Criteria

Patients must meet **all** of the following to be eligible:

1. Men or women ≥ 21 years of age
2. Sustained atrial fibrillation or atrial flutter (provided patient has history of atrial fibrillation)
3. Planned/scheduled direct current electrical cardioversion
4. Consumption greater than or equal to one cup of coffee per day sometime in the past 5 years
5. Willing and able to comply with coffee abstinence or continuation for at least 6 months
6. Life expectancy of at least 6 months
7. Willing and able to return and comply with scheduled phone follow up visits
8. Willing and able to provide written informed consent

2.3.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Established allergy or adverse reaction to coffee
2. Stated inability to comply with coffee abstinence or continuation
3. Atrial fibrillation ablation in preceding 3 months or planned in next 3 months
4. Recent cardiothoracic surgery in preceding 3 months
5. Pregnancy or desire to get pregnant within next 6 months.
6. Current enrollment in an investigation or study of a cardiovascular device or investigational drug that would interfere with this study
7. Any other criteria, which would make the patient unsuitable to participate in this study as determined by the Principal Investigator (e.g., an uncontrolled drug and/or alcohol addiction)

3.0 STUDY TREATMENT

After eligibility for the study has been confirmed, participants will be randomized to abstinence from coffee or continued consumption of caffeinated coffee. Participants will undergo this intervention until the primary endpoint of AF recurrence, end of study (month 6), or study withdrawal, after which they will consume or abstain from coffee at their discretion.

3.1 Coffee Abstinence

If allocated to coffee abstinence, patients will be encouraged to completely abstain from coffee and other caffeine-containing products as much as feasibly possible. As some decaffeinated coffee can also contain caffeine, patients will be encouraged to abstain from decaffeinated coffee as well. Other non-coffee caffeine-containing products to

avoid will include, but not be limited to, tea, cola, energy drinks, chocolate, chewing gum, and chocolate- or coffee-flavored foods (e.g. ice cream).

3.2 Continued Coffee Consumption

If allocated to continued coffee consumption, patients will be encouraged to drink at least one cup of caffeinated coffee (or one espresso shot) daily and other caffeine-containing products as per their usual lifestyle. It will be recommended that patients do not intentionally increase or decrease consumption of these products.

4.0 EARLY TERMINATION

If a randomized participant terminates participation in the study early (i.e., prior to completion of all follow-up), the Principal Investigator will determine the primary reason for early termination and report this. Participants who early terminate from the study will not be replaced with newly enrolled participants.

4.1 Randomized Participants – with exclusion found on day of cardioversion

A proportion of patients scheduled for electrical cardioversion do not convert to sinus rhythm, outlined in more detail below. Thus, randomization will be undertaken after successful cardioversion from AF to sinus rhythm in order to minimize exclusion of randomized patients for this reason.

In the event that another exclusion criterion is identified on the day of cardioversion after randomization has occurred, the participant may or may not continue to be treated as allocated as deemed appropriate by the Principal Investigator. All randomized patients will be included in the ITT analyses.

4.2 Unsuccessful cardioversion

Patients will be interviewed and consented prior to cardioversion occurring. However, a small proportion of patients do not have successful cardioversion. As a result, randomization will occur after successful cardioversion from AF to sinus rhythm. Patients will be excluded in the event that cardioversion is unsuccessful.

4.3 Participant Withdrawals

Each participant will be informed that participation in the study is voluntary and that he/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 randomization will be included in the ITT analyses.

4.4 Other Early Terminations

Participants who discontinue follow-up at any time after randomization will be included in the ITT analyses.

Lost to Follow-Up: If a participant is unable to be contacted via phone for follow-up (i.e. participants who become lost to follow up and whose status is unclear because they fail to appear for study visits without stating an intention to withdraw) for any other reason and the study team is unable to confirm the status of their atrial fibrillation post-cardioversion upon review of their medical record at study follow up visits, the participant will be designated an early termination. The clinical site Principal Investigator should 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.

In the absence of a stated intention to withdraw, the physician or other healthcare professional of participants may be contacted in an attempt to ascertain the presence or absence of AF recurrence.

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.

Early Study Closure: The study may be terminated due to safety concerns. Should this be necessary, participants currently in follow-up will be early terminated and scheduled for a Close-Out Visit, as soon as possible. The Principal Investigator will be responsible for informing the appropriate local Institutional Review Board of the early study termination.

5.0 STUDY PROCEDURES

Table 2 provides an overview of the evaluations to be performed at each study visit/follow-up. See also Figure 1, the study flow diagram, for details on timing of these evaluations.

Table 2. Schedule of Evaluations and Visits

	Screening	Baseline	Follow-Up Phone Calls		
	Visits 1a-1b	**Visit 1c**	**Visit 2**	**Visit 3**	**Visit 4**
			Month 1	Month 3	Month 6
		Cardioversion			
Initial inclusion/exclusion evaluation	X				
Screen for coffee consumption habits	X				
Screen for significant other caffeinated product consumption	X				
Informed consent	X				
Demographics		X			
Height and weight		X			
Detailed history of coffee consumption habits		X	X	X	X
Detailed history of alcohol consumption habits		X	X	X	X
Detailed medical history		X	X	X	X
Targeted medication history		X	X	X	X
Assessment of clinically available pre-cardioversion ECG		X			
Assessment of clinically available post-cardioversion ECG		X			
Randomization		X			
Detailed history of other caffeinated product consumption			X	X	X
AF symptoms			X	X	X
Assessment of AliveCor KardiaMobile or Apple Watch ECG strip			X	X	X
Assessment of clinically available ECG or ambulatory			X	X	X

ECG monitoring from physician/healthcare provider					
Adverse events/serious adverse events evaluation			X	X	X
Targeted medical care utilization			X	X	X
Vital status			X	X	X

5.1 Screening for Inclusion/Exclusion Criteria

Each potential participant's medical record will be briefly reviewed for available inclusion and exclusion criteria data. Potentially eligible patients will be subsequently approached to ascertain interest and coffee/other caffeinated product consumption. After informed consent is obtained, pre- and post-cardioversion ECGs will be assessed to record AF and sinus (or other appropriate non-AF underlying) rhythm respectively. Once this is confirmed, randomization will be undertaken.

5.5 Electrocardiogram (ECG)

Pre- and post-cardioversion electrocardiogram (ECG) data will be assessed at baseline. Results from the ECG test will be entered onto the case report form (CRF).

5.6 Physical Examination and Medical History

The screening evaluation will collect medical history data for assessment of inclusion/exclusion criteria, including coffee/other caffeinated product consumption history.

5.7 Targeted Medication Inventory

Current/regular use (since the last study follow up) of a specific list of concomitant medications/therapies will be documented at baseline (post cardioversion) and at all follow-up visits. Medication data will be collected by self-report and electronic medical record on a CRF and will include type of medication. The list of targeted medications/therapies includes AF-related medications (e.g., anticoagulants, antiarrhythmics, negative chronotropic agents).

5.8. Specific Adverse Events

Site personnel will review medical records to determine if any of the prespecified AEs occur:

1. Any death
2. Myocardial infarction
3. Stroke/transient ischemic attack
4. Heart failure exacerbation
5. Hospitalization
6. Syncope
7. Emergency Room Visit

6.0 Risks and Benefits of the Study

6.1 Cardioversion Procedure

The cardioversion procedure involves several risks, but each of these participants would experience these risks whether or not they choose to participate in DECAF or not, since inclusion is this trial requires already having a planned/scheduled cardioversion procedure. The known risks have been shown to occur in less than 1% of cases and include adverse reaction from administered medications for sedation/anesthesia, lack of success, induction of another arrhythmia, skin burn, or stroke or transient ischemic attack. Potential benefits of cardioversion include reduction in symptoms (such as palpitations, shortness of breath, and dizzy spells), improvement in energy/well-being, and strengthening of heart function (if AF is a major cause or contributor to weakened function).

6.2 Coffee Abstinence or Continuation

Abstinence from coffee and other caffeine-related products may result in caffeine-withdrawal, symptoms of which can include headache, fatigue, anxiety, difficulty concentrating, depressed mood, irritability, tremors, and low energy. It is not clear what effect, if any, coffee has on AF and AF recurrence; this forms the rationale for the present study. Potential benefits of coffee abstention may therefore include a reduction in AF recurrence. Conversely, it may be possible that coffee consumption is beneficial and abstinence may result in a greater likelihood of AF recurrence.

7.0 STUDY ROLES

The DECAF study has been developed by the Principal Investigator at the University of California, San Francisco (UCSF). The study investigators are committed to conducting this study in a uniform manner, adhering to the study protocol and the operations manual. Standardization, supervision, and coordination of all procedures will be enhanced through peer review and quality control mechanisms.

7.1 Administrative Organization

DECAF is organized and conducted by the coordinating center, the University of California San Francisco (UCSF) under the guidance of the Principal Investigator.

7.2 Enrolling Clinical Site

The study will be conducted at 3 sites.

The Coordinating Center for DECAF will be at the University of California, San Francisco. Another site is University of Adelaide, Adelaide, Australia. The final site is Sunnybrook Health Sciences Centre, Toronto, Canada.

7.2.1 Clinical Site Principal Investigator

This study protocol will be conducted by the Principal Investigator and his staff. The Principal Investigator has experience in and will be responsible for:

- Conducting the study protocol in accordance with the signed agreement with the UCSF, the study protocol, all applicable FDA regulations (21 CFR Parts 50, 54, 56, 812), GCP guidelines, and any conditions of approval imposed by the IRB
- Providing IRB Approval and an Approved Informed Consent
- Screening and selecting appropriate participants
- Collection and archiving of data obtained pursuant to the requirements of the study protocol during the course of the study and after the study has been completed

It is acceptable for the Principal Investigator to delegate one or more of the above functions to an associate or co-Investigator, however, the Principal Investigator remains responsible for the proper conduct of the study protocol, complying with the study protocol, and collecting all required data.

8.0 PROTOCOL DEVIATIONS

Principal Investigators are required to adhere to the study protocol, 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 major deviations from the study protocol will be reported, as soon as possible, but no later than 10 working days of notification of the event. In addition, all major deviations will be reported to the UCSF CC, as well as the local IRB as appropriate, per the IRB's reporting requirements.

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.

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 study participants
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant 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

Complete study files will be kept in a secure location. Participant files will include archives of completed CRFs and source documents. The CRFs are the primary data collection instrument for the study and are considered source documents. All data requested on the CRF will be recorded. 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

The data will be compiled into the central study database at UCSF. Sites will collect and enter study data onto electronic CRFs via the online study database, REDCap. The study data will be stored in the study database at UCSF and will be subjected to checks for completeness, consistency and validity. Data entry will occur in a timely manner.

For all procedures, clinical site personnel will only have access to their own site data.

9.5 Data Monitoring

[The investigators] will be responsible for monitoring procedures related to study conduct and data collection/reporting to ensure the quality and integrity of the study data. A representative will check the completeness of participant study records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, as per the DECAF Monitoring Guidelines.

To ensure data quality, we will perform the following Quality Assurance procedures: after the first two participants are randomized and the study intervention is performed, 100% of inclusion/exclusion criteria and key baseline data points will be reviewed against source documentation collected from the site (such as the participant's de-identified initial EP H&P, procedure note and first follow-up EP note). In addition, specified de-identified documentation will be requested from each site to perform source verification on a random 10% sample of key study data. If during the course of the study the error rate exceeds a 5% threshold, the percentage of source verification will increase until control is demonstrated.

10.0 STATISTICAL METHODS

10.1 Sample Size and Randomization

The goal of this trial is the enroll a total of 200 participants (n=100 per treatment group).

Assuming a 0.05 two-tailed alpha level, 1:1 randomization scheme, 50% recurrence rate in the absence of coffee, and potential 10% loss to follow-up, a sample size of n=200 (100 per arm) will provide approximately 80% power to detect a 1.63 times increased hazard of AF recurrence between the groups.

The table below summarizes the minimum detectable relative hazards in Cox models with binary predictor, by baseline AF recurrence rate (RR) (rows) and Percent Lost to Follow up (LTFU) (columns)

	5% LTFU	10% LTFU
50% RR	1.68	1.69
60% RR	1.62	1.63

Randomization will be performed 1:1 with stratification across sites.

10.2 Intention-to-Treat (ITT)

The main intention-to-treat (ITT) analysis set will include all randomized participants, whether or not they are compliant with the treatment allocation for this trial. Every attempt will be made to collect data until the end of the follow-up period for all randomized participants and these data will be included as part of the main ITT analysis. The analyses for the primary objective will be performed using the ITT dataset.

Although substantial crossover is not anticipated, as treated and per protocol analyses will also be conducted if failure to comply with allocated treatment assignments occurs in more than 10% of cases or if there is a significantly different proportion of assignment adherence in one group compared to the other.

11.0 PUBLICATION

Any presentation/publication of any data from this study must be approved by the Principal Investigator prior to release.

12.0 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.

12.1 Institutional Review Board (IRB) and Ethics Committee (EC) Approval

This protocol and any amendments will be submitted to a properly constituted independent IRB for each clinical site, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the Principal Investigator. The Principal Investigator at each site should also provide a list of IRB members and their affiliates to the UCSF CC.

12.2 Informed Consent

The investigator and/or study coordinator must explain to each participant 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.

This informed consent should 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 can enter the study before his/her informed consent has been obtained.

The informed consent form must be submitted by the investigator for IRB approval. An informed consent template will be provided to all of the clinical sites for their use. Any changes to the template consent form suggested by the Investigator must be agreed to by the UCSF CC before submission to the local IRB, and a copy of the approved version must be provided to UCSF CC after IRB approval.

12.3 Declaration of Helsinki

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

SUMMARY OF PROTOCOL CHANGES

Protocol Date	Description of Change	Brief Rationale
Sept 5, 2021	Original version	N/A
Oct 19, 2021	Study duration changed from 12 to 6 months	To facilitate recruitment given frequent reluctance of patients to abstain from coffee
	Addition of Month-1 follow-up visit	To add an earlier timepoint than Month-3 given reduction in study duration to 6 months
	Amendment of inclusion criteria: "sustained AF or atrial flutter (provided patient has a history of AF)"	Given previous lack of reference to atrial flutter, to clarify that patients in flutter at time of cardioversion were eligible if they also had a history of AF
	Amendment of exclusion criteria: "recent/planned AF ablation within 6 months"	Previously was 12 months - change to reflect reduction in study duration to 6 months
	Correction of remaining references to previous study title to "DECAF" throughout document	Completion of prior change not undertaken throughout document in some places
January 19, 2023	Addition of second site: University of Adelaide	To facilitate recruitment
	Clarification of primary objective: "time to first confirmed AF recurrence and/or Aflutter recurrence following cardioversion"	Given previous lack of reference of atrial flutter, to clarify that either recurrent AF or flutter would fulfil primary endpoint
October 9, 2023	Addition of previously approved Month-1 follow-up visit throughout document where missing	Completion of prior change not undertaken throughout document in some places
	Addition of option to call & enroll patients remotely within 1 week of cardioversion if clinical care did not allow time for coordinator to approach during hospital visit	To facilitate recruitment as busy clinical care settings were preventing many eligible patients being approached by coordinators before cardioversion
	Amendment of exclusion criteria: "recent/planned AF ablation within 3 months"	Previously was 6 months - to facilitate recruitment as many otherwise eligible patients had had ablation within 6 months
May 31, 2024	Addition of third site: Sunnybrook Health Sciences Centre	To facilitate recruitment
	Amendment of secondary objectives: removal of AF and coffee abstinence symptom assessments	These secondary assessments were initially planned at the time of initial study design but due to practical constraints were not collected
	Amendment of inclusion criteria: "life expectancy of at least 6 months"	Previously was 1 year – change to reflect prior reduction in study duration to 6 months
	Amendment of "Lost to Follow-Up" procedure: clarified that medical record review was also utilized in addition to physician/healthcare professional contact to confirm AF recurrence status	Clarification that, in addition to contacting physician/healthcare professional, medical record use was approved to confirm AF recurrence status if patient did not attend follow up visits
	Removal of SF-36, hrQOL, and physical activity questionnaires	These assessments were initially planned at the time of initial study design but due to practical constraints these data were not collected
	Removal of Section 5.9 Targeted Medical Care Utilization	The collection of these data are already described in Section 5.10 Adverse Event Collection
	Amendment of Section 5.7 Targeted Medication Inventory: reference to dosage and frequency removed	Clarified that medication type was collected but not dosage or frequency

June 12, 2025	Clarification of primary objective: "time to first confirmed clinical recurrence of AF recurrence and/or atrial flutter recurrence, or device-detected recurrence lasting longer than 30 seconds" –	Given previous lack reference to device-detected recurrence, to clarify that device data was also reviewed and a threshold of 30 seconds utilized
	Amendment of secondary objectives: addition of adverse events and separate AF/atrial flutter assessment, and removal of other arrhythmia assessment	Clarification that adverse events and assessment of AF and atrial flutter recurrence separately are prespecified secondary endpoints, and that collection of other arrhythmias was not systematically undertaken due to practical constraints and thus removed
	Amendment of Section 3.0 Study Treatment: addition that participants could consume or abstain from coffee at their discretion following primary endpoint being met, end of study (6 months), or study withdrawal	Clarification that patients could consume or abstain at their discretion after their involvement in the trial was complete
	Miscellaneous: removal of day 1 study visit that was not undertaken, addition of heart failure exacerbation that was collected as an adverse event, removal of remaining references to coffee abstinence symptom assessment, clarification of wording, minor grammatical errors	Correction of several minor errors and clarification of wording throughout document

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DECAF

Does Eliminating Coffee Avoid Fibrillation?

A randomized controlled trial to assess abstinence of coffee compared to continued consumption on recurrent atrial fibrillation following cardioversion

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1.0 STUDY OVERVIEW AND RATIONALE

This study is an investigator-initiated, prospective, open-label, randomized clinical trial of coffee abstention compared to continued caffeinated coffee consumption in patients with atrial fibrillation (AF). It will be conducted at multiple clinical sites in the United States, Australia, and Canada. The goal is to enroll and randomize two-hundred (200) adult men and women.

AF is the most common, sustained heart rhythm disorder experienced by humans. Coffee is one of the most ubiquitously consumed substances worldwide. Given both the increasing population impact of AF and the widespread use of coffee in society, determining any benefit, risk, or lack of any effect of coffee on AF would be of great interest to physicians, scientists, and individual consumers.

Prior observational studies have evaluated the role of chronic coffee consumption and incident AF with varied results. [1-3] However, established notions exist that coffee and caffeine contribute to AF and/or trigger AF episodes. In a large study of symptomatic patients with paroxysmal AF, caffeine was reported as the second most common triggering factor in almost one-third of individuals.[4] Prior surveys of physicians have also suggested reductions in caffeine to assist with arrhythmias.[5] Conversely, professional society guidelines either do not discuss coffee or caffeine[6] or suggest they are unlikely to contribute based on recent studies.[7] Interestingly, observational studies generally suggest that caffeinated coffee has no association with AF, or even may be associated with a *lower* risk of AF.[8] [2, 3, 9]

A key limitation of existing data on the effects of coffee and caffeine on AF has been their observational nature. This trial thus seeks assess the effect of random allocation to coffee abstinence compared to continued caffeinated coffee consumption in patients undergoing cardioversion for AF or atrial flutter, with patients being followed up for recurrent episodes of AF.

1.1. SCOPE FOR ANALYSIS

The trial analyses will assess the effect of coffee abstinence compared to continued caffeinated coffee consumption on AF recurrence in patients undergoing cardioversion.

2.0 STUDY AIMS AND ENDPOINTS

Hypothesis: Coffee abstinence will result in a lower recurrence of AF following cardioversion compared to continued caffeinated coffee consumption (mention of coffee for the SAP refers to caffeinated coffee; those randomized to avoid coffee were indeed randomized to avoid all coffee).

<u>Primary endpoint:</u>

- The number of people with first confirmed clinical recurrence of AF or atrial flutter, or device-detected recurrence lasting longer than 30 seconds, following cardioversion in the coffee abstinence group compared to the continued caffeinated coffee consumption group analyzed as a time-to-event outcome.

<u>Secondary endpoints:</u>

- Adverse events before censorship, including myocardial infarction, stroke or transient ischemic attack, heart failure exacerbation, syncope, emergency department visit, hospitalization, and death

- Atrial flutter and atrial fibrillation separately as incident outcomes

3.0 STUDY DESIGN

This study is a multicenter, investigator-initiated, prospective, open-label, randomized clinical trial. After screening and eligibility has been determined, participants will be randomized after successful cardioversion. Follow-up visits will occur at: Month 1, Month 3, and Month 6. See the DECAF protocol for the schedule of evaluations, data sources, and windows for each of the study visits. Clinical sites will make every possible effort to ensure that each study visit is conducted within the specified window.

4.0 STUDY POPULATION

The target population for this trial is adults in the United States, Australia, or Canada with AF.

Potential participants will be identified at each clinical site from lists of patients with a planned and/or scheduled direct current electrical cardioversion. Eligibility for the study will be confirmed, using the inclusion/exclusion criteria noted below, prior to randomization after successful cardioversion.

INCLUSION CRITERIA

Patients must meet **all** of the following to be eligible:
1. Men or women ≥ 21 years of age
2. Sustained atrial fibrillation or atrial flutter (provided patient has history of atrial fibrillation)
3. Planned/scheduled direct current electrical cardioversion
4. Consumption greater than or equal to one cup of caffeinated coffee per day sometime in the past 5 years
5. Willing and able to comply with coffee abstinence or continuation of caffeinated coffee for at least 6 months
6. Life expectancy of at least 6 months
7. Willing and able to return and comply with scheduled follow up visits
8. Willing and able to provide written informed consent

EXCLUSION CRITERIA

Patients will be excluded if they meet **any** of the following:
1. Established allergy or adverse reaction to coffee
2. Stated inability to comply with coffee abstinence or continuation
3. Atrial fibrillation ablation in preceding 3 months or planned in the next 3 months
4. Recent cardiothoracic surgery in preceding 3 months
5. Pregnancy or desire to get pregnant within next 6 months.
6. Current enrollment in an investigation or study of a cardiovascular device or investigational drug that would interfere with this study
7. Any other criteria, which would make the patient unsuitable to participate in this study as determined by the Principal Investigator (e.g., an uncontrolled drug and/or alcohol addiction)

4.1 ALLOCATION

After successful cardioversion, participants will be randomized (1:1) to one of the two arms: coffee abstinence or continued caffeinated coffee consumption.

The DECAF study-wide allocation scheme will be created by a statistician prior to the start of the trial. Randomization will be performed with 1:1 with stratification across sites.

Sites will be instructed to randomize a participant as follows:

- After primary eligibility has been confirmed
- After all screening measures have been performed
- As soon as possible after successful cardioversion

Participants who completed primary eligibility and screening measures but did not have a successful cardioversion (such as due to inability to convert AF or documented early recurrence of AF prior to leaving the procedure room) will be excluded prior to randomization.

4.2 BLINDING

Due to the nature of the intervention, it is not practical to have participants blinded to their randomized allocation.

5.0 SAMPLE SIZE AND POWER CALCULATIONS

The goal is to enroll a total of 200 participants (n=100 per treatment group) study-wide.

The sample size is based on the following assumptions: (1) a 50% incidence of AF recurrence; (2) 10% loss to follow-up; and (3) 0.05 two-tailed alpha level. Under these assumptions, a sample of 200 individuals randomized 1:1 to either coffee abstention or continued caffeinated coffee consumption will provide 80% power to detect a 1.63 times increased hazard of AF between the groups.

6.0 STATISTICAL METHODS

All analyses will be conducted upon completion of data collection and database lock. No interim analyses are planned.

The primary analysis will be by intention-to-treat (ITT), according to randomized allocation, without regard to participant compliance with this randomized allocation. Every attempt will be made to collect data for both primary and secondary endpoints until the end of the six month follow-up period for all randomized participants, and all data will be included as part of the primary ITT analysis.

Although substantial crossover is not anticipated, as treated and per protocol analyses will be conducted if failure to comply with the randomized allocation occurs in more than 10% of all participants or if there is a significantly different proportion of assignment adherence in one group compared to the other. The per protocol analyses will be restricted to a sub-sample excluding all the protocol violators, and adjust for any baseline factors that are imbalanced ($P<0.1$) in the per-protocol sub-sample.

Patient baseline characteristics will be summarized overall and by randomization assignment. Continuous variables will be summarized using means and standard deviations (SD) for normally

distributed measures or medians and quartiles for non-normally distributed measures. Categorical variables will be summarized using contingency tables that display counts and percentages.

All tests will be two-sided with a 0.05-level of significance. Adjustment for multiple comparisons will not be used.

6.1 PRIMARY ENDPOINT ANALYSIS

The primary endpoint, defined as the clinical recurrence of AF or device-detected AF lasting longer than 30 seconds, will be analyzed as a time-to-event outcome. Follow-up time for participants who do not experience the primary endpoint will be censored at the time of study withdrawal or end of study (month 6). Kaplan-Meier plots will be used descriptively to compare the survival distributions of the primary endpoint by randomization arm. Cox proportional hazards regression models including the randomization assignment will be used to formally analyze the primary endpoint (AF recurrence). These models will also include study site, used in the randomization procedure as a stratification factor, and additionally baseline patient characteristics in sensitivity analyses. Point estimates and Wald-based 95% confidence intervals and p-values will be reported. The primary ITT analysis will include all participants regardless of compliance with randomized allocation.

6.2 SECONDARY ENDPOINT ANALYSIS

Prespecified secondary endpoints include atrial flutter and atrial fibrillation separately as incident outcomes, and adverse events before censorship including myocardial infarction, stroke or transient ischemic attack, heart failure exacerbation, emergency department visit, syncope, hospitalization, and death. Kaplan-Meier plots will be used to describe the survival distributions of secondary time-to-event outcomes (e.g., death) by trial arm and Cox hazard regression will be used for analysis. Continuous secondary endpoints will be described by randomization assignment using means and SDs, or medians and quartiles and categorical endpoints will be summarized using counts and percentages. Generalized linear models, which accommodate a range of outcome types including dichotomous, continuous, and counts, will be used for analysis. Randomization assignment will be included in all models, as well as study site used as a stratification factor in the randomization procedure. Additional models will adjust for the baseline patient characteristics in sensitivity analyses.

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