Use of Dapagliflozin to Reduce Burden of Atrial Fibrillation in Patients Undergoing Catheter Ablation of Symptomatic Atrial Fibrillation
(DAPA-AF)
Prospective, Randomized, Multicenter, Placebo-Controlled Trial
Principal Investigator: Mehmet K. Aktas, MD
Co-Principal Investigator: Ilan Goldenberg, MD
Co-Principal Investigator: Steven Wittlin, MD

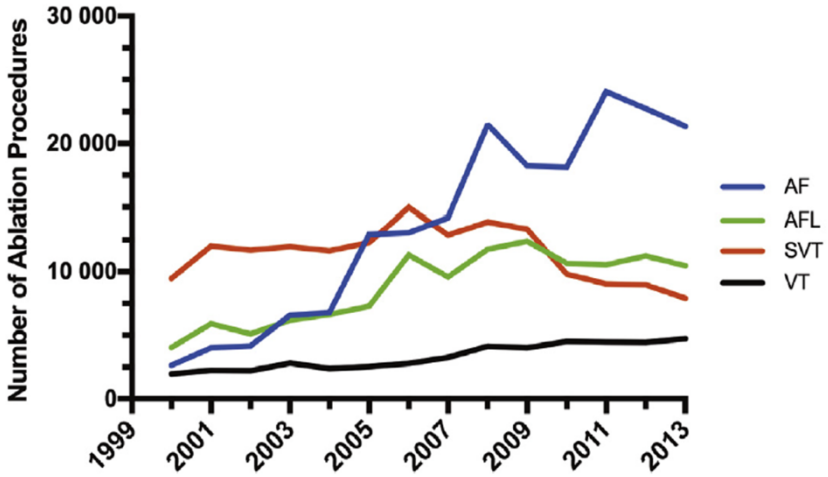
1. PURPOSE OF STUDY

To investigate the effect of dapagliflozin vs. placebo on the burden of atrial fibrillation (AF) in subjects undergoing catheter ablation of AF.

2. BACKGROUND AND RATIONALE

Atrial fibrillation (AF) is a major public health concern in the United States, affecting an estimated 2.3 million Americans.[1] The prevalence of AF in the U.S. is projected to reach 12.1 million by the year 2030.[2] AF is the most common sustained arrhythmia seen in clinical practice and accounts for approximately one-third of hospitalizations for cardiac dysrhythmias. AF is associated with significant mortality, morbidity, and healthcare costs.[3, 4] In total, the management of AF and its complications costs the U.S. healthcare system approximately $26 billion each year.[5] These costs are expected to increase dramatically unless AF is prevented and treated in a timely and effective manner. Antiarrhythmic drug therapy and catheter ablation (in select patients) has been the primary treatment for AF,[6] but these respective approaches may be associated with toxic sides effects[7] and procedural complications.[8-10] Furthermore, current approaches have limited efficacy and most patients require multiple interventions in order to achieve control, albeit often inadequate.[11, 12] Catheter ablation of AF is performed at many medical centers in the United States and throughout much of the developed world and the number of patients undergoing ablation of AF continues to rise (Figure 1 below).[13]

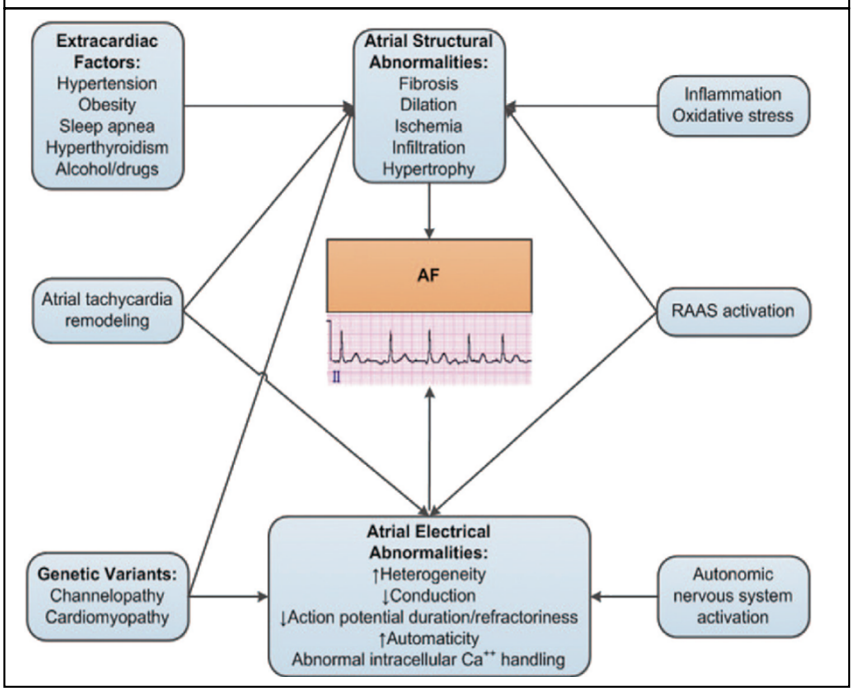
Figure 1 **Annual Volume of Catheter Ablation Procedures by Indication**



There are myriad of

pathophysiologic processes, both at the cellular and structural level, that have been shown to lead to the onset and maintenance of AF (Figure 2).[6] A commonly observed structural change in patients with AF is left atrial enlargement and dilatation. At the cellular level inflammation and fibrosis have been identified in patients with AF, even in the absence of structural heart disease.[14] Left atrial stretch secondary to HF results in neurohormonal activation, which in turn can activate multiple downstream profibrotic factors.[15] Oxidative stress has been linked to the onset and maintenance of AF.[16] It is recognized that the onset of AF begets adverse structural and electrophysiologic alterations which further begets AF.[17]

Figure 2: Mechanisms Predisposing to AF



The sodium-glucose cotransporter-2 (SGLT2) is expressed in the proximal convoluted tubules of the glomerulus and is responsible for reabsorption of the majority of filtered glucose.[18] Treatment with dapagliflozin, a selective SGLT2 inhibitor (SGLT2i), results in glucosuria and its use was initially approved in the treatment of hyperglycemia in patients with type 2 diabetes mellitus (T2DM).[19-21] Patients with T2DM treated with SGLT2i were shown to experience significant reductions in cardiovascular (CV) mortality,[22, 23] and more recent studies have shown that the CV and heart failure (HF) benefit of treatment with SGLT2i are independent of the presence of T2DM.[24, 25] Numerous pleotropic effects of SGLT2i treatment have been postulated,[26] including a reduction in preload by way of osmotic diuresis and natriuresis,[27] reduction in afterload via vascular effects that results in vasodilation,[28] inhibition of cardiac fibrosis,[29] reduction in atrial dilatation[30] as well reductions in inflammation[31] and oxidative stress.[32]

In a retrospective sub-analysis of the DECLARE-TIMI 58 trial, dapagliflozin treatment in patients with T2DM was associated with a significant 19% reduction in the risk of AF and atrial flutter events.[25] There are several putative mechanisms as to how dapagliflozin therapy may be

effective in controlling AF. First, natriuresis and diuresis caused by dapagliflozin may decrease LA volume and stretch,[27, 30] which is known to trigger AF. Second, dapagliflozin has been shown to attenuate the release of inflammatory cytokines such as TNF-α which induces apoptosis, chamber dilatation and scar formation.[31] Third dapagliflozin has been shown to reduce fibrosis and oxidative stress possibly rendering the atrial substrate less able to promote and maintain AF.[29, 32] Finally, SGLT2i have been shown to reduce epicardial fat,[33] which is closely interconnected with AF. Thus, it is possible that the pleotropic effects of SGLT2i on atrial function, inflammation, fibrosis, and oxidative stress may translate into a corresponding reduction in AF burden following catheter ablation of AF.

The DAPA-HF trial enrolled over 4,700 patients with heart failure with reduced ejection fraction (HFrEF) who were randomized to treatment with the SGLT2i dapagliflozin versus placebo which were given on top of usual treatment for HF.[34] After a median follow-up time of 18 months, a significant 26% reduction in the composite endpoint of worsening HF or CV death was observed in the dapagliflozin treated group. The beneficial effects of dapagliflozin on CV morbidity and mortality were observed regardless of the presence of T2DM. Based on the results of the DAPA-HF trial, the Food and Drug Administration (FDA) expanded and approved the use of dapagliflozin in patients with HFrEF (with and without T2DM) as an oral agent to reduce the risk of CV death and hospitalization for worsening HF.

The DAPA-CKD trial enrolled 4304 patients with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and urinary albumin-to-creatinine ratio of 200 to 5000 to receive dapagliflozin or placebo. After a median of 2.4 years, the independent data monitoring committee stopped the trial because of significant efficacy with dapagliflozin treatment. The primary outcome, which was a composite of sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes, was 39% lower among dapagliflozin treated patients when compared to placebo. Based on the results of the DAPA-CKD trial, the FDA further expanded and approved use of dapagliflozin to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for HF in adults with chronic kidney disease at risk of progression.

Dapagliflozin is an FDA approved oral agent used 1) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction, 2) to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular (CV) disease or multiple CV risk factors and 3) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, 4) to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for HF in adults with chronic kidney disease at risk of progression.

Our understanding of the risk factors and complications of AF is based mostly on studies that have evaluated AF in a binary fashion (present or absent) and have not investigated AF burden (quantity or amount of AF that a person has). AF burden was shown to be associated with increased risk of cardioembolic stroke, and other cardiac and noncardiac outcomes, including HF progression, hospitalizations, and mortality.[35-38] A reproducible definition of AF burden is the amount of time spent in AF divided by the total amount of time a patient is monitored. Cardiac implantable electronic devices (CIED) consisting of either a permanent pacemaker

(PPM), implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy with defibrillator (CRT-D) or an implantable cardiac monitor (ICM) are capable of tracking the amount of AF during specified time periods. Numerous studies have analyzed the diagnostic accuracy of AF detection by CIEDs and have found very high sensitivity and specificity as well as a strong positive predictive value.[39-41]

In this study we propose to evaluate the impact of treatment with dapagliflozin versus placebo following catheter ablation of AF on the burden of AF during 6-12 months of follow-up using CIEDs. We hypothesize that a treatment regimen that includes dapagliflozin in AF patients who undergo catheter ablation will decrease the subsequent burden of CIED detected AF when compared to placebo.

3. ADMINISTRATIVE ORGANIZATION

The University of Rochester is the Coordination and Data Center (CDC) for the multisite study. The University of Rochester Medical Center and 6 additional sites (7 total enrolling sites) will be participating in this trial. The University of Rochester CDC will provide each site with the study protocol and a model consent form, along other relevant subject study materials. As the Coordination and Data Center (CDC), the University of Rochester will provide comprehensive training on the study protocol, study operations, and the electronic data capture system (TrialMaster). All training will be documented for each enrolling site.

The Principal Investigator will oversee in conjunction with the CDC all research activities at the collaborating sites which will be conducted per the protocol, study operations instructions and study training. Research activities will include: subject screening, consenting, enrollment, conduct of baseline study procedures, conduct of follow-up study procedures, and drug dispensing via the UR Investigational Drug Services (IDS). The CDC is responsible for data management, analysis, and coordination of logistics. The enrolling sites will manage all subject recruitment activity and data collection per protocol as well as interact with the CDC and enrolling site study team regarding study operations. The CDC will be responsible for overall study management, data management, data reporting, and site communications for the study. The CDC will act as liaison between the UR Research Subject Review Board (RSRB) which will be the reviewing IRB for the study, and the UR-unaffiliated collaborating sites. The CDC will coordinate with these sites all reviewing IRB communications regarding initial and amendment protocol and consent reviews and approvals, as well as ongoing continuing reviews to ensure study and regulatory compliance. The PI in conjunction with the CDC will be responsible for overseeing notification to the UR-unaffiliated site investigators and delegated site personnel in writing of the RSRB review determinations. Additionally, the PI will conduct quarterly or ad hoc conference calls with site PIs and primary coordinators. Weekly internal team meetings will be held with the CDC and UR study team; these may be reduced to bi-weekly or monthly as the study progresses.

The University of Rochester is the Study Sponsor and is receiving funding from Astra-Zeneca for conducting this research study.

4. STUDY DESIGN

The study is a randomized placebo-controlled prospective multicenter clinical trial of symptomatic AF potential subjects who are scheduled to undergo catheter ablation of AF. Prior to undergoing ablation, potential subjects will be enrolled (consented) into the study. Following successful ablation, study subjects will be randomized in a 1:1 ratio to treatment with dapagliflozin (10 mg daily) versus placebo. Prior to randomization the subject must have had the AF catheter ablation and an implanted functional CIED in place as described below.

AF burden will be monitored by a CIED) either, 1) ICM, used as standard of care (SOC) for AF management or 2) existing PPM, ICD, or CRT-D that has remote monitoring capabilities.

Enrolled subjects will be followed for a minimum duration of 6 months and a maximum duration of 12 months following randomization in both the dapagliflozin and placebo arms as follows:

- CIED interrogation to quantitate AF burden will be performed during in office visits and during remote device interrogations. Interrogation results (PHI redacted by enrolling site) will be shared with the study coordination and database center (CDC) at the University of Rochester where it will be further reviewed by an independent study arrhythmia adjudication committee. AF burden will be quantified.

- Clinical data on medication, cardiovascular events, quality of life, and subject reported outcomes, will be collected at standard clinical visits.

Primary Endpoint

AF burden assessed at the final follow-up visit following catheter ablation of AF, **defined as percentage of time spent in AF (i.e. amount of time spent in AF divided by the total amount of time a subject was monitored).**

Secondary Endpoints

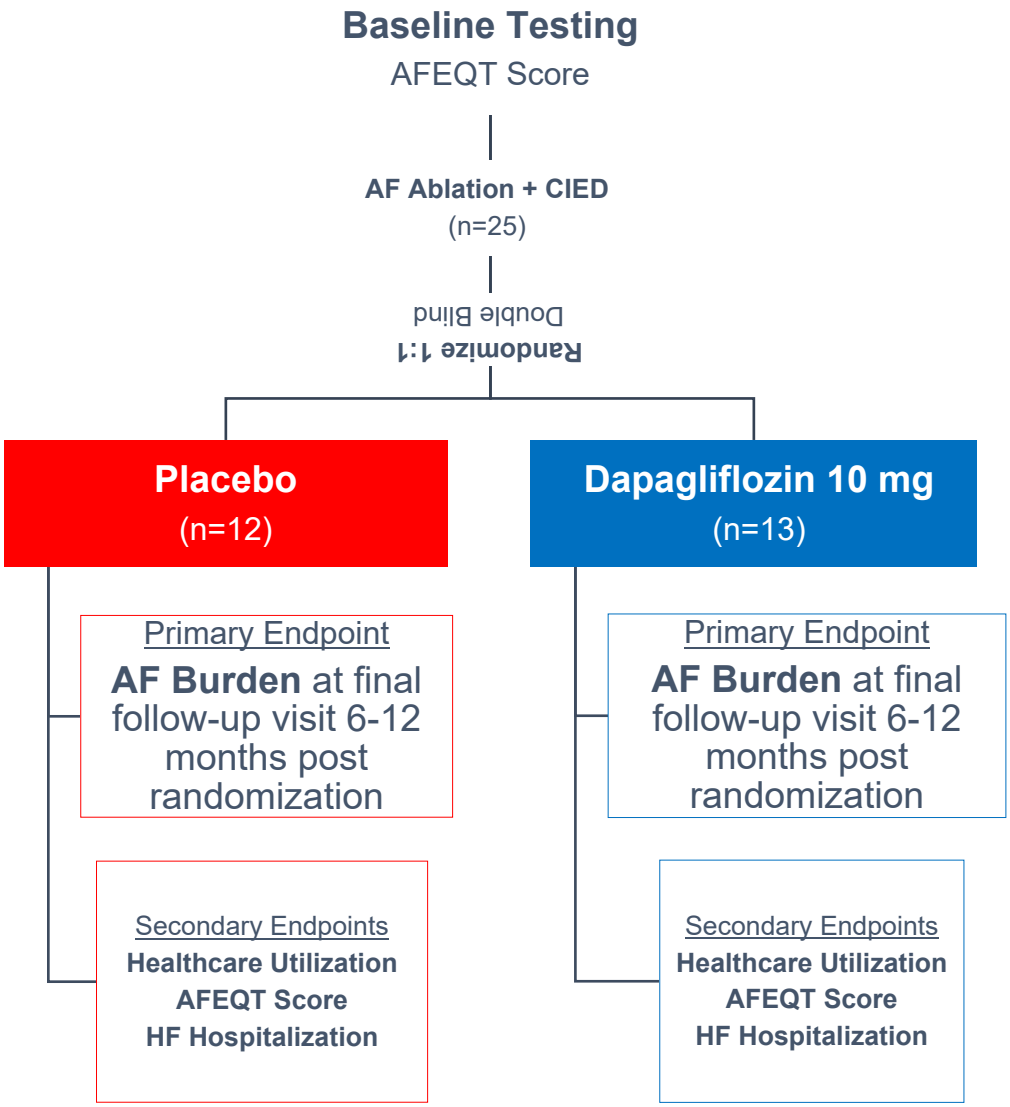
1. Rate of health care utilization (recurrent hospitalizations, unplanned office visits, unplanned remote visits, need for emergency room visits)
2. Post-ablation HF hospitalization
3. AF burden and impact on quality of life measured using the AFEQT score.

Tertiary (exploratory) Endpoints

We will acquire data on the effect of dapagliflozin treatment on clinical outcomes in diabetic and non-diabetic subjects with AF. Accordingly, the following exploratory outcomes will be compared between the two groups:

1. Other cardiovascular events such as stroke and myocardial infarction
2. Association of AF burden and AF type (paroxysmal vs persistent) with clinical decompensation defined as CV hospitalization, unplanned office visits, unplanned remote visits, emergency room visits or death.
3. Death

Figure 3: Study Design



4.1. SUBJECT POPULATION

The study population will include subjects undergoing catheter ablation of AF with an implanted CIED or indication for CIED that can be implanted prior to randomization per Figure 3.

Consented eligible subjects will be randomized in a 1:1 ratio to either intervention (dapagliflozin 10 mg once daily) or control (placebo); About 13 or 12 subjects enrolled to each group for a total of 25 subjects across all enrolling sites. After enrollment (consent), QoL assessment will be obtained using the AFEQT questionnaire. The subjects will then undergo the index catheter ablation of atrial fibrillation. If CIED does not exist prior to consent then CIED implant will occur prior to, during or within 24 hours of the ablation procedure. Following catheter ablation and successful CIED

implant, the subject will be randomized, baseline data collected and the subject will be followed over a minimum duration of 6 months and up to 12 months duration depending on date of randomization. Subsequent study visits visit will be virtual (through phone contact and/or videoconferencing) in which: a) remote de-identified CIED interrogations will be transmitted to the CDC by the site research coordinator; b) follow-up data on subject status, study drug accountability/compliance, and healthcare utilization/adverse events will be obtained. QoL testing will be repeated at the 12-month follow-up visit. We believe that the virtual approach to study visits and data collection will contribute to significantly higher acceptance and enrollment than in previous studies.

Follow-up visits will be done at 3, 6, 9 and 12 months following randomization.

The study duration is 3 years including a planned study startup period of 6 months, an enrollment period of 18 months, a follow-up period of 6 months, and 6 months for closeout and analysis.

4.2. STUDY INTERVENTIONS

Please see section 8 entitled study procedures that includes further study interventions.

This study is not studying CIEDs nor the AF ablation procedure but will utilize data already clinically used and available from the CIED. Subjects without a CIED in situ will undergo CIED implant at the time of, or within 24 hours following the ablation procedure. All consented subjects will be implanted with a CIED using standard of care procedures and indication and then undergo randomization. All CIEDs including future upgrades that are utilized in this study will be FDA approved and used per the current FDA indications as standard of care to monitor arrhythmias following catheter ablation. Subjects are consented as it is required that the QOL questionnaire be obtained prior to the AF ablation. Subjects will be screen failures and not undergo randomization if catheter ablation is not performed or if there is no existing functional CIED within 24 hours following the ablation procedure.

There are risks associated with the use of any medication. It is important to note that in this study, dapagliflozin will be administered in the intervention according to currently approved FDA indications for it use. Medications inherently may be associated with side effects. The clinical research team is experienced in cardiovascular trials and the clinical management of subjects with heart disease/heart failure and will be monitoring for any adverse effects. This is a Phase 4 study, and we are comparing two management strategies that are currently employed in clinical practice.

5. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Eligible for treatment with dapagliflozin per current FDA-approved indications, including: 1) heart failure (NYHA class II-IV) with reduced left ventricular ejection fraction (<50%), or 2) type 2 diabetes mellitus and established cardiovascular (CV) disease or multiple CV risk factors, or 3) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, 4) adults with chronic kidney disease at risk of progression as defined by the National Kidney Foundation as estimated GFR <60 ml/minute/1.73 m^2.

- Scheduled to undergo ablation of symptomatic paroxysmal or persistent AF prior to date of randomization per current guideline indications.
- A glycated hemoglobin level < 10.5% during the past 6 calendar months prior to consent only in patients with type 2 diabetes mellitus
- Age ≥ 18 years
- Existing functional CIED or planned to undergo CIED implant as SOC before or within 24 hours following the AF ablation procedure and prior to randomization date.

Exclusion Criteria

- Type 1 diabetes mellitus
- History of diabetic keto-acidosis
- Child Pugh Class C liver disease
- Last measured estimated GFR < 25 ml/minute/1.73 m^2
- Pregnancy, plan to become pregnant <1 year after consent or breast feeding
- Current therapy with an SGLT2 inhibitor
- Hypersensitivity to dapagliflozin
- On heart transplant list or likely to undergo heart transplant
- Unwilling or unable to cooperate with the protocol
- Participation in other clinical trials (observational registries are allowed with approval).
- Unwilling to sign the consent for participation
- Life expectancy <1 year after consent date for any medical condition

6. RECRUITMENT METHODS

Each site participating in the study will develop and implement recruitment methods that are appropriate to their institutional policies and guidelines, along with consideration to the rights and welfare of human subject research. An overall Recruitment Plan describing the use of recruitment materials and processes will be required as an addendum to the individual site's customized protocol for RSRB review and approval. Sites will utilize the IRB approved Study-related Documents customized with their individual site information which will be submitted for approval to the RSRB under their local site submission documents. Any additional site-specific recruitment materials the site develops outside of the approved Study-related Documents will be submitted to the RSRB for local site approval.

If the potential subject meets inclusion/exclusion criteria at time of consent, the study team will approach potential subjects for participation in the study based on the policies of the enrolling site. Enrolling site study staff will use a recruitment phone script and phone number obtained from a potential subject's records to contact a potential subject by phone. If during a clinic visit, the enrolling site staff will approach the potential subject with the same information as in the phone script to assess a potential subject's willingness to participate in the study.

7. CONSENT PROCESS

A model consent document as well as the study protocol will be provided to each site to obtain reviewing IRB approval specific to the enrolling site. Revisions to the model consent require approval from the Coordination and Data Center prior to submission of the consent to the reviewing IRB. Only the current site-specific reviewing IRB-approved consent form will be

provided to the potential subject for all consenting process options described below.

The informed consent process will be conducted by the Principal Investigator or individual authorized to conduct the process and will follow the local applicable laws, rules, regulations and guidelines. The informed consent process may be conducted in person or remotely using either a paper consent form or an electronic eConsent depending on the option that the potential subject prefers as indicated in the initial study recruitment contact with a study team member.

If using a paper consent form to remotely consent a potential subject, 2 copies of the consent should be mailed or e-mailed to the potential subject approximately 1 week prior to the telemedicine visit to allow the potential subject time to review the consent. A telemedicine appointment will be set up to discuss questions regarding the study with the potential subject and confirm the potential subject fully understands the study requirements. If the potential subject agrees to participate in the study, the potential subject will sign both consent forms and mail one back to the site team using the self-addressed envelope including postage that was provided by the site team. If the potential subject receives the consent via email, the potential subject will be asked to print 2 copies of the consent form and mail one back to the site team or bring the signed paper consent to the initial study visit.

The consent document will also be created using an electronic consent form that may be electronically signed by the potential subject. The site may consent a potential subject using a secure, web-based, HIPAA-compliant, TrialMaster data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. The study team member(s) delegated by the enrolling site PI for e-consenting would need to utilize uniquely assigned access website credentials to enter the potential subject's email address to enable the email to be sent by the website to the potential subject per the initial recruitment call. The website instructions, secured link, access credentials and unique signing code as identity verification assigned by the website system will be emailed to the potential subject. The potential subject may review the consent on the website and send questions to the study team via the website.

A telemedicine visit will be set up to discuss questions regarding the study with the potential subject and to confirm the potential subject fully understands the study requirements. If the potential subject decides to participate in the study, then the potential subject will be provided with a unique subject-assigned signing code to electronically sign the consent during the telemedicine visit. The website will indicate to the potential subject that this electronic signature is equivalent to a handwritten signature on a hard copy of the consent. The study coordinator will be able to print a final signed consent after completion of the e-signing process. The potential subject's access to the website will be restricted to only the consent and be disabled following consent signature.

The consent document will be used as a guide for discussion with the potential subject. The potential subject will be given sufficient time to ask questions and to consider participation. The study team provides contact information (email and phone) for potential subjects to contact a study team member with questions either in person, email or through the website that has a link for questions with a message sent to the PI and other delegated members of the study team. The study

team may respond to questions by email, phone or sending a message to the patient with a response to any questions in addition to the telemedicine visit specifically set up to discuss the study with the potential subject prior to consent signing. The potential subject's email will only be entered in the electronic system if the potential subject chooses to electronically sign the consent.

The potential subject's refusal to participate or subject's withdrawal from the study will not interfere with future medical treatment. All subjects will receive a copy of their signed informed consent and the original will be maintained at the enrolling site. Subject recruitment at an enrolling site may not begin until the reviewing IRB approval is obtained related to the enrolling site study protocol and consent.

Consent to Re-Contact:

Data collected may be used for the development of future research studies. The enrolling sites will maintain the confidentiality of the data throughout the process. Only authorized research personnel at the enrolling site working on the project will have access to the data. Consent for this purpose will be asked of subjects and response noted via checkboxes for subjects to indicate consent to future use of information and for "Consent to Re-Contact."

Subjects will be asked to consent to re-contact by the study physician, or someone from the study team, in the future about using information for research that is not described in the consent form. Additionally, they will be given the option to consent to future contact from the study team about participation in other research.

8. STUDY PROCEDURES

After signing consent, all subjects will undergo randomization and study related procedures, as well as standard of care procedures, per Table 1 and as indicated below.

All subjects will either have a functional CIED already implanted prior to AF ablation, at time of AF ablation or within 24 hours following AF ablation as standard of care.

All subjects enrolled in the study will remain on SOC medications and participation in the study will not require discontinuation of any SOC medications.

Intervention Management Arm (Dapagliflozin)

A block randomization method will be use to randomize subjects to treatment with dapagliflozin 10 mg once daily versus placebo. Subjects will take 1 blinded tablet of study drug (dapagliflozin) dosed once daily, per the randomization scheme, for a 6-12 month duration depending on date of randomization. All active and placebo tablets will be identical in appearance (same size, shape and color). Subjects will be encouraged to start study drug within 2 weeks of the date of randomization. Study subjects will be instructed to ingest all tablets whole and not to open them. Each subject will be dispensed 35 blinded doses per month, during each month of participation in the trial. Quarterly pill counts will be performed to track compliance. All drug dispensing (dapagliflozin and matching placebo) will be managed by the Investigational Drug Services (IDS) in the Department of Pharmacy at the University of Rochester Medical Center. The unit manages drug dispensing for numerous clinical trials and

has vast experience in this field. Any study related side effects will be reported to the independent Data and Safety Monitoring Board (DSMB) for review (details below). The cost of study drug will be covered by the study.

Patients with diabetes who are started on dapagliflozin will continue to undergo standard of care glucose monitoring as directed by the primary treating physician. The initiation of dapagliflozin does not require any incremental testing/monitoring beyond what is performed as standard of care.

IDS is in full compliance with federal, state, Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and American Society of Health-System Pharmacists (ASHP) requirements regarding control of investigational drugs. Investigational drugs will be stored in both the IDS and the Department of Pharmacy to ensure appropriate access, security, stability, and compliance with FDA guidelines. Drug order, receipt, and return forms will be maintained for all medications used in the clinical trial. Drug accountability records will be maintained for all study drug received, stored, dispensed and destroyed by the IDS. Study drug supplies will be inventoried on a regular basis for quality assurance purposes. IDS will maintain records after study completion according to FDA requirements, or as specified per protocol. JCAHO requires that anyone administering an investigational drug have a working knowledge of the drug, such as its purpose, side effects, precautions, and procedures for administration. All IDS personnel involved in the trial will receive the necessary training to ensure full compliance with good clinical practice guidelines.

Control Arm (Placebo)
Subjects will take 1 blinded tablet of placebo drug dosed once daily, per the randomization scheme, for a minimum duration of 6 months and maximum duration of 12 months.

Procedures for Both Groups – Regardless of Randomization:
Post-randomization, follow-up of subjects in each arm will include SOC visits at 3, 6, 9 and 12 months. When feasible these will be virtual (TeleHome) visits in order to minimize study related burden on enrolled subjects. Study related adverse events and protocol deviations will be recorded during each of these SOC visits. CIED interrogation data will be obtained either via remote CIED downloads or during in-office visits. The interrogation data will be acquired in a standardized PDF format. The interrogation report will de-identified. All protected health information will be removed and subject ID will be entered for tracking. The de-identified PDF file will be uploaded to the study web-based data management system in a HIPAA compliant manner. CIED interrogation reports will be reviewed by an independent Events Adjudication Committee, blinded to treatment assignment. The final SOC visit will take place in-office, during which time all study related procedures and assessments will be completed.

Standard of Care Procedures

- In-office or TeleHome follow up visits as scheduled will occur at 3, 6, 9 and 12 months. These visits will include a medical assessment, drug accountability/compliance, device interrogation, and subjects will be questioned about clinical and medical (adverse) events.

- 12 lead ECGs if performed as SOC at Baseline, 3 months, 6 months, 9 months and 12 months.
- Remote interrogation data from CIED will be collected.
- Echocardiographic data if performed as SOC.
- Blood sugar monitoring in diabetics per SOC.

Research Activities:

- Chart reviews will be performed by the study team at each time point and include data about clinical history, medications, ablation procedure, device implantation, and follow-up data will be collected from the medical record.
- Assessment of healthcare utilization (comprising the total of unplanned in-office visits, hospitalizations, repeat ablations, or death).
- AFEQT questionnaires will be completed by the subject at baseline and the final follow-up visit. The questionnaire should take the subject approximately ten minutes to complete. We will utilize an instrument specifically designed for patients with AF, the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT), a questionnaire focusing on symptoms, daily activities, treatment concerns and treatment satisfaction.

Method of Assigning Subjects to Treatment

Subjects will be randomized 1:1 to Dapagliflozin versus placebo. Randomization will occur electronically using the electronic data collection system, TrialMaster that is available 24/7 to all study personnel.

Follow-up 3, 6, 9, 12 months (See Table 1)

Following enrollment and randomization all subjects will have SOC follow-up in-office or TeleHome visits at 3, 6, 9 and 12 months. TeleHome videoconferencing visits may be replaced with in-office visits as needed.

All subjects will be followed for a time-period of a minimum of 6 months and maximum of 12 months.

The following study related data will be collected during SOC visits after ablation.

- *3 Months ± 1 calendar months from study drug initiation date*
    - Review of medical history including adverse events, hospitalization, unplanned office visits, and emergency room visits
    - Study drug accountability and compliance
    - Current cardiac medication
    - Blood sugar values in diabetic patients
    - Assessment of symptoms
    - 12-Lead ECG **(if done per standard of care)**
    - CIED Interrogation
- *6 Months ± 1 calendar months from study drug initiation date*
    - Review of medical history including adverse events, hospitalization, unplanned office visits, and emergency room visits

- Study drug accountability and compliance
- Current cardiac medication
- Blood sugar values in diabetic patients
- Assessment of symptoms
- 12-Lead ECG **(if done per standard of care)**
- CIED Interrogation
- AFEQT Questionnaire (if final follow-up visit)

- *9 Months ± 1 calendar months from study drug initiation date*
  - Review of medical history including adverse events, hospitalization, unplanned office visits, and emergency room visits
  - Study drug accountability and compliance
  - Current cardiac medication
  - Blood sugar values in diabetic patients
  - Assessment of symptoms
  - 12-Lead ECG **(if done per standard of care)**
  - CIED Interrogation
  - AFEQT Questionnaire (if final follow-up visit)

- *12 Months ± 1 calendar months from study drug initiation date*
  - Review of medical history including adverse events, hospitalization, unplanned office visits, and emergency room visits
  - Study drug accountability and compliance
  - Current cardiac medication
  - Blood sugar values in diabetic patients
  - Assessment of symptoms, NYHA functional class
  - 12-Lead ECG and Echocardiogram data **(if done per standard of care)**
  - CIED Interrogation
  - AFEQT Questionnaire

Communication at Randomization and the Conclusion of the Final Follow-up Visit

In order to maintain oversight and continued clinical management, the site PI will communicate by letter with the subject's treating physician that the subject is randomized and participating in the study. Also, at the conclusion of the final treatment visit, if the patient tolerated the study drug (Dapagliflozin or placebo), the site PI will communicate by letter with the subject's treating physician that it is recommended that the subject be treated with an SGLT2 inhibitor per FDA-approved indication.

Table 1: Schedule of Activities

Reportable Data Items	Screen/ Consent/ Randomization	Baseline	In-Office or TeleHome Visit 3 months	In-Office or TeleHome Visit 6 months	In-Office or TeleHome Visit 9 months	In-Office or TeleHome Visit 12 months
Timeframe	Confirm eligibility, consent, randomize	Following randomization	3 months (+/-1 calendar month) after date of study drug initiation	6 months (+/-1 calendar month) after date of study drug initiation	9 months (+/-1 calendar month) after date of study drug initiation	12 months (+/-1 calendar month) after date of study drug initiation
Inclusion/Exclusion	√					
Informed Consent	√					
Demographics		√				
Medical/Cardiac History		√				
Limited Physical Exam/NYHA		√				√
AF Ablation*		√				
CIED Device*		√				
AFEQT Questionnaire	√			√***	√***	√
CV and Diabetes Medication Log*		√	√	√	√	√
ECG*		√	√	√	√	√
LVEF (Echocardiogram)*		√				√
HbA1c** (per SOC)		√		√		√
Study Drug Initiation/ Accountability		√	√	√	√	√
CIED Interrogation and Activity Data*			√	√	√	√
Follow-up Contact/Cardiac Events/Procedures/ Glucose**		√	√	√	√	√
Adverse Events, HF hospitalization, Unplanned hospitalization, office, remote or ER visit, death		√	√	√	√	√
Protocol Deviations		√	√	√	√	√

* Standard of care procedures ** Diabetic subjects only ***If final follow-up visit

Plans for return of research results:

Research results will not be provided directly to subjects, but will be presented in national conferences and published in peer-reviewed papers after study completion. If requested by subjects we will send the published research results to subjects. Subjects will be notified if anything of medical importance is found.

9. RISKS TO SUBJECTS

The optimal treatment of patients undergoing ablation of AF remains an area of intense research. Patients undergoing ablation of AF experience a high rate of recurrent AF. There is evidence that dapagliflozin therapy may reduce the burden of AF. All patients enrolled in this study will have an FDA approved indication for dapagliflozin therapy. If a patient becomes pregnant during the course of the study, study drug should be discontinued immediately and CDC notified. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study medication.

The study is designed to prospectively evaluate whether dapagliflozin can reduce the burden of AF after ablation when compared to placebo.

Confidentiality Risk(s)

The risk to participating in this study may include a potential risk of a breach in confidentiality. Every effort will be made to keep the data confidential. To protect against this risk the information collected at each enrolling site will be entered by site personnel into a password protected electronic data capture (EDC) system. Subjects will be assigned a unique subject identification number at the time of registration, which is completed in the EDC system. The subject identification number is not connected with any PHI, such as date of birth or medical record.

Dapagliflozin Treatment Risks

Dapagliflozin has been studied in multiple clinical trials and has been found to be very well tolerated and has a high safety profile. However, the following serious risks have been associated with dapagliflozin treatment.

1. **Volume Depletion:** Dapagliflozin can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Diuretic dosing may be titrated according to symptoms, signs, weight and other information per standard clinical practice. Temporary interruption of study drug may also be considered in subjects at potential risk of volume contraction.
2. **Ketoacidosis in Diabetes Mellitus** has been reported in patients with type 1 and type 2 diabetes receiving dapagliflozin. Some cases can be fatal. If ketoacidosis is suspected, the study drug will be discontinued. Patients on dapagliflozin may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
3. **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with dapagliflozin. Patients on study drug will be evaluated for signs and symptoms of UTIs and will be treated promptly.
4. **Hypoglycemia:** dapagliflozin can increase the risk of hypoglycemia when co-administered with insulin and insulin secretagogues. Patients with type 2 diabetes at randomization will continue to take their glucose-lowering therapies but dose adjustments

may be required at the discretion of the treating primary care physician as per standard of care glucose monitoring in diabetic patients. The dose of insulin and/or sulfonylurea therapy may be reduced to minimize the risk of hypoglycemia at the discretion of the primary treating physician per standard clinical practice.

5. **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors including dapagliflozin. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Patients will be assessed for pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, prompt treatment will be instituted and study drug will be discontinued.
6. **Genital Mycotic Infections:** dapagliflozin increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Patients will be monitored and treat appropriately

The DAPA-HF trial enrolled 4,744 patients with heart failure with reduced ejection fraction (HFrEF) and randomized patients to treatment with dapagliflozin 10 mg once daily versus matching placebo. Dapagliflozin was stopped in 249 patients and placebo was stopped in 258 patients (10.5 vs 10.9%, P=0.71). Table below lists common adverse reactions associated with dapagliflozin therapy compiled from 12 placebo-controlled clinical trials. Standard of care monitoring of blood sugar values will be recommended for all diabetic patients enrolled in the study regardless of treatment allocation. Of note, treatment with an SGLT2 inhibitor was not shown to be associated with increased risk of hypoglycemia, and in the DAPA-HF study the rate of hypoglycemia was 1/2368 in the Dapagliflozin treatment arm vs. 4/2368 in the placebo arm. All adverse events during the trial will be prospectively collected and reviewed (detailed below in Table 2).

Table 2: Adverse reactions in placebo-controlled studies of glycemic control reported in ≥2% of patients treated with dapagliflozin

Adverse Reaction	**% of Patients**		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

Mitigation of risk associated with the Study Drug will follow drug labelling

recommendations per standard of care and procedures performed in the DAPA-HF clinical trial. These will include:

1. Glucose and HgBA1c monitoring in diabetic subjects will be performed as per standard of care. Patients with type 2 diabetes at randomization will continue to take their glucose-lowering therapies but these can be adjusted at the discretion of their diabetes health care provider. The dose of insulin and/or sulfonylurea therapy may be reduced to minimize the risk of hypoglycemia at the discretion of the primary treating physician per standard clinical practice.
2. Study drug will permanently be discontinued if pregnancy or diabetic ketoacidosis occur. Dose reduction (to dapagliflozin 5 mg daily or matching placebo) or temporary discontinuation may be considered in cases of acute, unexpected declines eGFR (while investigating other causes such as nephrotoxic drugs, urinary traction infection, or obstruction. Similarly, in cases of volume depletion and/or hypotension, alternative causes should be considered (e.g. gastrointestinal fluid loss, use of non-essential blood pressure-lowering drugs) and the dose of concomitant diuretic therapy re-assessed and reduced, if appropriate. Temporary interruption of study drug may also be considered, prophylactically, in subjects at potential risk of volume contraction/hypotension, such as subjects with an acute medical illness potentially causing volume depletion because of inadequate fluid intake or fluid/blood losses (e.g. gastroenteritis, gastrointestinal hemorrhage), or subjects undergoing major surgery.
3. Subject notification of possible adverse events at enrollment.
4. Adverse event data collection and independent DSMB monitoring.

Placebo Arm Treatment Risks

Subjects randomized to the placebo arm will undergo standard of care management following AF ablation. With regard to AF outcomes there are no known risks associated with not treating with dapagliflozin in the placebo arm.

10. POTENTIAL BENEFITS TO SUBJECTS

Subjects randomized to dapagliflozin may experience a lower burden of AF following ablation.

11. COSTS FOR PARTICIPATION

There are no additional costs to the subject. All office visit/procedures will follow standard of care guidelines and are covered by subject's medical insurance. The randomization process will not add to subject costs.

12. PAYMENT FOR PARTICIPATION

There will be no compensation for participation in this study.

13. SUBJECT WITHDRAWALS

Randomized subjects may be withdrawn prior to the study completion for a variety of reasons including:

a) Subject withdraws consent for any reason and will not be replaced.
b) Subject is lost to follow up despite best efforts to locate the subject and will not be replaced.
c) Subject withdrawn by physician.

Subjects may be considered lost to follow up after missing two consecutive follow-up visits with documented efforts to contact the subject.

These subjects will not undergo any additional study activities after withdrawal. Data collection will occur until the date of withdrawal and utilized in the study analysis. Withdrawn subjects who have been randomized will not be replaced. Withdrawn subjects will be requested to return all study drug at the time of withdrawal if contact is made with the subject. Subjects will not be required to withdraw from the study if the study drug is discontinued or unblinded. Subjects will not be required to be withdrawn from study if the subject decides not to take the study drug.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Data collected during this study will be obtained for research purposes and derived from study procedures, CIED interrogation data, subject records and subject visits. All study data will be stored in perpetuity in a password-protected database located at the CCRC per Section 15 and de-identified. Data will be accessible to the research sites and people who work with the University of Rochester which may use the results of the study for other research purposes. To protect confidentiality and privacy, subject data will be assigned a code using a unique subject ID number at the time of randomization and linked to subject identifiers that are stored separately in a study log solely maintained by the enrolling site study coordinator. The electronic data will be directly entered and extracted from computer system for data collection using encryption and physical controls. There is no plan to share, transmit or transfer the data. The subject's email address will not be stored nor transmitted with the study data if the subject opts for electronic consent signature via the study website.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

Study coordination, database management and statistical analysis will be performed by the Clinical Cardiovascular Research Center (CCRC) at the University of Rochester Medical Center (U of R) acting as the Coordination and Data Center for the study.

Data will be captured using TrialMaster, a HIPAA compliant secure web-based electronic data capture (EDC) system that is used to support the clinical research process. Data that are entered are validated against a set of rules to ensure the accuracy of the clinical data. The TrialMaster system is housed on CCRC servers that are housed behind the U of R firewall in the U of R Primary Data Center, where physical access and environmental controls are in place to protect the data. All access to the data is through an authentication process provided by the system and over the encrypted, secured U of R network, which both provide the necessary controls to prohibit unauthorized access to the clinical data. Continuous availability of the data is provided by mirroring the databases to servers located in a physically separate Secondary Data Center. Additional details are in the Data Safety Monitoring section below. Only authorized research personnel working on the project will have access to the data.

Only enrolling site personnel authorized by the site Principal Investigator will have access to the EDC system. Study personnel at each site delegated with EDC permission will be required to complete EDC training before receiving access to the system. Site personnel with EDC permission will have access to the system 24/7 for data entry. Study personnel will initially enter

all data related to the randomization and baseline data collection and will then complete data entry after each identified data collection timeframe per Table 1.

Data collected may be used for the development of future research studies. We will maintain the confidentiality of the data throughout the process. The subject will be given the option to agree or decline to be re-contacted in the future by the study doctor, or someone from the study team, about using the subject's information for research that is not described in the DAPA-AF study consent form; or to participate in other research. Re-contacting the subject may be made in person, by phone or by mail.

16. DATA AND SAFETY MONITORING PLAN

Adverse Event (AE) Data
An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to study drug, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study drug has been administered. The term AE is used to include both serious and non-serious AEs.

All adverse events will be collected after subject randomization at all subject contacts as indicated in Table 1. Adverse event data will be captured in the electronic data capture system and enrolling site investigators are responsible for reporting to and following reviewing Institutional Review Board (IRB) guidelines and reported to the DSMB. De-identified adverse event safety data will be provided to Astra-Zeneca, the study drug manufacturer as reported in a password-protected file per post-market FDA regulations.

Adverse Event Reporting
Enrolling site investigators shall report in the CDC electronic data collection system within five business days of PI awareness non-serious adverse events that are only related or suspected to be related to study activities and/or study medication, and all serious adverse events regardless of the relationship to the study activities and/or study medication per the serious event definitions below. Events leading to death or death (if event leading to death) of a subject must be reported as an adverse event, per the serious adverse event definition below. The enrolling site PI is aware that investigators are responsible for reporting to and following the guidance of any other applicable oversight bodies, including the reviewing Institutional Review Broad (IRB).

The CDC will be forwarding relevant documents to the Chair of DSMB for review and the Chair will determine whether individual case will require immediate assessment by the full DSMB committee or it could be assessed during electively scheduled DSMB meeting. Any SAEs meeting criteria for expedited reporting, the PI will be responsible for reporting to FDA and will notify AZ concurrently. We will also inform Astra Zeneca, the study drug manufacturer, about reported adverse events per FDA post-marketing regulation requirements.

Serious Adverse Event Definition

This population is at increased risk of heart failure, death, and poor clinical outcomes. A serious adverse event (SAE) is defined as any adverse medical experience that results in any of the following outcomes regardless of causal relationship with the study drug:
Results in death

- Is immediately life-threatening or results in death
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the
- ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical
- Intervention to prevent one of the outcomes listed above.

Unanticipated Problem Definition
An Unanticipated problem is any event, experience, issue, instance, problem or outcome that meets all 3 of the following criteria:

- Is unexpected in terms of the nature, severity or frequency given the research procedures that are described in the protocol–related documents AND in the characteristics of the population under study or if cause is study drug an adverse event or suspected adverse reaction is considered unanticipated if it is not listed in the study drug package insert or is not listed at the specificity or severity that has been observed per the study drug package insert.
- Is related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures and/or study drug involved in the research study.
- The incident suggests that the research places the subject or others at greater risk of harm (physical, psychological, economic or social) than was previously known or recognized OR results in actual harm of the subject or others. An unanticipated problem generally required a change in policy or procedure, warrants consideration of substantive changes to the protocol/consent or other immediate corrective actions in order to reduce the risk or eliminate immediate hazard.

Data and Safety Monitoring Board
A data and safety monitoring board (DSMB) will be appointed to independently monitor the conduct and the outcome of the trial. The DSMB will be responsible for monitoring the safety and well-being of the subjects participating in this study and ensuring the ethical conduct of the trial. The DSMB will be responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures and study drug, and for monitoring the overall conduct of the study.

The main focus of DSMB activity will be to monitor complications after randomization. For all randomized subjects, data on clinical events including adverse events, cardiovascular hospitalizations, and death will be collected and provided to the DSMB for evaluation of risks associated with participation in the trial.

The DSMB will be an independent group advisory to the Coordination and Data Center study principal investigator and asked to provide recommendations about starting, continuing, and

stopping the study. In addition, the DSMB asked to make recommendations, as appropriate, about:

- Efficacy of the 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 and consent forms
- Performance of individual sites
- Participant safety

The board will be comprised of 4 independent members: (1) 1 statistician with experience in clinical trials; (2) 1 cardiologist with expertise in clinical trials; (3) 1 electrophysiologist with expertise in ablation and arrhythmia treatment; and (4) 1 endocrinologist with expertise in diabetic monitoring and treatment. The DSMB will meet before trial commencement, after 25 subjects are enrolled and when the 6 month follow-up visit is completed on the last randomized subject. It is anticipated that these meetings will take place via conference call. One of the clinicians will be selected to chair the committee and will serve as the principal representative of the group. The Chair of the committee will be informed monthly about adverse events and will monitor safety of the subjects during interim time between formal meetings of DSMB.

Reports will be sent by the CDC to the DSMB chair, to report data on expected and unexpected adverse events as they are reported by the enrolling site. The Chair of the DSMB will have the right to convene additional meetings with all DSMB members when needed. The DSMB will carefully consider if these events are consistent with anticipated clinical outcome, i.e. unrelated, or a consequence of the study activity and/or study drug, i.e. related. Information on all these events will be sent to DSMB Chair as they occur and in addition, a full DSMB report including an adverse event summary will be prepared before every elective DSMB meeting.

17. DATA ANALYSIS PLAN

Descriptive statistics will be used to evaluate the rates related to the primary endpoint and health care utilization and HF hospitalization secondary endpoints for each group in the study population. Further, mean quality of life AFEQT scores will also be reported. General linear models will be used to identify factors associated with the risk of both AF burden and recurrent endpoints during follow-up.

For the primary endpoint of AF burden, defined as percentage of time spent in AF (i.e. **amount of time spent in AF divided by the total amount of time a patient was monitored**), the student's t-test will be used to statistically compare the placebo group vs. the active treatment group. This approach is subject to an examination of the distribution of the percent time in AF.

Currently, patients with persistent AF account for >60% of the AF ablation volume in each of the enrolling sites and therefore we anticipate a higher burden of AF than what has been reported in patients with paroxysmal AF, including CAPTAF (in which patients with paroxysmal AF

comprised 70% of the study population).[42]

Our preliminary data on 125 patients implanted with an ICM at URMC of whom 65% had persistent AF, show an overall AF burden of 25%. Other published studies have shown a higher burden of AF in persistent AF populations.[43] In the present study, enrollment will use a stratified proportionate allocation in a 2:1 ratio by type of AF (persistent vs. paroxysmal, respectively) to ensure a sufficient proportion of subjects with persistent AF.

Sample size

Our re-estimated power calculations are based on the following parameters:

1. 25 subjects randomized
2. Minimum follow-up of 6 months, average follow-up of 9 months.
3. Our preliminary interrogations suggest that we may have underestimated AF burden (possibly due to the higher risk characteristics of enrolled patients with heart failure, diabetes, and renal dysfunction). The revised AF burden estimate takes a conservative measure of at least 40%.

The Table below provides power calculations for a treatment effect in the range of 40% to 50%.

Reduce	Average AF burden: placebo	Average AF burden: Intervention	SD deviation	power	sample size	dropout	total sample
50%	**40%**	**20.0%**	15%	**85%**	23	10%	**25**
45%	**40%**	**22.0%**	15%	**76%**	23	10%	**25**
43%	**40%**	**22.8%**	15%	**73%**	23	10%	**25**
40%	**40%**	**24.0%**	15%	**66%**	23	10%	**25**

Based on our preliminary interrogation data above, the primary outcome of AF burden over an average follow-up of 9 months is assumed to be 40% in the placebo group and 20-24% in the intervention (dapagliflozin) group, with a standard deviation of 15% (a conservative estimate which allows for 10% drop-out). With a sample of 25 subjects randomized, a reduction from 40% to 20%-22% would provide 85%-76% power, respectively. Other possible scenarios are provided in the Table above.

We therefore, believe that the study may be the first to provide pilot prospective data on the possible antiarrhythmic properties of dapagliflozin following AF ablation.

The study power should not be affected by the association of diabetic status and cardiovascular medications with the study drug, Dapagliflozin, or AF burden, the primary outcome of the study. Further, prior publications have not shown differential effects of this drug within diabetic status or medication subgroups. Also, because the study drug and placebo groups will be randomly

assigned the distribution of diabetic patients and use of cardiovascular medications should be similar in the two. We will perform a sensitivity analysis where we adjust for diabetics and heart failure both parametrically and non-parametrically. Finally, the study was not designed to be powered to look for affects in subgroups of the study population, only in the overall enrolled study group.

18. COORDINATING CENTER TRACKING

Acting as Coordinating Center for the study, in order to ensure all required information is provided to the reviewing IRB, a Coordinating Center Tracking Spreadsheet will be submitted at the time of each annual progress review.

References:

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV and 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;285:2370-5.
2. Colilla S, Crow A, Petkun W, Singer DE, Simon T and Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *The American journal of cardiology*. 2013;112:1142-7.
3. Jackson SL, Tong X, Yin X, George MG and Ritchey MD. Emergency Department, Hospital Inpatient, and Mortality Burden of Atrial Fibrillation in the United States, 2006 to 2014. *The American journal of cardiology*. 2017;120:1966-1973.
4. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, Shah N, Chothani A, Savani GT, Mehta K, Parikh V, Rathod A, Badheka AO, Lafferty J, Kowalski M, Mehta JL, Mitrani RD, Viles-Gonzalez JF and Paydak H. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation*. 2014;129:2371-9.
5. Kim MH, Johnston SS, Chu BC, Dalal MR and Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4:313-20.
6. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM and Yancy CW. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1-76.
7. Zimetbaum P. Antiarrhythmic Drug Therapy for Atrial Fibrillation. *Circulation*. 2012;125:381-389.
8. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG and Sanders P. Complications of Catheter Ablation of Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology*. 2013;6:1082-1088.
9. Freeman JV, Tabada GH, Reynolds K, Sung SH, Liu TI, Gupta N and Go AS. Contemporary Procedural Complications, Hospitalizations, and Emergency Visits After Catheter Ablation for Atrial Fibrillation. *The American journal of cardiology*. 2018;121:602-608.
10. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, Grover P, Singh V, Vallurupalli S, Savani GT, Badheka A, Tuliani T, Dabhadkar K, Dibu G, Reddy YM, Sewani A, Kowalski M, Mitrani R, Paydak H and Viles-Gonzalez JF. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation*. 2013;128:2104-12.
11. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP and Tondo C. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med*. 2016;374:2235-45.
12. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P and Sanders P. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812-22.

13. Hosseini SM, Rozen G, Saleh A, Vaid J, Biton Y, Moazzami K, Heist EK, Mansour MC, Kaadan MI, Vangel M and Ruskin JN. Catheter Ablation for Cardiac Arrhythmias: Utilization and In-Hospital Complications, 2000 to 2013. *JACC Clin Electrophysiol*. 2017;3:1240-1248.
14. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA and Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*. 1997;96:1180-1184.
15. De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH and Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. *Cardiovascular Research*. 2010;89:754-765.
16. Samman Tahhan A, Sandesara PB, Hayek SS, Alkhoder A, Chivukula K, Hammadah M, Mohamed-Kelli H, O'Neal WT, Topel M, Ghasemzadeh N, Ko Y-A, Aida H, Gafeer M, Sperling L, Vaccarino V, Liang Y, Jones DP and Quyyumi AA. Association between oxidative stress and atrial fibrillation. *Heart Rhythm*. 2017;14:1849-1855.
17. Wijffels MCEF, Kirchhof CJHJ, Dorland R and Allessie MA. Atrial Fibrillation Begets Atrial Fibrillation. *Circulation*. 1995;92:1954-1968.
18. Wright EM, Loo DDF and Hirayama BA. Biology of Human Sodium Glucose Transporters. *Physiological Reviews*. 2011;91:733-794.
19. Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M and Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34:2015-22.
20. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K and Parikh S. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med*. 2012;156:405-15.
21. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ and Broedl UC. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*. 2014;37:1815-23.
22. Cavender MA, Norhammar A, Birkeland KI, Jørgensen ME, Wilding JP, Khunti K, Fu AZ, Bodegård J, Blak BT, Wittbrodt E, Thuresson M, Fenici P, Hammar N and Kosiborod M. SGLT-2 Inhibitors and Cardiovascular Risk: An Analysis of CVD-REAL. *J Am Coll Cardiol*. 2018;71:2497-2506.
23. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde A-M and Sabatine MS. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2018;380:347-357.
24. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C and Zannad F. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020.
25. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Budaj A, Kiss RG, Padilla F, Gause-Nilsson I, Langkilde AM, Raz I, Sabatine MS and Wiviott SD. Effect of Dapagliflozin on Atrial Fibrillation in

Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. *Circulation*. 2020;141:1227-1234.
26. Verma S. Potential Mechanisms of Sodium-Glucose Co-Transporter 2 Inhibitor-Related Cardiovascular Benefits. *The American journal of cardiology*. 2019;124 Suppl 1:S36-s44.
27. Ansary TM, Nakano D and Nishiyama A. Diuretic Effects of Sodium Glucose Cotransporter 2 Inhibitors and Their Influence on the Renin-Angiotensin System. *Int J Mol Sci*. 2019;20:629.
28. Li H, Shin SE, Seo MS, An JR, Choi IW, Jung WK, Firth AL, Lee DS, Yim MJ, Choi G, Lee JM, Na SH and Park WS. The anti-diabetic drug dapagliflozin induces vasodilation via activation of PKG and Kv channels. *Life Sci*. 2018;197:46-55.
29. Lee TM, Chang NC and Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med*. 2017;104:298-310.
30. Oldgren J, Laurila S, Åkerblom A, Latva-Rasku A, Rebelos E, Isackson H, Saarenhovi M, Eriksson O, Heurling K, Johansson E, Wilderäng U, Karlsson C, Esterline R, Ferrannini E, Oscarsson J and Nuutila P. Effects of 6 Weeks of Treatment with Dapagliflozin, a Sodium-Glucose Contransporter 2 Inhibitor, on Myocardial Function and Metabolism in Type 2 Diabetes Patients: A Randomized Placebo-Controlled Study. *Journal of the American College of Cardiology*. 2020;75:1610.
31. Bonnet F and Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. *Diabetes & Metabolism*. 2018;44:457-464.
32. Li C, Zhang J, Xue M, Li X, Han F, Liu X, Xu L, Lu Y, Cheng Y, Li T, Yu X, Sun B and Chen L. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. *Cardiovascular Diabetology*. 2019;18:15.
33. Sato T, Aizawa Y, Yuasa S, Kishi S, Fuse K, Fujita S, Ikeda Y, Kitazawa H, Takahashi M, Sato M and Okabe M. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol*. 2018;17:6.
34. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M and Langkilde AM. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381:1995-2008.
35. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, Noseworthy PA, Perez MV, Turakhia MP, American Heart Association Council on Clinical C, Council on C, Stroke N, Council on Quality of C, Outcomes R and Stroke C. Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. *Circulation*. 2018;137:e623-e644.
36. Chiang C-E, Naditch-Brûlé L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M and Steg PG. Distribution and Risk Profile of Paroxysmal, Persistent, and Permanent Atrial Fibrillation in Routine Clinical Practice. *Circulation: Arrhythmia and Electrophysiology*. 2012;5:632-639.
37. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP and Fonarow GC. Predictors and Prognostic Implications

of Incident Heart Failure in Patients With Prevalent Atrial Fibrillation. *JACC Heart Fail*. 2017;5:44-52.
38. Thihalolipavan S and Morin DP. Atrial Fibrillation and Heart Failure: Update 2015. *Progress in Cardiovascular Diseases*. 2015;58:126-135.
39. Hess PL, Healey JS, Granger CB, Connolly SJ, Ziegler PD, Alexander JH, Kowey PR, Ruff CT, Flaker G, Halperin JL, Hart RG and Lopes RD. The Role of Cardiovascular Implantable Electronic Devices in the Detection and Treatment of Subclinical Atrial Fibrillation: A Review. *JAMA Cardiology*. 2017;2:324-331.
40. Passman RS, Weinberg KM, Freher M, Schaechter A, Goldberger JJ and Kadish AH. Accuracy of Mode Switch Algorithms for Detection of Atrial Tachyarrhythmias. *Journal of Cardiovascular Electrophysiology*. 2004;15.
41. Solari D, Bertero E, Miceli R, Brunelli C, Ameri P and Canepa M. Methods, accuracy and clinical implications of atrial fibrillation detection by cardiac implantable electronic devices. *Int J Cardiol*. 2017;236:262-269.
42. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G, Rubulis A, Malmborg H, Raatikainen P, Lonnerholm S, Hoglund N and Mortsell D. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *Jama*. 2019;321:1059-1068.
43. Wechselberger S, Kronborg M, Huo Y, Piorkowski J, Neudeck S, Passler E, El-Armouche A, Richter U, Mayer J, Ulbrich S, Pu L, Kirstein B, Gaspar T and Piorkowski C. Continuous monitoring after atrial fibrillation ablation: the LINQ AF study. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2018;20:f312-f320.