

Protocol Title: Metformin as an Upstream Therapy in Atrial Fibrillation

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Drug Availability: Metformin hydrochloride (Glucophage®)
Commercially available.

Background:

Atrial fibrillation (AF) is the most common arrhythmia and its prevalence is projected to rise with the increase in age and comorbid disease in the patient population. AF is associated with significant morbidity and a nearly doubled risk of death.¹

As such the development of therapies which prevent or slow the progression of AF is imperative. In randomized controlled trials of therapies for AF, pharmacologic maintenance of sinus rhythm has not been demonstrated to be superior to therapies to control ventricular rates. In addition, medical therapy to maintain sinus rhythm was associated with significant cost and increased rates of hospitalization^{3,4}. However, in an "on treatment" analysis of the AFFIRM study which originally compared rhythm and rate control strategies, at an average of 3.3 years of follow up, the presence of sinus rhythm was associated with a significantly decreased risk of death (hazard ratio = 0.53)⁵. These findings suggest that the adverse effects of antiarrhythmic drugs in rate versus rhythm control studies offset the benefits of maintaining sinus rhythm when they are successful. Catheter ablation of the pulmonary veins and atria has been demonstrated to decrease the frequency of AF by 70-80% in several studies and provides a promising alternative to antiarrhythmic therapies.⁶⁹

Obesity is a known risk factor for AF and weight reduction through caloric reduction and exercise has been demonstrated to decrease the duration and symptomatic burden of AF in overweight and obese individuals in a randomized controlled trial.¹⁰ In a recently published retrospective cohort study of a physician led weight management intervention, successful reduction of 10% of body weight was associated with a six-fold increase in arrhythmia free survival.¹¹ Similarly, in a cohort study of overweight and obese patients undergoing catheter ablation for AF, a program of aggressive risk factor management prior to ablation led to improved glycemic control, blood pressure reduction, favorable left atrial remodeling and a nearly fivefold increase in AF free survival at two years with less use of antiarrhythmic medications.¹²

Metformin hydrochloride (hereafter referred to as metformin) is the first-line pharmacologic therapy of Type II diabetes and has been associated with modest but sustained weight loss in diabetic individuals^{13,14}. There has not been a randomized controlled trial to assess the weight effect of metformin on non-diabetic individuals who are overweight or obese. However in retrospective studies of metformin use in overweight and obese euglycemic individuals, metformin has been associated with modest weight loss (2.99.0 kg) without evidence of hypoglycemia.^{15,16} In a placebo controlled randomized controlled trial of metformin therapy of nondiabetic individuals with coronary disease and a large waist circumference, metformin use was associated with a 3.2 kg reduction at 18 months but did not improve other surrogate markers of cardiovascular disease.¹⁷ The known gastrointestinal side effects of metformin therapy occurred with the expected frequency in these studies.

In addition to obesity, there is significant epidemiologic and molecular data which implicates inflammatory, metabolic, and oxidative stress in the development and maintenance of AF. C-Reactive Protein (CRP) levels are known to be elevated in patients with AF and increasing CRP has been demonstrated to correlate with increasing AF burden. Development of AF was associated with a shift from glycolytic to ketolytic metabolism.¹⁸ In genome wide transcriptional studies, patients susceptible to AF demonstrated decreased expression of sets of genes related to metabolic and oxidative stress responses.²⁰

Metformin acts by decreasing hepatic glucose production and increasing skeletal muscle uptake of blood glucose. These effects are thought to be in part mediated by metformin induced activity of AMP-activated protein kinase (AMPK) alterations in atrial calcium channels.²¹ In canine models of atrial fibrillation AMPK activation limits AF promoting²² In murine models of atrial fibrillation in which liver kinase B1, an activator of AMPK, is deleted, AF develops spontaneously in an age dependent manner and progresses from a paroxysmal to a persistent form in a similar manner to that seen in AF patients.²³ Mutations in PRKAG2 gene, part of a subunit of AMPK have also been associated with early onset AF, and familial conduction diseases including Wolff-Parkinson-White syndromes.²⁴ In transcriptional studies of human atrial fibrillation, AMPK subunit expression is increased in patients susceptible to AF but who remain in sinus rhythm while AMPK subunit expression is decreased in patients persistently in AF. This further suggests AMPK activity is protective in human AF.²⁰

Given the benefits of weight loss in AF, the benefit of metformin for weight loss, and the experimental and genetic evidence linking AMPK activation to metformin therapy and reduction in AF risk, the potential of metformin as an upstream therapy is promising.

Trial Objective and Purpose:

The purpose of this trial is to determine if the upstream use of metformin in patients with atrial fibrillation and obesity undergoing a rhythm control strategy will increase the frequency of maintenance of sinus rhythm at six months. The primary endpoint is the number of patients in normal sinus rhythm after six months of follow up. Secondary endpoints are amount of weight loss, change in BMI, change in hemoglobin A1c, number of thromboembolic events, and burden of atrial fibrillation based on the Atrial Fibrillation Severity Score (AFSS).

Trial Design:

The proposed study will be a randomized control trial comparing metformin therapy to a control group in patients with a BMI ≥ 27 and atrial fibrillation who have elected to undergo a rhythm control strategy with ablation. Upstream therapy with Metformin will be used in a randomized fashion. The only variation to the standard of care will be the addition of Metformin therapy and additional blood draws for safety monitoring and EKGs for measuring outcomes in both the intervention and control groups.

Patients meeting the below inclusion and exclusion criteria who provide informed consent will be randomized to control versus metformin therapy six weeks prior to rhythm control.

At baseline all study patients will be assessed for:

Age, Gender, Weight, BMI, Tobacco Use, Hypertension, Hemoglobin A1c, Hyperlipidemia, serum CRP, glomerular filtration rate estimating equation (eGFR), B12, liver function tests (AST, ALT, ALP, bilirubin, albumin, INR), lactic acid, History of Coronary Artery Disease by MI, PCI, or CABG, History of Valvular Disease, History of Obstructive Sleep Apnea, Type of AF and duration, Number of Antiarrhythmic Medications (not including beta-blockers or calcium channel blockers).

In addition, patients will fill out a survey to determine their Atrial Fibrillation Severity Score (AFSS) – a validated tool to assess the symptomatic burden of AF - and will receive education on dietary changes and exercise.

Metformin will be initiated at 500 mg daily and increased as tolerated to 2000 mg daily over a three week period. Subjects will be instructed to hold Metformin on the day of any procedure or study requiring the administration of intravenous contrast and to resume 48 hours after the contrast administration and reinstituted only after renal function has been reevaluated and found to be at the patient's baseline. All patients will receive information on dietary changes to promote weight loss and will be encouraged to increase exercise activities. Patients will discontinue treatment at any time they are found to meet the baseline exclusion criteria for the study.

The initiation of the drug and the dosage increases will be overseen by a designee (mid-level cardiology practitioner) who will be responsible for stopping dosage increases if side effects occur. Six weeks after the initiation of drug the patient will undergo ablation with the intent of achieving rhythm control.

Patients will be followed up in regular intervals after the initial attempt at rhythm control. The minimum follow up interval is every three months. More frequent follow up may be scheduled as deemed necessary by the treating physician.

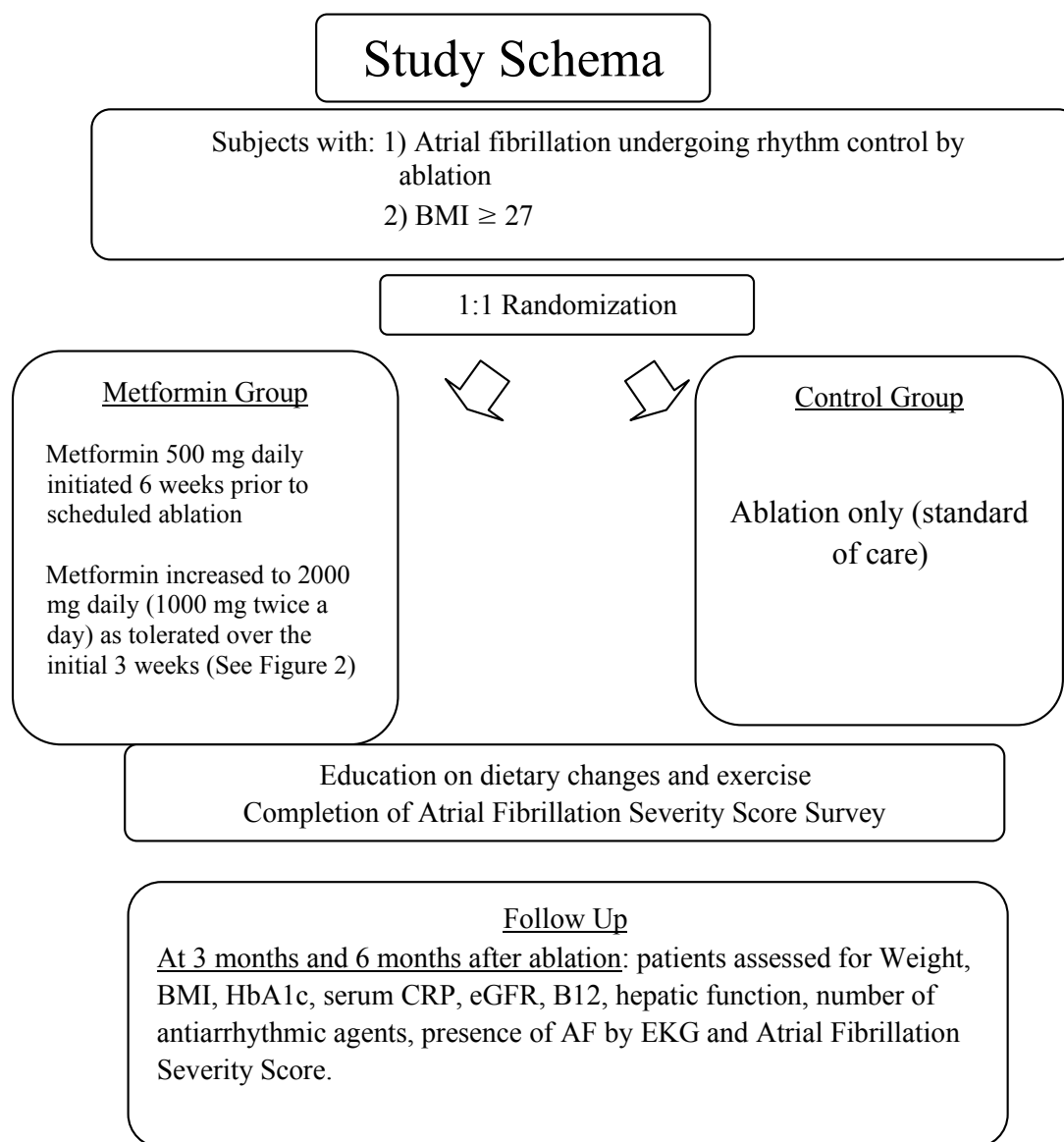
At the time of the first attempt at rhythm control, at the 3 month follow up, and at the 6 month follow up all study patients will be assessed again for:

Weight, BMI, Hemoglobin A1c, serum CRP, eGFR, liver function tests (AST, ALT, ALP, bilirubin, albumin, INR), B12, lactic acid, number of antiarrhythmic agents, presence of AF by EKG, and Atrial Fibrillation Severity Score.

At each 3-month and 6-month follow up, data will be reviewed by a designee who will use the criteria described below for reporting to the Medical Monitor. The patient will also be assessed for the occurrence of any adverse events as defined below and adverse events will be reported to the medical monitor.

At the end of 6 months of therapy, the decision to continue Metformin beyond 6 months will be made in conjunction with the patient's treating cardiologist and primary care physician.

Figure 1.



Investigational Product:

An investigational product is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, the investigational product is: GLUCOPHAGE® (metformin hydrochloride) tablets. The investigational product is available commercially. The outpatient pharmacy will obtain the investigational product.

The investigational product will be stored in a secure area according to local regulations. The investigator will ensure that investigational product is only dispensed to study subjects.

Storage and Dispensing:

The study drug is commercially available. Study drug will be stored in accordance with the package insert at 20°–25° C (68°–77° F); excursions permitted to 15°–30° C (59°–86° F).

Investigational product documentation will be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and storage temperatures.

Per package insert: The usual starting dose of GLUCOPHAGE® Tablets is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses.

In this study the starting dose will be 500 mg daily, given with meals. Over a 3 week period, the dosage will be increased to 2000 mg daily (given in a divided dose of 1000 mg twice a day) as tolerated by the patient, according to the schedule below.

Figure 2.

Study Drug	Week 1	Week 2	Week 3	Week 4
Number of pills in Morning	1	1	2	2
Number of pills in Evening	0	1	1	2
Total pills per day	1	2	3	4
Daily dose (of 500 mg tablet)	500 mg	1000 mg	1500 mg	2000mg

Method of Assigning Subject Identification:

The study design is a randomized control trial. After the subject's initial eligibility is established and informed consent has been obtained, the subject will be enrolled into the study by obtaining a randomly assigned subject number. The subject number will determine the randomization to the treatment or control arm.

Selection and Withdrawal of Subjects:

Inclusion criteria: All individuals diagnosed with Atrial Fibrillation and choosing to undergo a rhythm control strategy at Robert Packer Hospital with a BMI ≥ 27 will be eligible for the study. All subjects must be able to understand and willing to sign a written informed consent document.

Exclusion criteria: Individuals who are already taking metformin or other antidiabetic medications including insulin, have a diagnosis of diabetes, have a known allergy or FDA-labeled contraindication to taking metformin, eGFR below 30 mL/min per 1.73 m² or other clinical diagnosis of advanced renal disease, have acute or chronic metabolic acidosis (serum bicarbonate <22 mEq/L), have a history of significant alcohol use (>2 drinks/day on average), have a history of hepatic dysfunction (serum bilirubin 1.5X greater than the upper limit of normal), have a history of New York Heart Association (NYHA) Class III or IV heart failure, or are pregnant will be excluded from the trial.

Treatment of Subjects:

At baseline all study patients will be assessed for:

Age, Gender, Weight, BMI, Tobacco Use, Hypertension, Hemoglobin A1c, Hyperlipidemia, serum CRP, eGFR, liver function tests (AST, ALT, ALP, bilirubin, albumin, INR), History of Coronary Artery Disease by MI, PCI, or CABG, History of Valvular Disease, History of Sleep Apnea, Type of AF and duration, Number of Antiarrhythmic Medications (not including beta-blockers or calcium channel blockers).

In addition, patients will fill out a survey to determine their Atrial Fibrillation Severity Score (AFSS) – a validated tool to assess the symptomatic burden of AF - and will receive education on dietary changes and exercise.

Subjects will be randomized to receive either Metformin (500 mg tablet) or into the control group. Subjects will be instructed to take one tablet twice a day with meals. Over a 3 week period, the dosage will be increased to 2000 mg daily (given in a divided dose of 1000 mg twice a day) as tolerated by the patient.

Patients will be followed up in regular intervals after the initial attempt at rhythm control. The minimum follow up interval is every three months. More frequent follow up may be scheduled as deemed necessary by the treating physician.

At the time of the first attempt at rhythm control, at the 3 month follow up, and at the 6 month follow up all study patients will be assessed again for:

Weight, BMI, Hemoglobin A1c, serum CRP, eGFR, liver function tests (AST, ALT, ALP, bilirubin, albumin, INR), number of antiarrhythmic agents, presence of AF by EKG, Atrial Fibrillation Severity Score, occurrence of adverse events.

Study Drug Compliance:

Study drug dispensed to the subjects will be tracked. Subjects will return empty study drug containers and unused study drug at those visits when a new supply of study drug is to be received. Study drug accountability will be performed at each visit. Subjects should report any unintentional interruption or missed doses of 7 consecutive days or more to the study-site personnel at each visit. It is understood that subjects may occasionally miss a dose or that a subject may be placed on temporary discontinuation.

Outcomes and Assessment of Efficacy:

The primary outcome by intention to treat analysis will be maintenance of sinus rhythm by chart review, EKG, and Atrial Fibrillation Severity Score at 3 and 6 months after the initial attempt at rhythm control.

Secondary outcomes will include hospitalization related to arrhythmic events or medication side effects, number of antiarrhythmic medications, number of repeat ablations, BMI, Hemoglobin A1c, and number of thromboembolic events.

Pre-specified subgroup comparisons will include comparing patients randomized to metformin who have a 5% reduction in weight at 6 months to all control patients who achieve a 5% reduction in weight, and to all control patients.

Assessment of Safety:

A Medical Monitor will be utilized to provide general oversight and safety considerations for this study. The Medical Monitor will provide advice to the Sponsor-Investigator regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The Medical Monitor will be charged with assessing such actions in light of an acceptable risk/benefit profile for metformin. The Medical Monitor will act in an advisory capacity to the Sponsor-Investigator and will monitor subject safety data for the study.

All patients included in the study will have monitoring of renal function, hepatic function, and serum lactic acid at baseline, at the time of ablation or initiation of rhythm control, and at 3-month and 6-month follow ups. This data will be reviewed by an investigator who is not involved in the outcome analysis. This investigator will be a mid-level who will be assigned to check the routine labs. The parameters for immediate reporting to one of the study coordinators are the following- creatinine greater than or equal to 1.5 in males or 1.4 in females, elevated lactic acid, or serum bilirubin >1.5x the upper limit of normal. Exclusion criteria will also be reviewed at each follow up, and if at any point a patient meets the exclusion criteria for the study or has an unexpected adverse event they will be withdrawn from the study.

Routine reports will be provided to the Medical Monitor every 2 months and will include rates of disenrollment, reason for disenrollment, unexpected adverse events, and mortalities. If a statistically significant harm is detected in the analysis of the safety data collected at 2 month intervals the protocol will be terminated.

Adverse events will be solicited at routine follow-up with a designee and are defined as follows: .

Lactic Acidosis – lactic acid >2.1 mmol/L as measured at either routine follow up or if measured during a hospitalization for any reason

Thromboembolic event – any stroke, mesenteric ischemia, limb ischemia, or other event determined to be of an embolic etiology secondary to atrial fibrillation

Vitamin B12 levels and any change from baseline at the 3 and 6 month timepoints will be measured and submitted.

Adverse events will be reviewed every 2-months and a statistical analysis will be done. If the analysis finds that any of these adverse events have occurred more frequently in either group in a statistically significant manner, the trial will be stopped.

Potential Risks:

Per the Glucophage (metformin) package insert, metformin does not cause hypoglycemia in individuals with diabetes mellitus or normal subjects except in certain circumstances excluded by the study's exclusion criteria.²⁵

Metformin does have a warning for the risk of lactic acidosis. Per the insert:

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patientyears, with approximately 0.015 fatal cases/1000 patientyears). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypo perfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.²⁵

In a more recent review of pooled data from 347 trials and cohort studies an estimated risk of 4.3 cases of lactic acidosis in 100,000 patient years was calculated and this risk was equivalent with other anti-hyperglycemic agents.²⁶ The ultimate conclusion of this investigation was "There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other antihyperglycemic treatments if the drugs are prescribed under study conditions, taking into account contraindications".²⁶

Other known adverse reactions to metformin therapy include gastrointestinal side effects which include flatulence, diarrhea, nausea and vomiting, and abdominal discomfort. These symptoms are dose dependent and can be relieved by dose reduction. Approximately 50% of all patients can tolerate a maximal dose of metformin but a small minority of around 5% cannot tolerate any dose of metformin.²⁷

Potential Benefits:

The potential benefits to patients who agree to enroll in this study include the potential benefits of metformin therapy and the benefits of more frequent follow up. In addition the previously discussed evidence to show weight loss, metformin therapy has been demonstrated to have several potential beneficial effects including a decrease in progression from prediabetes to diabetes and improved cancer mortality compared to patients taking other diabetic therapies and non-diabetic individuals,^{28,29}

Statistics:

We expect a 30% recurrence of AF after patients undergo ablation. After ablation, we expect the recurrence of AF to be 30% less in the intervention group of patients on metformin than the control group.

Using an 80% power at a 95% confidence interval, the sample size of the control group (ablation only) and the intervention group (ablation plus metformin) will be 400 each for a two tailed study, accounting for up to a 3% attrition rate in each group. The total sample size of this study will be 800. It is estimated to take five years to accrue subjects.

Statistical methods employed to analyze outcomes will be a Pearson's X^2 test for categorical variables. Analysis of Variance will be used for continuous variables. All tests are two-sided and $P < .05$ will be used to indicate a statistically significant difference.

Direct Access to Source Data/Documents:

The investigator will permit trial-related monitoring, audits, IRB review and regulatory inspection(s) by providing direct access to source data/documents.

Record Retention:

In compliance with the ICH/GCP guidelines, the investigator will maintain all source documents that support the data collected from each subject, as well as all study documents.

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Ethics:

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Procedures to Obtain and Record Informed Consent:

All patients will be provided with a written consent document which will contain the purpose of the study, the procedures of the study, and the potential risks and benefits to participating in the study in language that is accessible to the lay public. This document will also clearly state that participation in the study is voluntary and the decision to participate will not affect other aspects of their care. The document will also clearly state that a patient may withdraw from the study at any time they choose. Each patient will meet with an investigator to assess the patient's understanding of the risks and benefits before providing verbal and written informed consent. Patients who are medically or cognitively incapacitated and cannot provide their own consent will be excluded from the study.

Subject Compensation:

Subjects will not receive any form of monetary compensation for participation in this study.

Procedures to Maintain Confidentiality:

The only identifying information that will be retained after the follow up period is the patient's medical record number. All data will be stored in password encrypted files. Any breaches of confidentiality will be reported to the IRB and Corporate Compliance Department.

Registration: The clinical trial will be registered with ClinicalTrials.gov an International Committee of Medical Journal Editors approved public registry.

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