Metformin as an adjunctive therapy to Catheter Ablation in Atrial Fibrillation

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PI: Hakan Oral, oralh@med.umich.edu

1. Background:

Atrial fibrillation (AF) is the most common arrhythmia and its prevalence is projected to rise with the increasing age of the population and comorbid disease prevalence. Obesity, diabetes, and the metabolic syndrome are known risk factors for AF.[1–3] Weight loss and cardiovascular risk factor modification, including glycemic control, has also been demonstrated to decrease AF burden and improve the long term success of catheter ablation for AF.[4–6] In addition to this patient level data, there is cellular evidence implicating metabolic and oxidative stress in the development and maintenance of AF. In genome wide transcriptional studies of human atria, patients susceptible to AF demonstrated decreased expression of genes related to metabolic and oxidative stress responses.[7] Similarly, metabolomic and proteomic studies of human atria demonstrate a shift towards ketolytic metabolism in persistent AF.[8]

Metformin hydrochloride is the first-line pharmacologic therapy of Type II diabetes. 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).[9] Because of the metabolic and weight loss effects of metformin, it may be a useful adjunctive therapy in the treatment of atrial fibrillation.

Role of AMPK on cardiomyocyte metabolism/electrophysiology:
In several animal and human studies, AMPK activity modulates susceptibility to AF. In murine models of atrial fibrillation in which liver kinase B1, an activator of AMPK, is deleted, AF develops spontaneously and progresses from a paroxysmal to a persistent form in a similar manner to that seen in AF patients.[10] Similarly, mutations of PRKAG2, a subunit of AMPK, is associated with the development of hypertrophic cardiomyopathy, atrial fibrillation, and ventricular pre-excitation.[11]

In studies of human atrial tissues, paroxysmal AF and metabolic stress both induced AMPK activation. However, this activity is suppressed in patients with long standing persistent AF suggesting that AMPK activation may protect against the progression of AF.[12,13] In these studies AMPK activity was associated with maintenance of L-type calcium channel activity and intracellular calcium handling.

Impact of metformin on AF/ cardiomyocyte electrophysiology:
In a retrospective cohort of newly diagnosed diabetics, metformin use was associated with a decreased incidence of AF when compared to other treatment modalities.[14] These authors performed subsequent in-vitro studies which demonstrated that metformin attenuated the oxidative stress and remodeling associated with tachypacing.[14] Similarly, in a retrospective cohort of diabetic patients undergoing catheter ablation, metformin use was associated with a lower risk of recurrence after ablation.[6]

Impact of metformin on weight loss in non-diabetics:
In randomized trials involving pre-diabetic individual's metformin therapy associated with modest but sustained weight loss (~2kg).[15,16] Similarly in a randomized controlled trial of metformin in

nondiabetic individuals with coronary disease and a large waist circumference, metformin use was associated with a 3.2 kg reduction at 18 months.[17]

2. Objective:

The purpose of this study is to determine if the use of metformin in patients with atrial fibrillation and obesity will decrease the recurrence of atrial fibrillation after catheter ablation.

Primary endpoint: Freedom from recurrent atrial arrhythmias at 12 months after a single ablation procedure to eliminate AF. There will be a 3 month blanking period after ablation during which recurrent atrial arrhythmias will not contribute to the primary endpoint. In clinical practice recurrence during this time may be one time and not correlate with long term outcome.

Secondary endpoints:

- Time to recurrence of AF (after the blanking period of 3 months)
- Freedom from recurrent atrial arrhythmias at 1 year after ablation (after the blanking period of 3 months)
- Freedom from recurrent atrial arrhythmias at 6 months after repeat ablation
- Assessment of patients' symptoms based on the Atrial Fibrillation Severity Score
- Percent change in weight at 3 and 6 months after ablation
- Percent change in HbA1c at 6 and 12 months after ablation
- Major procedural complications (major bleeding, vascular injury, myocardial perforation, stroke, mortality, etc)
- AF related morbidity during follow-up (ED visits and hospital admissions, due to AF, TIA/CVA, mortality).
- Burden of AF as assessed by AliveCor Kardia devices

3. Study Design:

Prospective, open label, single-center, randomized trial with 1:1 randomization to the study group (metformin) or control group (standard of care)

Inclusion criteria:

1. All patients with BMI >25 kg/m^2 with plan for rhythm control of atrial fibrillation by catheter ablation
2. All subjects must be able to understand and willing to sign a written informed consent document.
3. > or =18 years old

Exclusion criteria

- Individuals who are already taking metformin or other antidiabetic medications, including insulin
- Known diabetes
- Known allergy or FDA-labeled contraindication to taking metformin (estimated glomerular filtration rate <30 mL/min/1.73 m2, hypersensitivity to metformin, acute or chronic metabolic acidosis)
- Patients taking carbonic anhydrase inhibitors
- eGFR below 30 mL/min per 1.73m^2 or other clinical diagnosis of advanced renal disease
- Acute or chronic metabolic acidosis (serum bicarbonate <22 mEq/L)
- History of significant alcohol use (>2 drinks/day on average)

- History of hepatic dysfunction (serum bilirubin 1.5x greater than ULN)
- History of New York Heart Association (NYHA) Class III or IV heart failure
- Pregnancy or nursing

Intervention:

Patients meeting the below inclusion and exclusion criteria who provide informed consent will be randomized to control (standard of care) versus intervention (metformin therapy initiated between zero to six weeks prior to rhythm control with catheter ablation). All patients receiving metformin will be provided the Patients section of the Metformin drug label.

In addition, all subjects will receive education on lifestyle changes and exercise which are standard of care. This will include discussion with their treating electrophysiologist and the attached handout (Appendix 1).

Finally, all subjects will be provided with an AliveCor device in order to record an electrocardiogram during symptoms perceived to be AF. All patients will be instructed to transmit at least once per week.

Schedule of Events								
	Baseline (6-8 Weeks prior to ablation)	0-6 Weeks Prior to Ablation	1-2 Weeks prior to ablation	Ablation Procedure	3 Months Post Ablation (+/- 1 Month)	6 Months Post Ablation (+/- 1 Month)	9 Months Post Ablation (+/- 1 Month)	13 Months Post Ablation (+/- 1 Month)[6]
Physical Exam[1]	X			X	X	X		X
Medical History[2]	X			X	X	X		X
Medication Review	X Research visit			X	X	X	X	X
Informed Consent	X							
RFT [3]			X SOC	X SOC		X		
Hemoglobin A1c			X			X		X
ECG				X SOC	X SOC	X SOC		X SOC
Urine Pregnancy Test (if female of child bearing potential)	X							
Ablation Procedure				X				
Metformin Dosing[4,5]	All study paid	X						X[4]
AFSS Questionnaire	X			X	X	X	X	X
Recommendations for Lifestyle modification	X							
Review of drug diary		X		X	X	X	X	X
Review of adverse events		X		X	X	X	X	X

1: Including weight, height, BMI

2: Including History of Coronary Artery Disease by myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting, History of Valvular Disease, History of Obstructive Sleep Apnea, Type of AF and duration, Hypertension, Hyperlipidemia

3: Renal function test (RFT) X 4 X 75 (study arm patients on;t at 6 months)

4: Continuation of metformin after 12 months at the discretion of treating cardiologist and primary care provider.

5: Continuous dosing will occur from 6 weeks prior to the ablation procedure through the study period, except on the day of the procedure when it will be held.

6. Rhythm endpoints will be assessed

The Atrial Fibrillation Severity Score (AFSS) survey is a validated tool to assess the symptomatic burden of AF (Appendix 2). The assessment of the AFSS will be conducted by a study member.

Metformin immediate release will be initiated at 250 mg daily, oral dose, and increased as tolerated to 2000 mg daily over a three-week period. Patients will take metformin with a meal. The provided pills will be 500mg and will be split when taken as 250 mg. If patients tolerate the maximum dose of metformin they will require a total of 1465 pills for a 12-month supply (including the titration period).

If tolerated, subjects will increase their daily dose to 500 mg after 1 week (250 mg twice daily), to 1000 mg after 2 weeks (500 mg twice daily), and 2000mg after 3 weeks (1000 mg twice daily). If a patient is unable to tolerate a dose increase they will return to their last tolerated dose after omitting one days dosing. Patients in the intervention arm will be contacted bi-weekly during the dose titration period to assess for compliance with dose escalation.

Subjects will be instructed to hold Metformin on the day ablation for AF and before any procedure or study requiring the administration of intravenous contrast and to resume 48 hours after the procedure administration. 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. Patients will be asked to keep a drug diary which will be reviewed along with pill count in follow up to assess for compliance. The drug diary and adverse events will be reviewed as per the schedule of events.

The initiation of the drug and the dosage increases will be overseen by a member of the study team who will be responsible for stopping dosage increases if known or possible side effects of metformin occur. Drug initiation will occur between zero to six weeks before 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. Subjects will have follow up at least 30 days or longer post their last dose of metformin when administered as a study drug.

At each 6-month follow up, data will be reviewed by a designee who will use the criteria described below for reporting to an internal data safety monitoring board (DSMB). The patient will also be assessed for the occurrence of any adverse events as defined below and adverse events will be reported to the DSMB.

Assessment of Safety:

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

Allatients included in the study will have evaluation of prior renal function at the time of enrollment and monitoring in the peri ablation period. The intervention arm patients will have additional monitoring of renal function at 6-month follow up. 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. If found elevated lactic acid, or serum bilirubin >1.5x the upper limit of normal will also be reported. If these lab abnormalities are observed, repeat lab work or withdrawal from the treatment

arm of the study at the discretion of the investigator. 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 and related adverse event they will be withdrawn from the study.

Routine reports will be provided to the DSMB every 3 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 analyzed at 6 month intervals the protocol will be terminated.

All 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
Gastrointestinal side effects ascribed to metformin therapy requiring discontinuation

Adverse events will be reviewed every 3-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. For the infrequent but significant events of death and stroke, a difference of more than 3 deaths or more than 3 strokes in the intervention compared to control arm will result in assessment of the safety with the IRB with the consideration of termination of the trial.

4. 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.

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.[18]

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.[19]

Patients will be educated about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to metformin and report these symptoms to their healthcare provider.

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.[20]

5. 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. [21,22]

6. Statistics:

We expect a 10% rate of recurrent atrial arrhythmias in the intervention arm and a 30% rate of recurrent atrial arrhythmias in the control arm at 12 months post ablation. We plan to recruit patients over 2 years with a minimum follow up of 12 months for the last patient recruited. Using an 80% power at a 95% confidence interval, an estimated 10% drop out, and a 5% rate of non-tolerance of maximum dose metformin (with 50% efficacy at a reduced dose) we estimate 150 patients will be required for the study with a 1:1 randomization of patients to the control and intervention arms.

Randomization will be stratified on the basis of AF type (paroxysmal vs. persistent) and history of prior AF ablation.

The estimated recurrence is based on contemporary randomized trials of catheter ablation for AF in which recurrence rates were comparable (CABANA trial 58% recurrence at 18 months[23], CIRCA-DOSE trial with 52% recurrence at 12 months[24]) as well as published data from our center (49-59% recurrence at 21 months in persistent AF[25], ~30% at 2 years in paroxysmal AF[26]). The reduction in AF recurrence in the intervention arm is estimated based on observational data demonstrating reduction of AF recurrence in diabetic patients treated with metformin after catheter ablation (30% in unadjusted analyses, 15% with multivariate adjustment).[6] A comparable decrease in incident AF (19%) is seen in diabetic populations treated with and without metformin.[14]

Pre-specified subgroups for exploratory analyses include: Persistent AF, Pre-diabetes

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.

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

Drug Information
Drug name: Metformin (Glucophage®)

Drug product: Metformin hydrochloride immediate release, oral, 500mg

Availability: The study drug will be provided free of charge to the study patients via an internal study fund.

Preparation and Dispensing:

Drug Accountability
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the study drug (metformin). The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

The University of Michigan Outpatient Pharmacy will provide the drug supply and the study team will maintain accountability records according to the institution standard operating procedures.

Each subject will also be asked at each visit whether he or she has been compliant with dosing instructions. Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each visit, the Investigator or designee will evaluate the amount of metformin provided to each subject and any returned medication (as required for drug accountability purposes), and compare this accounting with the subject's dosing pattern to obtain an estimate of overall compliance. If it is determined that a subject is not compliant with study medication, then site personnel must re-educate the subject on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the subject.

ADVERSE EVENT REPORTING

Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment

b. *Probably related*: likely associated with study drug/treatment

c. *Possibly related*: may be associated with study drug or other treatment

d. *Unlikely to be related*, or

e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.

b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.

c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

d. A potential alternative cause does not exist.

Serious Adverse Events (SAE)

An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death.
b. A life-threatening adverse drug experience.
c. Inpatient hospitalization or prolongation of existing hospitalization.
d. A persistent or significant disability &/or incapacity.
e. A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose. Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience

when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the package insert (current edition) or in the study informed consent document.

Unexpected adverse events are those that:

a. Are not described in the package insert

b. Are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

Adverse Event reporting

Serious adverse events (SAEs) are defined above. All SAE forms must include the patient number, severity of reaction (e.g. mild, moderate, severe), relationship to study drug(s) (e.g. probably related, unknown relationship, definitely not related), date and time of administration of study drug(s) and all concomitant medications and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" as defined above are present. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up form. A final report to document resolution of the SAE is required.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations of all SAEs. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form as well as the Study Termination CRF. All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

The study will comply with the IRB & FDA reporting requirements and guidelines as appropriate.

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Appendix

1. Hand out regarding lifestyle changes for AF: The below text will be provided to all patients enrolled in the study

Living Well with Atrial Fibrillation

There are several lifestyle choices which can make atrial fibrillation less likely to happen or to cause symptoms. Many of these choices also can improve the control of atrial fibrillation by catheter ablation procedures:

• Weight loss - When overweight patients lose weight, they are less likely to have atrial fibrillation and symptoms from their atrial fibrillation. To lose weight (and keep it off), most patients need to make long term changes to the foods they eat (rather than short term diets). The DASH diet is a heart healthy eating style which is associated with improved blood pressure and weight loss (nhlbi.nih.gov/health-topics/dash-eating-plan, mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/dash-diet/)

- Sleep Apnea – Sleep apnea is a disorder of breathing during sleep and is about 5 times more common in patients with atrial fibrillation. Snoring, choking, or stopping breathing during sleep, daytime sleepiness, or morning headaches can be signs of sleep apnea. Diagnosing and treating sleep apnea can reduce blood pressure and help with atrial fibrillation. Talk to your cardiologist or primary doctor about sleep apnea testing.

- Exercise – Exercise may help with atrial fibrillation even when it does not lead to weight loss. The best exercise is one that you can do regularly and commit to long term. A goal would be to perform 150 minutes of moderate intensity exercise each week (brisk walking, water aerobics, slow biking, dancing) but you can work up to this goal.

- Blood pressure – If you have high blood pressure, getting this under control as directed by your doctors through dietary changes and medications can help lower the risk of atrial fibrillation.

- Alcohol – Alcohol may be a trigger for some patient's atrial fibrillation. Decreasing or eliminating alcohol intake can help with blood pressure control, weight loss, and atrial fibrillation.

- Tobacco – Cigarette smoking is associated with a higher risk for atrial fibrillation and stroke related to atrial fibrillation. Smoking harms almost every organ in the body. Quitting smoking has many health benefits including the chance to live longer with a lower risk of heart attack and stroke.

- Caffeine – Coffee and caffeine does not always affect atrial fibrillation but it may be a trigger for some patients, especially when in large quantities. You may find that cutting back on caffeine can help with atrial fibrillation.

2. Atrial Fibrillation Severity Score

PART A

Please answer the following questions as accurately as possible.

3. **Are you in atrial fibrillation currently?**
   - ○ Yes
   - ○ No
   - ○ I don't know

4. **How do you feel about your life at the present time?**

Worst possible life									Best possible life
○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10

5. **How often on average, does your irregular heart rhythm (atrial fibrillation) occur?**
   - ○ Continuously
   - ○ More than twice a day
   - ○ Daily or almost daily
   - ○ 4-5 times a week
   - ○ 2-3 times a week
   - ○ About once a week
   - ○ About twice a month
   - ○ About once a month
   - ○ About 2-4 times a year
   - ○ About once a year
   - ○ Less than once a year
   - ○ Not applicable, I have never had an irregular heart rhythm

6. **How long on average, do the episodes of the irregular heart rhythm last?**
   - ○ Continuously
   - ○ Several days or more
   - ○ All day
   - ○ Several hours, but less than a day
   - ○ About an hour
   - ○ 30-45 minutes
   - ○ < 30 minutes
   - ○ A few minutes
   - ○ Not applicable, I have never had an irregular heart rhythm

7. How severe was your *most recent* episode of irregular heart rhythm?

Not at all severe — Extremely severe

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

8. How severe was your *first* episode of irregular heart rhythm?

Not at all severe — Extremely severe

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

PART B

9. Have you ever been cardioverted (ie. been put to sleep and electrically shocked)?

○ Yes
○ No

If yes, how many times? ☐☐☐

10. How many times did you visit the emergency room within the past year because of an irregular heart rhythm?

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ more than 5 times ---------> ☐☐☐ times

11. How many times were you hospitalized within the past year because of an irregular heart rhythm?

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ more than 5 times ---------> ☐☐☐ times

12. How many times did you visit your specialist within the past year because of an irregular heart rhythm?

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ more than 5 times ---------> ☐☐☐ times

Please indicate how bothered you have been by the following symptoms (if at all) in the past 4 weeks. Fill in the answer that best describes your symptoms.

1. Palpitations:
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

2. Shortness of breath at rest:
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

3. Shortness of breath during physical activity:
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

4. Exercise intolerance (fatigue during mild physical activity):
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

5. Fatigue at rest
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

6. Lightheadedness/dizziness
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤

7. Chest pain or pressure
   How often have you been bothered by this symptom in the past 4 weeks?

I have not had this symptom in the past 4 weeks	Very little	A little	A fair amount	A lot	A great deal
⓪	①	②	③	④	⑤