IMPACT-AF SAP

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Optimizing primary care management of atrial fibrillation: The rationale and methods of the Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF) study

Statistical Analysis Plan, Version 1

January 9, 2019

Background

The burden of Atrial Fibrillation (AF), the most common sustained cardiac rhythm abnormality, is growing markedly such that the lifetime risk of acquiring this condition is now around 1 in 4.[1,2] AF is linked to increased mortality, substantial morbidity, high patient and health care costs,[3] as well as impaired quality of life.[4] In particular, AF is an important and independent risk factor for stroke, increasing the risk of such events by 5-fold and accounting for approximately 15-20% of all strokes.[5] Since at least a third of AF patients are asymptomatic,[6] many cases will be identified in outpatient settings when patients are being assessed for other conditions.

Traditionally, the major therapeutic interventions in AF patient care are directed at modifying or reversing the irregular rhythm and fast heart rate and in providing antithrombotic therapy to prevent strokes.[7-9]

Recently, multi-disciplinary approaches to AF management, centered on specialty AF clinics, have reported encouraging clinical results, including reductions in wait times for specialist assessment, emergency department (ED) visits, hospitalizations, and even mortality.[10-12] However, such clinics require expert staff, broad collaboration, and special resources including physical space that entail high costs.

Clinical Decision Support Systems (CDSS) are intelligent systems that digitize and operationalize evidence-based guidelines, clinical pathways and algorithms to provide personalized, timely and evidence-informed functions. While the utility of such heath informatics approaches to health care might seem intuitive, this is not always the case. The diversity in the design, functionality and implementation of CDSS in real-life care settings has precluded making sweeping judgments about their clinical effectiveness, particularly over the longer term. While such technologies offer promise, more robust systems need to be developed and their effectiveness assessed, ideally in randomized trials.

We have developed a CDSS tool that aims to empower improvement in overall AF-related care, not simply with regards to antithrombotic management, but also to support effective rate control and treatment of AF risk factors. The tool has been assessed in a preliminary fashion by a general cardiologist, electrophysiologist and primary care physician, working independently to assess the

utility and dependability of the CDSS using mock clinical cases. While it functioned accurately and with seeming efficacy, there remains the need to determine applicability, ease of use and clinical effectiveness in terms of whether AF patient care and outcomes would improve at the population level with its use.

The primary aim of Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF) study is to evaluate whether a CDSS tool, available to primary care physicians, and designed to support both practitioners and patients with evidence-based AF management, can improve clinical and patient-reported outcomes by comparison to usual clinical care. It further seeks to establish whether it will better standardize process of care so as to produce more efficient and cost-effective use of time and scarce health care resources as compared to usual care.

Methods

IMPACT-AF is a prospective, randomized, un-blinded, cluster design clinical trial, conducted in the primary care setting of Nova Scotia, Canada.

At least 200 primary care providers are being recruited and randomized at the level of the practice to control (usual care) or intervention (eligible to access to CDSS) cohorts. Over 1,000 patients of participating providers with confirmed AF will be managed per their provider's respective assignment.

Outcomes

Primary Outcome

The IMPACT-AF primary outcome is composite of any AF-related emergency department visit or unplanned CV hospitalization over 12 months.

Secondary Outcomes

Secondary outcomes include comparing the intervention versus usual care over 12 months on the following:

1. Any AF-related emergency department visit
2. Unplanned cardiovascular (CV) hospitalization
3. Strokes
4. Systemic embolism / major bleeding
5. Mortality
6. Anticoagulant therapy
7. Access to specialist consultation

8. Echo
9. Catheter ablations
10. EQ5D
11. Health care costs

The definitions of all outcome variables for the primary and secondary analyses are found in Appendix 1.

Analysis Plan

This statistical analysis plan follows the JAMA Guidelines for the Content of Statistical Analysis Plans in Clinical Trials [13]. A summary of all planned analyses is provided in **Table 1**.

Blinded Analyses

All statistical analyses will first be completed using blinded treatment groups (i.e. treatment X and Y).

Presentation of Data

The trial results will be presented according to the CONSORT guidelines for randomized controlled trials (RCTs) [14]. The baseline demographic characteristics of the patients will be summarized by group, reported as a mean (standard deviation [SD]) or median (first quartile, third quartile) for continuous variables and count (percent) for categorical variables (**Tables 2**). All statistical tests will be 2-tailed with α=0.05.

Primary Outcome Analysis

The primary efficacy analysis will be an analysis to compare rates of the composite of any AF-related emergency department visit or unplanned CV hospitalization between Intervention and Usual care over 12 months, with the outcome being treated as number of events (Tables 3). The analysis will follow the intention-to-treat (ITT) principle. While the unit of randomization is the practice/physician, the unit of analysis will be the patient. We will use Generalized Estimating Equations (GEE) –assuming exchangeable correlation structure for patients within the same practice and adjusting for urban and rural practice types to analyze all outcomes[15]. Unlike ordinary regression techniques, GEE allows us to estimate the intra-practice correlation among patients within each practice. For time-to-event analysis this is done using frailty-models. The results will be reported as estimate of the effect—reported as hazard ratio [HR], corresponding 95% confidence interval and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as p<0.001. The criterion for statistical significance will be set a priori at alpha = 0.05. The answers to the five questions in the EQ-5D-5L will be converted to health utilities using the Canadian scoring algorithm[16]. Cost effectiveness analysis

will be conducted by calculating the incremental cost per QALY gained by the CDSS arm compared with the usual care arm. Due to skewness of costs and health utility distributions, the non-parametric bootstrapping method will be used to estimate the 95% confidence interval for the incremental cost per QALY gained. All analyses will be performed using SAS version 9.4 (Cary, NC).

Secondary Outcomes Analysis

We will estimate the effect of CDSS (intervention) versus usual care (control) over 12 months on the following: any AF-related emergency department visit; unplanned CV hospitalization; strokes; systemic embolism / major bleeding; mortality; anticoagulant therapy; access to specialist consultation; echo; catheter ablations; EQ5D; health care costs (Table 3). The subgroup analyses will be performed by adding an interaction term of the subgroup variable and the intervention variable in the model. The criterion for statistical significance for subgroup analyses will be set at alpha = 0.05. This will not be adjusted for multiple testing as these analyses are exploratory.

Sensitivity Analyses

There are several methods for analyzing cluster RCTs[17, 18]. We will conduct sensitivity analyses in two ways. Firstly, we will perform sensitivity analyses using commonly used patient-level methods such as random-intercept model method (Table 4a). Secondly, we will also perform sensitivity analyses with the outcome (composite of any AF-related emergency department visit or unplanned CV hospitalization) being treated as a count assuming a Poisson distribution (Table 2). The results will be reported as incidence rate ratio [IRR], 95% CI and associated p-value. We hypothesize that our results will remain robust to the different sensitivity analyses.

Subgroup Analyses

A subgroup analysis will be conducted to compare the effect of CDSS (intervention) versus usual care (control) on the composite of any AF-related emergency department visit or unplanned CV hospitalization, as well as the of number AF Related ED Visits and CV Hospitalizations individually, by location of practice, patient sex, age, CHADS2, CHADS-VASC, hypertension, diabetes and years of practice of family doctor. We will perform these subgroup analyses by regression methods with appropriate interaction terms. This subgroup analysis will be conducted for all primary and secondary outcomes (Tables 5a, 5b and 5c). Our hypothesis is that the effects of the intervention on outcomes differ by subgroups. A sensitivity analysis will equally be conducted for all the different subgroup analyses with the outcome being treated as a count (Tables 5a, 5b and 5c). All the subgroup results will be presented using forest plots reporting estimates of effect as HR or IRR, 95% CI for each subgroup and a p-value of the interaction test.

Dissemination

Upon trial completion, the primary manuscript with the 12-month follow-up results, whether positive, negative or neutral, will be submitted for a peer-reviewed publication to a top medical journal. The final dataset will be shared through an open access data repository once all analyses are completed.

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Table 1: Statistical Analysis Plan Summary

Objective	Outcome	Hypothesis	Methods of Analysis
1) **Primary** To compare rates of the composite of any AF-related emergency department visit or unplanned CV hospitalization between Intervention and Usual care over 12 months	composite of any AF-related emergency department visit or unplanned CV hospitalization over 12 months	Intervention better than Usual Care	Generalized Estimating Equations (GEE) or frailty models
2) **Secondary** To compare I vs UC over 12 months on the following: any AF-related emergency department visit	any AF-related emergency department visit	Intervention better than Usual Care	GEE or frailty models
unplanned CV hospitalization	unplanned CV hospitalization	Intervention better than Usual Care	GEE or frailty models
strokes	strokes	Intervention better than Usual Care	GEE or frailty models
systemic embolism / major bleeding	systemic embolism / major bleeding	Intervention better than Usual Care	GEE or frailty models
mortality	mortality	Intervention better than Usual Care	GEE or frailty models
anticoagulant therapy	anticoagulant therapy	Intervention better than Usual Care	GEE or frailty models
access to specialist consultation	access to specialist consultation	Intervention better than Usual Care	GEE or frailty models
echo	echo	Intervention better than Usual Care	GEE or frailty models

catheter ablations	catheter ablations	Intervention better than Usual Care	GEE or frailty models
EQ5D	EQ5D	Intervention better than Usual Care	GEE or frailty models
health care costs	health care costs	Intervention better than Usual Care	GEE or frailty models
3) **Subgroup Analyses:** To compare the effect of I vs UC by different subgroups: location of practice, patient sex, age, CHADS2, CHADS-VASC, hypertension, diabetes and years of practice of family doctor	All primary and secondary outcomes	Effects on outcomes differ by location of practice	Regression methods with appropriate interaction term
4) Sensitivity Analyses: i) To assess the robustness of the results to different methods of adjusting for clustering; ii) To assess the robust ness of the results if the outcome is treated as the count (number of events)	composite of any AF-related emergency department visit or unplanned CV hospitalization	Results will remain robust	i) patient-level methods such as random-intercept model and cluster-level [i.e. random- and fixed-effects meta-analytic] ii) GEE using Poisson distribution

IMPORTANT REMARKS:

- The GEE is a technique that allows to specify the correlation structure between patients within a hospital and this approach produces unbiased estimates under the assumption that missing observations will be missing at random. An amended approach of weighted GEE will be employed if missing observations are found not to be at random.
- In all analyses results will be expressed as coefficient, standard errors, corresponding 95% and associated p-values.
- Goodness-of-fit will be assessed by examining the residuals for model assumptions and chi-squared test of goodness-of-fit.

Table 2. Characteristics of the Study Populations at Baseline

Characteristic	Variable	CDSS (N= 590)	Usual Care (N=543)
Age – years Median Interquartile range	Age at start		
Male sex - n (%)	Sex (Male)		
Height – cm - Mean (SD)	Height		
Weight – Kg- Mean (SD)	Weight		
Urban location of care - n (%)	Location		
Heart rate – BPM - Mean (SD)	Heart Rate		
Systolic Blood pressure - mmHg Median Interquartile range	Systolic BP		
Systolic Blood pressure - mmHg Median Interquartile range	Diastolic BP		
Type of atrial fibrillation - n (%) Paroxysmal Persistent Newly diagnosed/new onset	 AF Classification (Paroxysmal) AF Classification (Persistent/Chronic) AF Classification (First Episode)		
PREVIOUS MEDICATION USE - n (%)			
Aspirin	Ingredient (Aspirin)		
other antiplatelet	Ingredient (TICLOPIDINE) or (PRASUGREL) or (TICAGRELOR) or (CLOPIDOGREL)		
Vitamin K antagonist (Warfarin)	Ingredient (Warfarin)		
Non-vitamin K antagonist (NOAC)	Ingredient (DABIGATRAN) or (RIVAROXABAN) or (APIXABAN)		
Beta-blocker	Ingredient (TIMOLOL) or (LABETALOL) or (CARVEDILOL) or (PINDOLOL) or (ACEBUTOLOL) or (PROPANOLOL) or (NADOLOL) or (ATENOLOL) or (METOPROLOL) or (BISOPROLOL)		
Calcium channel blocker	Ingredient (NIFEDIPINE) or (FELODIPINE) or (AMLODIPINE) or (AMLODIPINE + ATROVASTATIN) or (DILTIAZEM) or (VERAPAMIL)		
Digoxin	Ingredient (DIGOXIN)		
Any other antiarrhythmic	Ingredient (DRONEDARONE) or (QUINIDINE) or (PROCAINAMIDE) or (MEXILETINE) or		

	(SOTALOL) or (LIDOCAINE) or (FLECAINIDE) or (PROPAFENONE) or (AMIODARONE)		
Nonsteroidal anti-inflammatory	Ingredient (SULINDAC) or (PETOPROPHEN) or (PIROXICAM) or (KETOROLAC) or (TENOXICAM) or (TIAPROFENIC) or (INDOMETHACIN) and (ETODOLAC) or (NEPAFENAC) or (IBUPROFEN) or (MELOXICAM) or (NAPROXEN) or (DICLOFENAC) or (CELECOXIB)		
OAC contraindication	OAC Contraindication (Yes)		
OAC other reason not prescribed	OAC reason not Rxd (Yes)		
BLEEDING AND STROKE RISK SCORES			
CHA_2DS_2 Score - Mean (SD) Score - n (%) 0 1 2 3 4 5 6 7	NOT the value REPORTED in PCP chart. CALCULATED using documented RFs.		
CHA_2DS_2-VASc Score - Mean (SD) Score - n (%) 0 1 2 3 4 5 6 7 8 9	NOT the value REPORTED in PCP chart. CALCULATED using documented RFs.		
Bleeding risk: HAS-BLED Score - Mean (SD) Score - n (%) 1 2 3 4 5 6			

7 8 9			
COEXISTING CONDITIONS - n (%)			
Previous stroke, systemic embolism or transient ischemic attack	Stroke (Yes) or SE (Yes) or TIA (Yes)		
Congestive heart failure	HF/LV Dysfunction (Yes)		
Hypertension	Hypertension (Yes) or (Yes-Treated) or (Yes-Not Treated)		
Diabetes mellitus	Diabetes (Yes-Not Documented) or (Yes-Type 1) or (Yes-Type 2)		
Previous myocardial infarction	MI (MM-YYYY) or (ND)		
Vascular disease (any) CAD PAD/PVD UA MI Aortic plaque	Vascular Disease (Yes) CAD (Yes) Aortic Plaque (Yes) PAD/PVD (Yes) UA (date) (MM-YYYY) or (ND) MI (date) (MM-YYYY) or (ND)		
Valvular Heart Disease	Replacement Type (Mechanical) or Mitral Stenosis Type (Moderate) or (Severe)		
Congenial Heart Disease	Congenital Heart Disease (Yes)		
OSA	OSA Dx (Yes)		
Tobacco use Former Current	 Tobacco use (Former) Tobacco use (Current)		
Alcohol abuse	Alcohol abuse (Yes)		
Pericarditis	Pericarditis (Yes)		
Pulmonary Disease	Pulmonary Disease (Yes)		
INTERVENTIONS/PROCEDURES - n (%)			
Vascular procedure (any) CABG PCI	Vascular Procedure (Yes) CABG (Yes) PCI (Yes)		
Ablation (for flutter or AF)	AF Ablation (Yes) or Previous Ablation for Aflu (Yes)		
Pacemaker / ICD	Pacemaker (Yes)		
Cardioversion # of patients # of events – median (IQR)	 Cardioversion (Yes) Cardioversions no.		
Bleeding History - n (%)			

Any bleeding	Bleeding History (Yes)		
Intracranial	IC-Intracerebral (Yes) or IC-Other (Yes)		
Non-intracranial	NIC-Epistaxis (Yes) or NIC-GI (Yes) or NIC-Other (Yes)		
Major bleeding	Major bleeding (Yes)		
PAST REFERRALS - n (%)			
AF Clinic	Referred to (AF Clinic)		
Cardiologist	Referred to (Cardiologist)		
Internist	Referred to (Internist)		
Electrophysiologist	Referred to (Electrophysiologist)		
Cath ablation	Referred to (Cath Ablation)		
ED visit for AF within the last 12 months # of patients - n (%) # of events - Mean (SD)	ER Visits (Yes) ED Visits 1 2 3 >3		
Cardiovascular-related hospitalization within the last 12 months # of patients - n (%) # of events - Mean (SD)	CV Hospitalization (Yes) CV Hospitalizations 1 2 3		
LAB VALUES			
eGFR – ml/min Median Interquartile range eGFR - n (%) < 30 ml/min 30-50 ml/min > 50 ml/min	Value *when* Blood Work (eGFR)		
Hemoglobin - g/L Median Interquartile range	Value *when* Bloodwork (Hemoglobin)		
Platelet - µmol/L Median Interquartile range	Value *when* Bloodwork (platelet count)		
TSH - mlU/L Median Interquartile range	Value *when* Bloodwork (TSH)		
INR			
CARDIAC ASSESSMENTS			
Prior ECHO - n (%)	ECHO (Yes)		
Ejection Fraction	The calculated EF		

Patients with EF - n (%) EF -Mean (SD) Normal (≥ 51%) Slightly Reduced (41-50%) Moderately Reduced (31-40%) Severely Reduced (≤ 30%)			
Stress Test	Stress Test (Yes)		
Holder or Loop - n (%)	Holter (Yes) or Loop (Yes)		
ECG within 12 months	ECG (Yes)		

Table 3. Primary and Secondary outcomes at 12-months

Outcome (Usual Care is reference)	Intervention Group (N=)		Usual Care Group (N=)		Primary analysis HR (95% CI); p-value	Sensitivity analysis IRR (95% CI), p-value
	No. of Patients	No. of Events	No. of Patients	No. of Events		
Primary						
AF related ED visits or CV hospitalizations						
Secondary						
AF related ED visits						
Heart Failure						
Syncope/Presyncope						
TIA/Stroke						
ACS (UA/MI)						
Rate/Rhythm						
Unplanned CV hospitalization						
Heart Failure						
Syncope/Presyncope						
TIA/Stroke/SE						
ACS (UA/MI)						
Rate/Rhythm						
Stroke						
Ischemic						
Other						
All-cause mortality						

Table 4a: Sensitivity analysis using commonly used patient-level methods such as random-intercept model and meta-analytic cluster-level methods.

Outcome (Usual Care is reference)	Random-intercept model HR (95% CI), p-value
Primary	
AF related ED visits or CV hospitalizations	
Secondary	
AF related ED visits	
Unplanned CV hospitalization	

Table 5a Subgroup analysis and subgroup sensitivity analyses of primary efficacy composite Outcome

Sub-Group (Usual Care is reference)	HR (95% CI), Interaction term p-value	IRR (95% CI), Interaction term p-value
Practice Location		
Rural		
Urban		
Patient Sex		
Female		
Male		
Age (years)		
<75		
≥ 75		
CHADS2		
0		
≥ 1		
CHADS-VASC		
0		
≥ 1		
Hypertension		
Yes		
No		
Diabetes		
Yes		
No		
Antithrombotics (baseline)		
Yes		
No		

Table 5b Subgroup analysis and subgroup sensitivity analyses of the number of AF Related ED Visits

Sub-Group (Usual Care is reference)	HR (95% CI), Interaction term p-value	IRR (95% CI), Interaction term p-value
Practice Location		
Rural		
Urban		
Patient Sex		
Female		
Male		
Age (years)		
<75		
≥ 75		
CHADS2		
0		
≥ 1		
CHADS-VASC		
0		
≥ 1		
Hypertension		
Yes		
No		
Diabetes		
Yes		
No		
Antithrombotics (baseline)		
Yes		
No		

Table 5c Subgroup analysis and subgroup sensitivity analyses of number of CV Hospitalizations

Sub-Group (Usual Care is reference)	HR (95% CI), Interaction term p-value	IRR (95% CI), Interaction term p-value
Practice Location		
Rural		
Urban		
Patient Sex		
Female		
Male		
Age (years)		
<75		
≥ 75		
CHADS2		
0		
≥ 1		
CHADS-VASC*		
0		
≥ 1		
Hypertension		
Yes		
No		
Diabetes		
Yes		
No		
Antithrombotics (baseline)		
Yes		
No		