**NOAC-AF Working Title  
Statistical Analysis Plan**Patrick Daniele  
**Created On:** October 2nd, 2018  
**Updated On:** October 23rd, 2018

**Preamble:**   
This document gives an outline of the necessary data manipulation tasks and statistical analyses to be performed for each objective. Definitions for groupings, cohorts, and outcomes are defined both overall and objective specific where appropriate.

**Deadlines:**

* **ESC 2019 (PARIS) – February 14th, 2019**
* **CCC 2019 (Montreal) – May 2019.**

**Objective 1 – Temporal Trends:**

|  |  |  |  |
| --- | --- | --- | --- |
| Task | Status | Date Completed | Filename |
| Define Cohort |  |  |  |
| Create research dataset   * Define outcome: Drug at Diagnosis |  |  |  |
| Analyses   * Describe cohorts by Age, Sex, SES * Initiation Trends * Trend Comparisons by Age, Sex, SES |  |  |  |
| Tables   * Baseline chars: Incident vs Prevalent * Baseline chars: I+P by Age, Sex, SES * Baseline chars: by NOAC type |  |  |  |
| Figures   * Flowchart * Inc. + Prev. cases over time * Drug intiation * Trends in drug initiation |  |  |  |
| Summary Report |  |  |  |

**Group Definitions**

1. Overall
   1. Incident AF Cases (2011-2016)
   2. Prevalent (<2011 + Incident Cases)
2. Age
   1. Continuous – Logistic models + Cox PH models
   2. Categorical – Kaplan Meier Curves + Stratified tables.
      1. >75 vs. <75 (In accordance with CHADS2)?
3. Sex
4. SES based on quintile

**Covariate Definitions:**

1. CHADS2 - (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke/transient ischaemic attack/systemic thromboembolism)
2. CHA2DS2–VASc [adding vascular disease, age 65–75, and sex category (female)]
3. Concomitant medications – prescription filled 180 days prior.
   1. Anti-platelets
   2. NSAIDS
   3. Anticoagulants
4. Comorbidities: X year lookback for each of
   1. Chronic Kidney Disease
   2. Dementia
   3. Ischemic Heart Disease
   4. MI
   5. Peripheral Vascular Disease
   6. Heart Failure
   7. Hypertension
   8. Diabetes
   9. COPD

**Incident Cases**

*Inclusions:*

* Index AF diagnosis between January 1, 2011 and December 31, 2016
* Age >= 20 years at time of index AF diagnosis
* BC or Alberta Resident

*Exclusions:*

* AF diagnosis 5 years prior (Multiple codes prior, or any codes prior?)
* Valvular AF
* Change in residency status within previous 5 years
* OAC prescribed prior to 2011?
* Chronic Kidney Disease?

**Prevalent Cases**

*Inclusions:*

* Index AF diagnosis between January 1, 2005 and December 31, 2016
* Age >= 20 years at time of index AF diagnosis
* BC or Alberta Resident

*Exclusions:*

* Valvular AF

**Questions:**

1. How to define non-valvular vs valvular AF?
2. Age Groups (One study uses <80 vs >80). Should we pick more narrow cuts for descriptive. Can include age as a continuous variable in any modeling.
3. Several studies exclude patients with total hip/knee replacement within 5 weeks and PE/DVT.
4. How to handle those on both Warfarin and a NOAC. Exclude?
5. How to handle OAC prior to AF diagnosis.
6. Can we take into account those who might be using NOAC for DVT/PE?
7. Minimum CHADs2 score for entry into the AF cohort?
8. Exclusion based on Chronic Kidney Disease?
9. Any contraindications for NOACs?

**Objective 1:** To describe the temporal changes in overall and sex- and age-specific prescription trends for warfarin, apixaban, rivaroxaban and dabigatran, between January 2011 and December 2016, in all newly diagnosed AF patients in British Columbia and Alberta. Furthermore, we will assess whether these trends vary by sex, age, and socioeconomic status.

**Cohort(s):**

1. Incident AF Cases
2. Prevalent AF Cases

**Outcome(s) / Endpoint(s):** First prescription defined as first OAC prescribed within XX days of diagnosis.

**Planned Analyses:**

* Describe incident and prevalent AF Cohorts stratified by age groups, sex, and SES over time.
  + χ2 Test, t-test, ANOVA for differences in baseline characteristics where appropriate
  + Test for Trend (Cochran–Armitage)
* Compute age and sex standardized rates of AF incidence and prevalence.
* Prescription initiation pattern over time (Warfarin vs. NOAC, and NOAC Specific) in incident cohort.
  + Test for trend (Cochran–Armitage)
* Compare trends by Age, Sex, and SES.
  + Graphical comparisons.

**Planned Figures:**

* Flowchart showing breakdown by Age, Sex, SES after exclusions
* Number of incident AF cases by year, prevalence over time.
* Percentage initiated on each drug. Overall, Age, Sex, SES. (Shows trends in incident cases)
* Percentage of total prescriptions each year (shows trends in prevalent cohort)

**Planned Tables:**

* Baseline characteristics of incident and prevalent cases by Age, Sex, and SES.
* Baseline characteristics (Age, Sex, CHADs, Comorbidities) by OAC treatment choice. Warfarin vs NOAC, or specific NOAC.

**Optional:**

* Dosages.

**EndNote Reference Group:** Objective 1 – Temporal Trends

**Notes:**

**Objective 2:** To describe the prescription patterns for warfarin, apixaban, rivaroxaban and dabigatran, focusing on the frequency and timing of patients’ prescription changes (i.e. switching to another anticoagulant) following their first anticoagulant prescription, during the study period. Furthermore, we will assess whether these prescription patterns vary by sex, age, and socioeconomic status.

**Cohort:** Incident AF Cases

**Outcome(s):**

* Prescription vs No Prescription (OAC vs. No Prescription)
* First prescription (NOAC vs. Warfarin)
* Time to first switch.
* Number of switches.
* Proportion of patients with NOAC and Warfarin who switch drugs during follow-up.

**Planned Analyses:**

* Explored factors associated with initial drug prescription using a logistic regression model.
  + Multinomial logistic model with No OAC, Warfarin, NOAC as outcomes.
* Model time to first switch using cox proportion hazards model.
* Compare number of switches between groups.

**Planned Figures:**

* Forest plot of unadjusted and adjusted odds ratios for initial drug prescription.
* Forest plot of unadjusted and adjusted hazard ratios for time to first switch.
* Kaplan Meier curves for time to first switch

**Planned Tables:**

* OR/HR with 95% confidence intervals
* Proportion of patients who switch from either Warfarin or NOAC.

**Options:**

* Within NOAC switching.
* Identify predictors of switching from warfarin to NOAC using a Cox PH model with time to switching among prevalent cases and cases initiated on NOAC.

**EndNote Reference Group:** Objective 2 – Prescription Patterns

**Notes:**

**Objective 3:** To examine patient adherence to oral anticoagulants following their AF diagnosis and determine whether the extent of adherence varies by anticoagulant type, sex, age.

**Cohort:** Incident AF Cases

**Outcome(s):**

*Adherence*

* Options:
  + Proportion of Days Covered
    - >0.8 threshold to indicate adherence vs. non-adherence
    - PDC = (Number of Days in Period “Covered”/Number of Days in Period)\*100
    - Pros: PDC is not inflated by early prescription fills.
    - Cons: Conservative measurement, may underestimate actual adherence.
  + Medication Possession Ratio (Capped at 1).
    - >0.8 threshold to indicate adherence vs. non-adherence
    - MPR = (Sum of days’ supply for all fills in period/number of days in period)\*100
    - Pros: Simple calculation. Not conservative, may closer reflect actual adherence.
    - Cons: May overestimate adherence since patients may refill early thereby increasing the numerator beyond the denominator.
* How do we handle dose adjustments in Warfarin?
* Limit adherence to first year of drug initiation?

*Persistence*

**Planned Analyses:**

* Describe adherence/persistence among incident AF cases using PDC or MPR, and time to discontinuation
  + Proportion with confidence intervals
* Compare rates of adherence by Age, Sex and SES adjusted for relevant confounders.
  + Simple Linear Regression – Model Adherence as a continuous variable
  + Logistic Regression – Model Adherence as binary variable (0.8< threshold to indicate adherence).
* Compare rates of Persistence/Discontinuation by Age, Sex and SES adjusted for relevant confounders.
  + Logistic regression to model binary outcome of discontinuation (first year post initiation).
  + Cox PH Model to model time to discontinuation.

**Planned Figures:**

* Forest plot of odds ratios and/or SLR coefficients – Adherence
* Forest plot of odds ratios – Discontinuation within first year
* Forest plot of hazard ratios – Time to discontinuation

**Planned Tables:**

**Options:**

* Within NOAC comparisons of adherence (Riva vs Dabi vs Apixa)
* Predictors of discontinuation and/or adherence.

**EndNote Reference Group:** Objective 3 – Adherence

**Notes:**

**Objective 4:** To examine and compare the rates of major adverse outcomes for warfarin, apixaban, rivaroxaban and dabigatran, and to determine if the outcomes vary by sex, age, socioeconomic status for the different anticoagulants.

**Cohort:** Incident AF Cases

**Outcome(s):** Major Adverse Cardiac Events (Major Bleeding, Systemic Embolism, Hemorrhagic Stroke, MI, All-cause mortality)

**Planned Analyses:**

* Describe rates of MACE at 30 days, 1 year, and 3 years.
* KM + Cox Proportional Hazards model
  + Option 1: Fixed exposure – Fix exposure to drug initiated at index diagnosis.
    - Pros: Simple
    - Cons: Ignores group changes, would likely need to reduce the length of follow-up
  + Option 2: Time varying exposure – Allow exposure to vary between groups (Warfarin, NOAC, no OAC)
    - Pros: Takes into account group changes, allows for longer follow-up
    - Cons: Increased complexity in interpretation and implementation
* Model Diagnostics
  + Proportional Hazards Assumption
    - KM Curves
    - Supremum Test
    - Log-log plots
  + Linearity + Additivity
    - Martingale Residuals

**Planned Figures:**

* Kaplan-Meier curves by Age Category, Sex, and SES
* Forest Plot of unadjusted and adjusted Hazard ratios for MACE

**Planned Tables:**

* Number of events, composite endpoint and individual components, by Age, Sex, and SES at 30 day, 1 year and 3 years with 95% confidence intervals
* Unadjusted and adjusted hazard ratios with 95% confidence intervals

**Options:**

**EndNote Reference Group:** Objective 4 – Outcomes

**Notes:**