

Supplemental Material

Table S1. Candidate covariates

Demographics

1. Age, years
2. Race – African American/Hispanic/White/Others
3. Gender – Male/Female
4. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate
5. Payer/Insurance – Medicare or Medicaid/private/Others

Medical History

1. Smoking – Current/Recent or Former/Non-smoker
2. Cancer – Yes/No
3. Hypertension – Yes/No
4. Osteoporosis – Yes/No
5. Diabetes – Yes/No
6. Hip Fracture – Yes/No
7. Hyperthyroidism – Yes/No
8. Hypothyroidism – Yes/No
9. GI Bleed – Yes/No
10. Obstructive Sleep Apnea – Yes/No
11. Dialysis – Yes/No
12. Hyperlipidemia – Yes/No
13. Anemia – Yes/No
14. Cognitive Impairment/Dementia – Yes/No
15. Frailty – Yes/No
16. Liver Disease – Yes/No
17. COPD – Yes/No
18. Alcohol Abuse – Yes/No
19. Drug Abuse – Yes/No

Cardiovascular History

1. Family History of AF – Yes/No
2. Peripheral Vascular Disease – Yes/No
3. Sinus Node Dysfunction/Sick Sinus Syndrome – Yes/No
4. Stroke or TIA – Yes/No
5. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
6. Significant Valvular Disease – Yes/No
7. Prior Valve Replacement/Repair – Yes/No

Coronary Artery Disease History

1. History of Coronary Artery Disease – Yes/No
2. Prior MI – Yes/No
3. Prior CABG – Yes/No
4. Any PCI – Yes/No

Vital Signs & AF status

1. Height, cm

2. Heart Rate, bpm
3. Diastolic Blood Pressure, mm HG
4. Systolic Blood Pressure, mm HG
5. Body Mass Index, kg/m² (For imputation purpose, we will impute individual components which are weight, height)
6. Intraventricular Conduction – RBBB/LBBB/Non-specific IVCD or Unknown-Ventricularly Paced/none

Echocardiographic Assessment (TTE or TEE)

1. LVEF – Normal ($\geq 50\%$)/Mild dysfunction ($>40\%$, $<50\%$)/Moderate dysfunction ($\geq 30\%$, $\leq 40\%$)/Severe dysfunction ($<30\%$)
2. LAD Type – Normal/Mild enlargement/Moderate enlargement/Severe enlargement

Laboratory Data

1. eGFR (MDRD), mg/dl (For imputation purpose, we will impute individual components which are age, gender, race, and serum creatinine)
2. Hematocrit, % (fill in from Hemoglobin by Hemoglobin*3 if missing)

Atrial Fibrillation Diagnosis

1. Type of AF – First Detected or New Onset/Paroxysmal AF/Persistent AF /Permanent AF
2. AF management strategy – Rate Control/Rhythm Control
3. Prior Cardioversions – Yes/No
4. Prior antiarrhythmic drug – Yes/No
5. Catheter Ablation of AF – Yes/No
6. AV Node or HIS Bundle Ablation – Yes/No

Functional Status

1. Functional Status – Living independently/Living with assistance or Resides in assisted living facility or Resides in skilled nursing home or Bedbound

Provider or Site

1. PI/Site Specialty – Cardiology/Electrophysiology/Family Practice or Internal Medicine

Table S2. Adjustment co-variates for multivariable models of each endpoint:

1. For EHRA score at baseline, adjusted for 15 risk factors (heart rate, height, systolic blood pressure, female, hip fracture, hyperlipidemia, frailty, COPD, any PCI, prior antiarrhythmic drug, catheter ablation of AF, AV Node or HIS bundle Ablation, race, congestive heart failure, PI/site specialty).
2. For all-cause death, adjusted for 21 risk factors in addition to linear splines of heart rate (level of education, current AF management strategy, cognitive impairment/dementia [CID], hyperlipidemia, linear spline of eGFR (when eGFR > 80), linear spline of eGFR (when eGFR ≤ 80), LAD type, cancer, truncated diastolic blood pressure [DBP] above 70 mm HG, intraventricular conduction, frailty, height, hematocrit, diabetes, smoking, linear spline of systolic blood pressure [SBP] (when SBP ≤ 120), COPD, truncated BMI above 30 kg/m², sex, congestive heart failure [CHF], age, functional status)
3. For cardiovascular death, adjusted for 14 risk factors in addition to linear splines of heart rate (diabetes, anemia, diastolic blood pressure, hyperlipidemia, AV Node/HIS bundle ablation, COPD, significant valvular disease, height, sex, LVEF type, functional status, eGFR, CHF, age)
4. For non-cardiovascular death, adjusted for 16 risk factors in addition to heart rate (Liver disease, sinus node dysfunction/sick sinus syndrome, linear spline of eGFR (when eGFR ≤ 60), linear spline of eGFR (eGFR > 60), intraventricular conduction, diabetes, COPD, cancer, sex, cognitive impairment/dementia, SBP, linear spline of BMI (when BMI ≤ 28), frailty, smoking status, hematocrit, functional status, age)
5. For all-cause hospitalization, adjusted for 23 risk factors in addition to heart rate (linear spline of age (when Age ≤ 70), linear spline of age (when age > 70), BMI, weight, osteoporosis, height, PCI, cancer, OSA, anemia, frailty, insurance status, history of CAD, PI/Site specialty, prior antiarrhythmic drug use, peripheral vascular disease [PVD], functional status, diabetes, hematocrit, linear spline of eGFR (when eGFR ≤ 80), COPD, truncated diastolic blood pressure above 70 mm HG, EHRA score, CHF)
6. For cardiovascular hospitalization, adjusted for 19 risk factors in addition to heart rate (BMI, history of coronary artery disease [CAD], prior valve replacement/repair, COPD, any PCI, AF management strategy, PVD, functional status, eGFR, LVEF type, DBP, diabetes, hematocrit, prior antiarrhythmic drug, LAD type, linear spline of age (when age ≤ 75 years), linear spline of age (when age > 75 years), PI/Site specialty, EHRA score, CHF)
7. For bleeding hospitalization, adjusted for 14 risk factors in addition to heart rate (obstructive sleep apnea [OSA], COPD, prior cardioversions, level of education, BMI, sex, prior valve replacement/repair, payer/insurance, AF management strategy, age, eGFR, anemia, hematocrit, GI bleed)
8. For other hospitalization, adjusted for 23 risk factors in addition to heart rate (Family history of AF, history of drug abuse, BMI, weight, anemia, linear spline of DBP (when DBP ≤ 75), PVD, liver disease, linear spline of SBP (when SBP ≤ 130), linear spline of SBP (when SBP > 130), PI/Site specialty, smoking status, level of education,

functional status, cancer, height, frailty, diabetes, OSA, hematocrit, CHF, age, linear spline of eGFR (when eGFR \leq 80), COPD)

9. For composite of stroke/major bleeding, adjusted for 22 risk factors in addition to heart rate (PVD, race, current AF management strategy, female, AV Node/HIS bundle ablation, hypertension, age, history of stroke/TIA, OSA, COPD, LAD type, cancer, functional status, level of education, intraventricular conduction, smoking, significant valvular disease, eGFR, insurance status, history of BI bleed, anemia, hematocrit)
10. For composite of MI/revascularization/Heart failure, adjusted for 16 risk factors in addition to heart rate (diabetes, eGFR, PVD, history of CAD, LVEF type, prior MI, prior cardioversions, history of CAD, prior antiarrhythmic drug use, EHRA score, insurance status, prior PCI, age, insurance status, significant valvular disease, anemia)
11. For composite of stroke/systemic embolism/heart failure/MI/revascularization/all-cause hospitalization/major bleeding/all-cause death, adjusted for 43 risk factors in addition to linear splines of heart rate (PVD, race, current AF management strategy, female, AV Node/HIS bundle ablation, hypertension, age, history of Stroke/TIA, insurance status, LVEF type, significant valvular disease, prior MI, eGFR, anemia, history of CAD, diabetes, prior cardioversions, prior antiarrhythmic drug use, EHRA score, insurance status, prior PCI, level of education, CID, hyperlipidemia, LAD type, cancer, truncated DBP above 70 mm HG, intraventricular conduction, frailty, height, hematocrit, smoking, linear spline of SBP (when SBP \leq 120 mm HG), COPD, BMI, CHF, functional status, OSA, history of GI bleed, hematocrit, weight, osteoporosis, PI/Site specialty)

Table S3. Adjusted association between baseline heart rate and baseline EHRA symptom class.

| Risk Factor | Adjusted OR (95% CI) | P-value | Overall P-value |
|---|-------------------------|--------------|-----------------|
| Congestive Heart Failure: NYHA Class III/IV vs. No CHF | 3.88 (2.97,5.06) | <.0001 | <.0001 |
| Congestive Heart Failure: NYHA Class II vs. No CHF | 1.83 (1.50,2.22) | <.0001 | |
| Site/PI provider specialty: Family Practice or Internal Medicine vs. Cardiology | 1.78 (1.47,2.16) | <.0001 | <.0001 |
| Female vs. Male | 1.73 (1.41,2.12) | <.0001 | |
| Frailty | 1.89 (1.43,2.51) | <.0001 | |
| Treated with Antiarrhythmic Drug in the Past | 1.42 (1.20,1.66) | <.0001 | |
| COPD | 1.47 (1.22,1.78) | <.0001 | |
| History of Any PCI | 1.38 (1.13,1.68) | 0.002 | |
| Prior interventional therapy for AF: Catheter Ablation of AF | 2.08 (1.32,3.27) | 0.002 | |
| Systolic Blood Pressure, mmHG (per 10 increase) | 0.93 (0.88,0.97) | 0.002 | |
| Prior interventional therapy for AF: AV Node or HIS Bundle Ablation | 1.78 (1.20,2.66) | 0.005 | |
| Heart Rate, bpm (per 5 increase) | 1.04 (1.01,1.08) | 0.007 | |
| Hip Fracture | 0.55 (0.35,0.87) | 0.01 | |
| Hyperlipidemia | 0.82 (0.69,0.97) | 0.02 | |
| Race: Others vs. White | 1.95 (1.08,3.51) | 0.03 | 0.049 |
| Height, cm (per 10 increase) | 1.10 (1.01,1.19) | 0.03 | |
| Race: Hispanic vs. White | 0.75 (0.53,1.06) | 0.1 | |
| Site/PI provider specialty: Electrophysiology vs. Cardiology | 0.88 (0.68,1.12) | 0.3 | |
| Congestive Heart Failure: NYHA Class I vs. No CHF | 1.05 (0.83,1.33) | 0.7 | |
| Race: African American vs. White | 0.99 (0.70,1.40) | 1.0 | |

Table S4. Adjusted association between increasing heart rate and outcomes for patients with all AF types.

| Endpoint | Adjusted HR (95% CI) per 5-bpm change in heart rate | P-value |
|--|--|----------------|
| All-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.06 (0.96,1.18) | 0.3 |
| Heart rate >65 bpm per 5-bpm increase | 1.11 (1.08,1.14) | <.0001 |
| Cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.13 (0.97,1.33) | 0.1 |
| Heart rate >65 bpm per 5-bpm increase | 1.10 (1.05,1.14) | <.0001 |
| Non-cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.00 (0.88,1.15) | 0.9 |
| Heart rate >65 bpm per 5-bpm increase | 1.12 (1.09,1.15) | <.0001 |
| All-cause hospitalization | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.06 (1.02,1.11) | 0.006 |
| Heart rate >65 bpm per 5-bpm increase | 1.05 (1.04,1.07) | <.0001 |
| Cardiovascular hospitalization | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.10 (1.04,1.16) | 0.0008 |
| Heart rate >65 bpm per 5-bpm increase | 1.06 (1.04,1.08) | <.0001 |
| Other hospitalization | | |
| Heart rate | 1.03 (1.01,1.05) | 0.0004 |
| Bleeding hospitalization | | |
| Heart rate | 1.03 (1.00,1.06) | 0.1 |
| SSE or major bleeding | | |
| Heart rate | 1.04 (1.01,1.07) | 0.02 |
| MI, revascularization, new onset heart failure | | |
| Heart rate | 1.07 (1.04,1.11) | <.0001 |
| SSE, major bleeding, new heart failure, MI, revascularization, all-cause hospitalization, all-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.07 (1.02,1.11) | 0.003 |
| Heart rate >65 bpm per 5-bpm increase | 1.06 (1.04,1.07) | <.0001 |

Adjustment co-variates for each outcome are identical to those used for the primary analysis with the following exception: AF type was added to the adjustment models of cardiovascular hospitalization, the composite of SSE/major bleeding, and the composite of SSE/major bleeding/heart failure/MI/revascularization/all-cause hospitalization/all-cause death.

HR: hazard ratio; CI: confidence interval; SSE: stroke or systemic embolism; MI: myocardial infarction.

Table S5. Unadjusted association between baseline-only heart rate and outcomes.

| Endpoint | Adjusted HR (95% CI) per 5-bpm change in heart rate | P-value |
|--|--|----------------|
| All-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 0.98 (0.85,1.13) | 0.8 |
| Heart rate >65 bpm per 5-bpm increase | 0.99 (0.94,1.04) | 0.7 |
| Cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 0.92 (0.72,1.19) | 0.5 |
| Heart rate >65 bpm per 5-bpm increase | 0.95 (0.87,1.03) | 0.2 |
| Non-cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.03 (0.80,1.31) | 0.8 |
| Heart rate >65 bpm per 5-bpm increase | 1.02 (0.95,1.09) | 0.7 |
| All-cause hospitalization | | |
| Heart rate per 5-bpm increase | 1.00 (0.98,1.02) | 0.9 |
| Cardiovascular hospitalization | | |
| Heart rate per 5-bpm increase | 1.01 (0.98,1.05) | 0.5 |
| Other hospitalization | | |
| Heart rate per 5-bpm increase | 0.99 (0.97,1.02) | 0.6 |
| Bleeding hospitalization | | |
| Heart rate per 5-bpm increase | 1.01 (0.96,1.07) | 0.7 |
| SSE or major bleeding | | |
| Heart rate per 5-bpm increase | 1.01 (0.97,1.06) | 0.5 |
| MI, revascularization, new onset heart failure | | |
| Heart rate per 5-bpm increase | 1.03 (0.97,1.10) | 0.3 |
| SSE, major bleeding, new heart failure, MI, revascularization, all-cause hospitalization, all-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.07 (0.97,1.19) | 0.2 |
| Heart rate >65 bpm per 5-bpm increase | 1.02 (0.99,1.05) | 0.1 |

Table S6. Unadjusted association between baseline-only heart rate and outcomes.

| Endpoint | Adjusted HR (95% CI) per 5-bpm change in heart rate | P-value |
|--|--|----------------|
| All-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.02 (0.87,1.19) | 0.8 |
| Heart rate >65 bpm per 5-bpm increase | 1.00 (0.96,1.05) | 0.8 |
| Cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 0.98 (0.72,1.35) | 0.9 |
| Heart rate >65 bpm per 5-bpm increase | 0.96 (0.87,1.05) | 0.3 |
| Non-cardiovascular death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.09 (0.85,1.39) | 0.5 |
| Heart rate >65 bpm per 5-bpm increase | 1.04 (0.96,1.12) | 0.3 |
| All-cause hospitalization | | |
| Heart rate per 5-bpm increase | 1.00 (0.97,1.02) | 0.7 |
| Cardiovascular hospitalization | | |
| Heart rate per 5-bpm increase | 1.00 (0.96,1.04) | 1.0 |
| Other hospitalization | | |
| Heart rate per 5-bpm increase | 0.99 (0.96,1.02) | 0.4 |
| Bleeding hospitalization | | |
| Heart rate per 5-bpm increase | 1.01 (0.95,1.07) | 0.7 |
| SSE or major bleeding | | |
| Heart rate per 5-bpm increase | 1.01 (0.96,1.05) | 0.7 |
| MI, revascularization, new onset heart failure | | |
| Heart rate per 5-bpm increase | 1.03 (0.97,1.09) | 0.4 |
| SSE, major bleeding, new heart failure, MI, revascularization, all-cause hospitalization, all-cause death | | |
| Heart rate ≤65 bpm per 5-bpm decrease | 1.11 (1.00,1.23) | 0.04 |
| Heart rate >65 bpm per 5-bpm increase | 1.02 (0.99,1.05) | 0.2 |

