

Curriculum Vitae

Elisabeth M. Oehrlein
eoehrlein@umaryland.edu

EDUCATION

University of Maryland, Baltimore

Ph.D., Pharmaceutical Health Services Research 08/2013 – 05/2018

M.S., Epidemiology

Franklin & Marshall College

5/2012

B.A., German Language & Literature

EXPERIENCE

University of Maryland, Baltimore

Research Assistant for Prof. Eleanor Perfetto, Ph.D., MS 6/2014 – present

Research Rotation with Prof. Julie Zito, Ph.D., MS 2/2014 – 6/2014

Teaching Assistant 8/2013 – 5/2014

National Health Council, Washington D.C.

1/2016 – 5/2016

Health Policy Intern

Bristol-Myers Squibb, Munich, Germany

1/2013 – 6/2013

Medical Information Intern

GlaxoSmithKline, Munich, Germany

5/2012 – 11/2012

Clinical Safety and Pharmacovigilance Intern

Franklin & Marshall College, Dept. of Chemistry, Lancaster, PA

9/2011 – 5/2012

Research Assistant for Prof. Katharine Plass, Ph.D

FUNDING

“Atrial Fibrillation Risk-Stratification Tools: Improving Patient Centeredness and Precision.”

Source: Pfizer (Research Agreement); January 2017 – September 2018;
\$62,599.

“Improving Atrial Fibrillation Real World Evidence through Stakeholder Engagement”

Source: PATIENTS Program at the University of Maryland, Baltimore (Agency for Healthcare Research and Quality R24HS022135; PI = C. Daniel Mullins, PhD); \$7,657.00.

“Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk Stratification Schemes and Shared Decision-Making.”

Source: PATIENTS Program at the University of Maryland, Baltimore (Agency for Healthcare Research and Quality R24HS022135; PI = C. Daniel Mullins, PhD); \$7,672.00.

“Using Patient Centered Outcomes Research and Epidemiology to Assess Atrial Fibrillation Treatment and Outcomes Among an Under-65 Privately Insured Population.”

Source: PhRMA Foundation Pre-Doctoral Fellowship in Health Outcomes, 2015-2017; \$50,000.

PEER-REVIEWED PUBLICATIONS

- **Oehrlein EM**, Perfetto EM, Love TR, Chung Y, Ghafoori P. Patient-Reported Outcome Measures in the FDA Pilot Compendium: Meeting Today’s Standards for Patient Engagement in Development? *Value Health*. (In Press)
- Law E, Harrington R, Alexander GC, Saha S, **Oehrlein EM**, Perfetto EM. Stakeholder Uptake of Comparative Effectiveness & Patient-Centered Outcomes Research: Conference Insights. *J Comp Eff Res*. (In Press)
- **Oehrlein EM**, Graff JS, Perfetto EM, Mullins CD, Dubois RW, Anyanwu C, Onukwugha E. Journal Editors’ Views on Real-World Evidence. *Int J Technol Assess Health Care*. 2018;1-9. doi:10.1017/S0266462317004408.
- Asche CV, Seal B, Kahler KH, **Oehrlein EM**, Baumgartner MG. Evaluation of Healthcare Interventions and Big Data: Review of Associated Data Issues. *Pharmacoeconomics* (2017) 35:759–765 doi: 10.1007/s40273-017-0513-5.
- Perfetto EM, **Oehrlein EM**, Boutin M, Reid S, Gascho E. Value to Whom? The Patient Voice in the Value Discussion. *Value Health*. 2017 Feb;20(2):286-291.
- **Oehrlein EM**, Burcu M, Safer DJ, Zito JM. National Trends in ADHD Diagnosis and Treatment: Comparison of Youth and Adult Office-Based Visits. *Psychiatr Serv*. 2016 Sep 1;67(9):964-9.
- Perfetto EM, Burke L, **Oehrlein EM**, Gaballah M. FDAMA Section 114: Why the Renewed Interest? *J Manag Care Spec Pharm*. 2015 May;21(5):368-74.
- Perfetto EM, Burke L, **Oehrlein EM**, Epstein RS. Patient-Focused Drug Development: A New Direction for Collaboration. *Medical Care*. 2015 Jan;53(1):9-17.
- Heller LE, Whiteleigh J, Roth, D, **Oehrlein EM**, Lucci FR, Kolonko KJ, Plass KE. Self-Assembly of Isomeric Monofunctionalized Thiophenes. *Langmuir*. 2012, 28, 14855-14859.

OTHER PUBLICATIONS

- **Oehrlein EM**, Hanna ML, et al. A Highlight of Similarities and Differences between the HTA Core Model 3.0 and the AMCP Format 4.0. *Value & Outcomes Spotlight*. 2017 Vol. 3, No. 5.
- **Oehrlein EM**, Perfetto EM, Hanna ML. Patient-Centeredness in Clinical Outcomes Assessment. *Value & Outcomes Spotlight*. 2017;3(1):16-17.
- Contributor: Comparative Effectiveness and Patient-Centered Outcomes Research: Enhancing Uptake and Use by Patients, Clinicians and Payers: Conference Report. PhRMA Foundation, March 2017. Available from: <http://www.phrmafoundation.org/wp-content/uploads/2017/01/2017-04-02-CER-Conference-Report-Final.pdf>
- Khan Z, Biltaji E, **Oehrlein EM**. Welcome Note from the ISPOR Student Network Advisor and Network Chairs, 2016-2017. *Value & Outcomes Spotlight*. 2016;3(3):24-25.
- Hanna ML, **Oehrlein EM**, Perfetto EM. An Introduction to Unit-of-Analysis Error. *Value & Outcomes Spotlight*. 2016;2(3):16-17.
- Burcu M, **Oehrlein EM**. Time-dependent confounders: Are they all the same? *Value & Outcomes Spotlight*. 2016;2(2):14-16.
- Perfetto EM, **Oehrlein EM**, Anyanwu, C, et al. Stakeholder Perspectives on Patient-Focused Drug Development: Insights from FDA, Patients, Industry, and Payers. University of Maryland, Baltimore. Available from: <http://www.pharmacy.umaryland.edu/centers/cersievents/patient-focused-drug-development/proceedings.html>
- Burcu M, **Oehrlein EM**, Ng X, Vandigo J. Promoting Health Services Research Across Disciplines: Role of Interprofessional Education. *Value & Outcomes Spotlight*, November/December 2015 Vol. 1, No. 6.
- Piniashko O, Kagan Atikeler K, ten Ham R, Vadziuk Y, van der Putten I, **Oehrlein EM**. Veni, vidi, vici! Student Activities at the 18th Annual European Congress. *Value & Outcomes Spotlight*, November/December 2015 Vol. 1, No. 6.
- Khan ZM, **Oehrlein EM**, Kelly B. Welcome Note from the ISPOR Student Network Advisor and Past and Present Chairs. *Value & Outcomes Spotlight*, September/October 2015 Vol. 1, No. 5
- Althemery A, Borse M, Garg R, Gharaibeh M, Jiao T, **Oehrlein EM**, Thompson J. ISPOR Student Network Database Fact Sheets. *Value & Outcomes Spotlight*, March/April 2015 Vol. 1, No. 2.

ORAL PRESENTATIONS

- **Oehrlein EM**, Perfetto EM, McCall D, Albrecht JS, Slejko J, Cooke C, dosReis S. Conceptualizing Patients' Experience with Atrial Fibrillation. Podium presentation at HTAi's Annual Meeting, June 1-5, 2018, Vancouver, Canada. (Accepted)
- **Oehrlein EM**, Perfetto EM, Love TR, Chung Y, Ghafoori P. Are Patient-Reported Outcome Measures Meeting Today's Standards? Podium presentation at HTAi's Annual Meeting, June 1-5, 2018, Vancouver, Canada. (Accepted)

- **Oehrlein EM.** Introduction to the EUnetHTA HTA Core Model® 3.0. Invited presentation, Regeneron Pharmaceuticals, Tarrytown, New York. November 14, 2017.
- **Oehrlein EM,** Sandhu G, McBurney R, Guilhaume C. Patient Powered Registries: Useful for Health Technology Assessment or not? Workshop at ISPOR 20th Annual European Congress, November 4-8, 2017, Glasgow, Scotland.
- **Oehrlein EM,** Harrington R, Wheeler R, Camp R, McBurney R. ISPOR Patient Centered Special Interest Group Open Meeting. Open Meeting at ISPOR 20th Annual European Congress, November 4-8, 2017, Glasgow, Scotland.
- **Oehrlein EM,** Asche CV. Updates from the ISPOR Digest of International Databases SIG. Open Meeting at ISPOR 20th Annual European Congress, November 4-8, 2017, Glasgow, Scotland.
- Perfetto EM, **Oehrlein EM,** Boutin M, Reid S, Gascho E. Improving the Patient Centricity of Value Assessments: A Rubric. Podium presentation at HTAi Annual Meeting, June 17-21, 2017, Rome, Italy.
- Best Student Oral Presentation Award
- **Oehrlein EM,** Graff JS, Perfetto EM, Mullins CD, Dubois RW, Anyanwu C, Onukwugha E. Are journal editors a barrier to publication of Real World Evidence? Oral vignette presentation at HTAi Annual Meeting, June 17-21, 2017, Rome, Italy.
- **Oehrlein EM,** Harris J, Labkoff N, Perfetto EM, Boutin M. Landscape Assessment: Patient Engagement in HTA. Oral vignette presentation at HTAi Annual Meeting, June 17-21, 2017, Rome, Italy.
- **Oehrlein EM,** Asche CV. ISPOR Digest of Databases. Open Meeting at ISPOR 22nd Annual Meeting, May 20-24, 2017, Boston, MA, USA.
- **Oehrlein EM,** Asche CV, Seal B. Uses, Applications, and Future Directions of the ISPOR Digest of Databases. Forum at ISPOR 19th Annual European Congress, Vienna, Austria.
- **Oehrlein EM,** Asche CV. ISPOR Special Interest Group on Digest of Databases. Open Meeting at ISPOR 21st Annual Meeting, Washington DC.
- **Oehrlein EM** on behalf of Eleanor Perfetto, PhD, MS. Segal J, Perfetto EM, Tambor E, Santanello N, Disney L. Patient and Patient Advocate Involvement When Generating and Synthesizing Evidence to Inform Decisions about Drugs: International Society for Pharmacoepidemiology Mid-Year Meeting, April 10-12, 2016, Baltimore, MD. *Panel Discussion.*
- **Oehrlein EM** on behalf of Eleanor Perfetto, PhD, MS. Patrick DL, Perfetto EM, Wheeler R. Patient Engagement: What Is in A Name? ISPOR 18th Annual European Congress, November 7-11, 2015, Milan, Italy.
- **Oehrlein EM,** Asche CV. ISPOR Special Interest Group on Digest of Databases Open Meeting. ISPOR 18th Annual European Congress, November 7-11, 2015, Milan, Italy.
- **Oehrlein EM,** Hanna ML, Perfetto EM. IQWiG Early Benefit Assessments of Type II Diabetes Therapies. ISPOR 20th Annual International Meeting. Philadelphia, PA, USA. May 2015. *Podium Presentation*

POSTER PRESENTATIONS

- **Oehrlein EM**, Desai B, Ngo M, Tang L, Love TR, Perfetto EM. Patient Stakeholder Involvement in the Clinical Practice Guideline Development Process. AMCP Annual Meeting, April 23-26, 2018, Boston, MA.
- Gold Medal Award
- **Oehrlein EM**, Albrecht J, Perfetto EM, et al. Listening to the “Patient Voice” to Improve Design and Interpretation of Secondary Analyses: An Example of Atrial Fibrillation. ISPOR 20th Annual European Congress, November 4-8, 2017, Glasgow, Scotland.
- **Oehrlein EM**, Harris J, Labkoff N, Perfetto EM, Boutin M. Landscape of Patient-Engagement Activities Across Thirteen Value-Assessment Bodies. ISPOR 22nd Annual International Meeting, Boston, MA.
- **Oehrlein EM**, Ganser TR, Perfetto EM, et al. Alignment Between Patient-Prioritized Symptoms and Endpoints Used in Clinical Trials: A Case Study on Sickle Cell Disease. ISPOR 22nd Annual International Meeting, Boston, MA.
- Perfetto EM, **Oehrlein EM**, Boutin M, Reid S, Gascho E. The Patient Voice in Value Assessment: A Rubric to Increase Patient Centricity. ISPOR 22nd Annual International Meeting, Boston, MA.
- **Oehrlein EM**, Hanna ML, Bjoernebo L, Perfetto EM. A Comparison of Insulin Degludec Clinical Evaluations and Recommendations Between Independent and National HTA Bodies. ISPOR 19th Annual European Congress, Vienna, Austria.
- Hanna ML, **Oehrlein EM**, Cooblall CA, Nguyen F, Perfetto EM, on behalf of Patient Centered Special Interest Group. Attributes Defining Patient Engagement and Centeredness in Health Care Research and Practice: A Framework Development by the ISPOR Patient-Centered Special Interest Group. ISPOR 19th Annual European Congress, Vienna, Austria.
- Perfetto EM, **Oehrlein EM**, Anyanwu CA, Kraska J on behalf of the UMB-NORD Project Team and Patient Advisory Board. Patient-Centered Outcomes Research (PCOR) Training: A Program for Rare Disease Patient Advocates. National Organization for Rare Disorders Annual Summit. Crystal City, VA, October 16-18, 2016.
- **Oehrlein EM**, Graff JS, Anyanwu CA, et al. Journal Editors: The Accelerator or the Brake for Real-World Evidence? AMCP’s Nexus 2016 Conference, October 3-6, 2016, National Harbor, MD.
 - Silver Medal Award
- **Oehrlein EM**, Perfetto EM, Chung Y, Ghafoori P, Harris R. Creating an inventory of risk factors for predicting stroke among atrial fibrillation patients: a systematic review. ISPOR 21st Annual Meeting, Washington DC. *Poster*.
 - Award Finalist
- Perfetto, EM, **Oehrlein EM**, M-CERSI PFDD Planning Committee. A proposed rubric for patient engagement in drug development: what constitutes “sound” engagement? ISPOR 21st Annual Meeting, Washington DC.
- Hanna ML, **Oehrlein EM**, Cooblall CA, Nguyen F, Perfetto EM. Patient Centered Special Interest Group. Definitions for patient engagement and

centeredness in health care research and practice: a systematic review by the ISPOR Patient Centered Special Interest Group. ISPOR 21st Annual Meeting, Washington DC.

- Mullins CD, Anyanwu C, **Oehrlein EM**, Graff J, Perfetto EM, Heath C. Do journal editors perceive real-world evidence as valuable? ISPOR 21st Annual Meeting, Washington DC.
- Gaitonde P, Lyttle Nguessan CJ, Cannon-Dang E, Shah AB, **Oehrlein EM**, Khan ZM. Opportunities for the ISPOR Student Network to Complement the Current Academic Curriculum. ISPOR 21st Annual Meeting, Washington DC.
- **Oehrlein EM**, Gaitonde P, Perfetto EM. The Merit-Based Incentive Payment System and Alternative Payment Models: Implications for Pharmacy Quality Measurement and Reporting. Pharmacy Quality Alliance Annual Meeting & Innovation Forum, May 18 - 20, 2016.
- **Oehrlein EM**, Hanna ML, Perfetto EM. A Comparison of Key Components of the HTA Core Model and the AMCP Format. ISPOR 18th Annual European Congress, November 7-11, 2015, Milan, Italy.
- Hanna ML, Pickering MK, **Oehrlein EM**, Albrecht JS, Patterson CR, Musallam, AJ, Perfetto EM. Twenty-Year Trends in Diagnosis and Treatment of Alzheimer's Disease. ISPOR 18th Annual European Congress, November 7-11, 2015, Milan, Italy.
- **Oehrlein EM**, Pickering MK, Perfetto EM, Anyanwu CU, Graff JS, Eichelberger B, Zagher RW. Meeting the Challenges of the Revised AMCP *Format*: Continuing Education on Comparative Effectiveness Research. AMCP's Nexus 2015 Conference, October 3-6, 2015, Orlando, FL.
 - Silver Medal Award
- Hung A, Gaitonde P, **Oehrlein EM**, Yang B, dosReis S, Zito JM. A Systematic Review of Observational Studies Evaluating Cardiovascular Outcomes of Testosterone Therapy in Men. DIA 51st Annual Meeting, June 14-18, 2015, Washington DC, USA.
- **Oehrlein EM**, Perfetto EM, Vandigo J. Engaging the Patient: The Need for Standardizing Terminology when Incorporating the Patient Voice in Research and HTA. 12th HTAi Annual Meeting, June 13-17, 2015, Oslo, Norway.
- **Oehrlein EM**, Burcu M, Safer D, Zito JM. National Patterns in ADHD Diagnosis and Treatment in Youth and Adults. American Academy of Child and Adolescent Psychiatry's 61st Annual Meeting in San Diego, CA, October 20-25, 2014. *Poster*.
 - Graduate Student Association Travel Awarded

HONORS

- HTAi Annual Meeting, Best Student Oral Presentation, 2017
- PhRMA Foundation Pre-Doctoral Fellowship in Health Outcomes, 2015-2017
- Patient-Centered Outcomes Research Institute (PCORI), 2016 Trainee Scholarship Awardee
- Donald O. Fedder Memorial Fellowship Awardee, June 2016
- ISPOR Student Network Chair, 2015-2016
- ISPOR Distinguished Service Award, May 2016

- ISPOR Student Leadership Award, May 2015
- Rho Chi Pharmacy Honor Society Inductee, April 2015
- FDA/Maryland Center for Excellence in Regulatory Science and Innovation (M-CERSI) Regulatory Talent Competition
 - 2015 – 1st Place - Mobile application conveying safety information to communicate risks of medications and devices (Bilal Khokhar, Elisabeth Oehrlein, Jan Sieluk, Priyanka Gaitonde, and Maya Hanna)
 - 2014 - 2nd Place - Enhancing the FDA Website for Consumer Information on Medication Safety/Efficacy (Melissa Ross, Xian Shen, Bilal Khokhar, Elisabeth Oehrlein, and Priyanka Gaitonde)
- United States Dept. of State Congress-Bundestag Youth Exchange Scholar (CBYX)
 - CBYX is a fellowship funded by the German Bundestag and U.S. Department of State that annually provides 75 American young professionals the opportunity to spend one year studying in Germany

PROFESSIONAL AFFILIATIONS

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2014 – present

- Co-Chair, Special Interest Group on Digest of Databases
- IT Advisory Group
- Student Network Chair 2015-2016
- Leadership Group, Patient Centered Special Interest Group, Patient Engagement in Research Working Group
- Leadership Group, Stated Preference Research in the European Union Working Group
- Contributor, ISPOR Code of Ethics, Chapter 7: Patient Centricity and Patient Engagement in Research

Health Technology Assessment International (HTAi) 2015 – present
Member, Patient Citizen Involvement Interest Group

Academy of Managed Care Pharmacy (AMCP) 2015 – 2017
Faculty for the Comparative Effectiveness Research (CER) Collaborative Certificate Program

PEER REVIEW

BMJ Innovations 2016 – present
Ophthalmology 2016 – present

LANGUAGE SKILLS

Fluent: English, German

COMPUTER/PROGRAMMING SKILLS

SAS

Microsoft Word, Excel, PowerPoint

Abstract

Title of Dissertation: Atrial Fibrillation Risk-Stratification Schemes: Improving Patient-Centeredness and Precision

Elisabeth Oehrlein, Doctor of Philosophy, 2018, Master's of Science, 2018

Dissertation Directed by: Eleanor M. Perfetto, PhD, MS, Professor, Pharmaceutical Health Services Research

Background: Despite treatment-guideline recommendations and availability medications to reduce stroke risk, widespread underutilization of oral anticoagulants (OACs) has been previously documented among individuals with atrial fibrillation (AF). Younger age and female gender are important in light of evidence that these groups, in particular, may not receive optimal AF care. The objective of this dissertation was to identify: 1) What are the barriers to patients initiating OACs? 2) Are providers aware of and using the RSSs and do disparities exist by age and gender? 3) Are RSSs predictive of stroke and OAC initiation among subpopulations (women and <65 years of age)?

Methods: In Aim 1, we invited patients and health care providers (HCPs) to participate in in-depth interviews. In aims 2 and 3, we conducted retrospective cohort studies using Optum's Clinformatic Data Mart (2008-2016). We used logistic regression to calculate odds ratios and 95% confidence intervals to identify whether RSSs were associated with OAC initiation and whether disparities exist by age or gender in aim 2. For Aim 3, we used a discrete time approach to estimate the risk of ischemic stroke associated with RSSs. Separately, we tested whether incorporating risk factors identified in the literature

as predictive of ischemic stroke improved prediction among women and patients ≤ 65 years.

Results: Themes from qualitative interviews include: specialists heightened perception of stroke risk compared to generalists and comorbidities/characteristics absent from RSSs also factor into risk consideration. The proportion of patients initiating OACs was only approximately 30%. CHADS₂, but not CHA₂DS₂-VASc, scores corresponded with higher odds of OAC initiation. We found no statistically significant differences between odds of initiating OACs among OAC-recommended males/females or age categories. Among women and those ≤ 65 years, all CHA₂DS₂-VASc scores >1 and CHADS₂ scores >0 were significant predictors of stroke. Prognostic models developed within subpopulations were no better at predicting stroke than existing RSSs.

Conclusions: RSSs are associated with ischemic stroke among newly diagnosed females and <65 years of age patients. Initiation of OAC treatment was consistently low. More research is needed to more clearly understand why RSSs might not be followed and why OACs are not initiated.

Atrial Fibrillation Risk-Stratification Tools:
Improving Patient Centeredness and Precision

by
Elisabeth M. Oehrlein

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2018

©Copyright 2018 by Elisabeth M. Oehrlein

All rights Reserved

Acknowledgements

This dissertation would not have been possible without my extraordinary advisor, Prof. Eleanor Perfetto. Your support and guidance have helped me reach my potential over the past five years. Thank you to my dissertation committee members: Debbe McCall and Professors Jennifer Albrecht, Catherine Cooke, Susan dosReis, and Julia Slejko. Each of you have provided me with extensive guidance, support, and feedback throughout this process and I am grateful. This work would not have been possible without the financial support from Pfizer, the PATIENTs program, and the PhRMA Foundation.

A very special thanks to my parents, Sharon and Gottlieb Oehrlein, my bother, Stefan Oehrlein, fiancé Lars Björnebo, Grandparents, Aunts and Uncles. I appreciate your high expectations, hard work, and encouragement. Thank you Lauren Gillespie, Patrick Brainard, Jess Gross, Susanne Jakobus, and Alex Samaan for your years of support and friendship.

Colleen Day, thank you for always going above and beyond. Priyanka Gaitonde and Jan Sieluk – I am grateful that we persevered through this stage of our lives together and I would not have wanted to do it without you. Thank you to other members of my PHSR family, especially Maya Hanna, Laura Bozzi, Chinenye Anyanwu, Joe Vandigo, and Mehmet Burcu.

I would also like to acknowledge several of my Professors at Franklin & Marshall College, including Professors Kate Plass, Jennifer Redmann, and Ed Fenlon. Thank you Prof. Plass for introducing me to research, Prof. Redmann for being supportive of me on

a day-to-day basis and in preparation for my post-graduation endeavors in Germany.

Thank you, Prof. Fenlon for being an excellent and engaging teacher who introduced me to drug synthesis, which led to me apply for an internship in the pharmaceutical industry and ultimately into this PhD program.

Finally, thank you Sabine Golke, Manuela Kruse, and Dr. Christine Kleemann. It is difficult to summarize the impact of all of the ideas you introduced me to and skills that you helped me develop. Vielen Dank!

Table of Contents

Acknowledgements	iii
List of Tables	vii
List of Figures.....	ix
List of Abbreviations	x
1. Statement of the Problem, Specific Aims, and Methodological Approach.....	1
2. Natural History of Disease and Outcomes Associated with AF.....	17
3. Preventing Stroke Among AF Patients: Medications, Procedures, and Decision-Making	27
4. Conceptual Models	45
5. Aim 1: Patient and Health Care Provider Perspectives on Atrial Fibrillation Diagnosis and Anticoagulant Initiation.....	51
6. Aim 2: Relationship between Risk-stratification-scores and Anticoagulant Initiation Following Atrial Fibrillation Diagnosis.....	70
7. Aim 3: Performance of the CHADS ₂ and CHA ₂ DS ₂ -VASc Atrial Fibrillation Anticoagulant Risk-Stratification-Schemes Among Newly Diagnosed Women and Patients Under-65 years of Age	91
8. Summary and Implications for Research and Clinical Practice	109
Appendix I. Stakeholder Feedback on Conceptual Model.....	122
Appendix II. Aim 1 – Internal Review Board Protocol.....	143
Appendix III. Aim 1 – Consent Document – Clinicians	154
Appendix IV. Aim 1 – Consent Document – Patients.....	158
Appendix V. Aim 1 – Interview Guide: Nurses	162
Appendix VI. Aim 1: Interview Guide – Patients	168

Appendix VII. Aim 1: Interview Guide – Pharmacists	176
Appendix VIII. Aim 1: Interview Guide – Physicians	182
Appendix IX. Aim 1: Patient Recruitment Language	187
Appendix X. Aim 1: Health care professional recruitment language.....	188
Appendix XI. Aims 2 and 3 variables	190
Appendix XII. Aim 2: Supplementary Tables and Figures.....	203
Appendix XIII. Aim 3: Supplementary Tables	217
References	222

List of Tables

Table 1. (1.1) Traditional versus novel risk factors for stroke.....	9
Table 2. (1.2) HAS-BLED variables.....	9
Table 3. (2.1) Classification of AF	19
Table 4. (3.1) Treatment options for AF ⁹	27
Table 5. (3.2) CHADS ₂ calculation	33
Table 6. (3.3) CHA ₂ DS ₂ -VASc calculation.....	33
Table 7. (3.4) Calculation of ATRIA.....	34
Table 8. (3.5) Bleeding risk prediction scores	35
Table 9. (3.6) Clinical practice guideline language on preventing thromboembolism.....	36
Table 10. (3.7) ESC's list of modifiable and non-modifiable risk factors for bleeding....	37
Table 11. (3.8) Characteristics of the CHADS ₂ , CHA ₂ DS ₂ -VASc, and ATRIA schemes	42
Table 12. (5.1) Overview of emerging themes	66
Table 13. (5.2) Interviewed patients' descriptions of the AF diagnosis experience	66
Table 14. (5.3) HCP-reported factors impacting whether patients receive warfarin or a NOAC	68
Table 15. (5.4) HCP-reported reasons for recommending aspirin.....	69
Table 16. (6.1) Proportion of patients receiving an OAC within 3-months of diagnosis.	90
Table 17. (6.2) Odds of initiating OACs within 3-months of diagnosis based on RSS scores.....	90
Table 18. (6.3) Impact of age and gender on OAC-initiation among OAC-recommended patients	90
Table 19. (7.1) Bivariate associations between risk factors and stroke within one year following diagnosis.....	106
Table 20. (7.2). Risk ratio of ischemic stroke during year following diagnosis by CHA ₂ DS ₂ -VASc score	107
Table 21. (7.3) Risk ratio of ischemic stroke during year following diagnosis with AF by CHADS ₂ score.....	108
Table 22. (7.4) Risk ratios for ischemic stroke among incident AF cohort.....	108
Table 23. (A4.1) Stakeholder feedback on draft conceptual model: ‘environment’	122
Table 24. (A4.2) Stakeholder feedback on draft conceptual model: ‘patient characteristics’	126
Table 25. (A4.3) Stakeholder feedback on draft conceptual model: ‘health behavior’ ..	136
Table 26. (A4.4) Stakeholder feedback on draft conceptual model: ‘patients outcomes’	140
Table 27. Study cohorts – inclusion criteria	190

Table 28. Study cohorts - exclusion criteria	190
Table 29. Study outcomes.....	190
Table 30. Risk scheme calculation.....	191
Table 31. Study covariates.....	197
Table 32. Bleeding adverse events (adapted from Wang et al. ¹¹).....	201
Table 33. (A6.1) OAC treatment initiation among OAC-recommended patients (2008-2014).....	203
Table 34. (A6.2) OAC treatment initiation among OAC-recommended patients (2015-2016).....	205
Table 35. (A6.3) Adjusted odds of initiating OACs within 3-months of diagnosis (2008-2014).....	206
Table 36. Table A6.4. Adjusted odds of initiating OAC within 3-months of diagnosis (2015-2016).....	207
Table 37. Table A6.3 Odds of initiating OACs within 3-months of diagnosis based on RSS scores	209
Table 38. Table A6.4. Adjusted odds of initiating an OAC by RSS component within 3-months of diagnosis (2008-2014)	209
Table 39. Table A6.5. Adjusted odds of initiating an OAC by RSS component within 3-months of diagnosis (2015-2016)	210
Table 40. Table A6.6. Odds of initiating OACs within 3-months of diagnosis based on RSS scores	210
Table 41. Table A6.7. Proportion of Patients Receiving an OAC within 6-months of diagnosis	212
Table 42. Table A6.8. Odds of initiating OACs within 6-months of diagnosis based on RSS scores	212
Table 43. Table A6.9. Odds of initiating OACs within 6-months of diagnosis based on RSS scores	213
Table 44. Table A6.10. Odds of initiating OACs within 6-months of diagnosis based on RSS scores	213
Table 45. Table A6.11 Pre-Update co-morbid condition medication utilization (CHADS2 ≥ 2).....	214
Table 46. Appendix A6.11. Odds of initiating OACs within 6-months of diagnosis among patients recommended to initiate OACs	215
Table 47. A7.1. Stroke within 12-months of AF diagnosis	219
Table 48. A7.2. Stroke within 12-months of AF diagnosis	220

List of Figures

Figure 1. (1.1) Research questions and rationale	3
Figure 2. (1.2) Overview of specific aims	3
Figure 3. (1.3) Description of data source for Aims 2 and 3	5
Figure 4. (1.4) Aim 2 overview	6
Figure 5. (1.5) Sample logistic model.....	10
Figure 6. (1.6) Overview of discrete time analysis.....	14
Figure 7. (1.7) Sample equation adapted from Albrecht JS. ¹⁷	15
Figure 8. (1.8) Split sample prognostic modeling approach.....	15
Figure 9. (4.1) Preliminary academic version of the Andersen model of the AF patient experience	48
Figure 10. (4.2) Preliminary patient-friendly version of the Andersen model of the AF patient experience	49
Figure 11. (4.3) Final patient-centered conceptual model of the AF patient experience..	50
Figure 12. (6.1) Study cohorts (3-month follow-up)	89
Figure 13. A6.1. Study cohorts (6-month follow-up)	212
Figure 14. A7.1. Ischemic stroke per 1,000 patients by follow-up month in the overall population (age)	217
Figure 15. A7.2. Ischemic stroke per 1,000 patients by follow-up month in the overall population (sex)	218
Figure 16. (A7.3) Women's prognostic model development	221
Figure 17. (A7.4) ≤ 65 years cohort's prognostic model development.....	221

List of Abbreviations

ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AP	Antiplatelet medication
ADRD	Alzheimer's disease and related dementias
AUC	Area under operating curve
BIC	Bayes Information Criterion
CDM	Optum Clinformatics Data Mart
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPG	Clinical practice guideline
EP	Electrophysiologist
ESC	European Society for Cardiology
ESRD	End-stage renal disease
HRS	Heart Rhythm Society
INR	International normalized ratio
IPA	Interpretive phenomenologic analysis
NOAC	Novel (direct-acting) oral anticoagulant
HCP	Health care provider
HR	Hazard ratio
HRQoL	Health-related quality of life
OAC	Oral anticoagulant
OR	Odds ratio
PCOR	Patient-centered outcomes research
RR	Risk ratio
RSS	Risk stratification schemes (CHADS ₂ and CHA ₂ DS ₂ -VASc)
RX	Prescription medication
TIA	Transient ischemic attack
UMB	University of Maryland, Baltimore
UMMC	University of Maryland Medical Center
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. Statement of the Problem, Specific Aims, and Methodological Approach

Background

Patients with atrial fibrillation (AF) are at a significantly higher risk of experiencing a stroke than individuals without AF. To reduce risk of stroke, oral anticoagulants (OACs) may be prescribed. While these drugs are effective in reducing risk of stroke, they also increase an individual's risk of adverse bleeding events. To help clinicians better assess the benefits and risks of anticoagulants among AF patients, researchers constructed stroke risk-stratification-schemes (RSSs). The models include "points" for comorbidities, including congestive heart failure, hypertension, diabetes mellitus, gender, and vascular disease, along with demographic characteristics, including age 65-74 years, age ≥ 75 years, and gender. While widely recommended in clinical guidelines, further critical evaluation of these RSSs is necessary, as some studies have shown that segments of the population are less likely to receive oral anticoagulants (OACs). In addition, validation studies for these RSSs were undertaken in elderly populations, making it unclear how applicable they are to younger AF populations. Given the availability of effective anticoagulants, it is important to verify that these disparities are not due to limitations in the risk-stratification schemes.

This multi-phase study consists of a patient-centered outcomes research (PCOR) qualitative study and quantitative, claims-based analysis. The qualitative portion of this study seeks to understand AF patients and providers views on the risk for stroke, the need for anticoagulant treatment, and the relevance of a conceptual model depicting the AF patient experience. The quantitative portion of this study examines (1) whether

anticoagulant treatment guidelines (e.g., CHADS₂ and CHA₂DS₂-VASc) predict OAC initiation and (2) whether existing risk schemes predictive of stroke could be improved for use among women or under-65 AF patients.

Study Goal

The overarching goal of this study is to improve the quality of care for AF patients. In particular, this study examines whether risk-stratification schemes for guiding anticoagulant prescribing to prevent stroke are sufficient for all patients and whether treatments guidelines that make use of the RSSs are adhered to. The results of this study will lead to improved health and patient experience by shedding light on stroke risk among two understudied AF patients, women and those under-65.

Further, this study addresses several key priorities identified by the National Heart, Lung, and Blood Institute to advance AF stroke prevention research.¹

- Enhance understanding of the epidemiology of AF in the population by systematically and longitudinally investigating symptomatic and asymptomatic AF in cohort studies;
- Further validate and improve on incident AF risk-prediction models across cohorts;
- Assess the role and basis of age, gender, racial/ethnic, and regional variations in AF onset and progression need to be better understood; and
- Understand non-clinical barriers to AF treatment

Problem statement

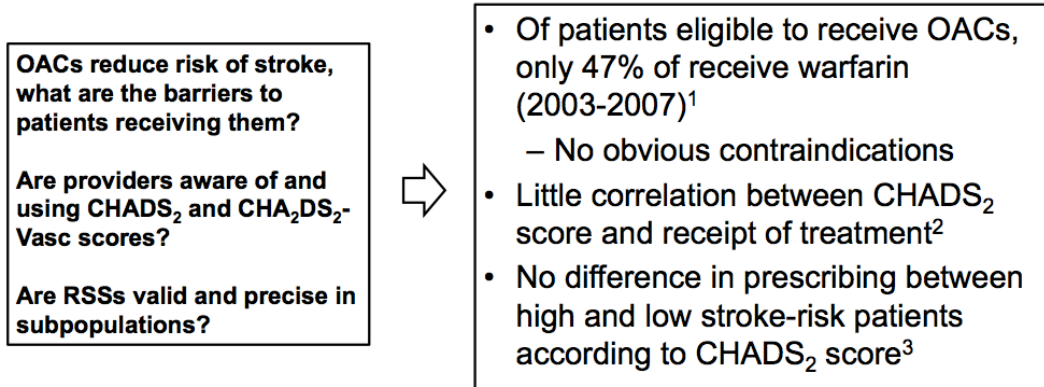
Effective medications for preventing stroke among AF patients are already available.

However, these medications are currently underutilized, especially among the under-65 population and in women, and many AF patients are still experiencing a high rate of stroke (see Figure 1).

1. Premise 1: RSSs exist to help identify which patients require preventive anticoagulation therapy. There are questions about how well the tools perform and how closely they are being followed. Improving both RSS precision and best practices in use could improve the effectiveness of preventive therapies.

2. Premise 2: Understanding the limitations of current RSSs provides information on how precision can be improved. Past research indicates age and gender may improve the precision of the tools.
3. Premise 3: Understanding the views of AF stakeholders, including patients, can provide information on how to improve precision and use of the RSSs.

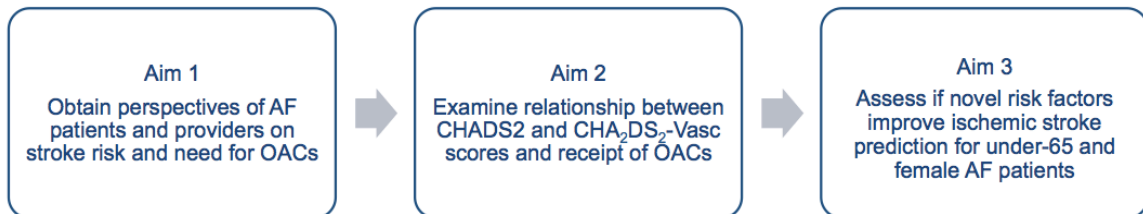
Figure 1. (1.1) Research questions and rationale



Research Approach

This study will be conducted in three phases, which collectively contribute to answering the research questions: *what are the barriers to patients initiating OACs? Are providers aware of and using the CHADS₂ and CHA₂DS₂-VASC? Are RSSs valid and precise in subpopulations?*

Figure 2. (1.2) Overview of specific aims



Aim 1: Obtain perspectives of AF patients and health care providers (HCPs) on stroke risk and need for OACs

Objective: To obtain the perspectives of AF patients and providers on the risk for stroke, the need for anticoagulant treatment, and the relevance of a conceptual model depicting the AF patient experience.

Data source: Patient and HCP interviews

Design: Patients and HCPs (cardiologists, electrophysiologists (EPs), general practitioners, nurses, pharmacists) will be invited to participate in a 1-hour interview on diagnosis, OAC treatment, risk of stroke, and a conceptual model of the patient journey. A target enrollment of 5 patients and 10 HCPs was sought for participation in in-depth, telephone interviews. Patients were recruited through the Atrial Fibrillation Support Forum on Facebook, and were eligible to participate if they stated they had been diagnosed with AF, had at least three AF-related health care visits since their initial diagnosis, are 18 years of age or older, can provide informed consent, and speak English. Participation was solicited by a Forum moderator by email. HCPs were eligible to participate if they are involved in the care of AF patients, able to provide informed consent, and speak English. HCPs were identified through recommendations from University of Maryland, Baltimore (UMB) faculty or listed on the University of Maryland Medical System's website.

Analysis plan: Audio recordings of interviews were transcribed and analyzed using interpretative phenomenological analysis (IPA) in an approach similar to Leahy et al.² In IPA, the researcher aims to learn about an individual's personal experiences, where participants are viewed as storytellers.^{2,3} This approach is particularly desirable for this study design, since IPA seeks to provide insights on how individuals experience major life events, for example diagnosis with AF. IPA is grounded in the belief that patients are

experts on their lived experiences.⁴ A narrative of the themes including verbatim phrases that best represented stakeholder perspectives was developed using Nvivo 11 qualitative data analysis software.

Aim 2: Examine relationship between CHADS₂ and CHA₂DS₂-VASc scores and receipt of OACs

Objective: To evaluate clinicians' (e.g., MD, DO's, NPs, and anyone with authority to prescribe) adherence to anticoagulant treatment guidelines (e.g., CHADS₂ and CHA₂DS₂-VASc) and the association between patient characteristics and receipt of anticoagulant treatment.

Data source: Medical and pharmacy claims within Optum LifeSciences database (see

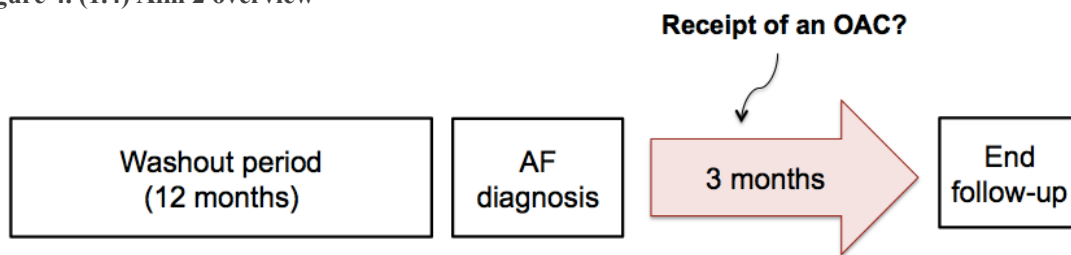
Figure 3. (1.3) Description of data source for Aims 2 and 3

Optum is a commercial data provider and care organization for the UnitedHealth Care Group. Optum's Clinformatics™ Data Mart (CDM) comes affiliated with Optum. The database includes approximately 12-14 million annual covered lives, for a total of over 65 million unique lives over a 17-year period (2001 through 2017). Clinformatics™ Data Mart is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum customer data-use agreements. These administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion. The claims data comprises both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states. In addition to medical claims and pharmacy claims, the claims data includes tables with member eligibility and inpatient confinements. The claims data also includes standard pricing for all medical claims, pharmacy claims, and inpatient confinements.

Design

We conducted a retrospective cohort study using Optum’s CDM administrative claims data for years 2008-2016 (see Figure 4 (1.4)). Patients with newly diagnosed AF were followed for three months post-diagnosis to identify presence of a pharmacy claim for OACs. Scores were calculated for patients diagnosed 2009-2014 (CHADS₂ pre-update cohort) or 2015-2016 (CHA₂DS₂-VASc, post-update cohort), respectively.

Figure 4. (1.4) Aim 2 overview



Our study cohort included patients with at least one inpatient or outpatient claim containing the international classification of diseases (ICD)-9 or ICD-10 codes for AF (427.31; I480, I481, I482, or I489) from 2008 to 2016. Date of diagnosis was considered the index date. Patients were required to have continuous enrollment in medical and pharmacy coverage for the entire 12-month pre-index washout and 3-months post-diagnosis. Patients were excluded if they have claims for oral anticoagulants, cardioversion therapy, catheter ablation, or valvular disease during the washout period to help identify incident AF diagnosis. Patients with hip or knee replacement surgery in the 6-weeks prior to diagnosis were also excluded because these surgeries can increase risk of stroke in the weeks immediately following surgery.⁵ Patients with pregnancy at any time during the study were also excluded since AF can be a complication of pregnancy.

6,7

1. Treatment Received (Dependent Variables)

For this analysis, treatment received was defined in the following ways:

“**Any OAC treatment received**” is the primary outcome of interest and was defined as a subject having at least one pharmacy claim for one of the following during follow-up:

- *Novel oral anticoagulants* (NOACs) were identified through pharmacy claims data. Relevant treatments in this category include apixaban, dabigatran, edoxaban, and rivaroxaban.
- *Vitamin K antagonists* (VKAs) were also identified through pharmacy claims data. Relevant treatments include: acenocoumarol, brodifacoum, coumatetralyl, dicoumarol, diphenadione, phenindione, phenprocoumon, pindone, tiocloamarol, and warfarin.

Medications were ascertained using pharmacy claims data using American Hospital Formulary Service Classification (AHFSC) codes (see Appendix XI). Although over-the-counter aspirin is commonly used among low-risk AF patients, it is not captured in claims. Therefore, analyses examining adherence to treatment guidelines only examined those patients recommended to receive prescription anticoagulants.

“**NOAC received**” was a secondary outcome and was defined by a subject having at least one pharmacy claim for one of the following during follow-up:

- *Novel oral anticoagulants* (NOACs) were identified through pharmacy claims data. Relevant treatments in this category include apixaban, dabigatran, edoxaban, and rivaroxaban.

“**VKA received**” was a secondary outcome and was defined by a subject having at least one pharmacy claim for one of the following during follow-up:

- *Vitamin K antagonists* (VKAs) were identified through pharmacy claims data. Relevant treatments include: acenocoumarol, brodifacoum, coumatetralyl, dicoumarol, diphenadione, phenindione, phenprocoumon, pindone, tiocloamarol, and warfarin.

2. Independent Variables

CHAD₂ or CHA₂DS₂-VASc Score

Between 2006-2014 (data set begins in 2008), ACC/AHA anticoagulant treatment guidelines recommended use of the CHAD₂, however, in late 2014, the newest guideline iteration recommended use of the CHA₂DS₂-VASc for patient risk stratification. The 2006 guidelines suggested either warfarin or aspirin were appropriate in the presence of one “moderate risk factor” (age \geq 75; hypertension; heart failure; LV; ejection fraction \leq 35%, or diabetes mellitus). Patients with one “high risk factor” (previous stroke, TIA, or thromboembolism; mitral stenosis; or prosthetic heart valve) or \geq 2 of the “moderate risk factors” were recommended to receive warfarin.⁸ The revised 2014 guidelines recommend “for patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA₂DS₂-VASc score of 2 or greater, oral anticoagulants are recommended.”⁹

A CHADS₂ (Years 2008-2016) or CHA₂DS₂-VASc (Years 2014-2016) score was calculated for each subject using covariates ascertained in the 12 months immediately preceding diagnosis with AF. For specific operationalization of variables, see Table 30. Risk scheme calculation (Appendix).

In addition to an individual's CHADS₂/CHA₂DS₂-VASc score, individual risk factors were also examined. These include both traditional risk factors (those included in stratification schemes) and novel risk factors identified through systematic review (see Table 1 (1.1)). Risk factors included in the HAS-BLED, which predicts bleeding risk amongst AF patients, are also considered. Although several of these overlap with risk factors for stroke, several are unique including abnormal liver function (See Table 2 (1.2)). In addition to risk factors, the HAS-BLED score includes medications that may predispose and individual to bleeding, such as antiplatelet agents or NSAIDs.

Table 1. (1.1) Traditional versus novel risk factors for stroke

<i>Traditional Risk Factors for Stroke</i>	<i>Novel Risk Factors for Stroke</i>
Variables included in the CHADS ₂ /CHA ₂ DS ₂ -VASc:	Identified through systematic literature review:
<ul style="list-style-type: none"> • Congestive heart failure • Hypertension • Age • Diabetes • Stroke • TIA • Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque) • Thromboembolism • Gender 	<ul style="list-style-type: none"> • Alcohol disorders • Chagas disease • Chronic obstructive pulmonary disease • Hyperhomocysteinemia • Hyperthyroidism • Left atrium dysfunction/strain • Left ventricular dysfunction • Low body weight • Obstructive sleep apnea • Race (black/Hispanic) • Renal disease/impairment • Smoking

Table 2. (1.2) HAS-BLED variables

<i>HAS-BLED Score</i>
<ul style="list-style-type: none"> • Hypertension • Abnormal renal/liver function • Stroke • Bleeding history or predisposition • Labile INR • Elderly • Drugs/alcohol concomitantly

Analysis Plan:

We calculated the proportion of individuals meeting CHADS₂ or CHA₂DS₂-VASc treatment-recommended criteria who received anticoagulant treatment within 3 months of diagnosis (“Any OAC treatment received”), stratified by age and sex. In addition, we calculated the proportion of subjects receiving OAC treatment by individual scores. For example, the proportion of subjects with a CHADS₂ score=1 receiving OAC treatment.

Sub-analyses with treatment types “NOAC received” and “VKA received” were also performed (see below).

To assess the role of individual risk factors in receiving treatment, we examined bivariate associations between covariates, including novel and traditional risk factors, and receipt of anticoagulant treatment (“Any OAC treatment received;” “NOAC received;” and “VKA received,” separately) within 3 and 6 months of AF diagnosis using Chi-square goodness of fit, Student’s T tests, or non-parametric methods, as appropriate. Differences between categorical variables were assessed using Chi-square tests and between continuous variables by using Student T tests. Non-parametric methods were used if, for example, there were many outliers.

Logistic regression modeling was used to identify important associations between covariates and receipt of: any anticoagulant treatment by 3 months post AF diagnosis, and NOACs-specifically or VKA’s-specifically, stratified by sex and age. A full model was developed for each of the stratified populations with odds ratios for individual risk factors, both traditional and novel, recorded (see Figure 5 (1.5)). A p-value below 0.05 was considered statistically significant.

Figure 5. (1.5) Sample logistic model

$$\text{logit } P(\text{OAC}) = \beta_0 + \beta_1(\text{CHADS}_2) + \beta_2(\text{Major bleeding}) + \beta_3(\text{Provider type}) + \dots$$

Stepwise selection was utilized for model selection for testing the following hypotheses:

Hypothesis #1: Men are more likely to receive guideline-adherent anticoagulant treatment than women upon diagnosis with AF

- $H_0: p_{\text{males}} = p_{\text{females}}$
- $H_A: p_{\text{males}} > p_{\text{females}}$

Hypothesis #2: Patients over the age of 65 are more likely to receive guideline-adherent anticoagulant treatment upon diagnosis with AF

- $H_0: p_{o65} = p_{u65}$
- $H_A: p_{o65} > p_{u65}$

To evaluate goodness of fit, the Hosmer-Lemeshow test assumes a X^2 distribution and will be utilized. This test assesses whether observed events match expected events and has been widely used in previous studies.

Sensitivity analyses

We conducted several sensitivity analyses to assess the rigor of our findings. First, we extended the follow-up time from 3-months post-diagnosis to 6-months to ensure that 3-months was a sufficient follow-up length to capture OAC initiation. We also examined if OAC-recommended patients, both those who initiated OACs and those that did not, initiated other prescription medicines to provide insights into whether patients might be filling prescriptions without adjudicating claims (e.g., low cost generics) or primary non-adherence. Specifically, we examined whether OAC-recommended patients with co-morbid hypertension initiated calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, beta blockers, thiazide diuretics, or direct antihypertensive agents pre- or post- diagnosis. We will also examine whether OAC-recommended patients with co-morbid diabetes initiated insulin or oral antidiabetics pre- or post-diagnosis stratified by OAC-initiation status. Finally, we will examine the impact of dichotomizing patients into RSSs <2 and ≥ 2 since guidelines recommend initiating OACs among all patients with scores ≥ 2 since CPGs recommend OACs for patients with scores ≥ 2 .

Aim 3: Assess if novel risk factors improve ischemic stroke prediction for under-65 years and female AF patients

Objective: To compare the prediction of ischemic stroke between prognostic models that include the novel risk factors with traditional RSSs (CHADS₂ and CHA₂DS₂-VASc) among under-65 and female AF patients.

Data source: Medical and pharmacy claims within the Optum LifeSciences database (see Figure 2)

Design: Our study cohort included patients with at least one inpatient or outpatient claim containing the international classification of diseases (ICD)-9 or ICD-10 codes for AF (427.31; I480, I481, I482, or I489) from 2008 to 2016. Date of diagnosis was considered the index date. Patients were required to have continuous enrollment in medical and pharmacy coverage for the entire 12-month pre-index washout and up to one year follow-up period. Patients were excluded if they have claims for oral anticoagulants, cardioversion therapy, catheter ablation, or valvular disease during the washout period to help identify incident AF diagnosis. Patients with hip or knee replacement surgery in the 6-weeks prior to diagnosis were also excluded because these surgeries can increase risk of stroke in the weeks immediately following surgery.⁵ Patients with pregnancy at any time during the study were also excluded since AF can be a complication of pregnancy.

6,7

Clinical outcome and covariates

Ischemic stroke following diagnosis with AF was identified through ICD-9 codes (ICD-9: 433.x1, 434.x1, 436.xx) and ICD-10 (I480, I481, I482, I489) codes between 2009 and 2016.^{10,11} Follow-up time was for up to one year post-diagnosis. Due to temporal

ambiguity and to avoid introducing protopathic bias, we excluded patients who experience stroke in the month immediately following diagnosis and begin follow-up for stroke at the start of month two.¹² A one-year follow up was selected, since the currently recommended risk stratification scheme, the CHA₂DS₂-VASc, was developed to predict one-year risk of stroke.¹³ Baseline characteristics including age, sex, comorbidities included in RSS's, history of bleeding adverse events, novel risk factors, diagnosis year, and provider type at diagnosis were used (see Appendix XI for operationalization of variables). See Table 1 for list of candidate novel risk factors.

The CHADS₂ and CHA₂DS₂-VASc will be estimated based on Wang and colleagues's methodology, which assigns points based on presence of codes within inpatient, outpatient, or pharmacy claims.¹¹ For example, history of diabetes mellitus (DM) is assigned to patients with at least 2 outpatient diagnoses of DM (ICD-9 250.X) or 1 hospital discharge diagnosis of diabetes or 1 diagnosis of DM and receipt of insulin or an oral antidiabetic. Other risk factors for stroke or conditions that may impact receipt of anticoagulants, such as Alzheimer's disease and related dementias (ADRD), will be identified using diagnosis or procedure codes.

Patients with claims for OACs and antiplatelet (AP) medications will be included as covariates in adjusted models, but not for prognostic modeling. OAC and antiplatelet use will be ascertained on a monthly basis post-index (diagnosis) date through pharmacy claims data using American Hospital Formulary Service Classification (AHFSC) codes (see Supplementary materials).

Analysis Plan:

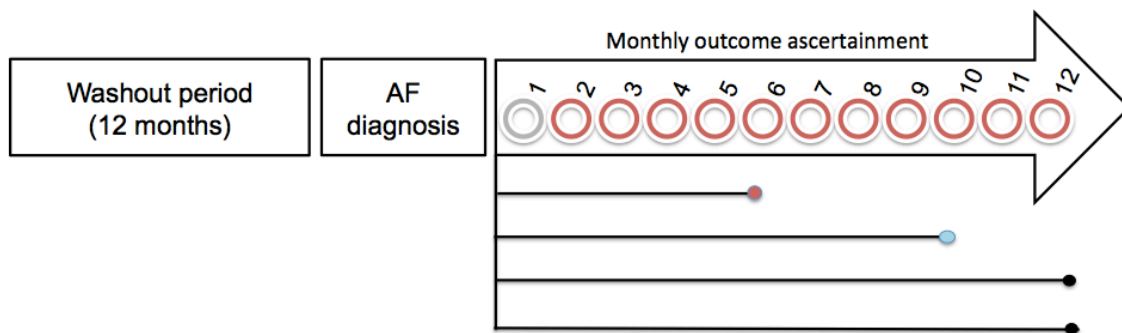
We calculated the proportion of individuals meeting CHADS₂ or CHA₂DS₂-VASc treatment-recommended criteria who experienced stroke during the 12 month follow up

period, stratified by age and sex. To assess the role of individual risk factors in experiencing stroke, we examined bivariate associations between covariates, including novel and traditional risk factors, and experiencing ischemic stroke within 12 months of AF diagnosis using Chi-square goodness of fit and Student's T tests as appropriate.

We used a discrete time approach to estimate the relative risk of ischemic stroke associated with CHADS₂ and CHA₂DS₂-VASc scores. Ischemic stroke, anticoagulant and antiplatelet use were captured on a monthly basis for up to one year following AF diagnosis (see Figure 6 (1.6)).

Hypothesis: Prognostic models incorporating novel risk factors will perform better than traditional models (CHADS₂ and CHA₂DS₂-VASc)

Figure 6. (1.6) Overview of discrete time analysis



Time to first ischemic stroke was modelled using generalized linear models with a binomial distribution and a complementary log-log link (see Figure 7 (1.7)).^{14,15} The complementary log-log link is used to analyze survival data and can account for censoring. This method allowed us to model the occurrence of the outcome of interest by month and to control for changing medication use as a time-varying exposure¹⁶ and to minimize selection bias in our cohort by including both OAC-initiators and non-initiators.

Patients were censored following first ischemic stroke, end of study follow-up or because their insurance status changed.

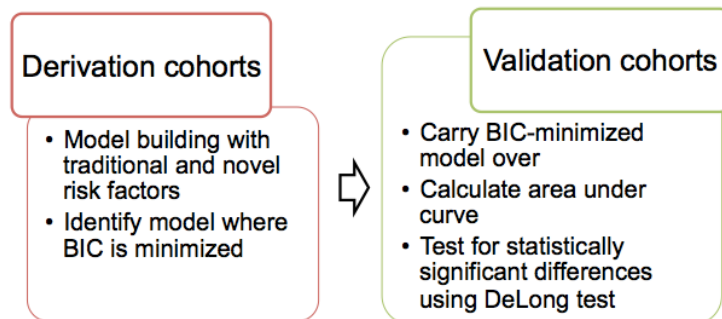
Figure 7. (1.7) Sample equation adapted from Albrecht JS.¹⁷

$$\text{Log}(-\log(1 - \text{Pit})) = \log \lambda_0(t) + \beta x_1 + \dots + \beta x_i$$

–Models first stroke

Separately, we excluded OAC and AP initiators and tested to see if novel risk factors that have been identified in the literature or reported during Aim 1 as predictive of ischemic stroke were predictors in the subpopulations and whether on their own or incorporating them with RSS risk factors improved predictive ability over existing RSSs. The overall study cohort, which includes all eligible patients, was stratified into two cohorts: gender and age. Among the stratified populations, two thirds of patients were randomly assigned to a strata-specific derivation cohort, while one third were randomly assigned to a validation cohort.¹⁸ Thus, two derivation and two validation cohorts were formed (women; ≤ 65 years).

Figure 8. (1.8) Split sample prognostic modeling approach



Minimization of the Bayes information criterion (BIC), which is a measure of “global fit” in prognostic modeling, was used to identify “best fit” models among derivation cohorts for further goodness of fit testing among validation cohorts (see Figure 8 (1.8)).¹⁹ The BIC attributes a “penalty” for increasing the quantity of variables in a statistical model.

This approach to model selection is adapted from Cook et al., Ridker et al., and Halabi et al.¹⁸⁻²⁰ Discrimination between cohort-specific models and the CHADS₂ and CHA₂DS₂-VASc RSS's will be calculated using receiver operating characteristic (ROC) curves and statistically significant differences identified using the Delong test.²¹ Models displaying perfect discrimination have an area under the curve (AUC) of 1.0, while models with an AUC of 0.5 have no discriminatory ability.²¹ The DeLong test is a non-parametric approach to test the hypothesis that ROC curves are equal.²²

Analyses were performed using SAS 9.2 (Cary, North Carolina). Statistical significance was set at $P < .05$.

$$H_0^{AUC}: AUC_p = AUC_{p-k}$$

$$H_A^{AUC}: AUC_p \neq AUC_{p-k}$$

2. Natural History of Disease and Outcomes Associated with AF

AF is the most common heart rhythm disorder, occurring when electrical signals originate in the pulmonary veins instead of the sinoatrial node, causing the atria to fibrillate. This results in an individual's heart beating either abnormally slow or fast, or contracting with irregularity.²³ The prevalence of AF increases with age with approximately 5% of individuals over 65 years affected and approximately 10% of individuals ≥ 80 .^{24,25} A recent study relying on a systematic literature review estimates that the global burden of AF in 2010 was approximately 33.5 million (~20.9 million men and ~12.6 million women).²⁶ The authors estimate that the prevalence rate of AF increased from 569.5 to 596.2 per 100,000 persons between 1990 and 2010. Among women, the authors estimate the prevalence per 100,000 persons increased from 359.9 in 1990 to 373.1 in 2010. In the United States, it is expected that the incidence of AF will double from an estimated 1.2 million cases in 2010 to 2.6 million cases in 2030.²⁷ Individuals with hypertension, coronary heart disease, heart failure, rheumatic heart disease, structural heart defects, pericarditis, congenital heart defects, sick sinus syndrome, hyperthyroidism, obesity, diabetes, and lung disease are at an increased risk of developing AF.²⁸

A multi-national study of AF patients found reduced health-related quality of life (HRQoL) as compared to general populations and roughly equivalent or worse HRQoL than post-myocardial infarction and heart failure patients.²⁹ Another study found that while AF patients have reduced HRQoL, this may be improved through effective heart rate or rhythm control strategies.³⁰

Diagnosis

According to the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines, the most common symptom of AF is fatigue. However, symptoms range from no symptoms to palpitations, dyspnea, hypotension, syncope, or heart failure.^{9,31} Additional symptoms of AF include palpitations, shortness of breath, weakness or difficult exercising, chest pain, dizziness or fainting, and confusion.³² Depending on whether the AF is symptomatic or asymptomatic, a diagnosis may occur following a routine physical exam or electrocardiogram (EKG) either as a result of suspicion of AF or for another reason.

AF can be diagnosed by a variety of different physicians including primary care doctors, cardiologists, and electrophysiologists (EPs). In order to detect AF, portable EKGs are typically used, since they allow monitoring for longer time periods.³³ Patients experiencing and reporting symptoms of AF report delayed diagnoses because their symptoms were not recognized as AF, but rather were diagnosed as anxiety, stress, or respiratory illnesses.^{34,35} In a qualitative study of forty atrial fibrillation patients in the Midwestern US, patients reported negative encounters with HCPs prior to diagnosis, including doubting participants stories, not recognizing symptoms, or dismissing concerns altogether. For example, one female patient reported that her doctor minimized her symptoms as a “woman thing” and stated that she was having a “panic attack.”³⁶ Patients sometimes attributed their own symptoms to “aging, excess work demands, physical deconditioning or stress” and used self-care strategies such as “rest, taking more time to accomplish tasks, avoiding particular activities or exercising harder to ‘get back into shape.’”³⁶

Types of AF

There are several types of AF and they are classified by the frequency and duration of episodes over time (see Table 3 (2.1)).⁹ In addition to these classifications, the term “lone AF” has been used historically to describe typically younger patients who did not have common comorbidities, such as cardiopulmonary disease, hypertension, or diabetes mellitus. The term originates from a study published in 1954, with 20 subjects (ages 38-72 years). Applying best clinical practices available at the time, the researchers were unable to identify any clinical characteristics typically associated with AF.³⁷ More recently, “lone AF” has been used to refer to patients under the age of 60 without clinical comorbidities.³⁸ However, due to increasing evidence that there is no unique mechanism for “lone AF”, the AHA/ACC/HRS guidelines do not recommend using this term since it is not a useful categorization for clinical decision-making.^{9,39}

Table 3. (2.1) Classification of AF

Term	Definition
Non-valvular AF	AF in individuals without a history of rheumatic mitral stenosis, mechanical/prosthetic heart valves, or mitral valve repairs.
Paroxysmal AF	AF terminating spontaneously or following intervention within 7 days of onset
Persistent AF	AF sustained for longer than 1 week
Long-standing persistent AF	AF sustained for longer than 12 months
Permanent AF	Does not represent a change in pathophysiology of AF, but rather a change in “therapeutic attitude”; decision to cease efforts to restore sinus rhythm
Valvular AF	AF related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.

*Adapted from January et al., Camm et al. Martins et al.^{9,40,41}

For the purpose of this study, the focus will be on patients with non-valvular, also known as non-rheumatic, AF.⁴² RSSs were developed for patients with non-valvular AF and NOACs are only indicated for patients with non-valvular AF. There is uncertainty over whether the mechanism of thrombogenesis is similar between non-valvular and valvular AF.⁴³ The risk of stroke associated with valvular AF is significantly higher than non-valvular AF and anticoagulation strategies differ between these two AF subtypes.⁴⁴

Risk of Stroke and Non-Valvular AF

Non-valvular AF is an independent risk factor for ischemic stroke. On average, across all ages, the presence of AF increases an individual's risk of experiencing stroke four to six-fold.⁴⁵ Among patients in the AMADEUS trial (median follow-up=11.6 months), Senoo et al. found that permanent AF patients had an increased risk of stroke or systemic embolism as compared to patients with nonpermanent AF (HR 1.68; 95% CI, 1.08–2.55; p=0.02).⁴⁶ Additionally, Wolf and colleagues estimate that over a 34-year follow-up period, Framingham Study participants with AF had twice the risk of developing stroke as compared to their AF-free counterparts.⁴⁷

Independent Risk Factors for Stroke Among AF Patients

The following patient characteristics and comorbidities are linked to an increased risk of stroke among AF patients:⁴⁸

Age

In an observational case-control study, Moulton et al. found that being 65 years or older increases the risk of stroke three-fold (RR: 3.3; 95% CI: 1.92 to 5.81), while Wang and colleagues estimated that each advancing decade is independently associated with stroke (RR of 1.32; 95% CI: 1.02 to 1.76).^{49,50} In a systematic review and meta-analysis of randomized controlled trials examining the efficacy of oral anticoagulants; van Walraven et al. found that each additional decade is associated with an increased risk of stroke (1.45, 95% CI: 1.26 to 1.66 per decade).⁵¹ A recent hospital-based cohort study by Chan et al. found that among Chinese patients with AF, the annual risk of stroke increased sharply with age. Among their sample, hazard ratios increased from 1.0 among the <50 years population to 13.0 (50-64 years), 19.3 (65-74 years), and 21.6 (\geq 75 years).⁵²

Biomarkers

A systematic review of studies examining the association between inflammatory or hemostatic biomarkers with stroke or thromboembolic events among AF patients found significant associations between circulating plasminogen activator inhibitor-1 (PAI-1) and thrombin-antithrombin (TAT) and increased risk of stroke; while higher levels of D-dimer were associated with increased thromboembolic event risk (pooled HR 2.90; 95% CI 1.22-6.90).⁵³ The review also stated additional biomarkers including interleukin-6, von Willebrand factor, P-selectin, and mean platelet volume were found to be predictive of stroke, albeit in studies with small populations. Hijazi et al. found that elevations in troponin I and NT-proBNP are associated with increased risk of stroke.⁵⁴ Pastori et al. found that increased levels of urinary 11-dehydro-TxB2 was associated with risk (HR 1.66 CI 1.36-2.02) of a composite cardiovascular event outcome (myocardial infarction and ischemic stroke, transient ischemic attack, cardiac revascularization, and CV death) in patients with AF despite anticoagulant treatment.⁵⁵

Congestive Heart Failure

Hughes et al. identified two studies where congestive heart failure (CHF) was found to be a significant predictor of stroke.^{48,56,57} In addition to these studies, common risk stratification schemes for stratifying AF patients into “high risk” categories where treatment is recommended, include CHF in their risk calculations, therefore most studies examining the predictive ability of these tools also report at least a univariate analysis of CHF as a risk factor.

Diabetes mellitus

In a systematic review of studies examining risk factors for stroke, Hughes et al. identified two studies where diabetes mellitus (DM) was found to be a significant

predictor of stroke.^{48,50,58} However, they also identified three additional studies where DM was not found to be a significant predictor of stroke: one among an elderly population and two among populations with no history of prior stroke or presence of CHF or left-ventricular dysfunction.^{59,60}

Female Gender

Although presence of AF increases the risk of stroke among all AF patients, women with AF are at an increased risk compared to men.⁶¹ An analysis of the ATRIA cohort study, which includes 13,559 AF patients treated within Kaiser Permanente of Northern California, found that after adjusting for confounders, untreated women had higher annual rates of thromboembolism than untreated men (adjusted rate ratio, 1.6; 95% CI, 1.3 to 1.9).⁶² Among men and women treated with warfarin, the study found that annual rates of thromboembolism were similar. Further, in a cohort study of AF patients over 65 in Quebec, Canada between 1998-2007, Tsadok and colleagues found that even among men and women treated with warfarin, the risk of stroke was higher among women than among men (adjusted hazard ratio, 1.14 [95% CI, 1.07-1.22]; $P < .001$).⁶³

History of Stroke/Transient Ischemic Attack (TIA)

Prior stroke or TIA is a well-documented risk factor for subsequent stroke among AF patients. In their systematic review of risk factors for stroke, Hughes et al. located seven studies identifying this risk factor.⁴⁸ Among these identified studies, risk ratios ranged from 2.1 ($p=0.04$) to 4.1 ($p=0.01$).^{57,64}

Hypertension

A systematic review of risk factors for stroke by Hughes et al. identified nine studies where either controlled or uncontrolled hypertension was found to be a significant

independent risk factor for stroke.⁴⁸ A study by Hart et al. found a significant association between history of hypertension and stroke (RR=3.4; p=0.003) among patients diagnosed with intermittent AF and sustained AF (RR= 1.8; p=0.008).⁶⁴ However, the authors did not find an association among patients with intermittent AF and uncontrolled hypertension (systolic BP >160).

Hyperthyroidism

There is currently clinical equipoise as to whether hyperthyroidism is a significant risk factor for stroke among AF patients. For example, in their review, Squizzato et al. found that three studies reported a higher frequency of stroke and systemic embolism among AF patients with hyperthyroidism. However, these studies were criticized for methodological flaws.⁶⁵

Intracranial hemorrhage

Nielsen et al. found that among a previously anticoagulated Danish cohort of AF patients, those experiencing first-time intracranial hemorrhage were at an increased risk for a composite outcome of ischemic stroke/systemic embolism/transient ischemic attack (RR 3.67 [95% CI, 3.12-4.31]) compared to those who did not experience intracranial hemorrhage.⁶⁶ The authors suggest this may be due to a decrease in anticoagulation post-intracranial hemorrhage.

Left atrial appendage morphology

Among a small sample of AF patients (n=50), Sakr et al. found that increased LAA orifice diameter (OR = 1.275 [1.102–1.748]; P = 0.028) and triangular LAA morphology (OR = 4.53 [1.629– 8.381]; P = 0.011) evaluated by transesophageal echocardiography (TEE) were independently associated with ischemic stroke among AF patients.⁶⁷

Left ventricular systolic dysfunction

The Atrial Fibrillation Investigators (AFI) Echo study found that abnormal left ventricular function is associated with stroke (RR 2.5 (1.5–4.4)). However other studies including the SPAF aspirin study, did not identify a significant association.^{68,69}

Low body weight

A recent study by Hamatani et al. among Japanese patients with AF found that over a median follow-up of 746 days, patients with a low body weight (defined as ≤ 50 kg) had a higher incidence of stroke/systemic embolism (HR 2.19; 95% CI: 1.57-3.04) after controlling for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, history of stroke, and OAC prescription at baseline.⁷⁰ Another study by Hamatani et al. also found an association between low body weight (defined by a BMI < 18.5 kg/m²) and a composite endpoint of death/stroke/systemic embolism (HR: 1.71, 95% CI: 1.25-2.32) among non-anticoagulated Japanese AF patients.⁷¹

Obstructive Sleep Apnea

In a retrospective analysis of patients referred to the Western Connecticut Health Network for polysomnography, Yaranov et al. found that obstructive sleep apnea (OSA) is strongly associated with frequency of stroke. After adjusting for age, male gender, and coronary artery disease, the authors found that the association between OSA and stroke remained statistically significant among AF patients (OR 3.65; 95% CI 1.252- 10.623).⁷²

Race

Kabra et al. analyzed Medicare claims data to examine the association between race and incidence of stroke among AF patients between 2010-2011. The authors found that even after adjusting for pre-existing co-morbidities, the hazard of stroke for blacks as

compared to whites remained statistically significant (HR = 1.46; 95% CI 1.38 to 1.55; p <0.001), as well as among Hispanics as compared to whites (HR = 1.11; 95% CI 1.03 to 1.18; p <0.001).⁷³

Red Blood Cell Distribution

Red cell distribution width has traditionally been used to differentiate among several causes of anemia, more recently; it has been identified as a novel predictor of cardiovascular morbidity and mortality. Among an Israeli AF population, Saliba et al. found an association between red cell distribution width >14.5% (HR 1.29 [95% CI, 1.17-1.42]) compared with those with red cell distribution width <14.5% and was similar in subjects with and without anemia. The HR for stroke was also significant when red cell distribution was analyzed by quartiles (HR 1.33 [95% CI, 1.15-1.53] highest vs. lowest).⁷⁴

Renal Impairment

The association between renal impairment and stroke remains unclear. For example, Guo et al. found that when comparing patients who were not receiving anticoagulants, male and female Chinese AF patients, renal dysfunction (HR 5.30; 95% CI 2.39–11.74, p<0.001) was a significant predictor of stroke, along with age and prior stroke.⁷⁵

However, in a study by Friberg et al. among Swedish AF patients, the authors found that when adjusted for other comorbidities, renal failure was not associated with stroke (HR 1.02; 95% confidence interval 0.95-1.10).⁷⁶

Smoking

In an analysis of the Atherosclerosis Risk in Communities (ARIC) study, Kwon et al. found a significant association between smoking and a composite endpoint of ischemic

stroke or CV death (HR 1.65; 95% CI 1.21–2.26) among a relatively young AF population (mean age: 63.4). Interestingly, the authors did not find a significant association (HR 1.05; 95% CI 0.69–1.61) in a similar analysis of the Cardiovascular Health Study (CHS), where the mean age was much older (mean age: 79.1).⁷⁷

Vascular disease

Olesen and colleagues examined whether vascular disease, including myocardial infarction and peripheral artery disease is independently associated with risk of stroke/thromboembolism among a Danish cohort not treated with warfarin or heparin. The authors found that vascular disease increased the risk of stroke/thromboembolism in their multivariate analysis (HR, 1.12; CI, 1.05-1.21). They also found that including vascular disease in the CHADS₂ score improved predictive ability of stroke.⁷⁸

Other Outcomes Associated with AF

AF is also independently associated with mortality. For example, in a sub-analysis of the Framingham Heart Study, among 296 men and 325 AF patients the OR for the association between AF and death was 1.5 (95% CI, 1.2 to 1.8) of among men (mean age=74) and 1.9 (95% CI, 1.5 to 2.2) among women (mean age=76) after controlling for age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack). Interestingly, the authors also found that while the risk of mortality did not significantly vary by age, AF did diminish the typically observed female survival advantage.⁷⁹

3. Preventing Stroke Among AF Patients: Medications, Procedures, and Decision-Making

AF treatment guidelines recommend prescribing oral anticoagulants (OACs), aspirin, or no medication based on an individual’s risk for developing stroke. There are two classes of antithrombotic agents: anticoagulants and antiplatelet medications.

In addition to antithrombotic agents for preventing stroke, AF patients may receive other medications or undergo procedures for rate or rhythm control (see Table 4 (3.1)).⁹ For example, sodium channel blockers, potassium channel blockers, catheter ablation, or cardioversion may be pursued to restore normal rhythm. In severe cases, surgical procedures may be pursued in combination with medications or other procedures. For rate control, beta-blockers, calcium channel blockers or digoxin may be prescribed.

Table 4. (3.1) Treatment options for AF⁹

Medication/Treatment Type	Use among AF patients
Medical devices	
Watchman	Prevent blood clot formation
Medications (examples)	
Anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban, warfarin)	Prevent blood clot formation
Antiplatelet (aspirin, clopidogrel)	Prevent blood clot formation
Beta blockers (atenolol, propranolol, metoprolol)	Heart <i>Rate</i> Control Medications
Calcium channel blockers (amlodipine, diltiazem hydrochloride, nifedipine, nicardipine)	Heart <i>Rate</i> Control Medications
Sodium channel blockers (flecainide, propafenone)	Heart <i>Rhythm</i> Control Medications
Potassium channel blockers (Sotalol, dofetilide, dronedarone, amiodarone)	Heart <i>Rhythm</i> Control Medications
Digoxin	Heart <i>Rate</i> Control Medications
Non-surgical procedures	
Electrical or chemical cardioversion	Heart <i>Rhythm</i> Control
Ablation (Catheter, cryo, radiofrequency)	Heart <i>Rhythm</i> Control
Surgical procedures	
Pacemakers/atrioventricular node ablation	Heart <i>Rhythm</i> Control
Open-heart maze procedure	Heart <i>Rhythm</i> Restoration

Adapted from the American Heart Association⁸⁰⁻⁸³

Anticoagulants

OACs are currently the primary method for preventing stroke among AF patients. These include vitamin k antagonists (VKA's), for example warfarin, and novel oral anticoagulants (NOACs), such as apixaban, dabigatran, edoxaban, and rivaroxaban.⁸⁴ Direct-acting oral anticoagulants (DOACs) is another term used to refer to NOACs.

Vitamin K antagonists (VKA's)

Warfarin is the most common VKA, other less commonly used VKA's include acenocoumarol, phenprocoumon, fluindione.⁸⁵ VKA's require close monitoring as they have a narrow therapeutic window, making the dose-response both within and across patients somewhat unpredictable. To achieve optimal dosing, patients receive regular international normalized ratio (INR) testing, which is a measure of the intensity of anticoagulation.⁸⁴ Despite documented efficacy of VKA's, patients are often outside of appropriate therapeutic range reducing effectiveness among real world populations. For example, Matchar et al. performed a randomized trial across six managed care organizations and estimated patients receiving chronic warfarin therapy were in target therapeutic range less than two-thirds of the time.⁸⁶ In a study examining incidence of low INR across 47 community-based clinics throughout the United States (years 2000 to 2002), Rose et al. found that women had an increased incidence of low INR as compared to men (incidence rate ratio 1.44; 95% CI 1.28-1.62).⁸⁷ Within their study population, just over half had a diagnosis for AF.

Novel oral anticoagulants (NOACs)

More recently, NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban have become available. This class of drugs is also referred to as direct oral anticoagulants (DOACs) in the literature. Dabigatran is an oral direct inhibitor of the enzyme thrombin

(which catalyzes numerous coagulation-related reactions), while rivaroxaban, apixaban, and edoxaban are oral direct inhibitors of enzyme Factor X (which is along the coagulation cascade).

NOACs have at least equivalent efficacy to VKA's, with apixaban considered superior and the others considered at non-inferior to warfarin.⁸⁸ Some consider NOACS advantageous over warfarin because dosing is more predictable and there are fewer drug-drug or drug-food interactions.^{84,89}

Stroke or Bleeding Risk

While VKAs and NOACs are effective in preventing stroke, they also carry an increased risk of bleeding.⁸⁰ A recent systematic review and meta-analysis of RCTs reporting major bleeding-related fatality among AF or venous thromboembolism (VTE) patients found that NOACs are associated with fewer fatality cases than VKAs. For example, the authors found that AF patients who survived major bleeding events and were treated with NOACs had lower mortality compared with patients treated with VKAs [OR 0.57; 95% CI 0.45 to 0.73].⁹⁰ The same study identified a 47% odds reduction in the risk of fatal bleeding [OR 0.53, 95% CI (0.42 to 0.68)] amongst AF patients receiving NOAC. The authors concluded that even in the absence of an antidote for NOACs their safety profile warrants their use. Through a systematic review, Lapner and colleagues found that risk of bleeding while on anticoagulants does not differ based on gender alone.⁹¹

Cost effectiveness

Shah et al. developed a Markov model to determine the cost effectiveness of various OACS (dabigatran (150 mg BID), rivaroxaban (20 mg QD), apixaban (5 mg BID), edoxaban (60 mg QD), and adjusted dose warfarin). Patient characteristics were based on a commercially insured population, outcomes were based on published RCTs, and costs

were based on rebated National Average Drug Acquisition drug cost estimates. The authors found that apixaban was the most cost-effective treatment (incremental cost-effectiveness ratio=\$25 816). A probabilistic sensitivity analysis found that apixaban had at least a 61% chance of being the most cost-effective strategy when the willingness to pay is \$100,000 per QALY. Among patients both under 65 years of age (ICER=(\$34,191) and ≥ 65 years (ICER=\$13,662), apixaban was determined to be the most cost effective strategy.⁹²

Adherence and Stroke or Bleeding Risk

Among patients taking warfarin, time in therapeutic range (TTR) is significantly associated with bleeding events and stroke. For example, a recent study among patients receiving VKA's utilizing a Finnish national registry found that among patients with a $TTR \leq 40\%$, the HR for experiencing a bleeding event was 1.6 (95%CI 1.5, 1.8) as compared to patients with a $TTR >80\%$ where the HR was 0.6 (95% CI 0.5, 0.7).⁹³ Similarly, patients with a $TTR \leq 40\%$ were at a significantly higher risk of experiencing a stroke [HR 1.8; 95% CI (1.7, 2.0)] as compared to those with a $TTR >80\%$ [HR 0.7; 95% CI (0.6, 0.8)]. In this study, TTR was calculated based on an individual's percentage of days with INR levels between 2.0, 3.0. Similarly, a recent study utilizing a commercial database in the United States found that risk of ischemic stroke or systemic embolism increases as the amount of time not taking any OAC (VKA or NOAC) increases. The study found that high-risk patients not taking an OAC for ≥ 6 months were at highest risk of developing the outcome [HR 3.66; (95% CI 2.68,5.01)] compared to patients at similar risk for developing stroke who had not taken an OAC for between 1 week and 1 month [HR 1.21 (95% CU 0.91–1.60)].⁹⁴

Antiplatelet Drugs

Aspirin

Although aspirin therapy is recommended in the current American College of Cardiology/American Heart Association (ACC/AHA) clinical guidelines for low-risk AF patients, a number of recent studies have concluded that aspirin is ineffective at preventing stroke among low risk patients. Lip et al. conducted a cohort study using Danish registry data and concluded that patients with even just one risk factor for stroke in addition to an AF diagnosis, the net clinical benefit of warfarin was higher versus aspirin.⁹⁵ A similar study evaluating apixaban versus aspirin among low risk patients had similar findings.⁹⁶ In a separate study, which utilized systematic review, Argulian et al. concluded, “current evidence clearly suggests that aspirin should no longer be used for stroke prevention in patients with atrial fibrillation.”⁹⁷ In addition, a recent analysis of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry, 10,126 AF patients from 176 US practices from June 2010 through August 2011, found that OAC with concomitant aspirin is associated with an increased risk of major bleeding (adjusted HR 1.53; 95% CI 1.20–1.96) and bleeding-related hospitalizations (adjusted HR 1.52; 95% CI 1.17–1.97).⁹⁸ Based on this evidence, the 2016 European Society for Cardiology’s AF treatment guidelines do not recommend aspirin for treating AF.⁹⁹

Comparative Efficacy/Effectiveness

A recent systematic review and network meta-analysis by Cameron and colleagues compared antithrombotic agents, including apixaban, dabigatran, edoxaban, rivaroxaban and VKAs, for prevention of stroke and major bleeding among RCT populations. The study found that dabigatran 150 mg twice daily [OR 0.66; (95% CI 0.53, 0.82)] and apixaban 5 mg twice daily [OR 0.78; (95% CI 0.65, 0.94)] are favored as compared to

adjusted dose VKA for stroke prevention. In terms of bleeding risk, NOACs were favored as compared to VKA for apixaban 5 mg twice daily [OR 0.69; (95% CI 0.6, 0.8)], edoxaban 60 mg daily [OR 0.79; 995% CI 0.69, 0.9)], dabigatran 110 mg twice daily [OR 0.8; (95% CI 0.69, 0.93)], and edoxaban 30 mg daily [0.46; (95% CI 0.4, 0.54)].¹⁰⁰ The same study found that aspirin was never favored over adjusted dose VKA among this population.

Risk Stratification Schemes (RSSs) in Atrial Fibrillation

Since OACs reduce risk of stroke, but may also increase risk of bleeding, cardiology professional societies recommend performing individualized benefit-risk assessments to determine which patients should receive OACs.^{9,99}

Predicting stroke risk

To aide clinicians in treatment decision-making, Gage and colleagues developed the CHADS₂ risk stratification scheme (RSS). They combined risk factors from two existing classification schemes, the Atrial Fibrillation Investigators (AFI) and Stroke Prevention and Atrial Fibrillation (SPAF), to create the CHADS₂ stroke prediction model.¹⁰¹

CHADS₂ is an acronym for the risk factors included: congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus (see Table 5 (3.2)). Patients are assigned “points” for the presence of comorbidities. The CHADS₂ prediction model has been widely recommended in clinical guidelines for screening patients for anticoagulants.^{8,101-105} Patients with a CHADS₂ “score” greater than three are considered to be at high risk for stroke. For example, an 80-year old patient with congestive heart failure and hypertension would have a CHADS₂ score of three indicating the patient should receive an anticoagulant. Despite emerging evidence that aspirin may be ineffective at preventing

stroke among “low risk” AF patients, clinical guidelines still recommend treating “high-risk” patients with OACs and lower-risk patients with aspirin.¹⁰⁴

Table 5. (3.2) CHADS₂ calculation

	Condition	Number of Points Assigned*
C	Congestive Heart Failure	1
H	Hypertension (above 140/90 mmHg); or Treated hypertension	1
A	Age \geq 75	1
D	Diabetes mellitus	1
S₂	Prior stroke, TIA, or Thromboembolism	2

*Score 0=low risk (no treatment or aspirin), Score 1=moderate risk (aspirin, anticoagulant), Score 2 or greater (anticoagulant)

Although the CHADS₂ appears predictive of stroke and was previously recommended in clinical guidelines, there has been criticism of the CHADS₂ for: (1) leaving out important risk factors for stroke and (2) too many patients being categorized as having intermediate risk of stroke resulting in an ambiguous recommendation of treatment with aspirin, warfarin, or other oral anticoagulants.¹⁰⁵¹³

Lip and colleagues expanded the CHADS₂ model by creating the CHA₂DS₂-VASc scoring system, which also adds “points” for female gender, vascular disease, and patient age (see Table 6 (3.3)).⁶ Giralt-Steinhauser et al. demonstrated that the CHA₂DS₂-VASc schema increases the percentage of patients who are recommended to receive anticoagulation compared with the CHADS₂.¹⁰⁶

Table 6. (3.3) CHA₂DS₂-VASc calculation

	Condition	Number of Points Assigned*
C	Congestive Heart Failure (or left ventricular systolic dysfunction)	1
H	Hypertension (above 140/90 mmHg); Treated hypertension	1
A₂	Age \geq 75(2 points); Age \geq 65 and <75 (1 point)	1 or 2
D	Diabetes mellitus	1
S₂	Prior stroke, TIA, or Thromboembolism	2

Table 6. (3.3) Continued

V	Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65-74	1
Sc	Sex category (female)	1

*Score 0=low risk (no therapy or aspirin), Score 1=moderate risk (consider oral anticoagulant), Score 2 or greater=high risk (oral anticoagulant)

More recently, researchers developed the ATRIA risk scheme for predicting stroke and other types of thromboembolism among AF patients (see Table 7. (3.4)). Although not yet recommended in clinical guidelines, the ATRIA scheme has begun gaining traction in the medical literature following several cohort studies demonstrating its predictive superiority to the CHADS₂ and CHA₂DS₂-VASc.¹⁰⁷ The ATRIA scheme developed by Singer and colleagues was developed in a large cohort of 13,559 patients diagnosed with AF and insured by Kaiser Permanente of Northern California between July 1, 1996, and December 31, 1997 and then followed through September 2003. Patients were followed until they experienced one of the outcomes of interest: ischemic stroke (defined as sudden onset of a neurologic deficit lasting > 24 hours and not attributable to other identifiable cause) or other thromboembolic events (defined as sudden occlusion of an artery to a visceral organ or extremity documented by imaging, surgery, or pathology and not attributable to concomitant atherosclerosis or other etiology) or censoring occurred.

Table 7. (3.4) Calculation of ATRIA

Risk factor	Points without prior stroke	Points with prior stroke
Age ≥85	6	9
Age 75–84	5	7
Age 65–74	3	7
Age <65	0	8
Female	1	1
Diabetes mellitus	1	1
Chronic heart failure	1	1
Hypertension	1	1
Proteinuria	1	1

Table 7. (3.4) continued

eGFR , 45 or ESRD 1 1	1	1
------------------------------	---	---

Predicting bleeding risk

In addition to risk stratification tools for predicting stroke, risk stratification tools for predicting bleeding have also been created. Since risk factors for bleeding often overlap with risk factors for stroke, application of these tools may be challenging.^{53,108} The HAS-BLED score was developed to predict 1-year risk of major bleeding among patients with AF (see Table 8 (3.5)). More recently, researchers have developed a biomarker-based bleeding risk score. The score, known as the ABC-bleeding score incorporates three biomarkers (haemoglobin, cTn-hs, and GDF-15 or cystatin C/CKD-EPI) in addition to age and history of bleeding.⁵³ In their external validation testing, the ABC score [c-index 0.71 (95% CI 0.68–0.73)] was found to be more predictive of major bleeding than the HAS-BLED [c-index 0.62 (95% CI 0.59–0.64)] or ORBIT [c-index 0.68 (95% CI 0.65–0.70)] scores. Despite the ABC score having high predictive ability, its’ calculation relies on an online calculator potentially hindering uptake into practice.¹⁰⁹

Table 8. (3.5) Bleeding risk prediction scores^{53,110,111}

HAS-BLED*		ORBIT [†]		ABC-Bleeding Risk	
Hypertension	1	Age ≥75 years	1	Age (ages 44 and up)	Complex – website-based calculation ¹¹²
Abnormal renal function; Abnormal liver function	1 or 2	Reduced hemoglobin/ hematocrit/ history of anemia	2	Biomarkers (GDF-15, cTnT-hs, and haemoglobin)	
Stroke history	1	Bleeding history	2	Previous bleeding	
Prior major bleeding or predisposition to bleeding	1	insufficient kidney function (estimated glomerular filtration rate <60 mL/ min/ 1.73 m ²)	1		
Labile INR Unstable/high INRs, time in therapeutic range < 60%	1	Treatment with antiplatelet	1		
Age > 65 years	1				
Medication usage predisposing to bleeding	1				

Antiplatelet agents, NSAIDs			
Alcohol or drug usage history ≥ 8 drinks/week	1		

*HAS-BLED score (≥3) indicates that patients should undergo regular clinical review¹¹³; †ORBIT score of 0 to 2 was “low risk,” a score of 3 was “intermediate risk,” and a score ≥4 was “high risk.”¹¹⁴

Treatment Guidelines

The American Heart Association/American Stroke Association recommends using the CHA₂DS₂-VASc in their 2014 guideline for the prevention of stroke (see Table 9 (3.6)).

¹¹⁵ This represents a change from the 2006 guidelines, where the CHADS₂ along with specific risk factors were described.

Table 9. (3.6) Clinical practice guideline language on preventing thromboembolism

Guideline Developer	Year	Language
AHA/ACC/HRS	2014	“In patients with nonvalvular AF, the CHA ₂ DS ₂ -VASc* score is recommended for assessment of stroke risk” ^{9,116}
AHA/ACC/HRS	2014	“For patients with CKD, dose modifications of the new agents are available; however, for those with severe or end-stage CKD, warfarin remains the anticoagulant of choice, as there are no or very limited data for these patients. Among patients on hemodialysis, warfarin has been used with acceptable risks of hemorrhage.” ⁹
AHA/ACC/HRS	2014	<ul style="list-style-type: none"> • “For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA₂DS₂-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (<i>Level of Evidence: A</i>), dabigatran (<i>Level of Evidence: B</i>), rivaroxaban (<i>Level of Evidence: B</i>), or apixaban. (<i>Level of Evidence: B</i>)”⁹ • “For patients with nonvalvular AF and a CHA₂DS₂-VASc score of 0, it is reasonable to omit antithrombotic therapy 183 and 184. (<i>Level of Evidence: B</i>).” • “For patients with nonvalvular AF and a CHA₂DS₂-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. (<i>Level of Evidence: C</i>)”

Table 9. (3.6) continued

AHA/ACC/HRS	2014	“Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable. (<i>Level of Evidence: A</i>)” ⁹	
ACC/AHA/ESC	2006 ⁸	Risk Category	Recommended Therapy for Patients with AF
		No risk factors	Aspirin, 81 to 325 mg daily

	One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)	
	Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)	
	Less validated or weaker risk factors	Moderate-risk factors	High-risk factors
	Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
	Age 65 to 74 y	Hypertension	Mitral stenosis
	Coronary artery disease	Heart failure	Prosthetic heart valve*
	Thyrotoxicosis	LV ejection fraction 35% or less	
		Diabetes mellitus	

Abbreviations: ACC= American College of Cardiology; AHA= American Heart Association; HRS= Heart Rhythm Society; INR= international normalized ratio; LV=lower ventricular

Current ESC guidelines recommend, “A high bleeding-risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected” (see Table 10 (3.7))⁹⁹

Table 10. (3.7) ESC's list of modifiable and non-modifiable risk factors for bleeding

Modifiable bleeding risk factors	Potentially modifiable bleeding risk factors	Non-modifiable bleeding risk factors
<ul style="list-style-type: none"> • Hypertension • Labile INR or time in therapeutic range <60% • Concomitant use of drugs predisposing one to bleeding (e.g., antiplatelet or non-steroidal anti-inflammatory drugs) • Excess alcohol consumption (≥8 drinks/week) 	<ul style="list-style-type: none"> • Anemia • Impaired renal function • Impaired liver function • Reduced platelet count or function 	<ul style="list-style-type: none"> • Age >65; Age ≥75 years • History of major bleeding • Prior stroke • Dialysis-dependent kidney disease or renal transplant • Cirrhotic liver disease • Malignancy

Adapted from Kirchhof et al.⁹⁹

Underuse of Anticoagulants

While medications effective in preventing stroke are widely available, under-prescribing remains a widespread problem. In a retrospective study examining warfarin underuse and nonadherence among a privately insured population between 2003-2007, Casciano et al.

found that 47% of patients who were eligible to receive warfarin and had no obvious contraindications to treatment did *not* receive medication. Only 40% of patients receiving warfarin had a high proportion of days covered (PDC) defined as >0.8 .¹¹⁷ Similarly, Zimetbaum et al. found that CHADS₂ score had little impact on receipt of warfarin therapy. For example, among patients at “high risk” for stroke according to their CHADS₂ score (3-6), 42.1% of patients received warfarin therapy. Among patients with lower CHADS₂ scores, including those with moderate (CHADS₂=1-2) and low risk (CHADS₂=0), the percentage of patients receiving warfarin therapy was 43.5% and 40.1%, respectively.¹¹⁸ Among persons not receiving warfarin, the ischemic stroke rate per 100 person years was 4.41, whereas among those with a high PDC, the rate fell to 1.62/100 person years.¹¹⁷

Ogilvie et al. conducted a systematic review comparing current treatment practices for stroke prevention with clinical practice guidelines. They identified nine studies where high risk-for-stroke was defined as individuals having a CHADS₂ score ≥ 2 . Among those studies, the range of underutilization was (39%-92%). Among the 29 studies they identified, 25 studies reported underutilization.¹¹⁹ Although this study received criticism for ignoring the nuances of identifying contraindications, many others have identified underuse of anticoagulants among the AF population.¹²⁰ For example, a medical chart review among patients with AF residing in northern Sweden found that 25% of sampled patients (n=296) not treated with an OAC did *not* have a reason for withholding treatment documented in their medical record. Acceptable reasons for withholding treatment included: no indication according to guidelines (CHA₂DS₂-VASc), “declined or adverse effects other than bleeding on warfarin,” terminal disease with a life expectancy of less than one year, predisposition for bleeding, inability to comply with INR monitoring,

persistent uncontrolled hypertension, liver or renal failure, or alcohol abuse, dementia or other cognitive dysfunction, or patients experiencing an isolated episode of AF. Among those patients without a documented reason for not receiving an OAC, 48% were under 75.¹²¹ Similarly, in a cross sectional study by Dreischulte and colleagues in the UK, patients with paroxysmal AF (OR=0.26; 95% CI=0.23 – 0.29), dementia (OR=0.25; 95% CI=0.20 – 0.30), or prior peptic ulcers (OR=0.79; 95% CI=0.72 – 0.88) were significantly less likely to receive OACs.¹²²

Possible Barriers to Appropriate Anticoagulation

Treatment Attributes

Although both VKA's and NOACs are demonstrated to be effective in preventing stroke among AF patients, certain characteristics of these medications may make it cumbersome for patients to maintain adherence. For example, warfarin requires regular INR monitoring and dose adjustment, which may be difficult to maintain for working individuals or individuals residing in rural areas, where warfarin clinics may be far away. NOACs do not required INR monitoring, but frequent visits to clinics may still be necessary for elderly patients or those with renal impairment, who will still require kidney function tests.¹²³ Dietary restrictions, including avoiding vitamin K found in leafy greens, is a barrier among warfarin patients, but this restriction is absent for NOAC users. Drug-drug or drug-alcohol interactions and restrictions on physical activities also serve as a barrier to patients. The absence of an antidote for apixaban and rivaroxaban may also impact decision-making towards warfarin or dabigatran.¹²⁴

In a series of in-depth interviews examining non-adherence to warfarin in the Midwest, health care professionals, including family physicians and cardiologists, stated that non-clinical characteristics beyond the CHADS₂ play an important role in treatment decision-

making. For example, affordability of the medication, family structure, risk of falls, and distance from health care clinics are important.¹²⁴ Clinicians also state that a patient's belief or knowledge may impact adherence to anticoagulants. Fortunately, clinicians also find that once patients have successfully initiated treatment, non-adherence becomes less problematic. However, if a patient believes that the medication is "difficult to manage," travel time is a "hassle," or that the patient is already taking numerous medications, treatment may be stopped. Since AF is typically asymptomatic, patients may also stop taking their medications because they no longer think there is a problem. Breakdowns in communication amongst different clinicians and healthcare settings, along with clinician reluctance to prescribe warfarin may also serve as barriers to optimum treatment.¹²⁴

Risk stratification schemes are inadequate or do not reflect patient experiences

Demographics and Risk Factors

In addition to previously mentioned barriers to adherence, risk stratification schemes may also prevent younger or female patients from being prescribed anticoagulants. The CHADS₂ and CHA₂DS₂-VASc were largely developed based on expert opinion and tested among elderly patient populations (see Table 11 (3.8)). However, comorbidities important for predicting stroke among elderly populations may differ significantly from younger populations, placing younger patients into "low risk" categories. For example, in a study using the Nationwide Inpatient Sample, Naderi et al found that co-morbidities differed dramatically between a younger (mean age 54 years) versus an older (mean age 78 years) subset of an AF population.¹²⁵ Specifically, they found that among the younger population, hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, and alcohol abuse were the most common co-morbidities. However, among the

older population, chronic kidney disease and obesity were among the most common comorbidities. While these comorbidities, or clusters of comorbidities may impact risk of stroke, they are not reflected in current stratification schemes.¹²⁵

Chao and colleagues found that among Taiwanese patients ages 50-64 years, the annual stroke risk was 1.78%, whereas among patients <50 years the annual risk was 0.53%. The authors suggested that patient's ages 50-64 may exceed the threshold for OAC use for stroke prevention and that the CHA₂DS₂-VASc's age cut-off of 65 may be inappropriate.

126

There are also questions about whether each of the risk factors contributing one point toward the CHA₂DS₂ –VASc score confer equal risk of stroke. For example, among a Chinese AF population, Huang et al. found that hypertension confers the highest risk of stroke among “low risk” AF patients (CHA₂DS₂ –VASc=1) and that among their study population, heart failure, diabetes mellitus, and vascular disease were not associated with stroke.¹²⁷

Additionally, not only may women experience AF differently than men, recent studies have demonstrated an increased risk of stroke among women with AF as compared to men. A recent analysis of the ORBIT-AF Registry found that female patients experience more symptoms than men. Women were significantly more likely to experience palpitations (p<0.001), syncope (p=0.11), and dyspnea during exertion (p=0.01) and while resting (P=0.001), exercise-intolerance (p=0.06), light-headedness (p<0.001), fatigue (p<0.001), and chest discomfort (p<0.001).¹²⁸ The same study found that women had a higher risk for stroke or non-CNS embolism as compared to men (adjusted HR=1.39; 95% CI, 1.05-1.84; P = .02). Further, in an observational study of general practices in the United Kingdom, Shantsila et al. found that among those not receiving an

OAC when indicated, the risk of stroke among women was significantly greater than among men (unadjusted $p=0.01$; adjusted $p=0.04$).¹²⁹

Finally, cutoff points may categorize patients erroneously into “low” -risk categories. For example, in an analysis of linked administrative databases in Alberta, Canada, the authors found that warfarin use is associated with a substantially lower rate cerebrovascular events or death among AF patients with a CHADS₂ score of 1 (OR 0.52, 95% CI 0.41 to 0.67).¹³⁰ However, according to treatment guidelines, these patients would not be recommended to receive treatment.

Possible Methodological Shortcomings of Derivation and Validation Studies

In addition, derivation and validation cohorts may suffer from selection bias as these studies included only untreated AF patients, potentially resulting in risk predictions suffering from confounding due to treatment (see Table 11 (3.8)).¹³¹ For example, if an RSS is derived from fitting a model to an untreated population, it may exhibit high predictive ability among other untreated populations, however, these populations do not reflect the entire AF population. In fact, these schemes may exhibit low predictive ability among those individuals at highest risk of experiencing the outcome of interest, since they were already receiving treatment.

Table 11. (3.8) Characteristics of the CHADS₂, CHA₂DS₂-VASc, and ATRIA schemes

	CHADS₂^{13,101,132}	CHA₂DS₂-VASc	ATRIA
Population (n)	Validation=1,733	Validation=1,577	Derivation cohort= 7,284 Validation cohort= 3,643
Age	Mean=81 years	Mean=66 years	<65=23.8%; 65-75=25.8%; 75-84=34.1%; ≥85=16.3% (entire ATRIA cohort, not reported separately)
Gender	Women=58%	Women=40.8%	Not reported as a percentage of population, only reported as percentage of person-years for entire ATRIA cohort (not specific to either derivation or validation cohorts) = 42.8%

Variable selection	Included independent risk factors from two prior risk schemes (AFI and SPAF)	Stepwise based on existing schema (AFI, SPAF, CHADS ₂ , ACC/AHA/ESC, 8 th ACCP guidelines, Birmingham	Preselected 10 candidate predictor variables (older age, female gender, prior ischemic stroke, diabetes, heart failure, hypertension, coronary artery disease (CAD), peripheral arterial disease (PAD), urine dipstick proteinuria, and low eGFR or end-stage renal disease (ESRD) requiring dialysis), total white blood cell count as an inflammatory marker and an episode of herpes zoster)
Outcome of interest	Hospitalization for ischemic stroke (ICD-9-CM as primary: 434, 435, 436)	Ischemic stroke was defined as a focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting 24 h and caused by ischemia	Ischemic stroke and other thromboembolism
Follow up time	Mean=1.2 years; median=1 year	1 year	Derivation= 32 609 person-years Validation= 26 263 person-years
Statistical analysis	(Validation) Exponential survival model • Censored deaths not accompanied by a hospitalization for stroke	(Validation) Multivariable logistic regression (age, gender, diabetes, coronary artery disease, heart failure, hypertension, prior stroke/TIA, prior other thromboembolism, and peripheral vascular disease)	(Derivation) Time-updated Cox proportional hazards model with the backward elimination method to determine predictors significant at the 0.05 level after variable selection

Table 11. (3.8) continued

Method of assessing good of fit	<i>c</i> statistic [0.82 (95% CI, 0.80-0.84)]	<i>c</i> statistic (0.606)	<i>c</i> statistic 0.74 (95% CI, 0.72-0.76)
Treatment status - derivation cohort	No warfarin; AFI = 38% prescribed aspirin; SPAF=100% prescribed warfarin	Not reported	No warfarin
Treatment status - validation cohort	No warfarin; 31% prescribed aspirin	No anticoagulation at baseline; antiplatelet medications taken by 74%	No warfarin

Finally, while the ATRIA scheme has been praised for improving predictive accuracy and the authors provided citations documenting the validity of their selected risk factors, they did not provide a rationale for why the specific risk factors were selected, while

other potential risk factors were left out. In developing the ATRIA scheme, Singer et al. “preselected 10 candidate predictor variables previously reported as stroke risk factors in AF: older age, female gender, prior ischemic stroke, diabetes, heart failure, hypertension, coronary artery disease (CAD), peripheral arterial disease (PAD), urine dipstick proteinuria, and low eGFR or end-stage renal disease (ESRD) requiring dialysis.”¹³² They also “considered total white blood cell count as an inflammatory marker and an episode of herpes zoster.”¹³² The authors found each of these risk factors, except herpes zoster to be significantly related to risk of stroke.

4. Conceptual Models

Developing a Patient-centered Conceptual Model of Atrial Fibrillation with Stakeholder Input

Approach

To support the development of a conceptual model for this research, preliminary models were developed based on the Anderson model of healthcare utilization. These were refined under Aim 1 by presenting the preliminary models to the patient and providers interviewed. Their input helped to shape the refinement of the preliminary models for use in this research.

Preliminary conceptual models

Two preliminary versions of the Andersen model of health care utilization were adapted to describe the AF patient experience: a standard, academic version, “Model 1” (see Figure 9 (4.1)) and “Model 2” is a patient-friendly version (see Figure 10 (4.2)). The decision to create a modified, patient-friendly version was based on the belief that patients are experts on their condition and research can have a greater impact if it addresses their needs and incorporates their experiences.¹³³ However, for patients to provide high-quality feedback, “research language” may need to be translated into lay language. For example, an important distinction between the models is the use of the abbreviation for describing AF. In academic circles, the acronym “AF” is typically used; however, based on feedback from our patient-advocate partner on this project, the patient-friendly version utilizes the term “afib” instead.

Model 1 (Figure 9 (4.1)) depicts an Andersen model for researcher and medical professional audiences. Black text indicates variables that can be identified through the Optum CDM, while grey text indicates unmeasured variables not found in the database. Column 1, “Environment,” depicts the healthcare system and external environment, it is

translated into “Things I can’t change” for Model 2. Model 1 separates “Patient Characteristics” into “predisposing characteristics,” “enabling resources,” and “perceived need” leaving “Health Behavior” as a separate column comprising “Personal health practices” and “use of health services.” For Model 2, these columns were simplified and combined into a single column “Things I may or may not be able to change.” Instead of describing “predisposing characteristics,” Model 2 describes, “what is it about me, or other afib patients” that could impact disease or outcomes; “enabling resources” is swapped for “helpful resources,” and “perceived need” is changed to “what impacts whether I believe I need to be treated.” “Personal health practices” is the same for each model, while “use of health services” is modified to “the health care services that I use.” The final column is entitled, “Outcomes,” in both columns, but “perceived health status” is modified to “my views about my health;” “evaluated health status” is modified to “things I’ve experienced” and “consumer satisfaction” is changed to “satisfaction with my care.” In some cases, differences between these models are limited to language; however, in other cases the content is slightly different. For example, under “personal health practices” an additional bullet “switching doctors if I have a bad experience” is included.

Conceptual models reflecting stakeholder experiences

In Aim 1, the qualitative portion of this research, interviewees provided suggestions for additions and modifications, which are reflected in Figure 11 (4.3). A summary of all stakeholder feedback is available in Appendixes I-VI. This study found that stakeholder engagement provides a different perspective than the peer-reviewed literature. For example, patients identified several modifiers that are not discussed in the peer-reviewed literature. Two patients independently identified mindfulness, meditation, and yoga for

their AF. Interestingly, although both patients credited this approach in improving their management of AF, the only mentions of any of these in relation to AF located on PubMed was a general article on yoga and cardiovascular disease, along with a 2013 poster presentation at the Symposium on Yoga Research.¹³⁴

There was overlap between patient and HCP input on the draft conceptual models; however, there were certain discrepancies in points of view and interpretations. For example, although all interviewed patients felt it is very important for them to understand their diagnosis and associated risks, HCP's disagreed amongst themselves on this point. Some felt that a patient understanding their diagnosis is key to adherence and disease management, while others felt that understanding their diagnosis is secondary and perhaps beyond the needs of some patients to achieve positive health outcomes. *"I mean, as long as they're compliant and they know when to ask questions... I think that's probably good enough."*

Several HCPs had difficulty understanding what was meant by some of the language included in the standard Andersen model, in particular what was intended by the "Environment" column and differentiating between "predisposing characteristics" and "enabling resources." In contrast, patients seemed to understand what was meant by each of the headings in the "patient-friendly" version. In the future, researchers may wish to utilize the modified "patient-friendly" or "plain language" Andersen model when engaging all stakeholders.

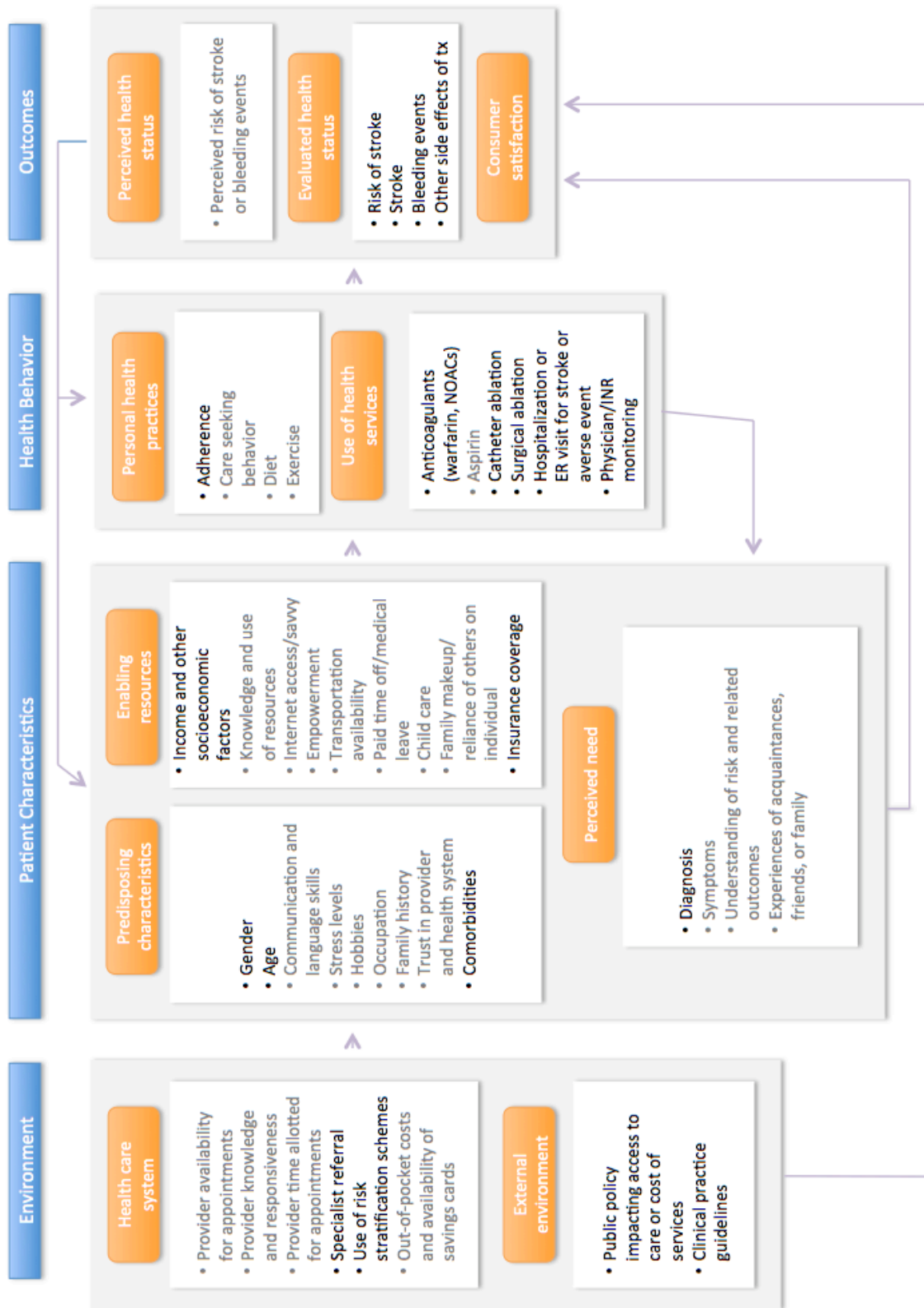


Figure 9. (4.1) Preliminary academic version of the Andersen model of the AF patient experience

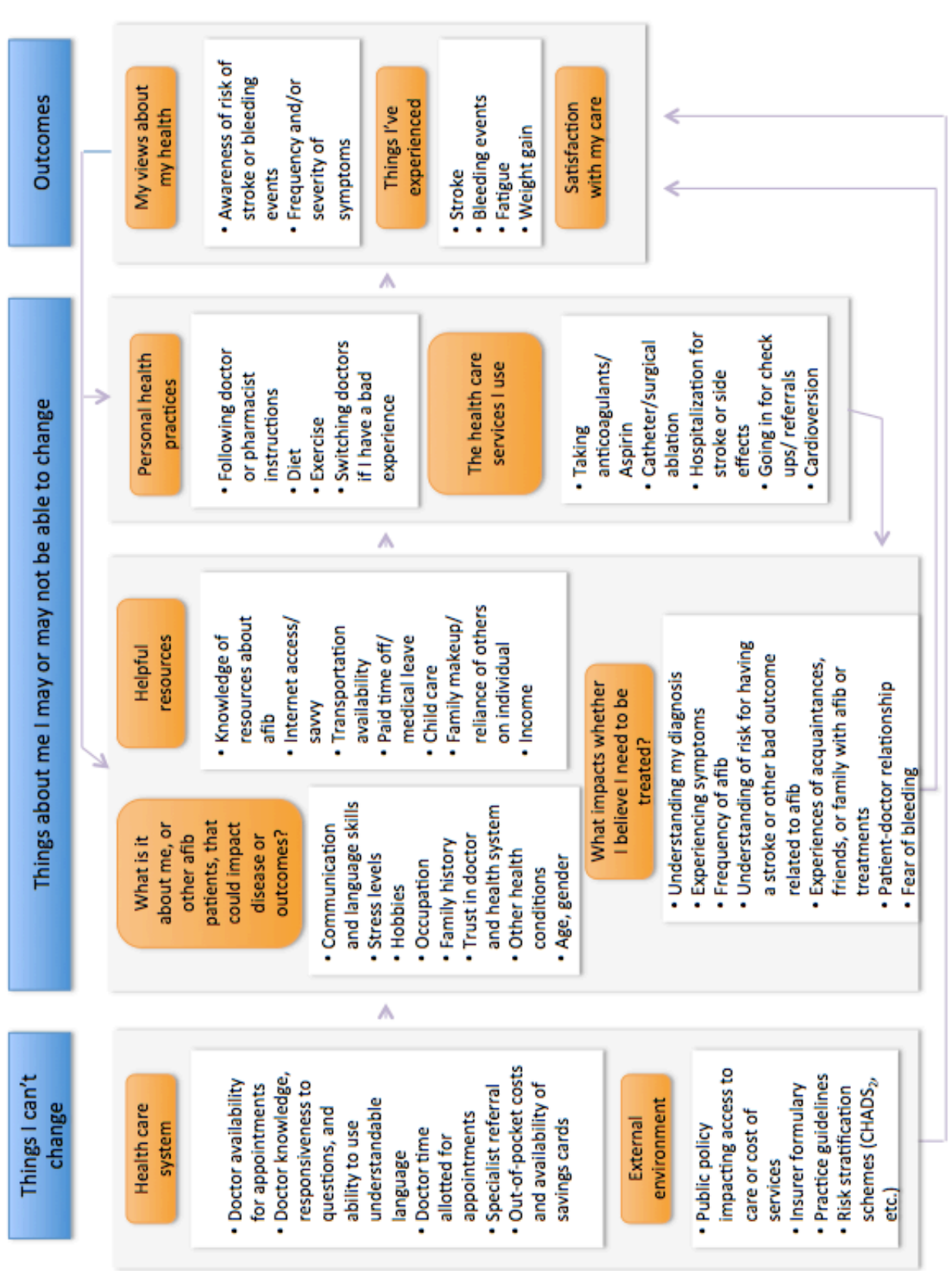


Figure 10. (4.2) Preliminary patient-friendly version of the Andersen model of the AF patient experience

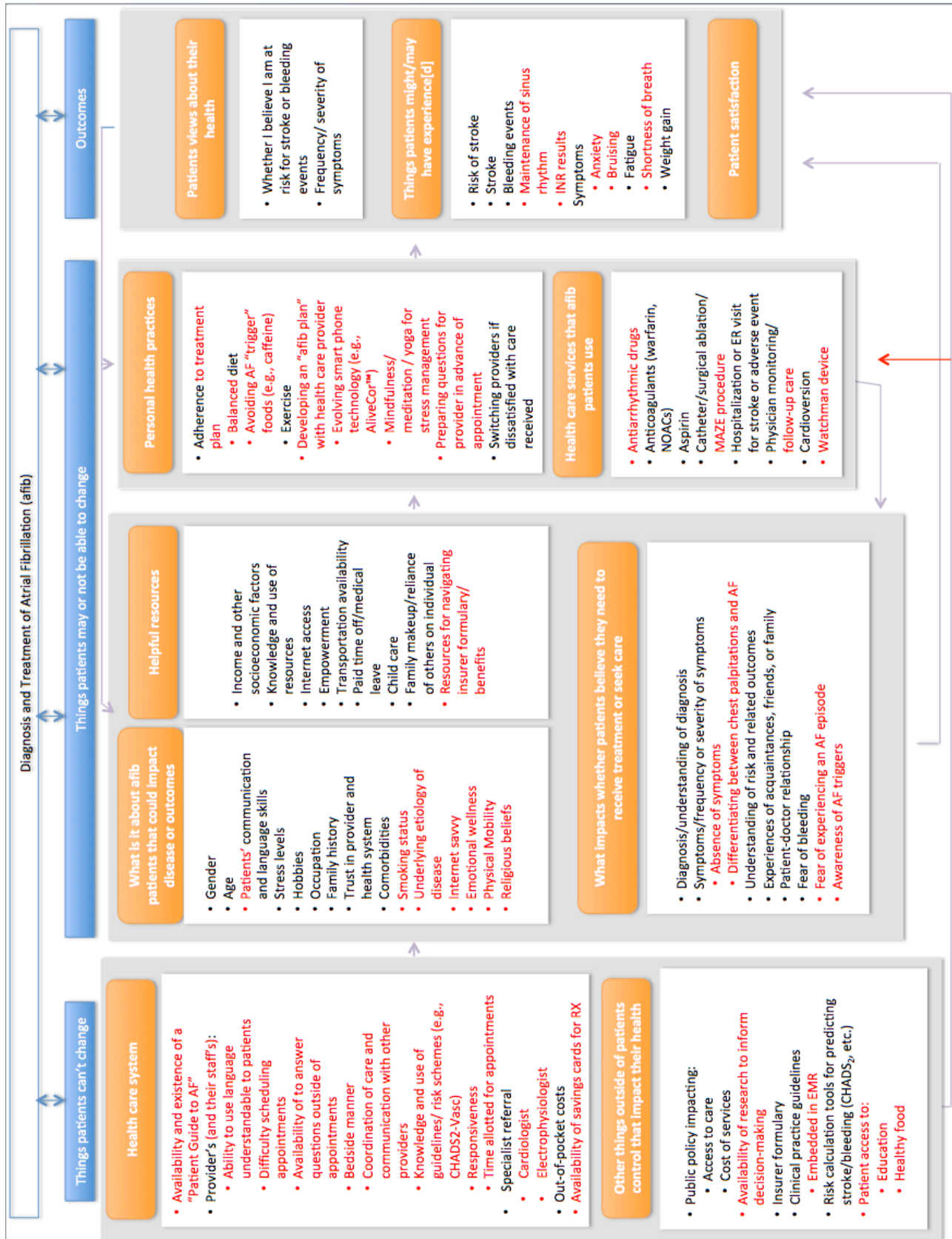


Figure 11. (4.3) Final patient-centered conceptual model of the AF patient experience

5. Aim 1: Patient and Health Care Provider Perspectives on Atrial Fibrillation Diagnosis and Anticoagulant Initiation

Abstract

Background: It is well known that anticoagulants reduce stroke risk in patients with atrial fibrillation (AF). Despite this, underutilization of anticoagulants among AF patients is widespread. Understanding the patient journey can help identify barriers to OAC initiation.

Objective: Conduct a pilot study to understand the patient journey and health care provider experiences from AF diagnosis forward and with anticoagulant-initiation decision-making.

Methods: Patients and health care providers were invited to participate in in-depth, telephone interviews. Perceptions of stroke risk, familiarity with and experience using RSSs, shared decision-making, and conversations about risk-stratification schemes were discussed. Interviews were recorded and transcribed. We used interpretative phenomenological analysis to identify thematic concepts.

Results: Fifteen interviews were conducted with 5 patients (2 male; 3 female) and 10 HCPs (2 cardiac nurses, 2 cardiologists, 2 EPs, 2 family doctors, and 2 pharmacists). Emerging themes included: 1) AF diagnosis challenges due to symptom variation and transience; 2) stroke-risk schemes are used more often than bleeding-risk schemes; 3) specialists have a heightened perception of stroke risk compared to generalists; 4) comorbidities and other patient characteristics absent from the CHADS₂ or CHA₂DS₂-

VASc also factor into risk consideration; 5) patients described need for more information upon initial AF diagnosis; 6) patients are interested in learning more about AF triggers.

Conclusion: Patient and HCP interviews improve awareness of challenges encountered and barriers to timely diagnosis, provide insights into factors influencing anticoagulant treatment initiation, and provide rationale for future research.

Keywords:

- [Patient-Centered Care*](#)
- [Qualitative Research](#)
- [Atrial Fibrillation*/psychology](#)
- [Atrial Fibrillation/drug therapy](#)
- [Anticoagulants/therapeutic use](#)

Background

Atrial fibrillation (AF) is the most common heart rhythm disorder and increases an individual's risk of experiencing ischemic stroke four to six-fold as compared to the general population.^{45, 23} In the United States, it is expected that the prevalence of AF will double from an estimated 1.2 million cases in 2010 to 2.6 million cases in 2030.²⁷

Individuals with hypertension, coronary heart disease, heart failure, rheumatic heart disease, structural heart defects, pericarditis, congenital heart defects, sick sinus syndrome, hyperthyroidism, obesity, diabetes, and lung disease are at an increased risk of developing AF.²⁸ Prior research suggests that health care professional-patient interactions occurring at the time of diagnosis have long-term effects on patient perceptions of their AF, psychological well being, and disease-management practices over the course of the disease.^{34,35,135} Patients report that fear and anxiety associated with receiving a diagnosis of AF can be reduced if providers clearly explain AF, provide easily understandable written and verbal information and encourage patients to be involved in their care.

Anticoagulants significantly reduce risk of stroke in AF patients and initiating prompt treatment may help alleviate fear and uncertainty among newly diagnosed AF patients.^{9,36} Despite this, underutilization of anticoagulants among AF patients is widespread.³⁶ In a retrospective study examining warfarin underuse and non-adherence between 2003 and 2007 in a privately insured population, Casciano et al. found that 47% of patients who were eligible to receive warfarin and had no obvious contraindications to treatment did *not* receive medication.¹¹⁷ The same study found that among patients *not* receiving warfarin, the ischemic stroke rate per 100-person years was 4.41; whereas among those with a high warfarin adherence, the rate fell to 1.62/100 person years.¹¹⁷

Understanding patient and health care provider (HCP) experiences at the time of AF diagnosis and perspectives on anticoagulant treatment initiation can inform care and interventions to reduce underutilization. Identifying patient and HCP needs and barriers can establish priorities for patient-centered outcomes research (PCOR). For example, breakdowns in communication between different clinicians and healthcare settings, along with clinician reluctance to prescribe warfarin, have been cited as barriers for patients with AF to receive optimum treatment.¹²⁴ Using qualitative research methods with a diverse group of stakeholders, including patients, the objective of this pilot study was to understand the patient and provider experiences with AF diagnosis and anticoagulant initiation decision-making.

Methods

A target enrollment of 5 patients and 10 HCPs [two of each of the following: cardiologists, electrophysiologists (EPs), general practitioners, pharmacists, and cardiac nurses] was sought for participation in in-depth, telephone interviews between December 2016 and April 2017. Patients, recruited through the Atrial Fibrillation Support Forum on Facebook, were eligible to participate if they stated they had been diagnosed with AF, had at least three AF-related health care visits since their initial diagnosis, were 18 years of age or older, could provide informed consent, and spoke English. Participation was solicited by a Forum moderator by email. HCPs were eligible to participate if they were involved in the care of AF patients, able to provide informed consent, and spoke English. HCPs were identified through recommendations from University of Maryland, Baltimore (UMB) faculty or listed on the University of Maryland Medical System's website.

Potential HCP participants were contacted by email in alphabetical order by last name to identify whether they were interested and eligible to participate in this study.

A general discussion guide was prepared and adapted to the role of each of the participant groups. Interviews built on existing qualitative research and included open-ended questions related to initial diagnosis with/of AF, follow-up care and patient trajectories post-diagnosis, and anticoagulant treatment decision-making.^{34,36,135} Perceptions of stroke risk, familiarity with and experience using RSSs, and conversations about risk-stratification schemes were included. All participants were offered a gift card in appreciation for their time.

Audio recordings of interviews were transcribed and analyzed using interpretative phenomenological analysis (IPA) in an approach similar to Leahy et al.² In IPA, the researcher aims to learn about an individual's personal experiences, where participants are viewed as storytellers.^{2,3} This approach is particularly desirable for this study design, since IPA seeks to provide insights on how individuals experience major life events, for example diagnosis with AF. IPA is grounded in the belief that patients are experts on their lived experiences.⁴ A narrative of the themes including verbatim phrases that best represented stakeholder perspectives was developed.

This study was reviewed and approved by the University of Maryland, Baltimore's (UMB) Internal Review Board. All participants were provided with an informed consent document prior to the interview and asked to provide verbal consent during the interview.

Results

In total, 6 patients and 24 HCPs (3 cardiac nurses, 10 cardiologists, 4 EPs, 4 family doctors and 3 pharmacists) were invited to participate. Of those invited to participate, 15 agreed to participate in interviews resulting in: 5 patient interviews (2 male; 3 female) and 10 HCP interviews (2 cardiac nurses, 2 cardiologists, 2 EPs, 2 family doctors, and 2 pharmacists). Interviewed patients were located in five states across the United States, while interviewed HCP's practiced in Maryland and Delaware. HCP clinical practice experience ranged from 2 to >30 years. Our analysis identified a number of themes centered on three areas: diagnosis, treatment, and patient desire for knowledge (see Table 12 (5.1)). Each is discussed in detail below.

Diagnosis

AF symptoms can be similar to those of other conditions, making diagnosis challenging

All interviewees described how symptoms can vary substantially between patients and include absence of symptoms, vague symptoms such as “effort intolerance,” or unusual symptoms in the chest area, making early diagnosis difficult (See Table 13 (5.2)).

Symptoms may also mimic a cold or viral infection. Among interviewed patients, three mistook their symptoms for other conditions and sought care for those: a suspected heart attack, indigestion, and an anxiety attack. One patient who had previously worked as a cardiac nurse measured her rapid heart rate and realized she was in AF. Since AF symptoms may be transient, it can be challenging to identify AF even among patients who see their HCP regularly.

AF diagnosis and treatment occurs across settings

Interviewed patients were all diagnosed in inpatient settings after experiencing symptoms and seeking care (see Table 13 (5.2)). However, HCPs report that occasionally patients are diagnosed during routine care. One HCP stated *“sometimes it’s luck. I mean, sometimes I’ve had a couple of folks where they just, you put your stethoscope on there, and you say, ‘Whoa, what’s that?’ And they don’t even know.”*

As follow up to their diagnosis, interviewed patients were referred to a general cardiologist. Depending on the patient’s insurance coverage or location, it may have taken several weeks for patients to schedule an appointment. In the interim, primary care providers may treat patients. Once a patient is stabilized, usually quickly, they typically are managed by their primary care doctor, except for an annual cardiology visit. HCPs reported that they would generally only refer to EPs the more complex cases or those they thought were good candidates for ablation or cardioversion procedures.

Patients want more information about AF upon initial diagnosis

HCPs reported difficulty explaining AF to patients, while patients reported receiving inadequate information related to AF from their HCP’s. One patient suggested that expressing “familiarity” with atrial fibrillation should not be interpreted as an “understanding” of AF.

“When I ended up at the first hospital, they sort of explained what it was, but my heart rate was going all over the place at that point. They didn’t really say anything. They’re like, ‘It’s kind of like you have atrial fibrillation.’ I’m like, ‘Oh, my dad had that,’ and that was kind of the end of the story. Maybe they thought I knew more just because my dad had AFib” – Patient

HCP's commented that often patients will retain only a small amount of the information they are told about AF or agree they understand when the HCP suspects that did not understand.

“What I find is that they nod their head and tell you that they understand, and we can document patient verbalizing understanding, – but you know that they got only a part of what it is that you said.” – HCP

Treatment Decision Making

Patients prefer to be treated by EPs instead of general cardiologists

Patients viewed EPs as experts on AF and better equipped than other HCPs to explain what AF is, treatment options, and possible outcomes. Patients reported feeling more at ease under the care of EPs and see them as central to their AF support network. *“A cardiologist could tell me that there are some issues with my heart, but I really felt more at ease under the care of the electro-physiologist because he could really understand what was going on.”* Three patients reported learning about EPs on the internet and thereafter seeking referrals for an EP from their cardiologists or primary care providers. Thus, a fourth pathway for referral to an EP may exist: patient knowledge and self-selection.

Perception of stroke risk versus bleeding risk is heightened among specialists compared to generalists

HCP's weigh the benefits and risks of anticoagulants differently. Specialists, especially those who referred to guidelines in treating AF patients, reported that, in general, the risk

of stroke is more important than an individuals' risk of bleeding. One clinician stated that he only considers risk of bleeding among "low risk" patients according to the CHADS₂-VASc: "when... the risks are relatively low, you weigh the risks of bleeding in that person, what they do, their hobbies, their occupation." However, general practitioners tended to worry more about the risk of bleeding.

"I think, at least in my opinion and the opinion of some other healthcare professionals that the risk of stroke is probably greater than the risk of a bleed from a fall." – Specialist

"If I see the risk of bleeding versus a stroke, if you look at it, bleeding hurts them much more." – General practitioner

Diverging views over age as a proxy for risk of bleeding

HCPs had diverging views on whether age is a good proxy for risk of falls or bleeding risk. One clinician alluded to the age of 70 years as an approximate age when she would begin to start considering patients as having an increased fall risk and switching patients to aspirin rather than anticoagulants. Another HCP stated that age does not factor into his decision-making, instead he relies on an individual's functional status, regardless of whether a patient is very young or elderly.

Stroke RSSs are widely used

Many HCPs reported using stroke risk stratification tools when considering anticoagulant prescribing. The CHADS₂ may be used for quick screening into a high- or low-risk category. However, when the risk score falls into a 'grey' treatment zone where no

specific recommendations are provided according to the CHADS₂ (e.g., score=1), the CHA₂DS₂-VASc may be used instead. While the majority of HCPs in this study described the importance of stroke risk-stratification tools in their treatment selection for a patient, one HCP stated that calculating a risk score disrupts the flow of communication with the patient and therefore rarely uses risk scores.

Comorbidities not included in the CHADS₂ or CHA₂DS₂-VASc are also considered

When asked if there are other comorbidities not included in the CHADS₂ or CHA₂DS₂-VASc that play a role in anticoagulant decision-making, the following comorbidities were mentioned: hypertrophic cardiomyopathy, rheumatic heart disease, and pulmonary hypertension. Also, the type and duration of AF may factor into how aggressively HCP's treat the disease.

Bleeding risk-stratification tools are not as important for decision-making

Of note, while many HCPs brought up either the CHADS₂ or CHA₂DS₂-VASc for stratifying patients as high or low risk for stroke, the HAS-BLED score for predicting risk of bleeding was not mentioned as a tool used in treatment decision-making. In fact, one clinician stated that he does not find the tool valuable:

"I don't use the HAS-BLED bleeding-risk calculator, per se. I don't find it valuable... it's – whether there's any history of major bleeding, GI bleeding, which is what it usually is. What – how, the age, frailty, balance, prior falls, are probably the things that I look at the most." – HCP

Novel oral anticoagulants (NOACs) preferred over warfarin

HCPs generally preferred prescribing NOACs instead of warfarin and reported a number of factors that drive HCPs toward or away from each (see Table 14 (5.3)). In general, HCPs reported that they do not have a preference for any particular novel, or direct acting, oral anticoagulant. They typically defer to the preferred NOAC on the patients prescription benefit formulary. One HCP mentioned estimated glomerular filtration rate (eGFR) and weight cut offs play a role in determining whether and which NOAC to prescribe. Patient preference also play an important role in treatment decision-making. For example, one patient stated that she chose to take a NOAC instead of warfarin because “*whether you drink something, eat something or the medications you take can always interfere with keeping in your INR range with warfarin.*” She also felt that because of all of these interactions, her stroke prevention would not be “consistent” and consistency would “*help better preventing a stroke than a medication that you never knew if you were going to be in your level or not.*” Neither HCPs nor patients in this study reported the availability of an antidote for bleeding as influencing their treatment decisions.

“One of the NOACs does have an antidote if you want it. The other ones will have an antidote within probably a few months at the most. And the bottom line is it wears off in 12 hours anyway.” – HCP

Use of aspirin

Despite emerging evidence that aspirin is inappropriate for stroke prevention among AF patients, it continues to play a prominent role in treatment. Several HCPs commented that they have noticed a reduction in aspirin prescribing over the past several years. However,

HCPs, even those who are familiar with updated recommendations, may still recommend aspirin to their AF patients (see Table 15 (5.4)).

Other Outcomes and Risks (beyond stroke and bleeding)

Patients are interested in learning more about AF triggers and other outcomes

In addition to better education and resources relating to stroke and bleeding risks, patients would like HCPs to provide them with more information about AF “triggers,” including foods and drinks to avoid. For example, one patient was unaware of possible associations between eating or drinking certain foods and increased risk of an AF episode until he became a member of the AF Patient Support Group on Facebook and watched online videos created by an English physician.

Patients cited risk of stroke, bleeding events, maintenance of sinus rhythm, and INR results as important outcomes. Symptoms directly associated with AF or anticoagulants, such as anxiety, bruising, fatigue, shortness of breath, and weight gain, were also important.

Discussion

Engaging patients and HCPs yielded insights about the challenges faced and barriers to prompt diagnosis and anticoagulant initiation for individuals with AF. The findings from this pilot study complement findings from other studies among the AF population.¹³⁵⁻¹³⁷ Our findings provide insights into the patient journey through diagnosis and treatment and experiences encountered along the way. Our HCP interviews identified considerations providers take into account when deciding whether or not to initiate

patients on anticoagulants. Both perspectives provide insights that can be leveraged to improve care, balancing stroke and bleeding risks.

Both patients and HCPs reported challenges in the diagnosis of AF due to variable and non-specific symptoms, and the transient nature of paroxysmal AF. Recent estimates are that between 10-27% of all patients with AF are undiagnosed.¹³⁸⁻¹⁴¹ While universal screening of the general population is unlikely to be cost effective, targeted EKG campaigns or emerging smartphone technology may be useful for early detection of AF.^{142,143} Hickey et al. is currently conducting a randomized, controlled trial examining mobile health (mHealth) EKG technology to detect AF episodes among an already-diagnosed AF cohort. If effective, it could provide the basis for future research to identify patients with undiagnosed AF.¹⁴⁴

In addition to challenges receiving an initial diagnosis, patients reported frustration with the short amount of time that providers dedicated to explaining AF immediately following their diagnosis. In parallel, most HCPs described difficulty communicating AF and risk of stroke to their patients. McCabe and colleagues have described the importance of early patient experiences on longer-term perceptions and trajectories.^{34,36,135} To improve patient experiences, HCPs should consider having handy a list of appropriate resources to recommend to patients at diagnosis. For example, the American Heart Association has published AF resources for patients and professionals, including an “*Interactive Afib Patient Guide*.” Many of these materials are available in both English and Spanish.¹⁴⁵ Along with practical guides for patients living with AF (e.g., exercise guides; interpreting lab results), Stopafib.org provides an online forum for patients to connect with one another.¹⁴⁶ Patient understanding of AF diagnosis and treatment

strategy is particularly important since care can occur across a range of healthcare settings.

Patients suggested that EPs are better able to explain diagnosis, trajectory, and outcomes associated with AF compared to other HCPs. Referring patients to EP's immediately following diagnosis, or suspicion of AF, at least for a single consultation, may help to put patients at ease. Fosbol et al. also found that EP's are more likely than general cardiologists or internal medicine/primary care providers to prescribe rhythm control or anticoagulant therapies for AF.¹⁴⁷ Thus early referrals to EPs may also reduce OAC underutilization.

While there has been substantial researcher interest in bleeding-risk scores such as the HAS-BLED and HEMORR₂HAGES scores, HCPs reported that they do not use these tools.¹⁴⁸ In fact, one HCP stated that he does not find the tools useful. Qualitative research with HCPs prior to risk-score development and co-development with practitioners can ensure that tools are not only highly predictive, but also well designed for the user. For example, one HCP described how risk schemes can get in the way of communicating with patients. Complex scoring mechanisms may be more predictive of stroke or bleeding events, but they also may be less likely to be incorporated into routine care. Incorporating RSSs into technology used at point-of-care could overcome this barrier.

Patients expressed an interest in learning more about AF triggers. These triggers are not well understood and much evidence is anecdotal. Small studies have identified associations between paroxysmal AF and increased alcohol use, as well as vagal

activation. Gastroesophageal reflux disease has been posited as a trigger.^{149,150} Weather patterns, such as cold or low humidity also have been linked to onset of AF.¹⁵¹ Since data on triggers are not routinely collected in traditional databases, researchers may wish to partner with online patient communities, such as participants in this study, or identify other potential data sources to investigate and enrich the evidence base on potential triggers.

This study has several important limitations that should be noted. We relied on a convenience sample and experiences of the study population may not be generalizable to other patients with AF or HCPs given that the objective of an IPA analysis is to understand individual person experiences. Patient participants may be more “activated” than typical AF patients since they are active participants of an online AF patient community. Furthermore, although stroke and bleeding events are commonly studied outcomes among AF patients, none of the AF patients enrolled in this study had experienced these outcomes.

Conclusions

Understanding patient and HCP experiences in AF improves awareness of challenges encountered and barriers to timely AF diagnosis, provides insights into factors considered in anticoagulant treatment initiation, and targets areas for future research. The findings serve as a first step in improving care for AF patients and future research aimed at improving use of underutilized preventive therapy and appropriately balance stroke and bleeding risks.

Table 12. (5.1) Overview of emerging themes

<p>Diagnosis</p> <ul style="list-style-type: none"> • AF diagnosis challenges due to symptom variation and transience; • Diagnosis and care occurs across settings
<p>Treatment Decision Making</p> <ul style="list-style-type: none"> • Stroke-risk schemes are used more often than bleeding-risk schemes; • Specialists have a heightened perception of stroke risk compared to generalists; • Comorbidities and other patient characteristics absent from the CHADS₂ or CHA₂DS₂-VASc also factor into risk consideration;
<p>Patient Desire for Information</p> <ul style="list-style-type: none"> • Patients described need for more information upon initial AF diagnosis; • Patients are interested in learning more about AF triggers

Table 13. (5.2) Interviewed patients' descriptions of the AF diagnosis experience

<i>Patient</i>	Quote
1	<i>“They did the pulse, took my blood pressure, and within ten minutes, I picked up that whatever they did – the EKG thing – because it was urgent care and I think my heart rate was 170 or something, they called 911 and took me to an emergency room. I spent two days in the hospital getting diagnosed, and then trying to convert me to sinus rhythm. I ended up at two hospitals because of insurance. That was fun. In the hospital, they said, “Oh, you have atrial fibrillation with RVR,” and they kept giving me diltiazem syrup, and it didn’t work, and as they went to release me, they told me I was in permanent AFib and I converted on my own.”</i>
2	<i>“I was out in the backyard, bending over, and I felt the quivering in my left neck, and I stood up and took my pulse, and it was going really fast. Being a cardiac trauma nurse for 30 years and having taught atrial fib 12-lead interpretation and arrhythmia to trauma nurses, I knew exactly what it was... I called an ambulance, went into the emergency room, they did the – I was there for 13 hours, and it showed the EKG ... The official diagnosis was actually in the emergency room.”</i>
3	<i>“I woke up on a Saturday thinking that I was having a normal panic attack. I had had panic attacks for years and something felt different so my mom talked me into going to the emergency room. Upon going to the emergency room, I was found to be in Atrial Fibrillation. I had never experienced it before that I know of. So, I was actually diagnosed with the first episode that day and I was admitted into the hospital. I was in the hospital for three days and they did all the tests. I had converted back to normal sinus rhythm.”</i>
4	<i>“There was no rhythm to it, so it was pretty scary so the first time that it happened I was really scared. I couldn’t figure out what was going on, but there were no other signs or symptoms for me. I wasn’t getting dizzy or loss of consciousness wasn’t an issue or anything like that so the first time that it happened I kind of just got it out. It tended to happen for me when I was going to sleep... Through my insurance I have kind of like a nurse advice line – when I lied down to go to sleep and my heart started going into my AFib again. So I explained to my wife that I was really scared and I’m going to call this nurse advice line. The nurse asked what my symptoms were and what was going on and how I was feeling. They said; we</i>

5	<p><i>do advise you to get to the emergency room as soon as possible. I went into the ER and I eventually came out of AFib while I was the ER.”</i></p> <p><i>“I had an event about – I guess six or seven years ago while driving down the road. Thought I was having a heart attack. Ended up in a – an ER, and they told me probably – I don’t know, eight hours after getting there that I was in Atrial Fibrillation.. I was hospitalized four days and while I was there, all they were telling me was I was in AFib, and they were trying to get my rate controlled, and to get me in – in a normal rhythm. They – tried a couple different drugs, and eventually the drugs set in, or eventually I went into normal rhythm on my own.”</i></p>
---	--

Table 14. (5.3) HCP-reported factors impacting whether patients receive warfarin or a NOAC

Experiences of family, friend, or acquaintance	<p><i>“Everyone knows somebody on either blood thinners or with Afib, or has bleeding, or has blood clots. That really affects their decision making tremendously.”</i></p> <p><i>“Depend on who the patient is... how much discomfort that comes from being on warfarin they will tolerate... sometimes they’re very... see [their] buddies getting bruises and [they] don’t like it. So they’re just not going to take it.”</i></p>
Cost of drug	<p><i>“If I don’t feel strongly enough that one has to be picked over all the others, then I will tend to say ‘You know what? Let’s not bankrupt you and just pick what is most affordable based on what is the first tier drug in your formulary.”</i></p>
Cost of INR monitoring	<p><i>“The cost of the drug versus the cost of the drug plus monitoring – I actually haven’t looked at the comparisons lately or run the dollars myself, but I don’t shy away from it because the initial drug is more expensive. I think there’s also long-term ways where it might not be as much with the monitoring aspect of things.”</i></p>
Dietary restrictions	<p><i>“Getting the dose just right can sometimes take a while – and changing the dietary restrictions, how their diet is going to influence taking the medication.”</i></p>
Drug-drug interactions	<p><i>“Other things that influence it are renal function, drug interactions, patient preference.”</i></p>
Likelihood of compliance	<p><i>“I don’t use DOACs if compliance is a question. So, warfarin for the pretty compliant patient.”</i></p>
Mobility	<p><i>“Any comorbidities certainly plays a role. Whether it has to do with being able to be mobile and go out and get INR checks or go to follow up appointments, etc.”</i></p>
Patient preference	<p><i>“Some of it is patient preference, so that’s a conversation with a patient that they can have with an understanding that they’ll have to have bloodwork taken every so often to monitor their levels.”</i></p>
Provider preference/ comfort	<p><i>“One big driver is provider preference and how comfortable the attending physician is of prescribing. That influences it.”</i></p>
Proximity to INR clinic	<p><i>“We’ve had instances where we intended to put somebody on warfarin, but they were unable to make it to routine follow-up appointments for their INR testing, and ended up switching agents because of that.”</i></p>
Renal function	<p><i>“What their renal function? Eliquis has an eGFR cut off, and also a weight cut off.”</i></p>
Transportation availability	<p><i>“Just thinking about whether other things might play into the decision, for example, costs, or transportation, accessibility, those types of things.”</i></p>

Table 15. (5.4) HCP-reported reasons for recommending aspirin

To “prescribe something”	Possibly unaware of emerging evidence on drawbacks of aspirin	Prescribed for AF patients for a reason other than stroke prevention
<p><i>“Most people these days from the data that I, I’ve read in, in sort of evolving data, I tend to push most of them towards anticoagulation. But if they choose not to, then we treat them with an aspirin for no good, for no good reason other than we do it and we keep an eye on them.”</i> – HCP</p>	<p><i>“I will usually tell them that some form of medication will be essential, whether it’s aspirin or Plavix or warfarin, that something will be needed just to make sure that he doesn’t end up with a stroke.”</i> – HCP</p> <p><i>“I fight this battle; it seems like, a couple of times a month. I feel like a lot of healthcare providers overestimate the benefit of aspirin and underestimate the bleeding risk that can be associated with it.”</i> - HCP</p>	<p><i>“[My EP] didn’t think I needed an anticoagulant, but then she encouraged me to stay on the aspirin anyways. I said, ‘I researched, and aspirin doesn’t seem to stop AFib-related stroke.’ She goes, ‘But you’ll be protected from other things.’”</i> – Patient</p>

6. Aim 2: Relationship between Risk-stratification-scores and Anticoagulant Initiation Following Atrial Fibrillation Diagnosis

Background: Despite treatment-guideline recommendations and availability of effective medications to reduce stroke risk, there is widespread underutilization of oral anticoagulants (OACs). Evidence suggests that current RSS may not be appropriate for AF patients who are younger or female. Thus, our objective was to identify if the RSS scores predict OAC initiation among newly diagnosed AF patients and whether disparities exist by age and gender.

Methods: We conducted a retrospective cohort study using Optum's Clinformatics™ Data Mart (CDM) administrative claims data for years 2008-2016. CDM is a de-identified database of administrative health claims for members of a large, national health insurer. Patients with newly diagnosed AF were followed for three months post-diagnosis to identify presence of a pharmacy claim for OACs. RSS scores were calculated for patients diagnosed 2009-2014 (CHADS₂ pre-update cohort) or 2015-2016 (CHA₂DS₂-VASc, post-update cohort), respectively. Logistic regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) of the association between risk scores and other covariates with OAC initiation, separately for the pre-update and post-update cohorts and stratified by gender and age.

Results: In the pre-update cohort (n=27,810), 30.1% of patients with a CHADS₂ ≥2 (n=16,893) initiated an OAC within 3-months of diagnosis; in the post-update cohort (n=9,569), 27.7% of those with a CHA₂DS₂-VASc ≥2 (n=8,272) initiated an OAC within 3 months. We found that CHADS₂ scores of both 1 [OR 1.326 (95% CI 1.198, 1.468)] and ≥2 [OR 1.689 (95% CI 1.534, 1.860)] are significantly associated with receipt of

OACs compared to those with CHADS₂ scores=0. In the post-update cohort, CHA₂DS₂-VASc score, including score of 1 [OR 0.910 (95% CI 0.685, 1.209)] or ≥ 2 [OR 1.181 (95% CI 0.926, 1.506)] trended towards, but did not correspond with higher odds of OAC initiation. After adjusting for co-morbidities and provider type at diagnosis, we found no statistically significant differences between odds of initiating OACs among OAC-recommended males and females or age categories across study years and cohorts.

Conclusion: Initiation of OAC treatment among newly diagnosed non-valvular AF patients was consistently low in pre- and post-update time periods. While high correlation would be expected, neither increasing CHADS₂ nor CHA₂DS₂-VASc scores correspond directly with increasing odds of treatment initiation. We did not identify treatment disparities based on age or sex. There is discordance between CHADS₂ and CHA₂DS₂-VASc scores and use of OAC treatment to prevent stroke. The reasons for this are unclear. Additional research is needed to elucidate why patients who are candidates for OAC therapy are not receiving therapy.

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder.²³ The prevalence of AF increases with age; approximately 5% of individuals 65-80 years and 10% of individuals ≥ 80 years of age are diagnosed with AF.^{24,25} AF increases an individual's risk of experiencing stroke four to six-fold.⁴⁵ Oral anticoagulants (OACs), such as warfarin and novel oral anticoagulants (NOACs), are effective in preventing ischemic stroke among AF patients; however, these medications also carry an increased risk of bleeding.⁸⁴⁸⁰ To balance OAC benefits of stroke prevention with risk of bleeding, clinical practice guidelines (CPGs) recommend performing individualized assessments to stratify non-valvular AF patients into categories of low, medium, and high risk-for-stroke.^{9,99} The American College of Cardiology/American Heart Association/European Society for Cardiology's (ACC/AHA/ESC)'s 2006 guidelines recommended the CHADS₂ RSS, which was updated to the CHA₂DS₂-VASc RSS in the 2014 ACC/AHA/Heart Rhythm Society's guideline.¹¹⁵ Importantly, the CHA₂DS₂-VASc also assigns "points" for female gender, vascular disease, and age 65-74 years. i.e., characteristics that were overlooked in the former risk stratification scheme.⁶

Despite treatment-guideline recommendations and availability of effective medications to reduce stroke risk, widespread underutilization of OACs has been previously documented, even patients at high-risk-for-stroke.^{119,152,153} Furthermore, prescriber reliance on characteristics other than those included in risk schemes to guide treatment decisions has been reported.^{119,152,153,154} While reasons for underuse of OACs are not well established, the veracity of RSSs and their uptake among HCPs could play a role. The addition of younger age and female gender are important considerations in light of evidence that these groups, in particular, may not receive optimal AF care. Despite the

lower prevalence of AF and risk of stroke among younger persons, Naderi and colleagues found that patients <65 years of age account for approximately one third of AF-related hospitalizations.¹²⁵ However, the authors did not look at OAC use prior to hospitalization. Thompson and colleagues examined the role of sex on initiation of OACs using the PINNACLE National Cardiovascular Data Registry (2008-2014) and found that women were significantly less likely to initiate OACs across CHA₂DS₂-VASc scores.¹⁵⁵ Among those with a CHA₂DS₂ score of 2, women were less likely to initiate OACs compared to men [risk ratio (RR) 0.95; 95% confidence interval (CI) 0.95, 0.96]. Similar results were observed for a CHA₂DS₂-VASc score of 2 [RR 0.67; 95% CI 0.66, 0.68]. However, since their data only went through 2014, the year that CHA₂DS₂-VASc was introduced, findings on the CHA₂DS₂-VASc were preliminary. Additionally, the data source was a registry of practices that voluntarily participate in a national, office-based cardiovascular quality improvement program. Thus, the findings are unlikely to be generalizable to all practices, in particular non-cardiology practices.

The objectives of this study were to (1) examine the relationship between RSS scores and receipt of OACs; (2) Determine whether patients over the age of 65 years are more likely than those under-65 years of age to initiate RSS-adherent OAC treatment upon diagnosis; and (3) Determine whether men are more likely than women to receive RSS-adherent treatment upon diagnosis with AF.

Methods

We conducted a retrospective cohort study to evaluate the association between CHADS₂ and CHA₂DS₂-VASc scores and initiation of OAC treatment within 3 months of

diagnosis with non-valvular AF. We also assessed whether there were disparities in OAC initiation based on age and sex.

Data source

We used the Optum Life Sciences administrative claims database for years 2008-2016. Optum is a commercial data provider for the UnitedHealth Care Group. Optum's Clinformatics™ Data Mart (CDM) includes approximately 12-14 million annual covered lives, for a total of over 65 million unique lives over a 17-year period (2001 through 2017). CDM is de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum customer data-use agreements. These administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion in the CDM. The CDM comprises both commercial and Medicare Advantage health plan claims data. The population is geographically diverse, spanning all 50 states. In addition to outpatient medical claims and pharmacy claims, the data includes member eligibility and inpatient confinements.

Study design and population

We identified the first AF diagnosis from service-encounter claims for ICD-9 (427.31) and ICD-10 (I480, I481, I482, I489) codes between 2009 and 2016. Individuals with claims for valvular disease, OACs, cardioversion therapy, or catheter ablation in the 12 months preceding the index AF diagnosis were excluded. Patients were also excluded if they had claims for pregnancy at any time during the study period or hip or knee replacement surgeries in the 6-weeks prior to diagnosis as OAC use may be contraindicated in these populations. AF patients also were required to have continuous

medical and pharmacy coverage during a 12-month washout period preceding the AF diagnosis and the 3-month follow-up period.

Calculation of CHADS₂ and CHA₂DS₂-VASc

The primary clinical practice guidelines for treatment of AF in the United States were updated in December 2014 and modified from recommending the CHADS₂ to CHA₂DS₂-VASc.⁹ Thus, we analyzed separately a pre-update cohort (diagnosed 2009-2014) where CHADS₂ scores were calculated and a post-update cohort (diagnosed 2015-2016) where CHA₂DS₂-VASc scores were calculated.¹¹⁶

CHADS₂ and CHA₂DS₂-VASc scores were estimated using covariates ascertained during the 12-month washout period preceding the index AF diagnosis. The CHADS₂ includes points for: congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, and prior stroke or TIA (two points if history of either). The CHA₂DS₂-VASc scores additionally includes a point for female sex, age ≥ 65 and < 75 , vascular disease, and two points for age ≥ 75 . We used the same coding scheme as Wang and colleagues, which relies on administrative and claims data (i.e., inpatient, outpatient, procedure codes, V codes, and pharmacy).¹¹

Other covariates

The HAS-BLED score, which predicts bleeding risk was also estimated, and includes hypertension, bleeding predisposition, abnormal renal or liver function, stroke, labile INR (unable to ascertain in our data), age > 65 , and concomitant medication (NSAIDs, aspirin, clopidogrel, prasugrel, ticagrelor) or excessive alcohol use.^{11, 110} A crosswalk table within the CDM was used to match ICD-9 and ICD-10 codes throughout the study period. We also gathered information on covariates previously observed to be associated

with increased risk of stroke (e.g., sleep apnea, chronic obstructive pulmonary disorder), bleeding or associated with receipt of anticoagulants. For example, Alzheimer’s disease and related dementias (ADRD) or provider type at diagnosis, were also ascertained during the washout period (see Supplement).¹⁵⁶

Receipt of OAC

Consistent with previous research, the main study outcome was a composite “receipt of an OAC” (NOAC or warfarin) endpoint within 3 months of diagnosis with AF.¹⁵⁷ We also examined receipt of NOAC and warfarin separately. OAC prescription fills were identified through pharmacy claims data using American Hospital Formulary Service Classification (AHFSC) codes. Since the first NOAC was introduced in the United States in 2010, NOAC follow-up also commenced in 2010.¹⁵⁸ The NOAC treatment category included apixaban, dabigatran, edoxaban, and rivaroxaban. During follow-up time, patients could have received both a NOAC and warfarin. In such cases, the subject would be counted once into the composite outcome based on first OAC received and would be included in both NOAC and warfarin sub-analyses.

Analyses

We estimated the proportion of individuals meeting OAC-recommended criteria [CHADS2 ≥ 2 (pre-update); CHA2DS2-Vasc ≥ 2 (post-update)] who received an OAC within 3 months of diagnosis. To assess the association of individual risk factors in receiving treatment, bivariate associations between covariates and receipt of an OAC during follow up were assessed using Chi-square goodness of fit or Student’s *T*-tests, as appropriate. These descriptive statistics were performed separately for OAC-recommended and not recommended cohorts.

We used logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess the association between risk scores and OAC initiation within 3-months of AF diagnosis. Potential confounders were included in our regression models if significantly associated with or clinically relevant for OAC decision-making (e.g., bleeding adverse events, and provider type). Separately, we also constructed models that incorporated the individual variables contributing to the CHADS₂ and CHA₂DS₂-VASc scores. Goodness of fit was assessed based on Hosmer-Lemeshow test, which is a measure of concordance between expected and observed outcomes.¹⁵⁹

We examine the following hypotheses: (1) Men are more likely to receive RSS-adherent OAC treatment than women upon diagnosis with AF; (2) Patients over the age of 65 are more likely to receive RSS-adherent OAC treatment upon diagnosis with AF. We stratified subjects into pre- and post-update cohorts that included only OAC-recommended patients (CHADS₂ ≥2; CHA₂DS₂-VASc ≥2) and tested whether OAC-recommended females had lower odds of initiating OACs than men when adjusting for other co-morbidities and demographic characteristics. We also tested whether OAC-recommended patients <65 years of age had lower odds of initiating OACs as compared to older OAC-recommended patients when adjusting for other co-morbidities and demographic characteristics. A *p*-value less than 0.05 was considered statistically significant. SAS 9.2 (SAS Corporation, Cary, NC) was used for all analyses.

Sensitivity analyses

We conducted several sensitivity analyses to assess the rigor of our findings. First, we extended the follow-up time from 3-months post-diagnosis to 6-months to assess whether the shorter time window may have misclassified people as not initiating an OAC. We

also examined if OAC-recommended patients in our cohorts, both those who initiated OACs and those that did not, initiated other prescription medicines to provide insights into whether patients might be filling prescriptions without adjudicating claims (e.g., low cost generics) or primary non-adherence. Specifically, we examined whether OAC-recommended patients with co-morbid hypertension initiated calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, beta blockers, thiazide diuretics, or other antihypertensive agents at any time in either pre- or post- diagnosis periods. We also examined whether OAC-recommended patients with co-morbid diabetes initiated insulin or oral antidiabetics pre- or post-diagnosis stratified by OAC-initiation status. Finally, we also examined the impact of dichotomizing patients into RSSs <2 and ≥ 2 since guidelines recommend initiating OACs among all patients with scores ≥ 2 .

Ethical approval

This study was approved by the University of Maryland, Baltimore's Institutional Review Board.

Results

Proportion of patients initiating OACs

We identified 37,379 commercial enrollees meeting eligibility criteria across all study years. In total, 27,810 were included in the pre-update (CHADS₂) cohort, while 9,569 were included in the post-update (CHA₂DS₂-VASc) cohort (Figure 12 (6.1)). In the pre-update cohort, 16,893 (60.7%) had a CHADS₂ score ≥ 2 and were classified into the OAC-recommended category. In the post-update cohort, 8,272 (86.4%) patients had a CHA₂DS₂-VASc ≥ 2 and were classified into the OAC-recommended category. In the pre-update cohort, 30.1% of OAC-recommended patients received an OAC within 3-

months, whereas among those with a CHADS₂<2, 24.3% received an OAC. In the post-update cohort, 27.7% of patients classified as OAC-recommended received an OAC within 3-months, while 24.1% of patients with a CHA₂DS₂-VASc <2 received an OAC (see Table 16 (6.1)).

Bivariate analysis

In the pre-update, OAC-recommended cohort, there were significant differences between patients who initiated OACs and those who did not in bivariate analysis (see Appendix Table A6.1). In the pre-update analysis, female gender (p<.0001) and age (p<.0001) were significantly different between non-initiators and OAC-initiators. Importantly, there was no significant difference between patients with a history of stroke/TIA or hypertension. There were also significant differences in: history of CHF, diabetes, and HAS-BLED score.

In the post-update, OAC-recommended cohort, there were no significant differences between patients initiating OACs and those who did not based on sex (p=0.3325), age ≥65 and <75 (0.3773), or history of stroke/TIA (0.2093) (see Appendix Table A6.2). Since additional comorbidities are assigned “points” in the CHA₂DS₂-VASc, comorbidities adding to OAC-recommended status varied between pre- and post-update populations. For example, in the pre-update cohort, a greater percentage of patients had hypertension (96.2% in no OAC and 96.8% in OAC), whereas in the post-update cohort, a smaller percentage of patients had hypertension (84.6% in no OAC and 89.3% in OAC).

RSSs and OAC initiation

In our adjusted results, CHADS₂ scores of both 1 and ≥ 2 were significantly associated with receipt of OACs compared to those with CHADS₂ scores=0 (see Table 17 (6.2)). There were no differences between increasing CHADS₂ categories. For example, 95% confidence intervals for patients with a CHADS₂ score=1 [OR 1.326 (95% CI 1.198, 1.468)] overlapped with patients who had a score=3 [OR 1.538 (95% CI 1.366, 1.732)] (see Appendix XII, Table A6.3). Thus, the odds of initiating were not significantly different between these groups. In the post-update cohort, CHA₂DS₂-VASc score >0 did not correspond with higher odds of OAC initiation compared to CHA₂DS₂-VASc score =0 (Table 18 (6.3)).

In our analysis of components of the CHADS₂ and/or CHA₂DS₂-VASc, neither CHF, female sex, nor vascular disease was associated with OAC initiation. In the pre-update study, CHF [OR 0.889 (95% CI 0.799, 0.990)] was associated with lower odds of initiating OACs, while female gender [OR 1.02 (95% CI 0.92, 1.08)] and age were non-significantly associated with OAC initiation (see Appendix XII, Table A6.4). In the post-update study, CHF also had lower odds of initiating OACs [OR 0.792 (95% CI 0.664, 0.944)], while neither female sex [OR 1.001 (95% CI 0.909, 1.103)], nor vascular disease [OR 0.962 (95% CI 0.843, 1.099)] were statistically significantly associated with OAC initiation (see Appendix XII, Table A6.5). Age ≥ 75 [OR 1.052 (95% CI 0.924, 1.199)] and prior stroke/TIA [OR 1.052 (95% CI 0.919, 1.204)], the two risk factors assigned greater weight in the CHA₂DS₂-VASc (2 points each), were not statistically significantly associated with initiating OACs in the post-update study. However, in sub-analysis that examined NOACs and warfarin separately, both older age and prior stroke were associated with increased odds of receiving warfarin, but not initiating NOACs. While

these clinical predictors were not significantly associated with initiating OACs, diagnosis in emergency or cardiology settings were strong predictors of initiating OACs across cohorts. In the post-update study, in particular, diagnosis in emergency [OR 1.626 (95% CI 1.347, 1.963)] or cardiology [OR 1.394 (95% CI 1.197, 1.623)] setting was strongly associated with NOAC initiation.

Role of Age and Sex on OAC-initiation Among OAC-Recommended Patients

After adjusting for co-morbidities and provider type at diagnosis, we found that there were no statistically significant differences between odds of initiating OACs among OAC-recommended males and females in our pre-update [OR 1.02; (95% CI 0.92, 1.08)] or post-update [OR 1.04 (95% CI 0.94, 1.16)] analysis (see Table 6.3). Similarly, we found no statistically significant differences in OAC initiation by age among OAC-recommended patients in pre-update [≥ 65 and < 75 years OR 0.99 (95% CI 0.88, 1.14); ≥ 75 years OR 0.92 (95% CI 0.82, 1.04)] or post-update [≥ 65 and < 75 years OR 1.09 (95% CI 0.91, 1.30); ≥ 75 years OR 1.09 (95% CI 0.92, 1.30)] analyses.

Sensitivity analyses

Since AF guidelines state that patients with a CHADS₂ ≥ 2 (pre-update) and CHA₂DS₂-VASc ≥ 2 (post-update) should initiate OACs, we performed a sensitivity analysis where RSSs were dichotomized into < 2 and ≥ 2 categories. Among patients with RSSs ≥ 2 , the odds of initiating OACs within 3-months was statistically significant in both pre-update [OR 1.382; (95% CI 1.299, 1.470)] and post-update [OR 1.261; 95% CI (1.092, 1.455)] cohorts (see Appendix Table A6.6).

In our sensitivity analysis in which follow-up time was extended from 3 months to 6 months post-diagnosis, the proportions of patients initiating OACs rose from 30.1% to

33.6% of patients with CHADS₂ ≥ 2 in the pre-update analysis and from 27.7% to 30.8% of patients with CHA₂DS₂-VASc ≥ 2 in the post-update analysis (see Appendix XII Table A6.7). The odds of initiating OACs within six-months was statistically significant among those with a CHADS₂ ≥ 2 in the pre-update [OR 1.691 (95% CI 1.535, 1.862)] but not among post-update patients with a CHA₂DS₂-VASc ≥ 2 [OR 1.263 (95% CI 0.968, 1.648)] (see Appendix XII, Table A6.8). Among patients indicated to initiate OACs, there was no statistically significant difference between men and women in the pre-update analysis [OR 0.992; (95% CI 0.920, 1.070)] or in the post-update analysis [OR 1.017; (95% CI 0.917, 1.129)]. Similarly, there were no statistically significant differences between patients <65 years and those 65-74 or patients ≥ 75 years of age (see Appendix XII Table A6.9). The six-month findings were consistent with results from the primary, three-month follow-up analysis.

The percentage of patients with co-morbid hypertension and co-morbid diabetes was similar among both OAC-non-initiators and OAC-initiators. However, in both pre- and post-update cohorts, the percentage of patients initiating prescription medicine treatments for their co-morbid conditions was lower among OAC-non-initiators (see Tables Appendix XII A6.11). For example, in the pre-update analysis, 62.3% of OAC-non-initiators with co-morbid hypertension had a prescription to treat hypertension in both pre- and post-diagnosis periods, whereas 84.1% of hypertensive OAC-initiators had prescriptions to treat their hypertension.

Discussion

This study's key findings have important implications for the management and risk stratification of AF patients. Irrespective of RSS score, initiation of OAC treatment

among newly diagnosed, non-valvular AF patients was consistently low. We identified substantial underutilization versus what would be expected based on RSS score.

Underutilization was not due to disparities in uptake of OACs by age or sex. There were no significant differences in OAC initiation between OAC-recommended men and women, nor among age categories. Although history of ischemic stroke/TIA is the most important predictor of subsequent ischemic stroke, it was only moderately associated with OAC initiation in the pre-update study and not statistically significantly associated with OAC initiation in the post-update study.

These findings corroborate prior evidence from US and more recent evidence among European populations, that OACs are widely underutilized.^{160,161} Most individuals at high risk for stroke for whom an OAC would be the most appropriate therapy did not receive treatment within the first three months of AF diagnosis. However, overall only 30.1% of AF patients with CHADS₂ ≥2 received an OAC within 3-months. These worrying findings are consistent with Haim and colleagues, who found that 22.8% of their AF cohort initiated warfarin within 90 days of index diagnosis.¹⁶² Despite the availability of newer OACs that are more convenient because they do not require frequent monitoring and are generally considered to have lower bleeding risk, initiation of OACs has not increased in initiation accordingly. While our proportions are unadjusted, it is unlikely this discrepancy can be sufficiently explained by routine contraindications to NOACs or warfarin. For example, O'Brien and colleagues analyzed the ORBIT-AF registry to identify factors associated with OAC contraindications in the US outpatient setting.¹⁶³ Among 10,130 patients, 13.1% had contraindications documented at baseline. Contraindications included prior bleed, patient refusal/preference, bleeding risk, and frequent falls/frailty, among others.

We found that neither younger age nor female sex reduce odds of initiating OACs, however widespread under-utilization remains a problem. Based on results from our 2015-2016 post-update analysis, it seems that many of the barriers to optimal OAC use and adherence identified during a 2012 Roundtable discussion sponsored by the AHA may remain today. ¹⁶⁴ Identified barriers included: knowledge gaps about stroke risk and lack of appreciation that aspirin has little ability to prevent stroke in people with AF. ¹⁶⁴

Although the CHA₂DS₂-VASc risk-stratification scheme has been shown to improve accuracy of stroke prediction over the CHADS₂, as measured by area under receiver operating curves, this improved accuracy did not translate into higher treatment initiation among patients in our study cohorts. ¹⁶⁵ While the CHA₂DS₂-VASc assigns points for additional comorbidities and demographic characteristics, placing a greater percentage of patients into the OAC-recommended category in the post-update study, a smaller proportion of these high stroke-risk patients appears to have actually initiated treatment (27.7% within 3-months). Our findings provide evidence supporting the AHA's quality improvement initiative to promote adherence to evidence-based guidelines for AF. ¹⁶⁶

While the initiative is currently directed at cardiology practices, we found that diagnosis by a cardiologist did increase odds of initiating OACs as compared to other provider types. Although patients often ultimately see a cardiologist, other HCPs such as family doctors also manage AF.(Aim 1) Thus, additional resources for educating other HCPs may be critical for improving population-level OAC initiation.

Many risk factors for stroke overlap with risk factors for bleeding, such as hypertension, creating a challenging situation for clinicians. ^{53,76} For example, elderly patients also are perceived to be at higher risk for bleeds, however, they also are at highest risk for stroke.

¹⁰⁸(Aim 1) We found that prior bleeding events and components of the HAS-BLED score reduced patients' odds of initiating treatment, whereas known risk factors for ischemic stroke, such as prior stroke, increasing age, CHF, female sex and vascular disease did not increase odds of initiating OACs across populations and in some cases reduced odds of initiating OACs. Concern for bleeding risk may be outweighing concerns over stroke risk in this population.

This failure to account for stroke risk in treatment decision-making is disturbing since increases in risk score are directly linked to increases in stroke. For example, Haim et al. found that the rate of ischemic stroke among non-valvular AF increased from 2 events/1000 person years among patients with CHA₂DS₂-VASc=0, to 58 events/1000 person years among those with a score=9.¹⁶² Results for other scores were not reported. While the CHA₂DS₂-VASc is more predictive of ischemic stroke than the CHADS₂ it also adds complexity to decision-making. Since the CHA₂DS₂-VASc assigns the most weight to prior stroke/TIA and age ≥ 75 , characteristics also included in the simpler CHADS₂, it is possible that promoting the CHADS₂ may have greater impact on the population level, in particular among patients diagnosed outside of emergency or cardiology settings. For example, as Lip described in his review of bleeding risk scores, researchers can often improve c-statistics, a measure of goodness of statistical model fit, by adding additional risk factors or biomarkers.¹⁶⁷ However, given limited time allotted to patient visits and existing strains on HCP work flows, these improvements in prediction may not be useful for clinical application unless they are directly imbedded into medical record software. For example, in Aim 1, a qualitative study of health care providers who care for AF patients, one stated he/she does not utilize RSSs, because the tools are cumbersome and impede direct communication with patients.

Although aspirin is not a recommended substitute for OACs among OAC-recommended patients, it is possible that the low proportion of OAC users may be partially explained by widespread use of aspirin instead of OACs. A retrospective, longitudinal observational cohort study conducted by An and colleagues using Kaiser Permanente Southern California data between January 1, 2006 and December 31, 2011, estimated that 30% of the population received only aspirin and an additional 23.5% of patients received no therapy.¹⁶⁸ Given growing evidence aspirin carries similar bleeding risk to OACs, while not providing equivalent stroke-risk reduction, this explanation is cause for concern. Recent studies have found that stroke risk when patients are *not* taking an OAC typically exceeds bleeding risk when patients *are* receiving an OAC. This held true even among elderly patients with frequent falls, frailty, and those with cognitive dysfunction.¹⁶⁹⁻¹⁷² In Aim 1, we found that HCPs are not aware of new evidence related to bleeding risk associated with aspirin and even HCPs aware of emerging evidence sometimes prescribe aspirin. (Aim 1) The 2016 ESC do not recommend aspirin for any patients, including low-risk patients.⁹⁹ Simplifying US CPGs, for example removing the intermediate risk category for whom both aspirin and OACs are recommended, may reduce aspirin prescribing and improve overall uptake of CPGs.

Our sensitivity analyses examining treatment of other comorbid conditions suggests that non-OAC initiators are less likely to initiate medications prescribed for other co-existing conditions. Underuse of OACs could be aligned with underuse of other medications for a variety of reasons, such as healthy user bias, access issues due to inability to pay out-of-pocket costs, access to a pharmacy, perceived lack of need, perceived risks, etc. (Aim 1) This could account for some of the discordance.

Patients with uncontrolled AF and/or hypertension and/or diabetes are at serious risk for stroke or other adverse events and should be flagged by their health plans for intervention. Larger participation in AHA's Get with the Guidelines[®] may help health plans increase RSS-adherent OAC initiation through quality measures that require documentation of RSS score and OAC prescription, or justification for not prescribing OACs.¹⁷³ In addition to such quality improvement initiatives, researchers should seek to better characterize the 70% of patients who do not initiate OACs and identify specific reasons for non-use.

Strengths and Limitations

Unlike prior similar studies, our study utilized data that captured post-CHA₂DS₂-VASc inclusion in US-based guidelines. We included data on patients who received treatment from a variety of prescribers, unlike previous studies that focused on patients treated by cardiologists.¹⁵⁴ This is important in avoiding selection bias, as not all patients receive their care from cardiologists or cardiology sub-specialties.

However, there are a number of limitations that should be considered. We used claims for OAC prescriptions as a proxy for initiation of OACs. It is possible that this study underestimates guideline-adherent prescribing, since patients may not have filled prescriptions they received from their providers. Additionally, current and past clinical practice guidelines recommend treatment with OACs among patient with risk scores ≥ 2 , versus aspirin, OACs, or no treatment among lower risk-for-stroke patients. Since aspirin is not captured in claims data, interpretation of our results should not be extrapolated to "treatment" initiation and should be limited to "OAC" initiation.

Additionally, there are several possible limitations associated with our data source that should be considered. Since administrative claims data are intended for reimbursement of medical services, misclassification bias or other biases may be present. Unmeasured confounding, such as out-of-pocket costs of medications, transportation availability, and frailty, all impact propensity to initiate OACs and are not captured by our study. Furthermore, these data represent commercially insured individuals and results may not be generalizable to the entire population.

Conclusion

Initiation of OAC treatment among newly diagnosed non-valvular AF patients was consistently low. Neither increasing CHADS₂ nor CHA₂DS₂-VASc scores corresponded directly with increasing odds of OAC initiation. We did not identify treatment disparities based on age or sex. There is discordance between CHADS₂ and CHA₂DS₂-VASc scores indicating preventive treatment is indicated and use of OAC treatment to prevent stroke. The reasons for this are unclear. While prescriber discretion is important in individualized treatment decision-making, treatment guidelines represent evidence of current best practice.¹⁶⁶ Additional research should try to elucidate why patients who are candidates for OAC therapy are not receiving therapy.

Figure 12. (6.1) Study cohorts (3-month follow-up)

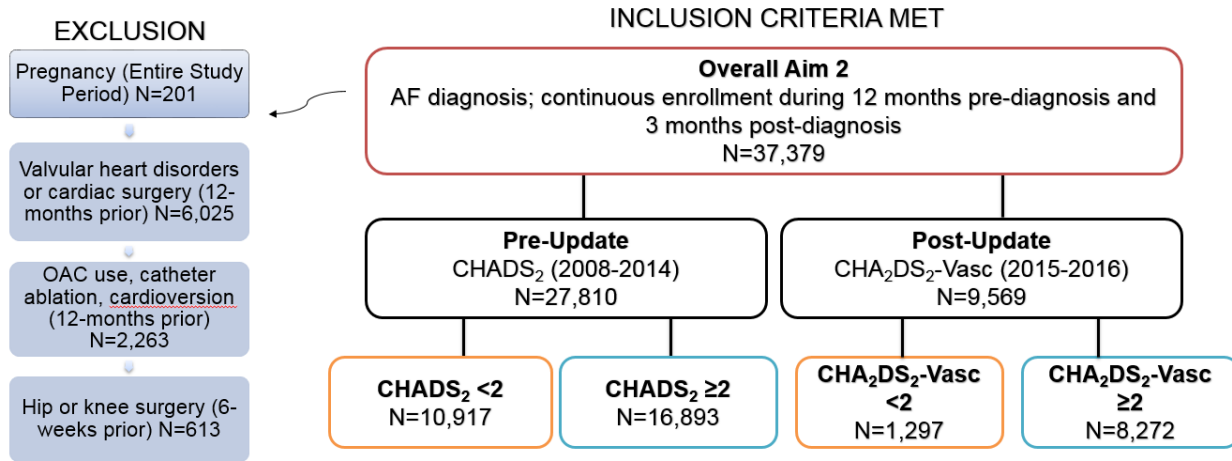


Table 16. (6.1) Proportion of patients receiving an OAC within 3-months of diagnosis
Pre-Update *Post-update*

	CHADS₂ <2	CHADS₂ ≥2	CHA₂DS₂-VASc <2	CHA₂DS₂-VASc ≥2
<i>All patients</i>	24.3%	30.1%	24.1%	27.7%
<i>Female</i>	21.4%	29.3%	14.8%	27.3%
<i>Male</i>	26.3%	31.0%	25.8%	28.2%
<i>Age <65</i>	20.5%	33.0%	24.9%	30.0%
<i>Age 65-74 years</i>	28.4%	30.2%	20.8%	29.0%
<i>Age ≥75</i>	25.7%	29.6%	¥	26.7%

Table 17. (6.2) Odds of initiating OACs within 3-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

CHADS₂ score	Adjusted Odds ratio (95% CI)	CHA₂DS₂-VASc score	Adjusted Odds ratio (95% CI)
0	Ref	0	Ref
1	1.326 (1.198, 1.468)	1	0.910 (0.685, 1.209)
≥2	1.689 (1.534, 1.860)	≥2	1.181 (0.926, 1.506)

Table 18. (6.3) Impact of age and gender on OAC-initiation among OAC-recommended patients
Pre-Update *Post-Update*

	Adjusted Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
Female		
Age (years)		
<65	1.02 (0.92, 1.08)	1.04 (0.94, 1.16)
≥65 and <75	Ref	Ref
≥75	0.99 (0.88, 1.14)	1.09 (0.91, 1.30)
	0.92 (0.82, 1.04)	1.09 (0.92, 1.30)

Adjusted for patient characteristics, including prior bleeding events, and provider type at diagnosis

7. Aim 3: Performance of the CHADS₂ and CHA₂DS₂-VASc Atrial Fibrillation Anticoagulant Risk-Stratification-Schemes Among Newly Diagnosed Women and Patients Under-65 years of Age

Background: Stroke risk-stratification-schemes (RSSs), such as the CHADS₂ and CHA₂DS₂-VASc are widely recommended in clinical guidelines to help clinicians assess atrial fibrillation (AF) patients' risk for stroke, which should guide decisions to initiate anticoagulants. Validation studies for these tools were primarily undertaken among male or elderly populations, making it unclear how applicable RSS's are to younger or female AF populations.

Objective: The objectives of this study were to (1) evaluate whether existing RSS's are predictive of ischemic stroke among AF patients who are female and those 65 years of age and younger; (2) test whether novel risk factors (chronic obstructive pulmonary disorder (COPD), hyperthyroidism, obstructive sleep apnea, or renal disease) identified in the literature as predictive of ischemic stroke are predictors among females and those ≤65 years of age and whether incorporating them improves prognostic models as compared to existing RSSs.

Methods: Optum's Clinformatics™ Data Mart (CDM) is de-identified database of administrative health claims for members of a large, national health insurer. We conducted a retrospective cohort study among newly diagnosed AF patients identified in the CDM (2008-2016). We identified patients with at least one claim for AF, who had no claims for oral anticoagulants, cardioversion therapy, catheter ablation, or valvular disease in the twelve months preceding diagnosis. Traditional risk factors included in RSS's, novel risk factors, and other patient characteristics were ascertained during this

washout period. We used a discrete-time approach to estimate the risk of ischemic stroke associated with CHADS₂ and CHA₂DS₂-VASc components and scores among a females and those ≤65 years of age. Separately, we developed prognostic models using novel and traditional risk factors in derivation cohorts. Based on minimization of the Bayes Information Criterion, test cohort models compared new to existing RSSs based on area under the curve (AUC).

Results: We identified 35,270 patients meeting inclusion criteria (16,560 women; patients ≤65 years). Overall, 4.11% (n=1,453) of subjects experienced an ischemic stroke within one year of their AF diagnosis. Among women and those ≤65 years, all CHA₂DS₂-VASc scores above 1 and CHADS₂ scores >0 were significant predictors of stroke. Neither vascular disease [overall risk ratio (RR) 1.07; (95% CI 0.94, 1.22)] nor female sex [overall RR 1.06 (95% CI 0.96, 1.18)] were significantly associated with ischemic stroke in adjusted models. Having Alzheimer's disease and/or a related dementia was a significant risk factor for ischemic stroke among women [RR 1.41; 95% CI (1.07, 1.84)] and those 65-years and younger [4.53; 95% CI (1.37, 14.96)]. Novel risk factors were not found to be predictive of stroke among female or ≤65 cohorts. Prognostic models developed within subpopulations were no better at predicting stroke than existing RSSs.

Conclusions: Both the CHADS₂ and CHA₂DS₂-VASc scores are associated with ischemic stroke among newly diagnosed AF patients who are female and for those ≤65 years of age. These findings align with and support AF guidelines that recommend OACs for AF patients who are perceived to be low risk. Novel risk factors were not found to be predictive of ischemic stroke and did not improve prediction as compared to the CHADS₂ or CHA₂DS₂-VASc.

Background

Atrial fibrillation (AF) is the most common arrhythmia and is associated with a five-fold increased risk of stroke.^{116,174} Despite widespread availability of anticoagulants (OACs), such as warfarin and apixaban, which have been demonstrated to reduce stroke risk by 64%, underutilization of these preventive treatments is widely recognized.⁶⁸ Studies have reported that certain AF subpopulations, including younger and female patients, may be less likely to receive OACs.¹⁷⁵ For example, despite observing that female gender (47%) was one of the most common CHA₂DS₂-VASC risk factors in their cohort of AF patients, Durham and colleagues found that female gender was protective against initiating OACs in a large AF cohort in the United Kingdom (n=23,018).¹⁵⁷ Disparities in OAC initiation may be due to limitations in the risk stratification schemes (RSSs) used by clinicians deciding when to treat AF patients with OACs.¹¹⁶

RSSs, such as the CHADS₂ and CHA₂DS₂-VASC, are widely recommended in clinical guidelines to help clinicians assess stroke risk in AF patients and guide decisions to initiate anticoagulants.^{116,13,176} The CHADS₂ and CHA₂DS₂-VASC assign “points” based on a patient’s comorbidities including congestive heart failure (CHF), hypertension, diabetes, stroke/transient ischemic attack (TIA), and vascular disease, along with age and gender. Guidelines recommend that patients with higher scores initiate OAC treatment, while patients with lower scores may initiate aspirin or no treatment.^{6,7}

Although RSSs are applied to all AF patients, including younger patients and women, they were initially developed and validated with primarily elderly patient populations. The CHADS₂ was validated in a population of 1,733 AF patients with a mean age of 81 years.¹⁷⁶ Risk factors included were selected from two existing RSSs developed among younger but primarily male populations (AF Investigators (AFI) mean age=69 years and

34% female; Stroke Prevention in AF (SPAF) mean age=69 years and 28% female). Comorbidities important for predicting stroke among elderly populations may differ significantly from younger populations. For example, in a study using the Nationwide Inpatient Sample (NIS), Naderi et al found that co-morbidities differed dramatically between a younger (mean age 54 years) versus an older (mean age 78 years) subset of an AF population.¹²⁵ These comorbidities may impact risk of stroke yet they are not reflected in current RSSs.¹²⁵

To improve the health and treatment of all AF patients, it is important to investigate whether risk-stratification-schemes (RSSs), such as the CHADS₂ and CHA₂DS₂-VASc, accurately predict risk of stroke in younger and female populations. Thus, the objectives of this study were to: (1) evaluate whether existing RSSs are predictive of ischemic stroke among AF patients who are female and those 65 years of age and younger; and (2) test whether incorporating novel risk factors (chronic obstructive pulmonary disorder (COPD), hyperthyroidism, obstructive sleep apnea, or renal disease) into existing RSSs that have been identified in the literature as predictive of ischemic stroke improves discrimination of prognostic models as compared to existing RSSs.

Methods

Data source

We conducted a retrospective, cohort study using the Optum Life Sciences Clinformatics™ Data Mart (CDM) for years 2008-2016. The CDM comes from a database of administrative health claims for members of a large national managed care organization. It includes approximately 12-14 million annual covered lives, for a total of over 65 million unique lives over a 17-year period (2001 through 2017). The CDM is statistically de-identified consistent with HIPAA and managed according to Optum

customer data use agreements. The administrative claims are verified, adjudicated, adjusted, and de-identified prior to inclusion. The CDM comprises both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states. In addition to medical claims and pharmacy claims, it includes member eligibility and inpatient stays.

Study population

Our study population comprised individuals with AF and meeting inclusion criteria. We identified AF patients as having at least one inpatient or outpatient claim containing the international classification of diseases (ICD)-9 or ICD-10 codes for AF (427.31; I480, I481, I482, or I489) from 2008 to 2016. This was the most recent data available at the time we began our study. Date of first diagnosis was considered the index date. Patients were required to have continuous coverage for the entire 12-month, pre-index washout and up to one year follow-up period. We excluded patients with claims for oral anticoagulants, cardioversion therapy, catheter ablation, or valvular disease during the washout period to help identify incident AF diagnosis. Patients with hip or knee replacement surgery in the 6-weeks prior to diagnosis were excluded due to increased post-surgical risk.⁵ Patients pregnant at any time during the study were also excluded as AF can be a complication of pregnancy.⁶⁷

Clinical outcome and covariates

Ischemic stroke following diagnosis with AF was identified through ICD-9 codes (ICD-9: 433.x1, 434.x1, 436.xx) and ICD-10 (I480, I481, I482, I489) codes between 2009 and 2016.^{10,11} The follow-up period lasted up to one year post-diagnosis. Due to temporal ambiguity and to avoid introducing protopathic bias, we excluded patients who experienced stroke in the month immediately following diagnosis and began follow-up

for stroke at the start of month two.¹² A one-year follow-up was selected for this study, since the the CHA₂DS₂-VASc was developed to predict one-year stroke risk.¹³ A CDM crosswalk table was used to match ICD-9 and ICD-10 codes.

Baseline characteristics were ascertained during the 12-month washout period¹¹ and included age, sex, comorbidities included in RSSs, history of bleeding events, novel risk factors, diagnosis year, and provider type at diagnosis (see Appendix XI for operational definitions of variables). Novel risk factors included: chronic obstructive pulmonary disorder (COPD), hyperthyroidism, obstructive sleep apnea, and renal disease.

The CHADS₂ and CHA₂DS₂-VASc were estimated based on Wang and colleagues's methodology, which assigns points based on inpatient, outpatient, and/or pharmacy claims codes.¹¹ For example, history of diabetes mellitus (DM) is assigned to patients with at least two outpatient diagnoses of DM (ICD-9 250.X) or one hospital discharge diagnosis of diabetes or one diagnosis of DM and receipt of insulin or an oral antidiabetic. Other risk factors for stroke or conditions that may impact receipt of anticoagulants, such as Alzheimer's disease and related dementias (ADRD), were identified using diagnosis or procedure codes.

Oral anticoagulants (OACs) and antiplatelet (AP) medications were included as covariates in adjusted models. OACs reduce risk of stroke by approximately 60%, whereas AP's reduce stroke event rates by approximately 20%.¹⁷⁷ Prior studies examining RSSs excluded patients receiving OACs and/or APs.^{13,132,176} Instead, we adjusted for medication exposure on a monthly basis. OAC and AP use was ascertained monthly post-index (diagnosis) date through pharmacy claims using American Hospital Formulary Service Classification (AHFSC) codes (see Appendix XI). Monthly proportion

of days covered (PDC) was used instead of fills because adherence to OACs is important in achieving stroke-risk reduction. Monthly PDC was calculated Consistent with Yao et al and Casciano et al and the following categories were used: $PDC \geq 0.8$, $PDC > 0$ but < 0.8 , and $PDC = 0$.^{117,178} To ensure temporality of medication use prior to stroke, OAC use was lagged by 7 days as the effect of warfarin is typically seen within 5 days of commencing treatment.¹⁷⁹

Analysis Plan

We calculated the proportion of individuals meeting CHADS₂ or CHA₂DS₂-VASc treatment-recommended criteria who experienced stroke during the 12 month follow up period, stratified by age and sex. To assess associations between individual risk factors and experiencing stroke, we examined bivariate associations between covariates, including novel and traditional risk factors, and experiencing ischemic stroke within post AF diagnosis using Chi-square goodness of fit and Student's *t*-tests as appropriate.

We used a discrete-time approach to estimate the relative risk of ischemic stroke associated with CHADS₂ and CHA₂DS₂-VASc scores. Ischemic stroke, OAC and AP use were captured on a monthly basis for up to one year following AF diagnosis. We modelled time to first ischemic stroke using generalized linear models with a binomial distribution and a complementary log-log link.^{14,15} This method allowed us to model the occurrence of stroke by month and to control for changing medication use as a time-varying exposure¹⁶ and allowed us to minimize selection bias by including both OAC-initiators and non-initiators. Patients were censored following first ischemic stroke, end of study follow-up, or because their insurance status changed.

Separately, we tested to see if novel risk factors identified in the literature as predictive of ischemic stroke were also predictors in subpopulations and whether, on their own, or with components of the RSSs improved predictive ability over existing RSSs. The overall study cohort, was stratified into two cohorts: female only and ≤ 65 years of age only. Among the stratified populations, two thirds of each were randomly assigned to a derivation cohort and one third to a validation cohort.¹⁸ Patients with claims for OACs during follow-up were excluded from analyses. Thus, two untreated derivation (female only and ≤ 65 years only) and two untreated validation (female only and ≤ 65 years only) cohorts were formed for a total of four groups.

Minimization of the Bayes information criterion (BIC), which is a measure of “global fit” in prognostic modeling, was used to identify “best fit” models among derivation cohorts. The model with the lowest BIC in the female only or ≤ 65 years only derivation cohort was transferred for further goodness of fit testing among female only and ≤ 65 years only validation cohorts.¹⁹ This approach to model selection is adapted from Cook et al., Ridker et al., and Halabi et al.¹⁸⁻²⁰ Discrimination between cohort-specific models and the CHADS₂ and CHA₂DS₂-VASc RSSs was calculated using receiver operating characteristic (ROC) curves and statistically significant differences identified using the Delong test.²¹ Models displaying perfect discrimination have an area under the curve (AUC) of 1.0, while models with an AUC of 0.5 have no discriminatory ability.²¹ The DeLong test is a non-parametric approach to test the hypothesis that ROC curves are equal.²²

Analyses were performed using SAS 9.2 (Cary, North Carolina). Statistical significance was set at $P < .05$. This study was approved by the University of Maryland, Baltimore's institutional review board.

Results

We identified 35,270 patients with AF in the OLS database between 2008-2016 meeting inclusion criteria. Overall, 4.11% ($n=1,453$) of subjects experienced ischemic stroke within one year of their AF diagnosis. Patients experiencing stroke were more likely to be female than male and ≥ 75 years of age (see Table 19 (7.1)). When stratified into CHA₂DS₂-VASc OAC-recommended categories (score ≥ 2), 4.74% of patients experienced stroke within one year, whereas among the OAC-discretionary category (score < 2), 0.93% of patients experienced stroke within one year (see Appendix XIII, Table A7.1). Across subpopulations, the highest incidence of stroke occurred during the second month following AF diagnosis (see Appendix XIII, Figures A7.1 and A7.2).

Risk stratification schemes and ischemic stroke

In the overall, female only, and age ≤ 65 years cohorts, a CHADS₂ > 0 and CHA₂DS₂-VASc > 1 among men and a CHA₂DS₂-VASc > 2 among women was significantly associated with increased risk of ischemic stroke (See Tables 20 (7.2) and 21 (7.3)). In the overall population, which included all sex and age groups, a CHADS₂=1 significantly predicted stroke [risk ratio (RR) 1.66 95% confidence interval (CI) (1.15, 2.40)] compared to CHADS₂=0. A similar increase in risk was observed with CHA₂DS₂-VASc=1 in the overall population [RR 1.79; (95% CI 1.48, 2.16)]. Among women and those ≤ 65 years, all CHA₂DS₂-VASc scores > 1 and CHADS₂ scores > 0 were significant predictors of stroke.

Among individual risk factors contributing to RSSs, vascular disease was not significantly associated with ischemic stroke among the overall or either subpopulation (see Table 22 (7.4)). Congestive heart failure was not significantly associated with stroke among women [RR 1.04; (95% CI 0.91, 1.19)] or patients under ≤ 65 years [RR 1.07; (95% CI 0.97, 1.19)], but had a barely significant association in the overall population [RR 1.11 (95% CI 1.01, 1.22)].

Female only cohort prognostic model

The female only cohort consisted of 16,560 patients with 753 patients experiencing stroke during the follow-up period. Within the female cohort, 15,591 patients were classified as having a CHA₂DS₂-VASc ≥ 2 and 10,906 (65.9%) were classified as having a CHADS₂ ≥ 2 . The majority of females were ≥ 75 years of age (57.2%), but there were also sizeable populations in the other age categories [< 65 years N=3074 (18.6%); ≥ 65 and < 75 N=4,016 (24.3%)].

The female derivation cohort consisted of 8,504 women (67%), while the validation cohort comprised 4,190 women (33%). In the fully adjusted female derivation cohort, significant predictors of ischemic stroke included age ≥ 75 [RR=2.75; (95% CI 1.81, 4.19)], diabetes [RR=1.40; (95% CI 1.09, 1.80)], and history of stroke/TIA [RR=2.75; (95% CI 2.15, 3.52)]. Aside from risk factors already included in the CHADS₂ or CHA₂DS₂-VASc, significant predictors of stroke included having Alzheimer's disease and related dementias (ADRD) [RR=1.60; (95% CI 1.17, 2.17)]. Since the RSSs are intended to guide OAC treatment decision-making and history of ADRD is generally perceived as a contraindication to OAC initiation, it was not included in prognostic model development.¹⁸⁰

The model where BIC was minimized in the female only derivation cohort included both age categories from the CHA₂DS₂-VASc, diabetes, and stroke (BIC=3993.2). The CHADS₂ (BIC=4003.5) had a smaller BIC than the CHA₂DS₂-VASc (BIC=4017.3). ROC curves were calculated using the female validation cohort for the derived model (AUC=0.6988), CHA₂DS₂-VASc (AUC=0.6825), and CHADS₂ (AUC=0.6809) (see Appendix XIII, Figure A7.3). Differences between the derived model and CHADS₂ (p=0.0001) or CHA₂DS₂-VASc (p=0.0003) were statistically significantly different.

Age (≤65 years) cohort prognostic model

The ≤65 years of age cohort included 6,970 patients with 206 patients experiencing ischemic stroke during follow-up. The majority of patients ≤65 years of age were male (64.9%). The percentage of patients CHADS₂ scores falling into lower (32.4% CHADS₂=0) moderate (38.4% CHADS₂=1), and higher risk (29.2% CHADS₂≥2) categories was fairly equal.

The ≤65 years derivation cohort consisted of 4,669 patients (67%), while the validation cohort comprised 2,301 patients (33%). In the ≤65 years of age derivation cohort, significant predictors of ischemic stroke included CHF [RR=2.48; (95% CI 1.24, 4.95)] and history of stroke/TIA [RR=5.20; (95% CI 3.04, 8.88)]. Female sex [RR=0.97; (95% CI 0.59, 1.58)], diabetes [RR=1.54; (95% CI 0.88, 2.67)], hypertension [RR=1.48; (95% CI 0.72, 3.04)], and vascular disease [RR=1.23; (95% CI 0.69, 2.22)] .

In the ≤65 years derivation cohort, the model including only CHF and stroke/TIA had the smallest BIC (1019.7) (see Appendix XIII, Figure A7.4). The BIC for the CHA₂DS₂-VASc was (BIC=1078.9) larger than for the CHADS₂ (BIC=1045.9). When ROC curves were calculated for the validation cohort, the BIC-minimized model was less predictive

of stroke (AUC=0.7604) compared to the CHADS₂ (AUC=0.8296; p<.001) and the CHA₂DS₂-VASc (AUC=0.8280; p<.0001). The difference between the CHADS₂ and CHA₂DS₂-VASc were not significantly different (p=0.218)

Discussion

CHADS₂ and CHA₂DS₂-VASc scores were associated with risk of ischemic stroke among newly diagnosed AF patients, including women and those ≤65 years of age. Not all individual comorbidities contributing to RSS scores were independent predictors of stroke across the AF population. However, novel risk factors did not improve prediction as compared to the CHADS₂ or CHA₂DS₂-VASc.

Results from this study suggest that both the CHADS₂ and CHA₂DS₂-VASc are appropriate for predicting stroke among AF patients who are under age 65 and/or women. However, current cut-off points for recommending OACs may not be appropriate in these subpopulations or overall populations. Current US guidelines recommend OAC treatment for patients with a CHADS₂ or CHA₂DS₂-VASc score of ≥2. However, we found that in the overall population and across subgroups, a score of ‘1’ was also predictive of stroke. In an analysis of linked administrative databases in Alberta, Canada, Sandhu and colleagues found that warfarin use is associated with a substantially lower rate of cerebrovascular events or death among AF patients with a CHADS₂ score of 1 (OR 0.52, 95% CI 0.41 to 0.67).¹³⁰ Current AHA/ACC guidelines recommend OAC treatment for patients with a score ≥2 and either aspirin or OAC for patients with a score of 1, whereas recently adopted European guidelines recommends that all patients except those with a CHA₂DS₂-VASc score of 0 receive OACs.¹⁶⁹⁻¹⁷² Thus, according to US treatment guidelines, these patients would not necessarily be recommended to receive OACs and

could instead receive aspirin. Future US-based guidelines should reconsider RSS cutoff points, as well as discourage the use of aspirin therapy.

Risk ratios for stroke among the overall population associated with CHADS₂ or CHA₂DS₂-VASc score were largely consistent with prior research.^{101,107,132,181}

Differences in study populations, outcome definition, and study design features are likely responsible for variation in study findings. For example, Gage and colleagues CHADS₂ validation study included a smaller (n=1733), elderly (mean age=81 years) population who were not prescribed warfarin at time of hospital discharge.¹⁰¹ In addition to risk estimates, their calculated c-statistic (0.82), which is equivalent to the AUC, was slightly higher than our estimate (0.77).

We found that components of the RSS's predictive of stroke varied across subpopulations. Among women, age, diabetes, and history of stroke were all important predictors. However, in the ≤65 years of age validation cohort, the only significant predictors of ischemic stroke contributing to RSS scores were CHF and history of stroke/TIA. Singer et al. also documented renal dysfunction and incorporated it into their ATRIA risk stratification scheme (c=0.71), which they found had greater predictive accuracy as compared to the CHADS₂ (c=0.66) or CHA₂DS₂-VASc (0.69).¹³² In our model, incorporating renal dysfunction did not improve predictive ability over other RSS's. Interestingly, we found that CHF, a comorbidity included in both RSS's, was not significantly associated with ischemic stroke in female cohort, but it was a significant predictor of stroke in the ≤65 years cohort. In the future, it may be possible to more accurately stratify patients into "high" or "low" risk categories based on differences in predictors among subpopulations. This could be achieved by incorporating

subpopulation-specific risk factor combinations into point-of-care systems. For example, Asberg and colleagues also found that CHF is not a significant predictor of stroke among a Swedish AF cohort [HR: 0.98; (0.94, 1.02)].¹⁰⁷ Their population was approximately equally male and female, but primarily elderly. It is possible that CHF may be an age-dependent predictor and therefore an important component of the RSSs.

In our overall cohort, female sex was not predictive of stroke. A recently published systematic review by Cheng and Kong identified 30 studies that examined female sex and thromboembolic risk. Among the 30 articles (5 randomized controlled studies; 24 observational studies), 17 reported a statistically significant difference between men and women.¹⁸² It is possible that female gender may have an additive effect on stroke risk, explaining why it is not an independent predictor, but still important for risk stratification.

Given the possibility of age- and sex-dependent predictors and the relatively low AUC for the CHA₂DS₂-VASc and CHADS₂ among females, it is likely that more predictive schemes can be developed. Future research using a more comprehensive data source may be able to use biomarkers or other measures for improved risk stratification.¹⁸³ However, given the low correlation between RSSs and OAC initiation, as further complexity is added to RSSs, it would be helpful for risk calculations to be automated within point-of-care software systems.

Limitations

There are several important limitations to this study. Concomitant aspirin use is an important unmeasured confounder in this study, since it decreases risk of stroke and is also prescribed based on perceived risk of stroke. Hsu and colleagues examined the

American College of Cardiology's quality improvement registry and found that hypertension, dyslipidemia, coronary artery disease, prior myocardial infarction, unstable and stable angina, recent coronary artery bypass graft, and peripheral arterial disease were associated with prescription of aspirin only. Whereas RSS components, including prior stroke, were predictive of initiating OACs. Thus, aspirin may be a more important confounder among individuals with a lower risk-for-stroke.¹⁸⁴

We used administrative claims data for this study, which allows a large sample size and provides "real world" estimates of ischemic stroke amongst AF patients. We also estimated anticoagulant and antiplatelet use based on pharmacy claims and did not have access to information on INR testing or documentation that patients were actually adherent to their medications. Similarly, we do not know if patients with history of hypertension had controlled or uncontrolled blood pressure.

Conclusion

We found that both CHADS₂ and CHA₂DS₂-VASc scores were predictive of ischemic stroke among newly diagnosed AF patients, including women and those ≤65 years of age. RSS scores below current cutoffs for OAC-recommended preventive treatment were also predictive of stroke. These findings align with and support AF guidelines that recommend OACs for AF patients who are perceived to be low risk. Novel risk factors were not found to be predictive of ischemic stroke and did not improve prediction as compared to the CHADS₂ or CHA₂DS₂-VASc.

Table 19. (7.1) Bivariate associations between risk factors and stroke within one year following diagnosis

	No Stroke	Stroke	p-value
Total (%)	33817 (95.9)	1453 (4.1)	
Female	15,807 (46.7)	753 (51.8)	0.0001
Age			
<65	8,595 (25.42)	178 (12.25)	<.0001
65-74	8,795 (26.01)	355 (24.43)	
≥75	16,427 (48.58)	920 (63.32)	
CHADS2			
0	4,345 (12.85)	49 (3.37)	<.0001
1	9,307 (27.52)	182 (12.53)	
≥2	20,165 (59.63)	1,222 (84.10)	
Congestive heart failure	3,812 (11.27)	287 (19.75)	<.0001
Hypertension	26,210 (77.51)	1,292 (88.92)	<.0001
Age ≥75	16,427 (48.58)	920 (63.32)	<.0001
Diabetes	8,457 (25.01)	510 (35.10)	<.0001
Stroke/TIA	4,965 (14.68)	558 (38.40)	<.0001
CHA2DS2-VASc			
0	1,878 (5.55)	13 (0.89)	<.0001
1	3,796 (11.23)	40 (2.75)	
≥2	28,143 (83.22)	1,400 (96.35)	
Age ≥65 and <75	8,795 (26.01)	355 (24.43)	0.1797
Age ≥75	16,427 (48.58)	920 (63.32)	<.0001
Vascular disease			
HAS-BLED			
0 or 1	9,672 (28.60)	151 (10.39)	<.0001
2	11,722 (34.66)	428 (29.46)	
≥3	12,423 (36.74)	874 (60.15)	
Renal disease	5,578 (16.49)	380 (26.15)	<.0001
Liver disease	1,781 (5.27)	97 (6.68)	0.0191
Stroke	3,669 (10.85)	505 (34.76)	<.0001
Prior bleeding/tendency	7,942 (23.49)	495 (34.07)	<.0001
Age >65	24,726 (73.12)	1,247 (85.82)	<.0001
Medications/alcohol excess	3,679 (10.88)	170 (11.7)	0.3258
History of bleeding			
Hemorrhagic stroke	151 (0.45)	30 (2.06)	<.0001
Major lower and unspecified GI	1,111 (3.29)	72 (4.96)	0.0005
Upper GI bleeding	262 (0.77)	15 (1.03)	0.2761

Major urogenital	4,076 (12.05)	272 (18.72)	<.0001
Major other bleeding	3,099 (9.16)	207 (14.25)	<.0001
Other possible predictors of stroke			
ADRD	1,727 (5.11)	160 (11.01)	<.0001
Atrial flutter	743 (2.20)	40 (2.75)	0.1591
Cancer	4,330 (12.80)	192 (13.21)	0.6473
Cardiomyopathy	192 (0.52)	**	0.4393
Coagulation defect	1,060 (3.13)	70 (4.82)	0.0004
COPD	2,114 (6.25)	122 (8.40)	0.0010
Hyperlipidemia	16,234 (48.01)	843 (58.02)	<.0001
Hyperthyroidism	412 (1.22)	18 (1.24)	0.9444
Obesity	1,666 (4.93)	87 (5.99)	0.0684
Obstructive sleep apnea	1,674 (4.95)	80 (5.51)	0.3400
Rheumatoid arthritis	655 (1.94)	34 (2.34)	0.2770
Ventricular arrhythmia	849 (2.51)	59 (4.06)	0.0003
Diagnosis year			
2009	4,167 (12.32)	196 (13.49)	0.3925
2010	4,052 (11.98)	184 (12.66)	
2011	4,408 (13.03)	194 (13.35)	
2012	4,821 (14.26)	222 (15.28)	
2013	5,628 (16.64)	221 (15.21)	
2014	5,238 (15.49)	212 (14.59)	
2015	5,503 (16.27)	224 (15.42)	
Provider type at dx			
Emergency	3,836 (11.34)	176 (12.11)	0.1628
General	6,875 (20.33)	290 (19.96)	
Hospital	8,205 (24.26)	382 (26.29)	
Cardiologist/EP	10,561 (31.23)	420 (28.91)	
Other specialist	1,647 (4.87)	60 (4.13)	
Other, unknown, or LTC	2,693 (7.96)	125 (8.60)	

Table 20. (7.2). Risk ratio of ischemic stroke during year following diagnosis by CHA2DS2-VASc score

	Overall		Women		≤65 years	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
0	Ref	Ref	**	**	Ref	Ref
1	1.49 (0.80, 2.79)	1.48 (0.79, 2.76)	Ref	Ref	1.17 (0.60, 2.30)	1.14 (0.58, 2.25)
2	2.85 (1.60, 5.06)	2.79 (1.57, 4.96)	4.48 (1.58, 12.67)	4.43 (1.56, 12.52)	2.89 (1.56, 5.35)	2.69 (1.43, 5.09)
3	4.70 (2.69, 8.22)	4.50 (2.57, 7.88)	5.86 (2.14, 16.00)	5.72 (2.09, 15.66)	5.19 (2.76, 9.74)	4.53 (2.33, 8.81)

≥4	9.88 (5.72, 17.08)	8.34 (4.80, 14.48)	15.24 (5.70, 40.73)	13.18 (4.91, 35.39)	13.92 (7.76, 24.95)	10.82 (5.62, 20.84)
----	--------------------	--------------------	---------------------	---------------------	---------------------	---------------------

Adjusted models controlled for: vascular disease, liver disease, renal disease, history of antiplatelet use or alcohol disorders, ADRD, COPD, hyperlipidemia, ventricular arrhythmia, cardiomyopathy, adverse bleeding events including hemorrhagic stroke, and provider type at diagnosis; **not a possible value or sample size too small; RR=risk ratio; CI=confidence interval

Table 21. (7.3) Risk ratio of ischemic stroke during year following diagnosis with AF by CHADS2 score

	Overall		Women		≤65 years	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.72 (1.25, 2.36)	1.76 (1.28, 2.42)	2.22 (1.32, 3.71)	2.27 (1.35, 3.81)	2.07 (1.23, 3.49)	2.02 (1.18, 3.44)
2	3.43 (2.55, 4.61)	3.49 (2.58, 4.71)	3.78 (2.31, 6.18)	3.92 (2.39, 6.44)	3.61 (2.11, 6.19)	3.47 (1.94, 6.20)
3	5.70 (4.21, 7.70)	5.52 (4.04, 7.54)	5.81 (3.51, 9.59)	5.69 (3.41, 9.50)	11.28 (6.67, 19.06)	10.28 (5.67, 18.62)
≥4	10.65 (7.94, 14.28)	9.81 (7.17, 13.40)	11.89 (7.28, 19.42)	11.18 (6.72, 18.62)	18.72 (11.18, 31.36)	17.51 (9.41, 32.55)

Adjusted models controlled for: female sex (overall, age), vascular disease, liver disease, renal disease, history of antiplatelet use or alcohol disorders, ADRD, COPD, hyperlipidemia, ventricular arrhythmia, cardiomyopathy, adverse bleeding events including hemorrhagic stroke, and provider type at diagnosis; **not a possible value; RR=risk ratio; CI=confidence interval

Table 22. (7.4) Risk ratios for ischemic stroke among incident AF cohort

Risk factors from RSS's	Overall	Women	≤65 years
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted RR (95% CI)
Congestive heart failure	1.30 (1.12, 1.50)	1.15 (0.94, 1.42)	2.00 (1.34, 2.98)
Hypertension	1.54 (1.29, 1.83)	1.43 (1.12, 1.84)	1.95 (1.25, 3.02)
Age (years)			
<65	Ref	Ref	
≥65 and <75	1.61 (1.34, 1.93)	1.56 (1.17, 2.08)	**
≥75	2.09 (1.77, 2.47)	2.17 (1.67, 2.82)	**
Diabetes mellitus	1.24 (1.10, 1.39)	1.24 (1.05, 1.47)	1.19 (0.87, 1.65)
Stroke/TIA	2.95 (2.63, 3.31)	2.84 (2.41, 3.33)	5.02 (3.64, 6.93)
Vascular disease	1.07 (0.94, 1.22)	1.11 (0.93, 1.32)	0.98 (0.68, 1.43)
Female	1.06 (0.96, 1.18)	**	1.08 (0.81, 1.44)

** Not possible values

8. Summary and Implications for Research and Clinical Practice

This multi-phase research consisted of a qualitative study followed by two quantitative, administrative claims-based analyses. This study was based upon the premises that RSSs help identify which patients require preventive OAC therapy, but there are questions about how well RSSs perform, especially among subpopulations, and how closely HCPs follow guidelines concerning them. Improving both RSS precision and best practices in use could increase uptake of preventive therapies. Understanding the views of AF stakeholders, including patients, can provide information on how to improve RSSs and their use. Furthermore, if low OAC use was due to suboptimal RSS performance, especially in female and younger groups, understanding the limitations of current RSSs could provide information on how they can be improved.

We confirmed, as was found in past research, that OAC treatment to prevent stroke in AF appears to be widely underutilized. Underutilization was not related to disparities in initiating OACs based on gender or age. We also considered that disparities may be related to HCPs not perceiving RSSs as useful or insufficient since they have recently been modified. However, the HCPs interviewed stated that they do use RSSs and find them helpful. It also appears that disparities are *not* due to poor RSS performance. The RSS performed quite well in predicting risk of future stroke among a larger cohort of AF patients. They also performed reasonably well in a female cohort and very well among a younger cohort. We could *not* improve RSS performance with the added, novel risk factors available in the claims database. However, we believe there is still opportunity to improve them with additional factors not available to us, based upon the qualitative input of patients and HCPs.

Underutilization of OACs

The most striking finding is that approximately 70% of patients, who appear to be suitable candidates for OAC treatment, did not initiate OACs following AF diagnosis. Whether follow-up was 3-months or 6-months post-diagnosis, the proportion of patients initiating OACs, including those at high risk for stroke, was only approximately 30% of patients. This proportion includes all of those with at least one claim for an OAC during follow-up, thus the proportion of patients with high adherence is likely lower.

Possibly overestimated, but still problematic

The actual proportion not initiating appropriate OACs therapy may be lower than 70%. For example, some patients may have contraindications to OACs or they may fill prescriptions through low-cost generic programs (LCGPs). As described below, prior literature indicates that these justifications only account for a minority of non-initiation.

CONTRAINDICATIONS TO OACs

While we did not examine contraindications specifically, they are unlikely to account for a large proportion of underutilization. For example, O'Brien and colleagues analyzed the ORBIT-AF registry to identify factors associated with OAC contraindications in the US outpatient setting.¹⁶³ Among 10,130 patients, 13.1% had contraindications documented at baseline. Contraindications included prior bleed, patient refusal/preference, bleeding risk, and frequent falls/frailty, among others. Our analyses adjusted for prior bleeding adverse events.

LOW-COST GENERIC PROGRAMS

Within the high-risk population, we found that a lower percentage of non-initiators as compared to initiators had claims for antihypertensive or diabetes medications given they had co-morbid hypertension or diabetes, respectively. This could indicate nonadherence across the board for all

medications or that some of the non-initiators were filling their prescriptions elsewhere, for example through LCGPs offered by certain pharmacy chains. Pauly and Brown conducted a retrospective cohort study using the Medicare Expenditure Survey and found that approximately 20% of warfarin fills were through LCGPs for which claims would not be adjudicated and therefore not appear in our data set.¹⁸⁵ The authors found that older patients with more comorbidities (indicating a higher RSS) were more likely to fill prescriptions through LCGPs. Thus, some of the low utilization might be explained by use of LCGP. Since our research focus was on younger AF patients, LCGPs may be less of a concern than it would be for studies focusing on elderly AF populations.

Barriers to OACs: Implications for Clinical Practice and Research

In Aim 2, we identified discordance between CHADS₂ and CHA₂DS₂-VASc scores and actual initiation of OAC treatment to reduce stroke risk. When patients were categorized into 0 (low risk), 1 (moderate risk), and ≥ 2 (high risk), we found that neither increasing CHADS₂ nor CHA₂DS₂-VASc scores corresponded directly with increasing odds of treatment initiation. This contradicted the Aim 1, qualitative research findings, because HCPs stated that they use RSS scores to guide treatment. Suboptimal use of OACs might be occurring due to: (1) RSSs not being used appropriately in practice; (2) complexity of RSSs and CPGs; (3) insufficient communication skills and awareness of resources; and (4) OAC costs. Concerns over bleeding risk are interwoven with each of these barriers.

RSSs are not used appropriately in practice – generalists heightened concern for bleeding risk

HCPs who see fewer AF patients, for example family doctors versus cardiologists, may be less familiar with or likely to use RSSs. In our qualitative study, we heard that specialists consider stroke risk as more important than bleeding risk, whereas generalists tend to weight bleeding risk

as more important than stroke risk. In our claims analyses, we found that diagnosis by a cardiologist or EP increased patients' odds of initiating OACs as compared to general practitioners. This may reflect generalists heightened concern for bleeding risk as compared to specialists concern for stroke risk.

RSSs are not used appropriately in practice – reducing their complexity may improve uptake

One HCP suggested that the RSSs are cumbersome and impede direct communication with patients. Currently, an individual's CHADS₂ or CHA₂DS₂-VASc score can be a number between 0 and 7 for the CHADS₂ or 0 and 9 for the CHA₂DS₂-VASc. However, according to clinical practice guidelines, the only important numbers are 0, 1, and ≥ 2 . In our study, we found that CHA₂DS₂-VASc score was not significantly associated with OACI initiation, whereas CHADS₂ score was associated with OAC initiation.

To reduce complexity and HCP burden, it may be possible to simplify scores or recommendations. For example, our qualitative interviews described how despite emerging evidence that aspirin carries similar risk of bleeding to OACs without the corresponding reduction in risk of stroke, aspirin continues to be commonly prescribed among AF patients.^{99,186} Interviewed HCPs, even those who were familiar with this evidence, still recommend aspirin to for stroke patients to “prescribe something.” The complicated numbering system and three options for treatment (OACs, aspirin, or no treatment) add to the complexity of treating AF patients and simplification could reduce provider burden and possibly improve uptake of guidelines.

These recommendations were incorporated into recent European guidelines recommending OAC initiation among patients with scores >0 .⁹⁹ The European guidelines do not recommend aspirin as a treatment option. Our analysis found that all scores >0 are predictive of stroke and this

simplification may help reduce HCP confusion. Thus, future US guidelines could remove the ambiguous “intermediate risk” category and instead have two options: very low risk (no treatment) or $RSS >0$ (OAC).

RSSs are not used appropriately in practice – improving HCP awareness through quality improvement initiatives

Discordance between RSSs and OAC initiation identified in this study provide further evidence of the need for initiatives such as the AHA’s Get With The Guidelines[®] quality improvement initiative. In 2016, the AHA updated their AF clinical performance and quality measure set to include measures related to the CHA₂DS₂-VASc. For example, Performance Measure (PM)-1 and PM-4: “CHA₂DS₂-VASc Score Documented (Inpatient and Outpatient)” require HCPs to record an individual’s RSS. Further, PM-5: “Anticoagulation prescribed” requires HCPs to provide rationale for not prescribing OACs when indicated to do so according to RSS.¹⁷³

Currently, this quality improvement initiative is limited to cardiology practices and is not linked to reimbursement. Expanding these measures to non-cardiology settings and linking them to reimbursement could be extremely effective in promoting better quality of care for AF patients. A recent analysis of implementation of a physician dashboard and pay-for-performance program to improve venous thromboembolism prophylaxis rates among hospitals found a significant improvement in clinical practice guideline compliance following implementation of these programs.¹⁸⁷

Insufficient communication skills and/or awareness of resources as a barrier to OACs

Patients described EPs as better communicators and that they preferred to be treated by EPs as compared to other HCP-types. Most HCPs described difficulty communicating AF and risk of stroke to their patients, in particular asymptomatic patients. HCPs also described limited

availability or knowledge of patient education resources, either online or in print. Prior qualitative research indicates that health care professional-patient interactions occurring at the time of diagnosis have long-term effects on patient perceptions of their AF, psychological well-being, and disease-management practices over the course of their disease.^{34,35,135} Consistent with a recent study by Clarkesmith and colleagues in the United Kingdom, in Aim 2, we found that specialists have greater odds of initiating CPG-adherent OAC treatment as compared to family doctors.¹⁸⁸ This may be a result of EPs better awareness of RSSs, but it may also be a result of EPs better ability to communicate AF and associated risks to patients.

In the absence of effective communication between patients and their HCPs, patients may be influenced by unreliable or non-generalizable sources of information. For example, participants identified lawyer ads describing adverse bleeding events experienced as a possible reason for not initiating OACs. Patients and HCPs alike described how experiences of family members or acquaintances (e.g. first hand knowledge of ischemic stroke or hemorrhagic stroke) can impact initiation and adherence to OACs. This also indicates that studies examining OAC initiation may suffer from health user bias, since better informed, more activated patients may be less likely to be influenced by anecdotes and possibly seek out additional data.

To ensure that patient and HCP communication is not a barrier to preventive measures against stroke, future research should examine which examples and language are most effective at communicating AF and stroke risk to patients. One HCP described using jello as an example visual for patients. Identifying the most effective examples can help facilitate well-informed shared decision-making between patients and providers. Additionally, certain patient-specific resources already exist and should be more widely disseminated to patients through their HCPs. For example, a partnership between stopafib.org and the AHA developed “MyAfibExperience,”

which includes a variety of patient resources.¹⁴⁶ Resources include “What is Afib?”, “Why Afib Matters”, “Understand Your Risk,” and “Treatment and Prevention.” These patient-friendly resources could also guide HCPs in learning a patient-friendly vernacular.

Cost as a barrier to convenient NOACs – transition to generic versions may improve OAC initiation

We found that NOAC-initiators tended to have lower RSSs than warfarin-initiators. This is consistent with Schoof and colleagues analysis of channeling and anticoagulants using medco claims data.¹⁸⁹ During interviews, a patient mentioned that Medicare patients eligible to use RX savings cards, resulting in an increased out-of-pocket cost. This may partially explain why older patients are being channeled to warfarin instead of NOACs. This is important as elderly patients are at highest risk for both bleeding adverse events and stroke risk. They may have limited mobility and/or access to transportation. Apixaban, one of the NOACs, is associated with lower risk of bleeding than warfarin and NOACs do not require as frequent monitoring as warfarin requires. Both of these factors could be advantageous for elderly patients. However, if patients are unable to afford NOACs, perceived as unlikely to be adherent to warfarin and simultaneously perceived to be at a high risk for falls due to their age and possible frailty, they may be prescribed aspirin in place of an OAC. Since HCPs may be concerned with bleeding risk (Aim 1), especially for the elderly, they avoid the warfarin and prescribe aspirin since it is also inexpensive and perceived as having lower risks. The cost of NOACs is expected to decrease as generic versions become available, potentially removing an important barrier to OAC initiation. For example, in 2018 the first approved NOAC, dabigatran etexilate, will begin losing certain patent protections and the cost of NOACs is expected to decrease substantially between 2020 and 2025.¹⁹⁰ This may improve uptake of OACs in the future.

RSSs can likely be improved

In Aim 1, HCPs described several comorbidities beyond those included in RSSs that impact the propensity of patients to initiate OACs. These include hypertrophic cardiomyopathy, rheumatic heart disease, and pulmonary hypertension. While rheumatic heart disease patients were excluded as a result of only examining non-valvular AF patients, cardiomyopathy and pulmonary hypertension may be examples of important risk factors in this population, or at least among AF subpopulations. Our data source did not have sufficient sample size to examine these or other potential risk factors. However, it is important that research is conducted to verify that comorbidities beyond those included in RSSs that contribute to HCP decision-making are in fact predictors of stroke among AF patients.

Our finding that diabetes is a predictor of stroke among women, but not in the <65 cohort, while CHF is a predictor among those <65, but not the female cohort, indicates that subpopulation-specific risk stratification may be important in balancing benefits and risks of OACs. Our data set did allow us to examine four novel risk factors for stroke that had previously been identified through a systematic literature review. These included COPD, obstructive sleep apnea, renal disease, and hyperthyroidism. While none of these were identified as significant predictors of stroke among our cohort, given the relatively low AUC, especially among women, the CHADS₂ and CHA₂DS₂-VASc can likely be improved. Other researchers have begun analyzing the role of biomarkers in improving risk prediction among AF patients.¹⁸³ Biomarkers may be especially important in reclassifying patients currently thought to be at low risk for stroke. However, as the complexity of RSSs increases, to facilitate uptake of improved scores, it is critical that the resulting recommendations are automatically displayed in point-of-care systems for HCPs to act upon.

Importance of stakeholder engagement for research and clinical practice

This study provides further evidence of the importance of engaging patients, HCPs, and other stakeholders in research. While secondary analyses of administrative claims data provides population-level insights, interviews provide context and highlight the many variables impacting health care that are traditionally unmeasured within databases. Improved methods for co-developing real world evidence with patients can improve validity of studies and help identify important limitations.

Engaging patients and HCPs helped to identify many variables that factor into treatment decision-making, but are often unmeasured in traditional claims databases. Among these are experiences of others, out-of-pocket costs, likelihood of patient adhering to dietary restrictions or their medication, patient mobility, patient or provider preferences, patients' proximity to an INR clinic, and transportation availability. These variables are consistent with a recent study by Ferguson et al. in cardiac nurses in New Zealand aimed to assess perceived barriers and enablers for patients to receive OACs.¹⁹¹ However, these variables are not accounted for or discussed in recent observation studies.¹⁹² For example, a recent study utilizing the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry to examine absence of OACs and subsequent outcomes did not directly examine or qualitatively discuss any of these variables. They examined frailty, possibly a proxy for patient mobility, but the others were captured only under a catchall phrase of "our analysis was observational and thus subject to residual or unmeasured confounding."¹⁹³ This study also did not examine provider type, a measured variable in this dataset that had previously been identified as an important variable in determining treatment strategy within the ORBIT-AF registry.¹⁴⁷

To quantitatively address unmeasured confounding, novel techniques, such as adjusting for residual confounding by linking data sources have been piloted.¹⁹⁴ Patient-centered conceptual models can help researchers identify which variables they can address quantitatively and which can only be addressed qualitatively.

Limitations

Relevance to Base AF Population

The literature describes challenges diagnosing AF since it is often transient in nature and symptoms may indicate other diagnoses. Symptoms range from unusual chest feelings to feelings of indigestion. In our study, we heard first-hand of the challenges associated with receiving an AF diagnosis. For example, prior to diagnosis, one interviewed patient sought care for a panic attacks, while another patient thought she may have a virus. Thus, there may be a sizable population of undiagnosed AF patients in the US. This population may include patients at either high or low risk of stroke, for example, a recently published retrospective analysis documented underutilization of ambulatory electrocardiogram (EKG) monitoring post-stroke or TIA. They concluded that there is likely over-diagnosis of strokes as cryptogenic, whereas there is likely under-diagnosis of AF-related stroke.¹⁹⁵

Since standard approaches for identifying AF patients using ICD-9 or ICD-10 codes rely on existing diagnosis, they are not sufficient in identifying all patients with AF. Depending on the research question, other approaches to identifying AF patients may have a role in sensitivity analyses.

In addition to patients who have not yet received an AF diagnosis, our study's focus on younger patients and use of private insurance claims database means that our findings may not be generalizable to all elderly patients, the category with the highest prevalence of AF. Advancing

age is the most prominent risk factor for developing AF.¹⁹⁶ For example, in the Framingham study, the hazard of developing AF increased with every ten years of life [Ref=50-59 years; 60-69 HR: 4.98 (95% CI 3.49, 7.10); 80-89 HR: 9.33 (95% CI 6.68, 13.0)].¹⁹⁷ Our cohort consisted of patients with private or Medicare Advantage insurance. Thus, our study cohorts may be somewhat younger and healthier than the base AF population. Since age is also an important risk factor for stroke and contributes to RSSs, our study cohorts may have a lower risk of stroke and therefore lower RSS-scores than the base AF population.

We also did not have access to information on race within our dataset. However, a cohort stemming from a similar dataset, the OptumLabs Data Warehouse (OLDW), were predominantly white [84% white, 8%, African American, and 8% other (Hispanic, Asian, multiple races)].¹⁹⁸ While European ancestry is a known risk factor for developing AF, it is possible that this could be due to lower detection rates among minority populations.¹⁹⁹

Other limitations

There a number of additional important limitations to our study. While the purpose of IPA analysis is not to gather a generalizable sample, but rather understand individual experiences, it is important to understand this as it applies to interpretation of Aims 2 and 3. Patient and HCP participants in qualitative interviews may be more “activated,” or knowledgeable of clinical practice guidelines than typical AF patients or HCPs. It is possible that the discrepancy in HCPs reporting that they use RSSs and our quantitative findings are a result of our qualitative sample including predominantly HCPs with cardiology expertise (2 EPs, 2 cardiologists, 2 cardiac nurses, 2 pharmacists working in cardiology).

Aims 2 and 3 utilized administrative claims data intended for reimbursement of medical services; hence, misclassification bias or other biases may be present. Unmeasured confounding, such as

out-of-pocket costs of medications, transportation availability, and frailty, all impact receipt of OACs and are not captured by our study, but impact patients' propensity to initiate OACs. Furthermore, since the data stem from privately insured individuals, more complex cases, such as those enrolled in Medicare who are under-65 will be missing. Therefore, the findings may not be generalizable to all persons.

We used claims for OACs as a proxy for initiation of OACS in Aim 2. It is possible that this study underestimates guideline-adherent prescribing, since patients may not have filled prescriptions that they received from their providers. Since aspirin is not captured in claims data, interpretation of our results should not be extrapolated to "treatment" initiation and should be limited to "OAC" initiation. Similarly, in Aim 3, we estimated OAC and antiplatelet use based on pharmacy claims and did not have access to information on INR testing or documentation that patients were actually adherent to their medications. Importantly, we do not know if patients with history of hypertension had controlled hypertension or not.

Conclusion

RSSs (CHADS₂ and CHA₂DS₂-VASc) for identifying appropriate candidates for preventive treatments and OAC stroke-preventive treatments are highly effective at predicting stroke, yet they do not appear to correspond with OAC initiation. We found that both CHADS₂ and CHA₂DS₂-VASc scores are highly associated with ischemic stroke among newly diagnosed AF patients, including females and those <65 years of age. However, initiation of OAC treatment among newly diagnosed non-valvular AF patients was consistently quite low across time and subpopulations. While high correlation would be expected, neither increasing CHADS₂ nor CHA₂DS₂-VASc scores correspond directly with treatment initiation. Suspected treatment disparities by age or sex were not found. While a number of factors, such as contraindications and LCGPs, could account for some of the underutilization, it is unlikely it accounts for such a

large amount. More research is needed to more clearly understand why RSSs might not be followed and why OAC are not being initiated.

Patient and stakeholder insights are critical to this effort. For example, we learned that generalists and specialists approach balancing the benefits and risk of OACs differently. These findings offer some insights as to why OACs are not being initiated as would be expected and can be foundational to answering these important questions.

Appendix I. Stakeholder Feedback on Conceptual Model

Interviewees provided suggestions for additions and modifications, which are reflected by revised conceptual models found in Chapter 4.

Environment

Participants generally agreed with the original bulleted points, however, several additions were suggested and are also included in the Table.

Table 23. (A4.1) Stakeholder feedback on draft conceptual model: ‘environment’

	HCP	Patient	Participant comments
Environment			
Health care system			
Provider availability for appointments	✓	✓	“So availability of provider is absolutely huge. I think it also helps to have some consistency in the provider. Also, 'access to primary care'. The PCPs often get involved.” – HCP
Provider knowledge and responsiveness, and ability to use language understandable to patients	✓	✓	“Yeah, I think that is very important, as well. I would say, I’m not sure the doctors are necessarily that great when it comes to communicating on a level that patients understand. But, I do think that’s important. I think it’s so common, that most of us

			<p>have a schpeel that we use that's pretty mundane." – HCP</p> <p>"Doctors' knowledge, responsiveness – that's two." – Patient</p>
Provider time allotted for appointments	✓	✓	<p>"I have an Integrative Health doctor – so ... whenever I go, I get an hour of her time. And it's – it's amazing the way it works... I hate going to my EP. I'm gonna wait forever, and I'm – and he's gonna be rushed when I'm there." – Patient</p>
Specialist referral	✓	✓	<p>"Specialist referral, yeah, I think that is a big deal. I think sometimes, depending on the situation, sometimes it's tough to produce a cardiologist within a short period of time." – HCP</p>
Out-of-pocket costs and availability of savings cards	✓	✓	<p>"Out-of-pocket costs and availability of saving cards I think is huge. I think the cost of medications is a huge player in this, and whether or not there's coupons. I know that depending on what the medication is, we can even send them to one pharmacy for one drug and a different pharmacy for another drug for better costs, which is, in my mind,</p>

			ridiculous, but that’s where we’re at. So, I think cost containment is very challenging and a huge factor.” – HCP
Suggested additions			<ul style="list-style-type: none"> • Availability and existence of a ‘Patient Guide to AF’ • Bedside manner • Coordination of care and communication with other providers • Knowledge and use of guidelines/ risk stratification schemes • Responsiveness • Specifying referral to either a cardiologist or electrophysiologist
External environment			“And I didn’t have too many on the ‘External Environment.’ I don’t even know what some of that means.” – Patient
Public policy impacting access to care or cost of services	✓	✓	“So, public policy is obviously a big deal. With ACA, who knows what’s going to happen with that, so I think that’s obviously a very important thing, depending on how the folks have access. That may change.” – HCP
Insurer formulary	✓	✓	“The insurance formulary is certainly important. I think the nice thing about it is that there were a couple of different options.” – HCP
Clinical practice guidelines	✓	✓	“Yeah, I guess, guidelines are guidelines. They help tailor our practice and they’re not the end-all, be-all. So, I think so. I think it gives us – the clinical

			practice guidelines really the biggest driver is anticoagulation.” – HCP
Risk stratification schemes	✓	✓	“I think that helps to simplify the decision making process, even for those who are not cardiologists.” - HCP
Suggested additions	<ul style="list-style-type: none"> • Availability of research to inform decision-making • Whether practice guidelines are embedded in electronic medical records • Patient access to education and healthy foods 		

(✓) = yes, important; (-) no, not important; (0) = neither agree nor disagree; ≠ = contradicting viewpoints

A number of themes related to the conceptual framework emerged during the course of the formal interviews and feedback on the conceptual models. They are grouped according to the relevant sub-headers below.

Environment: Health Care System

- Many HCP’s are unaware of AF-specific resources for their patients

Environment: External Environment

- Patients and providers alike found that there are limited resources for AF patients
- Cost-sharing/ position on formulary factors into HCP’s decision-making
- Amongst HCPs familiar with current risk stratification schemes, they thought they were accurate and their simplicity makes them easy to use in providing care

Structure of Conceptual Model

Several interviewees struggled to connect “external environment,” in particular public policy, to AF.

"So, that always should be considered. External environment, public policy impacting access to care, cost of services. I guess, in a global way, yes. With respect to AFib and – alright, this has been around so long, I can't think of any – yeah, I can't say, no. But, I can't think of anything directly that would impact it. But, in some global sense, I'm sure we can think of something that could impact the care." – HCP

"Public policy for AFib, I don't know. I mean, for a lot of other diseases, I'd say, that's [inaudible]. So, this one, I'm not sure as much. I wanna say, [inaudible] is critical for this [inaudible]."

AF Patient Characteristics

Interviewees struggled to differentiate between 'predisposing characteristics' and 'enabling resources.' In addition to these points, a number of suggested additions are found in the Revised Conceptual Models.

Table 24. (A4.2) Stakeholder feedback on draft conceptual model: 'patient characteristics'

Patient Characteristics	HCP	Patient	
Predisposing Characteristics			
Gender	✓	()	"So, moving up to predisposing characteristics, gender, we talked about briefly already. It certainly influences it in some situations." – HCP
Age	✓	()	"Age, yes, I think more critical than gender. If you're about 75, be a 2 point. So, age is more critical than gender." – HCP
Communication and Language Skills	✓	()	"So, that's why they need a layperson's guide to AFib. You read some of it in this really high

			language, so – High stuff. I don't know half the medical terms.” – Patient
Stress levels	✓	✓	<p>“Stress levels, I could see stress levels influencing it simply from a compliance standpoint.” – HCP</p> <p>“Vacation helps AFib.” – Patient</p>
Hobbies	≠	✓	<ul style="list-style-type: none"> ○ (+) “Hobbies I guess may have some impact into what treatment options we choose.” – HCP (-) “Hobbies, I'm not seeing that one.” – HCP ○ “If you have an atrial fibrillation attack and, you know, you have a medical set-up guideline with your specialist who said, well, I don't want you to waste your time going to the emergency room unless you've having new symptoms. Try to keep your mind off of it and that's where hobbies come in. So, watch a comedy, color, do something to keep your mind busy.” – Patient
Occupation	≠	()	<ul style="list-style-type: none"> ○ (+) “Occupation is something to think about because it gives you a sense of how much information they can handle.” – HCP ○ (-) “Occupation, yes. I don't – I have to be honest with you. In my practice, I don't see a kind of this coming into play.” – HCP
Family History	≠	()	“Family History doesn't play a role in decision-making though it may play a role in how a person

			<p>reacts to it if they have family members who have dealt with it already.” – HCP</p> <p>“I’m not sure, once you’re treating AFib, and you’re in the care of a physician, that the family history makes a difference.” - HCP</p>
Trust in provider and health system	✓	✓	<p>“Trust in Provider obviously has an impact in outcomes in every patient and every interaction.” – HCP</p> <p>“That totally impacts it. If I would have stayed with that – I didn’t trust the cardiologist, and now that I have someone I know I can go to.” – Patient</p>
Comorbidities	✓	✓	<p>“Yes, and comorbidities, of course. How about separating out emotional illness under comorbidities?” – HCP</p>
Suggested additions	<ul style="list-style-type: none"> • Smoking status • Underlying etiology of disease • Internet savvy • Emotional wellness • Physical mobility • Religious beliefs 		
Enabling Resources			
Income and other socioeconomic factors	≠	()	(+) “Income and other factors, of course.” – HCP

			(-) “I think if you have insurance, it doesn’t really matter. Because usually the drugs are cheap and your generic are all cheap... It may limit your ability to use a DOAC, but, I would say this was a medium.” – HCP
Knowledge and use of resources	≠	✓	(+) “Knowledge and use of resources, I think that absolutely plays a role.” – HCP (-) “Knowledge and Use of Resources? That, that has not a lot of impact.” – HCP “I underlined ‘knowledge’ – that’s – that’s the key to me about everything – just if – if somebody could’ve handed the data” – Patient
Internet access/ savvy	-	✓	“I don’t know, I don’t want to get folks down the wrong path, or you’ll put them on medication that’s right for them, then they’ll read something on the internet about side effects.” – HCP “Internet access/savvy” because the Facebook page has been everything, and that – that’s led me to all sorts of other resources. I think I mentioned the doctor in the U.K that posts Facebook videos – all things that make you feel better.” – Patient

Empowerment	✓	✓	“Empowerment, that's a big term. Yeah, a lot of people don't feel very empowered in the healthcare system, and that is difficult. And every experience we expose them to that doesn't get them where we thought it should is going to affect that.” – HCP
Transportation availability	✓	✓	“Transportation is a big one. I think that's a big thing for folks, to be able to get that, transportation and mobility services.” – HCP
Paid time off/ medical leave	✓	✓	“Paid time off, medical leave, yeah, I think physicians underestimate how making it to clinic performance affects their work life.” – HCP
Child care	≠	✓	(+) “Child care, sure, I mean, I'm sure that has some impact, at some level. I guess the average patients we see are kind of beyond the toddler parent age. But, yeah.” – HCP (-) “No, I don't think that's really important with this.” – HCP “Sometimes you have to get creative with that. I do a lot for my son, but my son goes to a really good school, so if I ended up in emergency rooms or in a hospital, I have a really good school where I called, and – I'm a single parent, so I'm like, ‘Hey, I'm not

			going to be able to get him from lunch today because I'm in the hospital right now. Don't worry; I'll take care of it." – Patient
Family makeup/ reliance of others on individual	≠	✓	(+) "Sure, the social support is critical no matter what diagnosis. It's always harder when you're doing it alone. It's harder for us to treat them. It's harder for them to do well." – HCP (-) "No, I don't think that should be very important either with AFibs. Again, it's not too much needed with AFib, it's more just the individual." – HCP "I think it helps too if your family members are involved and they know exactly what atrial fibrillation is and what the side effects are so they kind of know what you're going through so they can help better." – Patient
Suggested addition	<ul style="list-style-type: none"> Resources for navigating insurer formulary/benefits 		
Perceived Need			
Diagnosis/ understanding of diagnosis	≠	✓	(+) "Diagnosis and understanding of the diagnosis. I would completely agree" – HCP

			(-) “I find that most patients don’t understand much about diagnosis at all. If even my patients were educated, they would have a hard time understanding their diagnosis. So, I’ll give this a kind of low to medium. I mean, as long as they’re compliant and they know when to ask questions, and they kind of have a [inaudible], I think that’s probably good enough.” – HCP
Symptoms/ frequency or severity of symptoms	✓	✓	<p>“Symptoms, frequency, severity, that definitely gets their attention more if they have symptoms. If they don’t have symptoms, then they don’t prioritize” – HCP</p> <p>“I went to ERs five different times before I finally had somebody look at me and go, ‘Look, with AFib, they’re not overly worried about you until your pulse gets over 120.’ Just hearing that piece of data ... then I know, if my heart’s bouncing around but I’m at 70, I’m – I’m not going to get too worried about it... That was huge.” – Patient</p>
Understanding of risk and related outcomes	✓	✓	“Understanding of the risk and related outcomes, I think is very accurate truly understanding the risk of

			stroke and a number of other comorbidities with AFib.” – HCP
Experiences of acquaintances, friends, or family	✓	()	“Yeah. I think that’s really important. That everyone knows somebody on either blood thinners, or with AFib, or has bleeding, or has blood clots. That really affects their decision making tremendously.” – HCP
Patient-doctor relationship	✓	✓	<p>“Yeah, that’s really important. I think they have to trust you. They’re taking this medicine. They don’t know for sure if it’s gonna help them. They wanna feel better. They really need to trust you and know that you’re gonna look after their best interest. That you’re not just about prescribing drugs.” – HCP</p> <p>“I have a good patient-doctor relationship now. I’ve learned that it’s perfectly okay to interview your doctor, which I did.” – Patient</p>
Fear of bleeding	≠	≠	<p>(+) “I think bleeding events are huge. That tends to be one of the bigger concerns. And then, who to contact if they just get scared.” – HCP</p> <p>(-) “Fear of bleeding is very, generally not much of a problem. There are rare people that they’re so worried about that but most of the time when one</p>

			<p>explains those risks, it's not a particular issue." – HCP</p> <p>(+) "Fear of bleeding. I guess that's really big for some people too because Coumadin, like I never had an issue with bleeding, but I've heard some people just bleed. Like they'll cut themselves shaving and just bleed for hours and hours and hours. – Patient</p> <p>(-) "Bleeding events - I think people are scared to take blood thinners, again, because they're scared they're going to have an accident and bleed to death, which then turn, they're the ones that generally end up with TIAs or mini strokes or a stroke." – Patient</p>
Suggested additions			<ul style="list-style-type: none"> • Absence of symptoms • Differentiating between chest palpitations and AF • Fear of experiencing an AF episode • Awareness of AF triggers • Sleep habits

(✓) = yes, important; (-) no, not important; (0) = neither agree nor disagree; ≠ = contradicting viewpoints

A number of themes related to the conceptual framework emerged during the course of the formal interviews and feedback on the conceptual models. They are grouped according to the relevant sub-headers below.

AF Patient Characteristics: Predisposing Characteristics

- Patients seeking information about AF on the internet is a concern for HCP's, while patients state that they have learned a tremendous amount about AF from resources such as Google Scholar, YouTube, and Facebook.

AF Patient Characteristics: Perceived Need

- HCP's do not feel that most patients understand AF diagnosis and patients do not feel that AF is adequately explained
- HCP's struggle to convey risk of stroke to AF patients

Two areas where HCP's commented that it is particularly challenging to modify AF patient's perceived need for anticoagulants to reduce stroke risk are: (1) when a patient does not know what a stroke is or how severe strokes can be for an individual's health; and (2) when patients have few AF symptoms and feel healthy.

“Sometimes we don't assume that they know what a stroke is. Then we have to kind of give very vivid descriptions of someone who has a droopy face, or can't talk, or can't use the left side of their body. And then, that kind of conjures up some recollection of someone they know that had that. The other thing is that their only experience of stroke is someone who had a stroke, and then has no manifestations, and they're doing fine. So, for them to also understand the Russian roulette of stroke and the next one could be extremely devastating. And if you're fortunate, then you can – you don't have side effects, but you can't take that chance.” – HCP

One HCP commented “a tricky thing that always comes up in conversation is the risk of stroke when you're feeling perfectly well [it] is a very hard thing to convey to people.”

Structure of Conceptual Model

HCP's found the language included in the standard Andersen Model somewhat difficult to understand. For example, there was confusion over the header “predisposing characteristics.”

When you say “Predisposing characteristics,” what do you mean? Predisposing to what?” – HCP

“Predisposing characteristics –” I guess, when I looked at these, I was thinking predisposing for them to be compliant, for them – I guess I was unsure” – HCP

Patients' Health Behavior

Participants generally agreed with the original bulleted points, however, several additions were suggested and are also included in the Table.

Table 25. (A4.3) Stakeholder feedback on draft conceptual model: ‘health behavior’

Health Behavior			
Personal health practices			
Adherence	✓	✓	<p>“Yeah, adherence is really important as we talked about ... people who are known to be mild adherents, and people who are mildly non-adherents, we don’t use the DOAC.” – HCP</p> <p>“Definitely follow your doctor or pharmacist’s instructions.” - Patient</p>
Diet	✓	✓	<p>“So, diet and exercise are good in general, for just good overall health. I’m not sure has a big impact on AFib outcomes.” - HCP</p> <p>“Diet, especially with warfarin, yeah, I think that’s accurate.” – HCP</p> <p>“Eat[ing] healthy is a good thing anyway, no matter what but do what you can and can’t have if you choose to take Warfarin because that will keep your levels normal.” – Patient</p>

Exercise	✓	✓	<p>“Exercise, yeah, I think people underestimate the value of losing weight and how it can impact AFib. I don’t think many patients understand that. I don’t think that’s related to many patients, but it’s definitely something that plays a role.” – HCP</p> <p>“Exercise is harder because boy, those medications do affect – I feel like I’m walking through water, like I’m in a water aerobics class. Exercise is also a mental thing because I exercise, come home, relax, and go into atrial fib. That was my pattern. It gets scary, but I’m pushing through that.” – Patient</p>
Switching providers if dissatisfied with care received	✓	✓	<p>“I always encourage second opinions. And where I practice, there’s no shortage of doctors. And so, I’ve had patients get different opinions from me to see another provider sometimes. Sometimes, I’m the second opinion.” – HCP</p> <p>“I had to switch doctors because I had a bad experience, but it was at the – my husband and the people at work encouraged me to do it. “Don’t put up with it, change doctors.” – Patient</p>
Suggested additions	<ul style="list-style-type: none"> • Balanced diet • Avoiding AF “trigger” foods • Developing an “afib plan” with health care provider • Evolving smart phone technology 		

	<ul style="list-style-type: none"> • Mindfulness/ meditation for stress management • Preparing questions for provider in advance of appointments 		
Use of health services			
Anticoagulants	✓	✓	
Aspirin 𠄎	✓	✓	<p>“I do not take anticoagulants, but I did take aspirin, knowing that the aspirin is not going to do anything for the stroke prevention. It’s a nice anti-plaque thing, so I take –for the arthritis, so I take aspirin.” – Patient</p>
Catheter/ surgical ablation	✓	✓	<p>“Catheter surgical ablation, yeah, so being in the setting where you can have options to address what the issues are.” – HCP</p>
Hospitalization/ER visit for stroke or adverse event	✓	✓	<p>“Hospitalization or visit for stroke or adverse event, yeah, I think that’s a very real concern.” – HCP</p>
Physician monitoring	✓	✓	<p>“When you say “physician monitoring,” does that mean that follow-up or phone availability, or are you talking about actually telemetry monitors? Both ways are fine, but they might be two separate items then, essentially.” – HCP</p>

Cardioversion	✓	✓	“Physician monitoring and cardioversion, both of those make sense. I feel like they fit there.” – HCP
Suggested additions	<ul style="list-style-type: none"> • Antiarrhythmic drugs • Watchman device 		

(✓) = yes, important; (-) no, not important; () = neither agree nor disagree; ≠ = contradicting viewpoints; †Note: Disagreement over whether this *should be* a treatment, not whether it *is* a treatment

A number of themes related to the conceptual framework emerged during the course of the formal interviews and feedback on the conceptual models. They are grouped according to the relevant sub-headers below.

Patients’ Health Behavior: Personal Health Practices

- HCPs take an individual’s likelihood of being adherent into account when determining which type of rhythm or anticoagulant drugs an individual should receive

“The patient education is reinforcing the stroke risk. We’re determining compliance with the anti-rhythmic – I mean, with the anti-coagulant. With the Warfarin, it is easy to see. With the DOACs, it’s – we just have to kind of take it on blind faith that they’re taking it correctly. And we just remind them how important it is to take every single dose.” – HCP
- Mindfulness, meditation, and developing an ‘afib plan’ can be helpful strategies to help patients manage AF episodes and stress

One clinician stated, “*Stress levels, I’m not sure how that matters. It’s not a stress-related arrhythmia.*” However, patients report stress related to their afib. For example, one patient reported developing acrophobia because of a concern of what would happen if they were to go into afib while outside. To overcome this fear, the patient reported mindfulness and having an “afib plan” as invaluable: “*I have my atrial fib plan, and if I go into it – be mindful of it when you’re in it and how you handle it when you’re in it. “Look, I got through this episode, and this is what I did. I’ll be okay; I can do this again.” That’s how you handle it. So, that – what impacts the outcome is that mental part. It really impacts that outcome.*” Another patient credits yoga

with helping him manage his AF: “I do a form of yoga every morning. It is an amazing – the – the impact is just amazing. Does it cure my AFib? The answer is ‘No’. Does it allow me to sleep through an AFib event? Absolutely”- Patient

Patients’ Health Behavior: Use of Health Services

- HCP’s do not have a clear preference for one NOAC versus another, they typically rely on the individual’s formulary

Patients Outcomes

Participants generally agreed with the original bulleted points, however, several additions were suggested and are also included in the Table.

Table 26. (A4.4) Stakeholder feedback on draft conceptual model: ‘patients outcomes’

Outcomes	HCP	Patient	
Perceived health status			
Perceived risk of stroke or bleeding events	✓	✓	“Awareness of risk for stroke or bleeding. Yeah, that kind of – it does kind of bother me.” – Patient
Frequency/ severity of symptoms	✓	✓	“Frequency and severity of symptoms. Again, that always gets their attention.” – HCP
Evaluated health status			
Risk of stroke	✓	✓	“Risk of stroke. That wasn’t made clear to me in the – in the early rounds. I get it now, but again, I think

			some simple handouts could get data in people's hands on." – Patient
Stroke	✓	✓	
Bleeding events	✓	✓	"Bleeding events are a factor that limit the available treatments, so if the person had bleeding issues, or they want to be on a drug, but they have contraindications to that, or they're worried about side effects." – HCP
Fatigue	✓	✓	"Fatigue, yeah, I guess some people feel fatigue. Yeah, I think fatigue would happen with this disease." – HCP
Weight gain	-	✓	"I don't think weight gain has been much of an issue." – HCP "I don't really per say think it's the medications or what they're doing that's causing the weight gain as much as it is the fear of exercising with atrial fibrillation. A lot of people are scared to exercise and afraid of getting their heartrate up too high. I think that's where doctors maybe need to prescribe or recommend cardio rehab." – Patient

Consumer satisfaction	✓	()	“Yeah, I think definitely consumer satisfaction will influence health behavior too. You’ve got that here on top.” – HCP
Suggested additions	<ul style="list-style-type: none"> • Maintenance of sinus rhythm • INR results • Symptoms: anxiety, bruising, shortness of breath 		

(✓) = yes, important; (-) no, not important; () = neither agree nor disagree; ≠ = contradicting

viewpoints

Appendix II. Aim 1 – Internal Review Board Protocol

Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk Stratification Schemes and Shared Decision-Making: Study Protocol

Introduction/Objective

To determine which patients should receive anticoagulation therapy for AF, researchers constructed stroke risk-prediction models that score a patient's risk by giving "points" for comorbidities and demographic characteristics, including congestive heart failure, hypertension, age 65-74 years, age ≥ 75 years, diabetes mellitus, gender, and vascular disease. While widely recommended in clinical guidelines, further critical evaluation of these tools is necessary as some studies have shown that segments of the population are less likely to receive anticoagulants. For example, validation studies for these risk-stratification schemes were undertaken in elderly populations, making it unclear how applicable the tools are to younger AF populations. Given the availability of effective anticoagulants, it is important to verify that disparities in treatment are not due to limitations in the risk-stratification schemes.

We consider this **PCOR pilot study** as a first step to PCOR patient engagement to solicit perspectives from patients, physicians, and pharmacists to inform an administrative claims-based analysis of the utility of risk-stratification schemes for preventing stroke among AF patients. The results will be used to inform future steps in the research.

The specific aims of this study are to:

1. Understand stakeholder (patient, physician, and pharmacist) perceptions of risk and treatment in AF and gather self-reported information from these stakeholders on decision-making and risk-stratification tools for stroke in AF
2. Enable stakeholders to provide feedback on a conceptual model related to risk stratification in AF

3. Prioritize research questions in AF risk stratification based on stakeholder opinions/needs

This study constitutes our **pre-engagement** steps to solicit initial stakeholder input from patients, physicians, and pharmacists to inform methods and dissemination of a secondary data analysis of risk-stratification in AF. Example questions will probe on issues such as:

- What do patients know about AF risk factors?
 - When they were diagnosed and when treatment decisions were being made, was the patient included in decision-making?
 - Were risk-stratification schemes explained to and discussed with the patient at the time of diagnosis? Was there transparency? Did patients understand their use?
 - What was their comfort level with the information? Do they believe it helped them understand their disease, risk, and/or treatment options?
 - How do physicians utilize risk-stratification schemes for treatment decision-making? Do they discuss the risk-stratification score with the patient?
 - Do they approach this decision differently based on patient characteristics? If so, which characteristics?
 - What is each clinician's role in risk stratification and communication of that information to patients?
-
- Research design and sampling

Overview:

This project initiates pre-engagement activities in prioritization, framing the questions, selection of comparators and outcomes, and creation of a conceptual framework. This project allows Elisabeth Oehrlein, a graduate student studying CER-PCOR to gain experience in patient pre-engagement, engagement activities, and qualitative research. It will help establish partnerships between the School of Pharmacy, the School of Medicine and AF patient organizations, such as

stopafib.org. It will also provide information that will guide the next level of engagement activity (e.g., a survey of various stakeholders or a more in-depth engagement of clinicians).

- Subjects and method of data collection

Clinician Interviews

A total of 10 clinician interviews will be conducted.

Physicians (cardiology (2x), electrophysiology (2x), and family medicine (2x)): AF patients are typically treated by cardiologists, electrophysiologists, and family doctors. These expert interviews will discuss perceptions of risk in AF, familiarity with and experience in use of risk-evaluation schemes and shared decision-making, and conversations about risk-stratification schemes (see Attachments for Interview Guide).

Pharmacists (2x): Pharmacists, especially those working in anticoagulation clinics, have a great deal of experience with adverse events, treatment options, and appropriate prescribing in AF. This expert interview will collect these perceptions with particular attention to patient risk for stroke or bleeding events, and risk-stratification schemes (see Attachments for Interview Guide).

Cardiac Nurse (2x): An interview with a cardiac nurse from the University of Maryland Heart and Vascular Center will be conducted in fall 2016. The purpose of this interview is to better understand barriers to appropriate treatment among AF patients (see Attachments for Interview Guide). Cardiac nurses are on the front line of care and may be more approachable to patients than physicians. Patients may be more likely to talk to nurses about lifestyle barriers to appropriate treatment. For example, a patient interviewed about treatment decision-making felt

comfortable bringing up a concern related to eating strawberries (which may reduce effectiveness of warfarin) during a nursing consultation.²⁰⁰

Clinician Inclusion Criteria:

- Involved in the care of AF patients

Clinician Exclusion Criteria:

- Unable to give informed consent
- Non-English speaking

AF Patient Interviews:

A total of 3 patient interviews will be conducted.

In depth interviews of three stopafib.org members will be conducted in fall 2016 by telephone.

An advertisement (see Attachment) will be posted on their online forum. Eligible patients will be 65 years or younger with at least three AF-related health care visits since diagnosis. Patients will identify which risk factors and comorbidities they find most worrisome in terms of developing stroke. They will be asked to identify educational resources they have been provided related to these risk factors and which risk factors their physicians and pharmacists emphasize. Particular attention will be paid to the language used by patients to describe their patient experience.

These discussions will focus on the AF patient experience with the healthcare system. We will discuss when patients were diagnosed, what information they received about their diagnosis and related risk factors, if risk-stratification scheme scoring was discussed, how shared decision-making factored into their treatment selection, and barriers to adequate treatment. Finally, participants will be requested to provide feedback on how and where they access information about AF. In addition to these interviews, patients will be asked to provide feedback on a conceptual framework (see Appendix).

Patient Inclusion Criteria:

- Men and women ages 18-65 with a diagnosis of AF
- Minimum of 3 health care visits where AF was discussed since diagnosis

Patient Exclusion Criteria:

- Unable to give informed consent
- Non-English speaking

Study Outcomes:

- Participant knowledge, attitudes, and experiences with AF treatment decision-making and risk stratification
- Comprehensive conceptual framework to guide future analyses and interpretation of results

- Recruitment

Clinicians: Health care providers will be identified in two ways: (1) recommendations from School of Pharmacy faculty; and (2) by examining the University of Maryland Medical Center's website. Potential participants will be contacted by email two times to identify whether they are interested and eligible to participate in this study. Potential participants identified through the UMMC website will be contacted in alphabetical order by last name. See Attachment for recruitment advertisement/email.

Patients: We will post an advertisement to participate in this study (see Attachment) on the Atrial Fibrillation Support Group on Facebook. Debbe McCall, MBA, our AF patient partner, also serves as Administrator for the Atrial Fibrillation Support Group and has granted permission for this advertisement to be posted once IRB approval has been granted. Patients will be requested to contact Elisabeth Oehrlein by email or telephone (listed on the advertisement). Elisabeth will screen participants by telephone to ensure they meet inclusion criteria.

Compensation: Patients will be provided a \$50 honorarium for their participation, while health care providers will be provided with a \$100 honorarium. Both amounts will be provided as visa gift cards.

- Data Analysis

Audio recordings of interviews will be transcribed and analyzed using interpretative phenomenological analysis (IPA) in an approach similar to Leahy et al. (Leahy, Desmond, Coughlan, O'Neill, & Collins, 2016) In IPA, the researcher aims to learn about an individual's personal experiences, where participants are viewed as storytellers. (Leahy et al., 2016; Smith JA., Flowers P., & Larkin M., 2009) Themes will be identified from experiences and incorporated into the Conceptual Framework. This approach is particularly desirable for this study design, since the sample size is small.

A narrative of the themes including verbatim phrases that best represent stakeholder perspectives will be developed. The identified themes will further define and describe subjects' experiences with diagnosis and treatment of AF.

- Reporting Procedures

Findings will be presented at future professional meetings and conferences as submitted abstracts for peer review for posters or podium presentations, and submitted as manuscripts to peer-

reviewed journals. Participants will receive appropriate acknowledgement for their contributions either in name or as anonymous subject based upon their preference.

Participants will be notified of all results, presentations, and publications as they become available.

- Protection of subjects

Risks

The risk of a breach of confidentiality is minimal. The data collected during this study will be kept confidential. Only Elisabeth Oehrlein will have access to identifying information on study participants that will be used only during recruitment (e.g. names, addresses, and phone numbers). No other identifying information will be collected, and all identifying information will be destroyed following conclusion of the interviews. The research team will receive a transcript of the interviews without any participant personal identifiers. The transcriptions will remain in a password-protected private folder with access restricted to the research team only.

The risk of breach of privacy is minimal. The research team (Elisabeth Oehrlein excepted) will have no contact with the participants except for conducting the interviews. Elisabeth Oehrlein will handle all recruiting, schedule the facilities, conduct the interviews, and audio record the interviews. No information gathered or reported will contain any personal identifiable information of the participants. The research team will receive a transcript with no personal

identifiers. The participants will be identified generically as participant A, B, C etc. The interview will take place in a private room or on the telephone with one or two research team members present.

There is a potential for psychological discomfort. To minimize this risk, we will proceed as follows: participants will be told that they can stop at any time. They also will be reminded of their right to remain silent if they do not feel comfortable answering some questions. They will be told that it is fine to not answer questions when they do not feel comfortable answering them.

Benefits

There will be no direct benefit to the participants involved in these interviews. They will benefit indirectly by knowing that they are contributing insight to a topic that affects them. The proposed study could lead to identification and implementation of strategies to improve the quality of care for patients with AF.

Risk Benefit Ratio

The potential benefits of this study outweigh the minimal risks to participants.

Participant Withdrawal

Participants will be able to stop participating in the interview at any point. They will not be penalized in any way and will receive compensation regardless of their level of participation in the interview.

- Informed Consent Process

Alteration of Consent

We are requesting a waiver of written documentation of informed consent for participants in this study.

- 1) The study is minimal risk. The probability & magnitude of harm/discomfort anticipated in the interviews are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.
- 2) The waiver or alteration will not adversely affect the rights and welfare of the participants. The only record linking the participant and the study would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Removing this link further minimizes risks.

Waiver of HIPAA Authorization

We are requesting a HIPAA waiver in order to recruit study participants using email.

Informed Consent Process

Healthcare provider who treats patients with AF: A consent form describing in detail the procedures and risks of the study will be provided to the participants. The PI will verbally describe the procedures and allow ample time to read the consent form, ask questions and consider if they want to participate in the study. The subject will verbally consent before the interview begins but after the recording is initiated. The participant will receive a copy of the informed consent document. The participant may withdraw consent at any time during the interview.

Patients with AF: A consent form describing in detail the procedures and risks of the study will be provided to the participant. The PI will read the consent form aloud prior to commencing the interview study. If they agree, participants will provide verbal consent before the interview begins but after the recording is initiated. The participant may withdraw consent at any point in the study.

- Data Collection, Handling and Storage

All interviews will be audio-recorded. To protect the privacy of participants, they will be referred to by a letter (e.g. participant A, B, C). The researchers will receive a verbatim transcript of the interviews from a professional transcription service that will not contain identifiable participant information. The researchers will not be able to trace back to any specific participant through this information. Audio recordings will be kept in a secure password-protected server with access only by research team members. The audio recordings of the interviews will be held until

completion of analyses in case questions arise regarding the transcripts and then they will be destroyed.

References

- Siouta, E., Hellstrom Muhli, U., Hedberg, B., Brostrom, A., Fossum, B., & Karlgren, K. (2015). Patients' experiences of communication and involvement in decision-making about atrial fibrillation treatment in consultations with nurses and physicians. *Scandinavian Journal of Caring Sciences*, doi:10.1111/scs.12276 [doi]
- Leahy, D. M., Desmond, D., Coughlan, T., O'Neill, D., & Collins, D. R. (2016). Stroke in young women: An interpretative phenomenological analysis. *Journal of Health Psychology*, 21(5), 669-678. doi:10.1177/1359105314535125 [doi]

Appendix III. Aim 1 – Consent Document – Clinicians

RESEARCH CONSENT FORM

Protocol Title: Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk

Stratification Schemes and Shared Decision-Making

Protocol Number:

Principal Investigator: Jennifer Albrecht, PhD (Elisabeth M. Oehrlein's Dissertation)

This is a research study involves an interview. Your participation is completely voluntary. You may choose not to participate or continue in this study at any time.

PURPOSE OF STUDY

- To gather information on your experiences with the diagnosis and treatment of afib and to help us develop a conceptual framework of afib patient's experiences

WHAT YOU WILL BE ASKED TO DO

- You are being asked to participate in this study because you treat patients with afib
- This interview will last approximately 1 hour. I am also interviewing a number of health care providers involved in the care of persons with afib, along with afib patients themselves
- This interview will be audio-recorded, but you will not be asked to give your name
- Answer to the best of your ability
- Please participate for the entire interview, but you do not have to respond to any questions you are not comfortable answering.

POTENTIAL RISKS

- Breach of confidentiality. This risk is unlikely and would be minimal due to the type of information we will be collecting. To minimize this risk:
 - Written documents from the interview will not include your name. The files will be saved in a password-protected file that will be accessible to authorized study team members only.
- Breach of privacy. This risk is also minimal. The lead investigator (myself) will handle all recruiting, scheduling, conducting, and audio recording the interviews. No information gathered or reported will contain any personal identifiable information on any of the participants.
- Psychological discomfort. You may feel uncomfortable with some of the topics or questions asked during this interview. This risk is unlikely; but, to minimize this risk:
 - It is fine to not answer questions when you do not feel comfortable answering them and
 - You can stop participating in the interview at any time.

POTENTIAL BENEFITS

- You will not directly benefit from participating in this interview. However, you are contributing your insights on a topic that affects you. This could help improve the quality of care for individuals with afib in the future.

ALTERNATIVES TO PARTICIPATION

- Your alternative is to not take part in the interview.

COSTS TO PARTICIPANTS

- It will not cost you anything to take part in this study.

PAYMENT TO PARTICIPANTS

- You will receive \$100 for participating in this study

CONFIDENTIALITY AND ACCESS TO RECORDS

- This study will not involve confidential information. We will gather information on your experiences with the diagnosis and treatment of afib

- The data from the study may be published. However, you will not be identified by name.

RIGHT TO WITHDRAW

- You do not have to take part in this research. You are free to withdraw your consent at any time during the interview. If you decide to stop taking part, or if you have questions, concerns, or complaints, please contact me, Elisabeth Oehrlein, at 410-706-0908.
- There are no adverse consequences (physical, social, economic, legal, or psychological) if you decide not to participate in this interview or if you decide not to participate for the entire length of the interview.

Can I be removed from the research?

- We do not anticipate removing any person from this study as their participation in this interview discussion will only happen once. A person may be asked to leave early from the interview if they are unable to follow instruction from the research staff.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research all rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. The research has been reviewed and approved by the UMB Institutional Review Board (IRB). Please call the IRB if you have questions about your rights as a research participant.

The research described in this consent form has been classified as minimal risk by the IRB of UMB. The IRB is a group of scientists, physicians, experts, and other persons. The IRB's membership includes persons who are not affiliated with UMB and persons who do not conduct research projects. The IRB's decision that the research has minimal risk does not mean that the

research is risk-free. You are assuming risks of injury as a result of research participation, as discussed in the consent form.

If you are harmed as a result of the negligence of a researcher, you can make a claim for compensation. If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the staff of the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office
800 W. Baltimore Street, Suite 100
Baltimore, MD 21201
410-706-5037
hrpo@umaryland.edu

Appendix IV. Aim 1 – Consent Document – Patients

RESEARCH CONSENT FORM

Protocol Title: Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk

Stratification Schemes and Shared Decision-Making

Protocol Number:

Principal Investigator: Jennifer Albrecht, PhD (Elisabeth M. Oehrlein's Dissertation)

This is a research study involves an interview. Your participation is completely voluntary. You may choose not to participate or continue in this study at any time.

PURPOSE OF STUDY

- To gather information on your experiences with the diagnosis and treatment of afib and to help us develop a conceptual framework of afib patient's experiences

WHAT YOU WILL BE ASKED TO DO

- You are being asked to participate in this study because you have a diagnosis for afib
- This interview will last approximately 1 hour. I am also interviewing two other persons with afib and a number of health care providers involved in the care of persons with afib
- This interview will be audio-recorded, but you will not be asked to give your name
- Answer to the best of your ability
- Please participate for the entire interview, but you do not have to respond to any questions you are not comfortable answering.

POTENTIAL RISKS

- Breach of confidentiality. This risk is unlikely and would be minimal due to the type of information we will be collecting. To minimize this risk:
 - Written documents from the interview will not include your name. The files will be saved in a password-protected file that will be accessible to authorized study team members only.
- Breach of privacy. This risk is also minimal. The lead investigator (myself) will handle all recruiting, scheduling, conducting, and audio recording the interviews. No information gathered or reported will contain any personal identifiable information on any of the participants.
- Psychological discomfort. You may feel uncomfortable with some of the topics or questions asked during this interview. This risk is unlikely; but, to minimize this risk:
 - It is fine to not answer questions when you do not feel comfortable answering them and
 - You can stop participating in the interview at any time.

POTENTIAL BENEFITS

- You will not directly benefit from participating in this interview. However, you are contributing your insights on a topic that affects you. This could help improve the quality of care for individuals with afib in the future.

ALTERNATIVES TO PARTICIPATION

- Your alternative is to not take part in the interview.

COSTS TO PARTICIPANTS

- It will not cost you anything to take part in this study.

PAYMENT TO PARTICIPANTS

- You will receive \$50 for participating in this study

CONFIDENTIALITY AND ACCESS TO RECORDS

- This study will not involve confidential information. We will gather information on your experiences with the diagnosis and treatment of afib

- The data from the study may be published. However, you will not be identified by name.

RIGHT TO WITHDRAW

- You do not have to take part in this research. You are free to withdraw your consent at any time during the interview. If you decide to stop taking part, or if you have questions, concerns, or complaints, please contact me, Elisabeth Oehrlein, at 410-706-0908.
- There are no adverse consequences (physical, social, economic, legal, or psychological) if you decide not to participate in this interview or if you decide not to participate for the entire length of the interview.

Can I be removed from the research?

- We do not anticipate removing any person from this study as their participation in this interview discussion will only happen once. A person may be asked to leave early from the interview if they are unable to follow instruction from the research staff.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research all rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. The research has been reviewed and approved by the UMB Institutional Review Board (IRB). Please call the IRB if you have questions about your rights as a research participant.

The research described in this consent form has been classified as minimal risk by the IRB of UMB. The IRB is a group of scientists, physicians, experts, and other persons. The IRB's membership includes persons who are not affiliated with UMB and persons who do not conduct

research projects. The IRB's decision that the research has minimal risk does not mean that the research is risk-free. You are assuming risks of injury as a result of research participation, as discussed in the consent form.

If you are harmed as a result of the negligence of a researcher, you can make a claim for compensation. If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the staff of the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office
800 W. Baltimore Street, Suite 100
Baltimore, MD 21201
410-706-5037
hrpo@umaryland.edu

Appendix V. Aim 1 – Interview Guide: Nurses

Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk

Stratification Schemes and Shared Decision-Making: Nurse Interview Discussion Guide

Nurse Interview Discussion Guide

Hello, my name is Elisabeth Oehrlein and I am a graduate student at the University of Maryland School of Pharmacy. I would like to thank you for agreeing to speak with me today. I'd like to hear your valuable opinions and experiences related to the diagnosis and treatment of atrial fibrillation (AFIB) among your patients. Your opinion is valuable and you will help us to learn more about the things that may affect whether or not a person is treated for afib. We will also ask for your advice about a flowchart we created that shows the types of things that impact whether or not afib patients receive treatment. We want to know if you think we got it right.

I want to begin by providing you with some background information about this project. This work is funded by the University of Maryland's PATIENTs program, which is a program to involve patients in research as experts on their health condition.

The information you give us is completely confidential. We will not associate your name with anything you say during this conversation.

You can decide not to answer a question. That is fine. If at any time you want to stop the interview, please just let me know and we will stop.

We will not identify you by name, but we will use the information you provide to help us better understand patients' experiences with afib treatment.

This interview is being recorded so that we do not get anything wrong when we write our research report. Your identity will remain anonymous, meaning we will not use your name in any written documents and we will not link your name to any comments in the report. In order to protect your privacy, please don't mention any afib patients or healthcare providers by name.

I am going to read the informed consent document aloud and have provided a copy to you by email. Once we have gone through the consent document, I will need you to either agree or disagree to participate out loud. If you agree to participate, we will continue to the interview. (Informed consent here – see Appendix 1)

Do you have any questions?

I am going to start the tape recorder and would like you to state that you are an afib patient and that you agree to participate in this interview. **START TAPE RECORDER - HAVE PARTICIPANT STATE THEIR AGREEMENT. PROCEED WITH THE INTERVIEW:**

If there are no further questions, I would like to begin the interview.

Domain 1 – Diagnosis and Understanding

DG1: About how many afib patients do you see in a week/month?

DG2: In your experience, what is a typical sequence of events leading to diagnosis of patients with afib? When you first see afib patients, where are they coming to you from (e.g., what types of specialists or settings)? Could you please describe to me the most common pathways they take to get to you?

DG3: Following diagnosis, what happens?

- Are patients usually referred to a specialist?
 - Which type of specialist?

DG4: Are there specific questions that afib patients ask you following diagnosis?

- Do you believe patients with afib leave the doctor's office with all the information they need? With having all of their questions answered? What are the barriers that you think are preventing your patients from getting all the information they need and having all of their questions answered?
- How are you a resource for newly diagnosed patients? How could you be better utilized
- Do your patients understand what afib is? How do they describe afib to others? Please elaborate.

Domain 2 – Treatment Decision-Making

TX1: In your experience, what are the most common treatments for preventing stroke among afib patients?

- Probe: Are there treatments besides the NOACs and VKA's that you feel are important or widespread?

TX2: What goes into a decision to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX3: What goes into your decision *not* to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX4: How does the patient's age play into the decision to treat or not treat? Do you think that younger patients, for example those in their 50's, have the same likelihood of being treated as those with similar disease who are in their 70's?

TX5: In what way does gender impact treatment decision-making?

TX6: Are you familiar with risk-stratification tools for deciding which afib patients to treat?

Probe: Have you used the CHADS tool?

- If so, which are you familiar with?
 - Where did you learn about these tools?
 - Do you find that your peers are generally familiar with these tools?
 - Are these tools helpful?
 - Do you believe these tools are missing important risk factors, could you please describe them to me and describe why they are important?
 - Do you believe there are risk factors included in these tools that you think should be left out?
 - Do you talk with patients about these tools or your findings regarding their scoring on the tools and how that information might guide treatment? If, yes, what is their reaction? If not, why not?
- If you are not familiar with these tools, what is it about specific patients that make you decide to not treat them?

In your experience, what makes the difference between using aspirin versus a prescription anticoagulant?

TX7: If patients are treated with anticoagulants, what do you think impacts the type of anticoagulant they receive?

- Probe: What is your primary source of information about the safety or efficacy of newer drugs?
 - Do patients have a "voice" in which treatments they receive? Do you discuss costs during these conversations?

TX8: Could you describe for me if patients voice concerns over their medications? If so, which concerns?

- If they voice concerns over *not* being prescribed medications for their afib, could you describe those for me?

TX9: In conversations you have with other clinicians, what concerns do they have?

- Are risk factors or risk-stratification tools mentioned during these conversations?
 - If yes, do you believe patients understand these conversations?

TX10: Which resources do you use for learning about treating afib patients?

- Are there particular documents or websites you rely on?
- Are there other resources that would be helpful to you?

Domain 3 – Feedback on Conceptual Framework

CF1: I'm trying to get a sense of what might help patients receive treatment in the best way possible so that they can reduce their likelihood of having a stroke. In order to understand your experiences in terms of implementing and monitoring treatment, I'm creating a document that shows what makes afib patients more likely or less likely to receive optimal treatment. Also, I want to know what might get in the way of patients getting treated in the best way possible.

- Could you take a look at the document I sent to you before this interview. Let me walk through it with you.
- Do you think it fits with your experiences? If yes, how? If no, why not? Are there things that are missing?

(Refer to standard Andersen conceptual model)

Is there anything you would like to add? Anything you think I should have asked that I didn't ask?

Closing

Thank you again for participating in this interview and providing insights into your experiences, it has been very helpful. Once I've concluded this project would you like a copy of the results?

Would it be okay for me to contact you about future studies?

If you have any questions or comments, please feel free to contact me by phone or email.

Appendix VI. Aim 1: Interview Guide – Patients

Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk

Stratification Schemes and Shared Decision-Making

Patient Interview Guide

Hello, my name is Elisabeth Oehrlein and I am a graduate student at the University of Maryland School of Pharmacy. I would like to thank you for agreeing to speak with me today. I'd like to learn from your experiences in living with atrial fibrillation, also called afib. Your opinion is valuable and you will help us to learn more about the things that may affect whether or not a person is treated for afib. We will also ask for your advice about a flowchart we created that shows the types of things that impact whether or not afib patients receive treatment. We want to know if you think we got it right.

I want to begin by providing you with some background information about this project. This work is funded by the University of Maryland's PATIENTs program, which is a program to involve patients in research as experts on their health condition.

The information you give us is completely confidential. We will not associate your name with anything you say during this conversation.

You can decide not to answer a question. That is fine. If at any time you want to stop the interview, please just let me know and we will stop.

We will not identify you by name, but we will use the information you provide to help us better understand patients' experiences with afib treatment.

This interview is being recorded so that we do not get anything wrong when we write our research report. Your identity will remain anonymous, meaning we will not use your name in any written documents and we will not link your name to any comments in the report. In order to protect your privacy, please don't mention any afib patients or healthcare providers by name.

I am going to read the informed consent document aloud and have provided a copy to you by email. Once we have gone through the consent document, I will need you to either agree or disagree to participate out loud. If you agree to participate, we will continue to the interview. (Informed consent here – see Appendix 1)

Do you have any questions?

I am going to start the tape recorder and would like you to state that you are an afib patient and that you agree to participate in this interview. **START TAPE RECORDER - HAVE PARTICIPANT STATE THEIR AGREEMENT. PROCEED WITH THE INTERVIEW:**

If there are no further questions, I would like to begin the interview.

Domain 1 - Diagnosis and Understanding

DG1: To start off, would you describe for me how you came to be diagnosed with afib, beginning when you first had signs or symptoms until the time when you first saw a doctor who diagnosed you with afib

- Probe: Did you seek medical advice before being diagnosed
- How did your doctor explain afib to you?
- How do you learn about afib? Where did you learn about it from?

DG2: When you learned about your afib, how did you explain it to family members or friends?

DG3: Do you feel like you leave the doctor's office having all of your questions related to your afib answered?

- If not, what gets in the way of you having all of your questions answered?
- Do you have suggestions for how this could be improved?
 - For example, would you be interested in discussing with another clinician at your doctor's office? For example, a nurse or nurse practitioner?

Domain 2 – Treatment Decision-Making

TX1: What types of treatments for afib do you know about?

- How are the medications supposed to help your afib?
- How did you learn about the different treatments available to you?
- Any others you can think of?

TX2: Are you currently being treated with any medications for afib? Which medicines?

- When you were prescribed the medication, what was the conversation like between you and your doctor?
- Did he/she talk about other medications? Or give you options?
- If you are taking a medication, are you able to take it as your doctor recommended? Is there anything that interferes with you taking it the way your doctor or pharmacist recommends?

TX3 (NOT receiving meds): *If patient reports they are not receiving medications:* Can you explain for me how you and your doctor came to decide not to use medication?

- **Probe:** Did you feel like you had a say in whether you were given a medication or not?

TX4: How did you feel about the decision to treat (or not treat) your afib?

TX5: Can you describe for me how you are able to have a voice in the type of afib treatment that you receive? What helps you be heard? What gets in the way of you having a voice?

TX6: Can you describe for me if you have you ever heard of any tools that can help your doctor make a decision about whether to prescribe afib medications?

- Probe: Have you ever heard of something called the CHADS?
- Did your doctor discuss your risk for stroke with you in any detail? Do you know what your risk factors are? If yes, can you tell me what they are?
- Did your doctor talk ever talk with you about the benefits and risks of treatment so you could decide which was best for you?

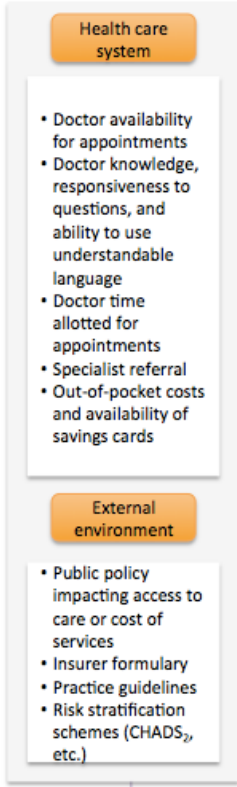
TX7: If you're concerned about your afib, who would you talk to?

- Probe: Could you describe for me your network of support? How does your network help with your care?
 -

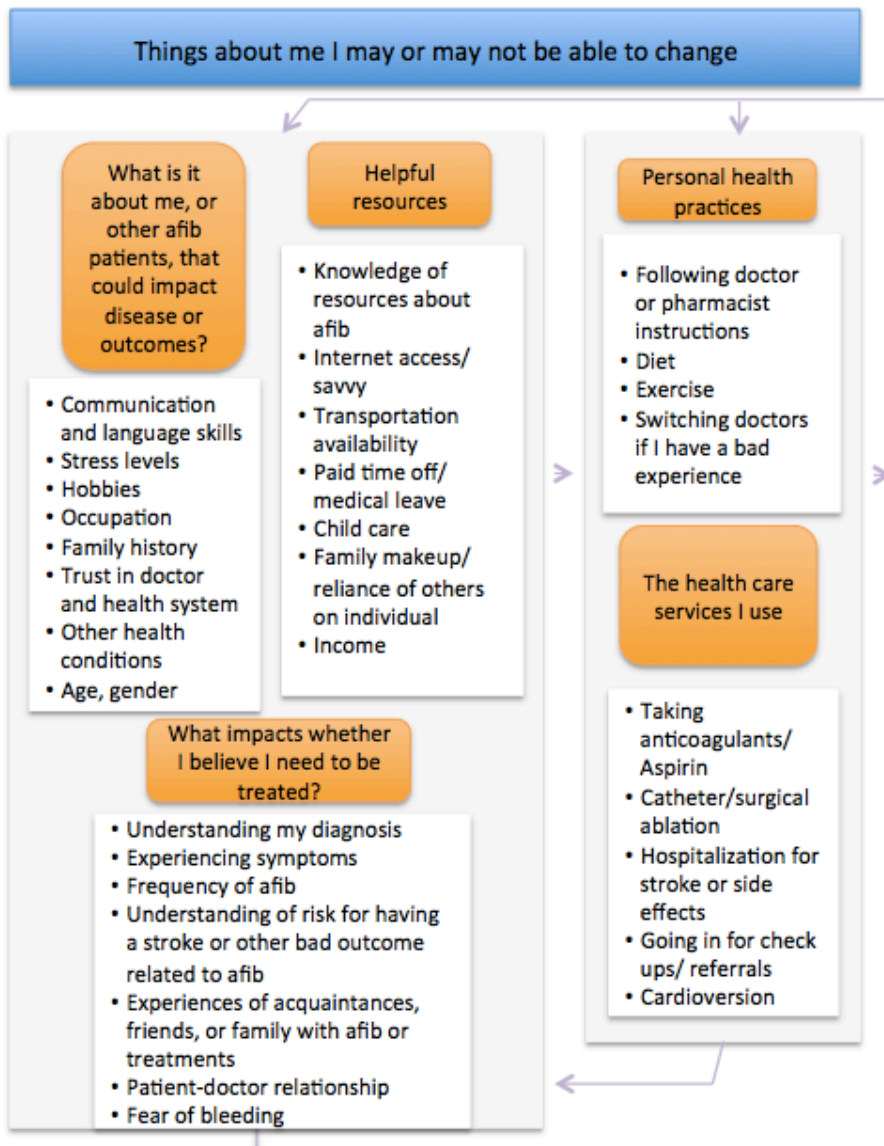
Domain 3 – Feedback on Conceptual Framework

- I'm trying to get a sense of what might help you receive treatment in the best way possible so that you can reduce your likelihood of having a stroke. In order to understand your experiences in terms of getting treated, I'm creating a document that shows what makes afib patients more likely or less likely to receive optimal treatment. Also, I want to know what might get in the way of getting treated in the best way possible.
- Could you take a look at the document with the diagram I sent to you before this interview? Let me walk through it with you.
- Let's start with the first column. Do you think it fits with your experiences? Are there things that are missing?
 - Does the language make sense? Or are there words that are better?

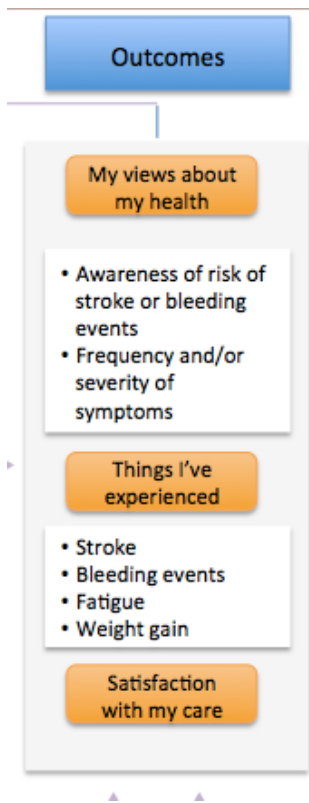
Things I can't change



- Now, let's take a look at the second section. Again, do you think it fits with your experiences? Are there things that are missing?
 - Does the language make sense? Or are there words that are better?

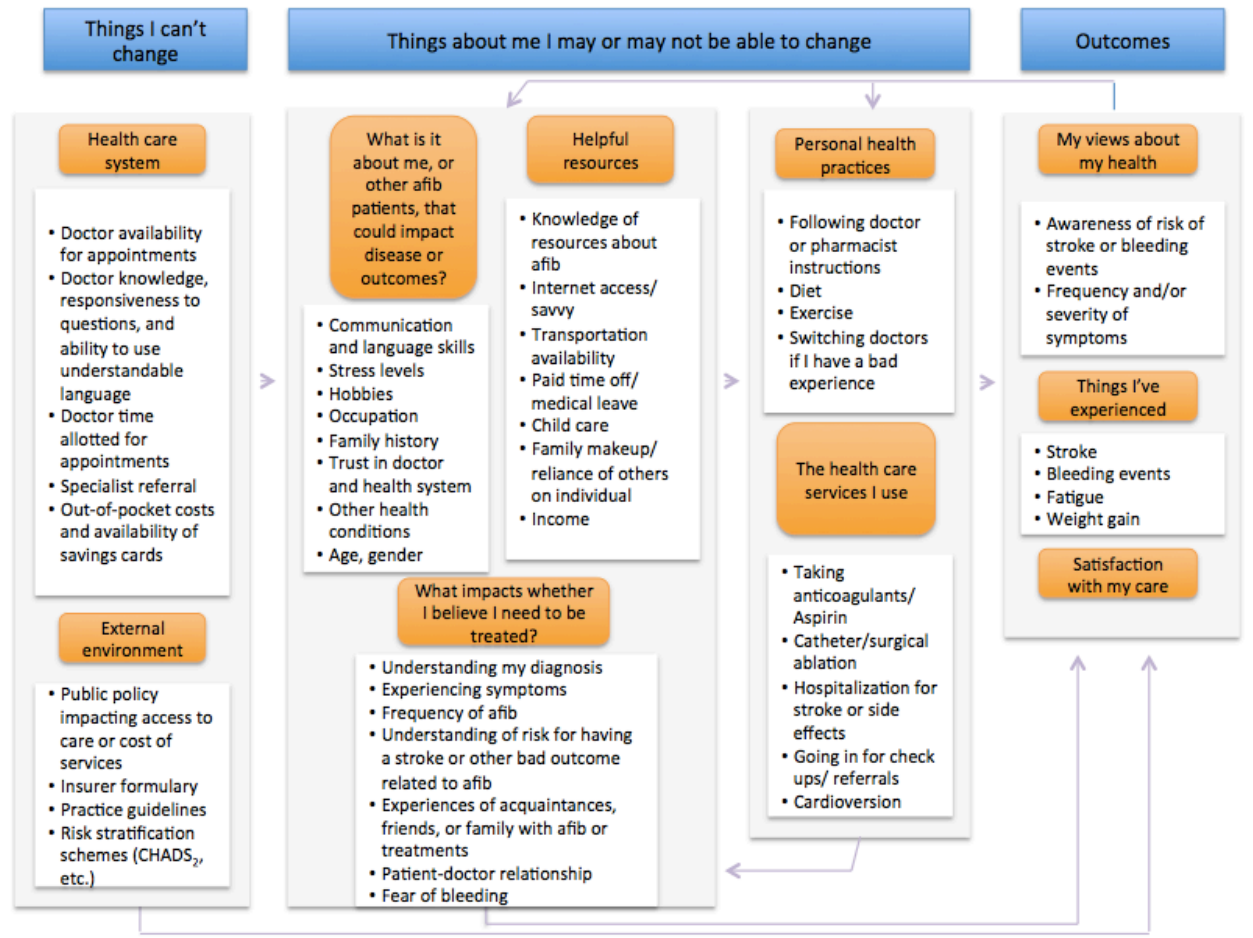


- Now, let's take a look at the last column. Are there things that are missing?
 - Does the language make sense? Or are there words that are better?



Lastly, let's take a look at the pieces together. This is how I thought about them, but do you think they are somehow out of order, or grouped incorrectly?

Are the arrows pointing in the right directions and connecting the correct boxes?



Is there anything you would like to add? Anything you think I should have asked that I didn't ask?

Thank you again for participating in this interview and providing insights into your experiences. It has been very helpful. Once I've concluded this project, would you like for me to send a copy of the results to you? Would it be okay for me to contact you about future studies?

If you have any questions or comments, please feel free to contact me by phone or email.

Appendix VII. Aim 1: Interview Guide – Pharmacists

Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk

Stratification Schemes and Shared Decision-Making: Nurse Interview Discussion Guide

Pharmacist Interview Discussion Guide

Hello, my name is Elisabeth Oehrlein and I am a graduate student at the University of Maryland School of Pharmacy. I would like to thank you for agreeing to speak with me today. I'd like to hear your valuable opinions and experiences related to the diagnosis and treatment of atrial fibrillation (AFIB) among your patients. Your opinion is valuable and you will help us to learn more about the things that may affect whether or not a person is treated for afib. We will also ask for your advice about a flowchart we created that shows the types of things that impact whether or not afib patients receive treatment. We want to know if you think we got it right.

I want to begin by providing you with some background information about this project. This work is funded by the University of Maryland's PATIENTs program, which is a program to involve patients in research as experts on their health condition.

The information you give us is completely confidential. We will not associate your name with anything you say during this conversation.

You can decide not to answer a question. That is fine. If at any time you want to stop the interview, please just let me know and we will stop.

We will not identify you by name, but we will use the information you provide to help us better understand patients' experiences with afib treatment.

This interview is being recorded so that we do not get anything wrong when we write our research report. Your identity will remain anonymous, meaning we will not use your name in any written documents and we will not link your name to any comments in the report. In order to protect your privacy, please don't mention any afib patients or healthcare providers by name.

I am going to read the informed consent document aloud and have provided a copy to you by email. Once we have gone through the consent document, I will need you to either agree or disagree to participate out loud. If you agree to participate, we will continue to the interview. (Informed consent here – see Appendix 1)

Do you have any questions?

I am going to start the tape recorder and would like you to state that you are an afib patient and that you agree to participate in this interview. **START TAPE RECORDER - HAVE PARTICIPANT STATE THEIR AGREEMENT. PROCEED WITH THE INTERVIEW:**

If there are no further questions, I would like to begin the interview.

Domain 1 – Diagnosis and Understanding

DG1: About how many afib patients do you see in a week/month? Do you engage them in conversations about their AF medications or vice versa?

DG2: In your experience, what is a typical sequence of events leading to diagnosis of patients with afib? When you first see afib patients, where are they coming to you from (e.g., what types of specialists or settings)? Could you please describe to me the most common pathways they take to get to you?

DG3: Following diagnosis, what happens?

- Are patients usually referred to a specialist?
 - Which types of specialist?

DG4: Are there specific questions that afib patients ask you following diagnosis?

- Do you believe patients with afib leave the doctor's office with all the information they need? With having all of their questions answered? What are the barriers that you think are preventing your patients from getting all the information they need and having all of their questions answered?
- How are you a resource for newly diagnosed patients? How could you be better utilized
- Do your patients understand what afib is? How do they describe afib to others? Please elaborate

Domain 2 – Treatment Decision-Making

TX1: In your experience, what are the most common treatments for preventing stroke among afib patients?

- Probe: Are there treatments besides the NOACs and VKA's that you feel are important or widespread? Are there other medications that your patients have questions about not directly related to treating AF, for example NSAIDS, inhalers, etc.?

TX2: What goes into a decision to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX3: What goes into your decision *not* to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX4: How does the patient's age play into the decision to treat or not treat? Do you think that younger patients, for example those in their 50's, have the same likelihood of being treated as those with similar disease who are in their 70's

TX5: In what way does gender impact treatment decision-making?

TX6: Are you familiar with risk-stratification tools for deciding which afib patients to treat?

Probe: Have you used the CHADS tool?

- If so, which are you familiar with?
 - Where did you learn about these tools?
 - Do you find that your peers are generally familiar with these tools?
 - Are these tools helpful? How?
 - Do you believe these tools are missing important risk factors, could you please describe them to me and describe why they are important?
 - Do you believe there are risk factors included in these tools that you think should be left out?
 - Do you talk with patients about these tools or your findings regarding their scoring on the tools and how that information might guide treatment? If, yes, what is their reaction? If not, why not?
- If you are not familiar with these tools, what is it about specific patients that make you decide to not treat them?

In your experience, what makes the difference between using aspirin versus a prescription anticoagulant?

TX7: If patients are treated with anticoagulants, what do you think impacts the type of anticoagulant they receive?

- Probe: What is your primary source of information about the safety or efficacy of newer drugs?
 - Do patients have a "voice" in which treatments they receive? Do you discuss costs during these conversations?

TX8: Could you describe for me if patients voice concerns over their medications? If so, which concerns?

- If they voice concerns over *not* being prescribed medications for their afib, could you describe those for me?

TX9: In conversations you have with other clinicians, what concerns do they have?

- Are risk factors or risk-stratification tools mentioned during these conversations?
 - If yes, do you believe patients understand these conversations?

TX10: Which resources do you use for learning about treating afib patients?

- Are there particular documents or websites you rely on?
- Are there other resources that would be helpful to you?

Domain 3 – Feedback on Conceptual Framework

CF1: I'm trying to get a sense of what might help patients receive treatment in the best way possible so that they can reduce their likelihood of having a stroke. In order to understand your experiences in terms of implementing and monitoring treatment, I'm creating a document that shows what makes afib patients more likely or less likely to receive optimal treatment. Also, I want to know what might get in the way of patients getting treated in the best way possible.

- Could you take a look at the document I sent to you before this interview. Let me walk through it with you.
- Do you think it fits with your experiences? If yes, how? If no, why not? Are there things that are missing?

(Refer to standard Andersen conceptual model)

Is there anything you would like to add? Anything you think I should have asked that I didn't ask?

Closing

Thank you again for participating in this interview and providing insights into your experiences, it has been very helpful. Once I've concluded this project would you like a copy of the results? Would it be okay for me to contact you about future studies?

If you have any questions or comments, please feel free to contact me by phone or email.

Appendix VIII. Aim 1: Interview Guide – Physicians

Patient, Pharmacist, and Physician Perspectives on Atrial Fibrillation Risk Stratification Schemes and Shared Decision-Making: Physician Interview Discussion Guide

Physician Interview Discussion Guide

Hello, my name is Elisabeth Oehrlein and I am a graduate student at the University of Maryland School of Pharmacy. I would like to thank you for agreeing to speak with me today. I'd like to hear your valuable opinions and experiences related to the diagnosis and treatment of atrial fibrillation (AFIB) among your patients. Your opinion is valuable and you will help us to learn more about the things that may affect whether or not a person is treated for afib. We will also ask for your advice about a flowchart we created that shows the types of things that impact whether or not afib patients receive treatment. We want to know if you think we got it right.

I want to begin by providing you with some background information about this project. This work is funded by the University of Maryland's PATIENTs program, which is a program to involve patients in research as experts on their health condition.

The information you give us is completely confidential. We will not associate your name with anything you say during this conversation.

You can decide not to answer a question. That is fine. If at any time you want to stop the interview, please just let me know and we will stop.

We will not identify you by name, but we will use the information you provide to help us better understand patients' experiences with afib treatment.

This interview is being recorded so that we do not get anything wrong when we write our research report. Your identity will remain anonymous, meaning we will not use your name in any written documents and we will not link your name to any comments in the report. In order to protect your privacy, please don't mention any afib patients or healthcare providers by name.

I am going to read the informed consent document aloud and have provided a copy to you by email. Once we have gone through the consent document, I will need you to either agree or disagree to participate out loud. If you agree to participate, we will continue to the interview.

(Informed consent here – see Appendix 1)

Do you have any questions?

I am going to start the tape recorder and would like you to state that you are an afib patient and that you agree to participate in this interview. **START TAPE RECORDER - HAVE**

PARTICIPANT STATE THEIR AGREEMENT. PROCEED WITH THE INTERVIEW:

If there are no further questions, I would like to begin the interview.

Domain 1 – Diagnosis and Understanding

DG1: About how many afib patients do you see in a week/month?

DG2: In your experience, what is a typical sequence of events leading to diagnosis of patients with afib? When you first see afib patients, where are they coming to you from (e.g., what types of specialists or settings)? Could you please describe to me the most common pathways they take to get to you?

DG3: Following diagnosis, what happens?

- Are patients usually referred to a specialist?
 - Which type of specialist?

DG4: Are there specific questions that afib patients ask you following diagnosis?

- Do you believe patients with afib leave the doctor's office with all the information they need? With having all of their questions answered? What are the barriers that you think are preventing your patients from getting all the information they need and having all of their questions answered?
- How are you a resource for newly diagnosed patients? How could you be better utilized
- Do your patients understand what afib is? How do they describe afib to others? Please elaborate.

Domain 2 – Treatment Decision-Making

TX1: In your experience, what are the most common treatments for preventing stroke among afib patients?

- Probe: Are there treatments besides the NOACs and VKA's that you feel are important or widespread?

TX2: What goes into your decision to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX3: What goes into your decision *not* to treat a patient with anticoagulants?

- Probe: Are there specific comorbidities or demographic characteristics that you look for in patients?

TX4: How does the patient's age play into the decision to treat or not treat? Do you think that younger patients, for example those in their 50's, have the same likelihood of being treated as those with similar disease who are in their 70's?

TX5: In what way does gender impact treatment decision-making?

TX6: Are you familiar with risk-stratification tools for deciding which afib patients to treat?

Probe: Have you used the CHADS tool?

- If so, which are you familiar with?
 - Where did you learn about these tools?
 - Do you find that your peers are generally familiar with these tools?

- Are these tools helpful?
- Do you believe these tools are missing important risk factors, could you please describe them to me and describe why they are important?
 - Do you believe there are risk factors included in these tools that you think should be left out?
- Do you talk with patients about these tools or your findings regarding their scoring on the tools and how that information might guide treatment? If, yes, what is their reaction? If not, why not?
- If you are not familiar with these tools, what is it about specific patients that make you decide to not treat them?

In your experience, what makes the difference between using aspirin versus a prescription anticoagulant?

TX7: If you decide to treat a patient with anticoagulants, what makes you decide to prescribe a specific type of anticoagulant?

- Probe: Are you familiar with novel oral anticoagulants? When would you decide to prescribe one over the other?
 - What is your primary source of information about the safety or efficacy of newer drugs?

TX8: Could you describe for me if patients voice concerns over their medications? If so, which concerns?

- If they voice concerns over *not* being prescribed medications for their afib, could you describe those for me?

TX9: In conversations you have with other prescribers, what concerns do they have?

- Are risk factors or risk-stratification tools mentioned during these conversations?
 - If yes, do you believe patients understand these conversations?
 - Do patients have a “voice” in which treatments they receive? Do you discuss costs during these conversations?

TX10: Which resources do you use for learning about treating afib patients?

- Are there particular documents or websites you rely on?
- Are there other resources that would be helpful to you?

Domain 3 – Feedback on Conceptual Framework

CF1: I'm trying to get a sense of what might help patients receive treatment in the best way possible so that they can reduce their likelihood of having a stroke. In order to understand your experiences in terms of implementing and monitoring treatment, I'm creating a document that shows what makes afib patients more likely or less likely to receive optimal treatment. Also, I want to know what might get in the way of patients getting treated in the best way possible.

- Could you take a look at the document I sent to you before this interview. Let me walk through it with you.
- Do you think it fits with your experiences? If yes, how? If no, why not? Are there things that are missing?

Is there anything you would like to add? Anything you think I should have asked that I didn't ask?

Closing

Thank you again for participating in this interview and providing insights into your experiences, it has been very helpful. Once I've concluded this project would you like a copy of the results? Would it be okay for me to contact you about future studies?

If you have any questions or comments, please feel free to contact me by phone or email.

Appendix IX. Aim 1: Patient Recruitment Language

Subject: Opportunity to Participate in Health-Related Interviews

Opportunity: Patient Perspectives on Atrial Fibrillation Treatment and Decision-Making

The goal of this study is to understand patient, physician, and pharmacist views on risk for stroke for people with atrial fibrillation or what some people call A-fib, and how risk factors into how patients get treated

Who is Eligible?

- Men and women ages 18-65 with a diagnosis of afib
- Minimum of 3 health care visits where your afib was discussed since diagnosis

What will you be asked to do?

- Complete a very brief telephone questionnaire to determine if you are eligible
- Attend a 1-hour 15 minute telephone interview (if eligible)
- Discuss what you know about risk factors for having a stroke; describe the kinds of conversations you had with your doctor when you discussed any treatments that were being considered or that you are now on; what you might know about any stroke risk tools your doctor might use; and what barriers might be getting in the way of you taking a medication.

Compensation:

- All information is confidential. You will receive a \$50 Visa gift card for your time.

If interested, contact Elisabeth Oehrlein at eoehrlein@umaryland.edu or (410) 706-0908

Appendix X. Aim 1: Health care professional recruitment language

Subject: Opportunity to Participate in Atrial Fibrillation-Related Interview

Opportunity: Health Care Professional Perspectives on Atrial Fibrillation Risk Stratification Schemes and Shared Decision-Making

The goal of this study is to understand patient, Cardiologist, Family Doctor, Electrophysiologist, Pharmacist, and Nurse perceptions of risk for stroke among atrial fibrillation patients and how this feeds into treatment decision-making

Who is Eligible?

- Cardiologists, Family Doctors, Pharmacists, Electrophysiologist, and Nurses involved in the treatment of atrial fibrillation patients.

What will you be asked to do?

- Complete a very brief telephone questionnaire to determine if you are eligible
- Attend a 1 hour 15 minute in-person or telephone interview (if eligible)
- Discuss what you know about risk factors for stroke and which resources you use for this information.
 - Your familiarity with risk-stratification tools for atrial fibrillation and how you use them in your decision-making.
 - How you approach treatment decision-making differently based on individual patients characteristics and which characteristics you consider.
 - Your discussions of these characteristics with patients, and the decision to either treat or not treat them.
 - Your opinions on a research approach, or what is called a conceptual model, for treating patients with Atrial Fibrillation, especially on how to improve that approach from your perspective.

Compensation:

- All information is confidential. You will receive a \$100 honorarium for your time.

If interested, contact Elisabeth Oehrlein at eoehrlein@umaryland.edu or (410)706-0908

Appendix XI. Aims 2 and 3 variables

Table 27. Study cohorts – inclusion criteria

Characteristic/Condition	MDC/ICD-9/V/Other
Atrial fibrillation	At least one diagnosis of ICD-9 427.31
Age	≥18 years

Table 28. Study cohorts - exclusion criteria

Characteristic/Condition	MDC/ICD-9/V/Other
Cardiac Surgery	V42.2, V43.3, 35.05-35.09, 35.20-35.28 and 35.97
Hip and Knee Replacement Surgery	V43.64, V43.65, 81.40, 81.51, 81.52, 81.53, 81.54, 81.55
History of anticoagulant use (during washout); cardioversion; catheter ablation	Any claim during “Wash-out” <ul style="list-style-type: none"> • V58.61 (Long-term/current use of anticoagulants) 3 to 12 months prior to diagnosis¹⁷⁸
Pregnancy	630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, 796.5; ICD-9 CM procedure codes: 72-75.99, or HCPCS codes: 59000-59350, 76801-76828, 83661-83664
Valvular Heart Disease	394.x, 396.0, 396.1, 396.8, 396.9, 424.0, 745.xx, V42.2, V43.3

Table 29. Study outcomes

Outcome	MDC/ICD-9/V/Other
Ischemic stroke	Any of the following (primary discharge diagnosis):

	ICD-9: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436.xx ^{10,11}
Systemic embolism	Any of the following: 444.x Arterial embolism
Receipt of anticoagulant	<p>“AnyOAC” – any oral anticoagulant received during study period</p> <ul style="list-style-type: none"> • Sub: “AnyNovOAC” – any prescription for apixaban, dabigatran, edoxaban, or rivaroxaban • Sub: “AnyVKA” – any prescription for warfarin, others

Table 30. Risk scheme calculation

CHADS₂		
Congestive heart failure	<p>1 inpatient or 2 outpatient claims:</p> <ul style="list-style-type: none"> • 428.x (heart failure), 398.91 (rheumatic heart failure (congestive)), • 402.x1 (hypertensive heart disease with heart failure: 402.01 malignant, 402.11 benign, 402.91 unspecified) • 404.x1 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage I-IV or unspecified: 404.01 malignant, 404.11 benign, 404.91 unspecified) <p>404.x3 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage V or end stage renal disease: 404.03 malignant, 404.13 benign, 404.93 unspecified)^{10,11}</p>	1 point
Hypertension	<p>One of the following:</p> <ul style="list-style-type: none"> • 401.x (essential hypertension) • 402.x (hypertensive heart disease) • 403.x (hypertensive chronic kidney disease) • 404.x (hypertensive heart and chronic kidney disease) • 405.x (secondary hypertension) <p>OR</p> <ul style="list-style-type: none"> • At least 1 dispensing of a CCB, ACEI, ARB, BB, a thiazide diuretic or a direct antihypertensive agent¹¹ 	1 point

Age ≥75 years	Administrative data	1 point
Diabetes mellitus	At least two outpatient: <ul style="list-style-type: none"> • ICD-9 250.X; OR One inpatient stay: <ul style="list-style-type: none"> • ICD-9 250.X; OR One diagnosis of ICD-9 250.X plus an insulin or oral antidiabetic dispensing ^{11,201}	1 point
Stroke/TIA	ICD-9 codes for stroke/TIA: <ul style="list-style-type: none"> • 433.xx (occlusion and stenosis of precerebral arteries), 434.x (occlusion of cerebral arteries), 435.x (transient cerebral ischemia), 436.x (acute but ill-defined cerebrovascular disease), 437.x (other and ill-defined cerebrovascular disease) ICD-9 codes for thromboembolism: <ul style="list-style-type: none"> • VTE: 451.x (phlebitis and thrombophlebitis), 453.x (other venous embolism and thrombosis) PE: 415.11 (iatrogenic pulmonary embolism and infarction), 415.12 (septic pulmonary embolism), 415.19 (other pulmonary embolism) ¹¹	2 points
CHA₂DS₂-VASc		
Congestive heart failure/LV dysfunction	1 inpatient or 2 outpatient claims: <ul style="list-style-type: none"> • 428.x (heart failure), 398.91 (rheumatic heart failure (congestive)), • 402.x1 (hypertensive heart disease with heart failure: 402.01 malignant, 402.11 benign, 402.91 unspecified) • 404.x1 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage I-IV or unspecified: 404.01 malignant, 404.11 benign, 404.91 unspecified) 	1 point

	404.x3 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage V or end stage renal disease: 404.03 malignant, 404.13 benign, 404.93 unspecified) ^{10,11}	
Hypertension	362.11, 401.xx – 405.xx, 437.2, 642.0x-642.2x, 642.7x, 642.9x, 760.0, 997.91, E942.6 ¹⁰	1 point
Age ≥75 years	Administrative data	2 points
Diabetes mellitus	At least two outpatient: <ul style="list-style-type: none"> • ICD-9 250.X; OR One hospital discharge: <ul style="list-style-type: none"> • ICD-9 250.X; OR One diagnosis of ICD-9 250.X plus an insulin or oral antidiabetic dispensing ^{11,201}	1 point
Stroke/TIA/TE	ICD-9 codes for stroke/TIA: <ul style="list-style-type: none"> • 433.xx (occlusion and stenosis of precerebral arteries), 434.x (occlusion of cerebral arteries), 435.x (transient cerebral ischemia), 436.x (acute but ill-defined cerebrovascular disease), 437.x (other and ill-defined cerebrovascular disease) ICD-9 codes for thromboembolism: <ul style="list-style-type: none"> • VTE: 451.x (phlebitis and thrombophlebitis), 453.x (other venous embolism and thrombosis) • PE: 415.11 (iatrogenic pulmonary embolism and infarction), 415.12 (septic pulmonary embolism), 415.19 (other pulmonary embolism) ¹¹ 	2 points

Vascular disease (prior MI, PAD or aortic plaque)	<ul style="list-style-type: none"> • ICD-9: 412.x (old myocardial infarction) 410.XX²⁰² (acute myocardial infarction) • ICD-9: 440.20 - 440.24 (atherosclerosis of native arteries of the extremities—with intermittent claudication, with rest pain, with ulceration, with gangrene), 440.29 (other atherosclerosis of native arteries of the extremities), 440.30-440.32 (atherosclerosis of bypass graft of the extremities: of unspecified graft, of autologous vein bypass graft, of nonautologous biological bypass graft), 443.9x (peripheral vascular disease unspecified) • ICD-9: 444.x (arterial embolism and thrombosis), 445.x (atheroembolism), Atherosclerosis: 440.x¹¹ 	1 point
Age 65–74 years	Administrative data	1 point
Sex category (i.e. female)	Administrative data	1 point
HAS-BLED		
Hypertension (i.e. uncontrolled BP)	“highBP” 362.11, 401.xx – 405.xx, 437.2, 642.0x-642.2x, 642.7x, 642.9x, 760.0, 997.91, E942.6 ¹⁰	1 point
Abnormal renal/liver function	Abnormal renal and liver function ¹¹ : <ul style="list-style-type: none"> • ICD-9 diagnostic codes: 580.xx (acute glomerulonephritis), 581.xx (nephrotic syndrome), 582.xx (chronic glomerulonephritis), 583.xx (nephritis and nephropathy not specified as acute or chronic), 584.xx ((acute kidney failure), 585.xx (chronic kidney disease), 586.xx (renal failure unspecified) • ICD-9 procedure codes: 39.95 (hemodialysis), 54.98 (peritoneal dialysis), • V-codes: V56.0 (aftercare involving extracorporeal dialysis), V56.8 (aftercare involving other dialysis) 	1 or 2 points

- CPT-4 codes: 90935-90993 (hemodialysis, miscellaneous dialysis procedures), 99512 (home visit for hemodialysis), 99559 (home infusion, peritoneal dialysis, per visit)

Abnormal liver function:

- ICD-9 diagnosis codes: 070.x (viral hepatitis), 571.x (chronic liver disease and cirrhosis), 572.x (alcoholic cirrhosis of liver), 573.x (other disorders of liver), 576.8x (other specified disorders of biliary tract), 456.0x - 456.2x (esophageal varices with bleeding, without bleeding, in diseases classified elsewhere), 155.0x (malignant neoplasm of liver primary), 155.1x (malignant neoplasm of intrahepatic bile ducts), 155.2x (malignant neoplasm of liver not specified as primary or secondary)
- ICD-9 procedure codes: 39.1x (intra-abdominal venous shunt), 42.91 (ligation of esophageal varices)

Stroke

ICD-9 codes for stroke/TIA 433.xx (occlusion and stenosis of precerebral arteries), 434.x (occlusion of cerebral arteries), 435.xx (transient cerebral ischemia), 436.x (acute but ill-defined cerebrovascular disease), 437.x (other and ill-defined cerebrovascular disease) ¹¹ 1 point

Bleeding tendency or predisposition

- ICD-9 codes¹¹: 430.x (subarachnoid hemorrhage), 431.x (intracerebral hemorrhage), 432.x (other and unspecified intracranial hemorrhage), 531.0x (acute gastric ulcer with hemorrhage), 531.2x (acute gastric ulcer with hemorrhage and perforation), 531.4x (chronic or unspecified gastric ulcer with hemorrhage), 531.6x (chronic or unspecified gastric ulcer with hemorrhage and perforation), 532.0x (acute duodenal ulcer with hemorrhage), 532.2x (acute duodenal ulcer with hemorrhage and perforation), 532.4x (chronic or unspecified duodenal ulcer with hemorrhage), 532.6x (chronic or unspecified duodenal ulcer with
- 1 point

hemorrhage and perforation), 533.0x (acute peptic ulcer of unspecified site with hemorrhage), 533.2x (acute peptic ulcer of unspecified site with hemorrhage and perforation), 533.4x (chronic or unspecified peptic ulcer of unspecified site with hemorrhage), 533.6x (chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation), 534.0x (acute gastrojejunal ulcer with hemorrhage), 534.2x (acute gastrojejunal ulcer with hemorrhage and perforation), 534.4x (chronic or unspecified gastrojejunal ulcer with hemorrhage), 534.6x (chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation), 578.0 (gastrointestinal hemorrhage); 455.2x (internal hemorrhoids with other complication), 455.5x (external hemorrhoids with other complication), 455.8x (unspecified hemorrhoids with other complication), 562.02 (diverticulosis of small intestine with hemorrhage), 562.03 (diverticulitis of small intestine with hemorrhage), 562.12 (diverticulosis of colon with hemorrhage), 562.13 (diverticulitis of colon with hemorrhage), 568.81 (hemoperitoneum nontraumatic), 569.3 (hemorrhage of rectum and anus), 569.83 (perforation of intestine), 569.85 (angiodyplasia of intestine with hemorrhage), 569.86 (dieulafoy lesion (hemorrhagic) of intestine), 578.1x (blood in stool), 578.9 (hemorrhage of gastrointestinal tract unspecified); 599.7x (hematuria), 719.1x (hemathrosis), 423.0x (hemopericardium), 786.3x (hemoptysis), 784.7x (epistaxis), 459.0x (hemorrhage unspecified)

- ICD-9 procedure code: 44.43 (endoscopic control of gastric or duodenal bleeding)
- CPT code 43255 (upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate) with control of bleeding, any method)

	<ul style="list-style-type: none"> Anemia ICD-9 codes: 285.0x (sideroblastic anemia), 285.1x (acute posthemorrhagic anemia), 285.9x (anemia unspecified) 	
Labile INR (if on warfarin)	(Cannot calculate with available data)	
Age (e.g. >65 years, frail condition)	Administrative data	1 point
Drugs (e.g. concomitant aspirin or NSAIDs) or alcohol excess	<ul style="list-style-type: none"> NSAIDs, Aspirin, clopidogrel, prasugrel, ticagrelor¹¹ ICD-9 codes: 94.61 – 94.63 – alcohol rehabilitation and detoxification 94.67-94.69 – combined alcohol/drug rehabilitaion and detoxification 303.0x – 303.9x – alcoholism 291.xx – alcohol-induced mental disorders 357.5x – alcoholic polyneuropathy 425.5x – alcoholic cardiomyopathy 571.1x – acute alcoholic hepatitis 571.2x – alcoholic cirrhosis of liver 571.3x – alcoholic liver damage, unspecified 305.0x -alcohol abuse 	1 point

Table 31. Study covariates

Condition/Characteristic	MDC/ICD-9/V
Demographics	
Age	Administrative data
Sex	Administrative data
Comorbid Conditions	
Acute coronary syndrome	410.XX, 411.XX ²⁰²
Adrenal hemorrhage	772.5x ¹⁴
Alcohol dependence/Drug Use or Induced Mental Disorders	MDC 20, ICD-9: 94.61 – 94.63; 94.67-94.69; 303.0x – 303.9x; 291.xx – ; 357.5x; 425.5x; 571.1x; 571.2x; 571.3x ; 305.0x -alcohol abuse ^{11,203,204}

Alzheimer's disease and related dementias	290.0, 290.10–290.13, 290.20–290.21, 290.3, 290.40–290.43, 294.0, 294.1, 294.10, 294.11, 294.8, 331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 797 ^{156,205}
Angina	411.1, 413.0, 413.1, 413.9 ²⁰⁶
Atherosclerosis of aorta	440.0 ²⁰⁷
Atrial flutter	427.32 ¹⁴
Cancer	hematologic (ICD-9-CM: 200–208), gastrointestinal (ICD-9-CM: 150–159), or respiratory cancer (ICD-9-CM: 170–176) or 1 inpatient claim with a primary cancer diagnosis (ICD-9-CM: 140–209) ²⁰⁸
Cardiomyopathy	425.0, 425.1, 425.2, 425.3, 425.5, 425.7, 425.8, 425.9 ²⁰⁹
Carotid artery stenosis	00.61, 00.63 ²¹⁰
Chronic kidney disease	585, 585.3, 585.4, 585.5, 585.6, 585.9, 403, 403.0, 403.00, 403.01, 403.1, 403.10, 403.11, 403.9, 403.90, 403.91, 250.4, 404, 404.0, 404.00, 404.01, 404.02, 404.03, 404.1, 404.10, 404.11, 404.12, 404.13, 404.9, 404.90, 404.91, 404.92, 404.93, 582, 582.0, 582.1, 582.2, 582.4, 582.8, 582.81, 582.89, 582.9 ²¹¹
Chronic liver disease	571.2x, 571.5x, 571.6x, 070.0x, 070.2x, 070.4x, 070.6x, 070.71, 348.3x, 456.00–456.2x, 572.20–572.4x, 782.4x, 789.59, 155.x, V42.7, 50.5, 471.35, 471.36 ¹⁴
Chronic obstructive pulmonary disease	491, 491.0, 491.1, 491.2, 491.2x, 491.8, 491.9, 492, 492.0, 492.8
Cirrhosis	456.0, 456.1, 456.2, 456.21, 567.23, 571.2, 571.5, 572.2, 572.3, 572.4, 789.59 ²¹²

Coagulation defect	286.x, 287.x ¹⁴
Congestive heart failure	<p>1 inpatient or 2 outpatient claims:</p> <p>428.x (heart failure), 398.91 (rheumatic heart failure (congestive)),</p> <p>402.x1 (hypertensive heart disease with heart failure: 402.01 malignant, 402.11 benign, 402.91 unspecified)</p> <p>404.x1 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage I-IV or unspecified: 404.01 malignant, 404.11 benign, 404.91 unspecified)</p> <p>404.x3 (hypertensive heart and chronic kidney disease, with heart failure and with chronic kidney disease stage V or end stage renal disease: 404.03 malignant, 404.13 benign, 404.93 unspecified)^{10,11}</p>
Coronary occlusion without myocardial infarction	411.81 ²⁰⁶
Diabetes	<p>At least two outpatient:</p> <p>ICD-9 250.X; OR</p> <p>One hospital discharge:</p> <p>ICD-9 250.X; OR</p> <p>One diagnosis of ICD-9 250.X plus an insulin or oral antidiabetic dispensing^{11,201}</p>
Deep vein thrombosis	451.1x, 451.2x, 453.0x, 453.2, 453.3x, 453.40, 453.41, 453.42, 453.8x, 997.2x ²¹³
Fibrinolysis	286.6
Heart transplant or left ventricular assist device	37.5x, 33.6, 37.6x, V42.1 ²⁰⁹

Hypercoagulopathy	289.8 ¹⁴
Hyperlipidemia	272.0, 272.1, 272.2, 272.4, and 272.9 ²¹⁴
Hypertension	362.11, 401.xx – 405.xx, 437.2, 642.0x-642.2x, 642.7x, 642.9x, 760.0, 997.91, E942.6 ¹⁰
Inflammatory bowel disease	555.x, 556.x ²¹⁵
Ischemic heart disease (Coronary artery disease)	411.89 ²¹⁶
Ischemic stroke	433.xx, 434.xx, 435.xx, 437.0x, 437.1x ¹⁴
Mitral valve disorders	424.0 ²¹⁷
Neurological disorders	332.x, 340.x, 342.x-344.x, 436.x ¹⁴
Obesity	278.0, 278.00, 278.01 ²¹⁸
Obstructive sleep apnea	327.23 ²¹⁹
Other hemorrhage	568.81, 719.1x, 423.0x, 455.2x, 455.5x, 456.0x, 456.20, 455.8x, 459.0x, 530.21, 530.7x, 535.x1, 537.83, 562.12, 562.13, 569.3x, 569.85, 578.0x, 578.1x, 578.9x, 596.7x, 599.7x, 782.7x, 784.7x, 786.3x, 853.xx ¹⁴
Peripheral ischemic disease	459.9 ²²⁰
Peripheral vascular disease	443.9 ²²¹
Renal insufficiency	285.21, 403.xx-404.xx, 405.xx, 458.21, 581.xx-583.xx, 582.xx, 585.1-585.6, 585.9, 586, 588.1, 588.8x-588.9, 590.00-590.01, 590.11, 591, 593.71-593.73, 593.81, 599.7, 792.5, 996.56, 996.68, 996.73, 996.81, E879.1, V42.0, V45.1x, V56.xx ¹⁰
Rheumatoid arthritis	714.xx ²²²
Sleep disorders	780.50 ²²³

Thyrototoxicosis	242.90 ²²⁴
Transient ischemic attack	435.x ²²⁵
Vascular disease history of myocardial infarction, peripheral vascular disease, or aortic plaque	<p>ICD-9: 412.x (old myocardial infarction) 410.XX²⁰² (acute myocardial infarction)</p> <p>ICD-9: 440.20 - 440.24 (atherosclerosis of native arteries of the extremities—with intermittent claudication, with rest pain, with ulceration, with gangrene), 440.29 (other atherosclerosis of native arteries of the extremities), 440.30-440.32 (atherosclerosis of bypass graft of the extremities: of unspecified graft, of autologous vein bypass graft, of nonautologous biological bypass graft), 443.9x (peripheral vascular disease unspecified)</p> <p>ICD-9: 444.x (arterial embolism and thrombosis), 445.x (atheroembolism), Atherosclerosis: 440.x¹¹</p>
Valvular heart disease	394.x-397.x, 398.9x, V42.2, V43.3 ¹⁴
Ventricular arrhythmia	427.1, 427.4x, 427.5 ²⁰⁹

Table 32. Bleeding adverse events (adapted from Wang et al. ¹¹)
Composite “major bleeding” (any of the outcomes listed in this table)

Hemorrhagic stroke	430.xx-432.xx ¹⁴
Major upper GI bleed	<p>Hospitalization with</p> <ul style="list-style-type: none"> • Diagnosis of: 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 578.0 • ICD-9 procedure code: 44.43 • CPT code 43255

Major lower and unspecified GI bleed	Hospitalization with <ul style="list-style-type: none"> • Diagnosis of: 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9
Major urogenital bleed	Hospitalization with <ul style="list-style-type: none"> • Diagnosis of 599.7 • 626.2x and secondary diagnosis indicating acute bleeding: anemia (280.0, 285.1, 285.9)
Major other bleed	Hospitalization with <ul style="list-style-type: none"> • Diagnosis of: 719.1x, 423.0x, 786.3x, 784.7x, 459.0x, 285.1x • ICD-9: esophageal hemorrhage, 530.82; hematemesis, 578; gastroduodenitis with bleeding, 535.01- 535.61; intracranial hemorrhage, 430-432; intraocular, 379.23; hemorrhage not specified, 459²⁰¹
Pulmonary embolism	415.1x ²¹³
Composite endpoint “major bleeding”	HEMSTROKEdx or MAJUPPGIdx or MAJLOWGIdx or MAJUROdx or MAJOthBLEEdx or PEMBdx

Appendix XII. Aim 2: Supplementary Tables and Figures

Table 33. (A6.1) OAC treatment initiation among OAC-recommended patients (2008- 2014)

OAC recommended population (n=16,893)			
	No OAC received	OAC received	p-value
Total (%)	11,802 (69.86)	5,091 (30.14)	
Female	6115 (51.81)	2533 (49.75)	0.014
Age			0.0074
<65	1389 (11.77)	685 (13.46)	
65-74	2156 (18.27)	933 (18.33)	
≥75	8257 (69.96)	3473 (68.22)	
CHADS2			
Congestive heart failure	2278 (19.30)	686 (13.47)	<.0001
Hypertension	11,357 (96.23)	4929 (96.82)	0.0593
Age ≥75	8257 (69.96)	3473 (68.22)	0.0239
Diabetes	4846 (41.06)	1948 (38.26)	0.0007
Stroke/TIA	3222 (27.30)	1409 (27.68)	0.6153
HAS-BLED			
0 or 1	689 (5.84)	312 (6.13)	
2	4948 (41.93)	1820 (35.75)	
≥3	6165 (52.24)	2959 (58.12)	
Hypertension	11,357 (96.23)	4929 (96.82)	0.0593
Renal disease	2836 (24.03)	947 (18.60)	<.0001
Liver disease	684 (5.80)	200 (3.93)	<.0001
Stroke	2780 (23.56)	888 (17.44)	<.0001
Prior bleeding/tendency	3665 (31.05)	1084 (21.29)	<.0001
Age >65	10,307 (87.33)	4348 (85.41)	0.0007
Medications/alcohol excess	696 (5.90)	1747 (34.32)	<.0001
History of bleeding			
Hemorrhagic stroke	116 (0.98)	19 (0.37)	<.0001
Major lower and unspecified GI	543 (4.60)	110 (2.16)	<.0001
Upper GI bleeding	148 (1.25)	15 (0.29)	<.0001
Major urogenital	2095 (17.75)	520 (10.21)	<.0001
Pulmonary embolism	123 (1.04)	226 (4.44)	<.0001
Major other bleeding	1503 (12.74)	397 (7.80)	<.0001
Other possible predictors of tx			
Acute coronary syndrome	896 (7.59)	251 (4.93)	<.0001

ADRD	1044 (8.85)	174 (3.42)	<.0001
Atrial flutter	282 (2.39)	161 (3.16)	0.0039
Cancer	1658 (14.05)	603 (11.84)	0.0001
Cardiomyopathy	96 (0.81)	23 (0.45)	0.0099
Coagulation defect	422 (3.58)	175 (3.44)	0.6553
COPD	997 (8.45)	275 (5.40)	<.0001
Hyperlipidemia	7011 (59.41)	2869 (56.35)	0.0002
Hyperthyroidism and Thyrotoxicity	142 (1.20)	61 (1.20)	0.9782
Inflammatory bowel disease	83 (0.70)	25 (0.49)	0.1123
Neurological disorders	424 (3.59)	109 (2.14)	<.0001
Obesity	700 (5.93)	307 (6.03)	0.803
Obstructive sleep apnea	631 (5.35)	279 (5.48)	0.7239
Pericarditis	134 (1.14)	40 (0.79)	0.0389
Rheumatoid arthritis	292 (2.47)	83 (1.63)	0.0006
Vascular disease	2469 (20.92)	689 (13.53)	<.0001
Venous thromboembolism	598 (5.07)	661 (12.98)	<.0001
Ventricular arrhythmia	454 (3.85)	117 (2.30)	<.0001
Diagnosis year			0.0005
2009	1752 (14.84)	696 (13.67)	
2010	1675 (14.19)	641 (12.59)	
2011	1840 (15.59)	749 (14.71)	
2012	1990 (16.86)	907 (17.82)	
2013	2334 (19.78)	1113 (21.86)	
2014	2211 (18.73)	985 (19.35)	
Provider type at dx			<.0001
Emergency	1219 (10.33)	525 (10.31)	
General	2361 (20.01)	1184 (23.26)	
Hospital	3193 (27.05)	1125 (22.10)	
Cardiologist/EP	3383 (28.66)	1520 (29.86)	
Other specialist	587 (4.97)	294 (5.77)	
Other, unknown, or LTC	1059 (8.97)	443 (8.70)	

Table 34. (A6.2) OAC treatment initiation among OAC-recommended patients (2015-2016)

OAC recommended population (n=8,272)				
	No OAC received	OAC received	p-value	
Total (%)	5,978	2,294		
Female	3239 (54.18)	1218 (53.10)	0.3746	
Age			0.0325	
	<65	644 (10.77)	276 (12.03)	
	65-74	1752 (29.31)	714 (31.12)	
	≥75	3582 (59.92)	1304 (56.84)	
CHA2DS2-VASc				
	Congestive heart failure	804 (13.45)	245 (10.68)	0.0007
	Hypertension	5061 (84.66)	2049 (89.32)	<.0001
	Age ≥65 and <75	1752 (29.31)	714 (31.12)	0.1058
	Age ≥75	3582 (59.92)	1304 (56.84)	0.0109
	Diabetes	1847 (30.90)	763 (33.26)	0.0383
	Stroke/TIA	1193 (19.96)	475 (20.71)	0.4468
	Vascular disease	1331 (22.26)	455 (19.83)	0.0162
HAS-BLED			<.0001	
	0 or 1	1008 (16.86)	297 (12.95)	
	2	2247 (37.59)	921 (40.15)	
	≥3	2723 (45.55)	1076 (46.90)	
	Hypertension	5061 (84.66)	2049 (89.32)	<.0001
	Renal disease	1339 (22.40)	429 (18.70)	0.0002
	Liver disease	369 (6.17)	105 (4.58)	0.0052
	Stroke	1015 (16.98)	323 (14.08)	0.0013
	Prior bleeding/tendency	1735 (29.02)	537 (23.41)	<.0001
	Age >65	5266 (88.09)	1990 (86.75)	0.0961
	Medications/alcohol excess	251 (4.20)	465 (20.27)	<.0001
History of bleeding				
	Hemorrhagic stroke	64 (1.07)	**	0.0111
	Major lower and unspecified GI	216 (3.61)	51 (2.22)	0.0014
	Upper GI bleeding	59 (0.99)	**	0.0241
	Major urogenital	884 (14.79)	234 (10.20)	<.0001
	Pulmonary embolism	65 (1.09)	78 (3.40)	<.0001
	Major other bleeding	683 (11.43)	189 (8.24)	<.0001

Other possible predictors of tx			
Acute coronary syndrome	322 (5.39)	88 (3.84)	0.0036
ADRD	426 (7.13)	93 (4.05)	<.0001
Atrial flutter	143 (2.39)	86 (3.75)	0.0008
Cancer	846 (14.15)	291 (12.69)	0.0829
Cardiomyopathy	79 (1.32)	31 (1.35)	0.9155
Coagulation defect	242 (4.05)	61 (2.66)	0.0026
COPD	333 (5.57)	108 (4.71)	0.118
Hyperlipidemia	3170 (53.03)	1345 (58.63)	<.0001
Hyperthyroidism	93 (1.56)	22 (0.96)	0.038
Inflammatory bowel disease	52 (0.87)	16 (0.70)	0.437
Neurological disorders	199 (3.33)	49 (2.14)	0.0044
Obesity	395 (6.61)	216 (9.42)	<.0001
Obstructive sleep apnea	386 (6.46)	170 (7.41)	0.121
Pericarditis	74 (1.24)	**	0.0022
Rheumatoid arthritis	123 (2.06)	45 (1.96)	0.7819
Venous thromboembolism	231 (3.86)	188 (8.20)	<.0001
Ventricular arrhythmia	133 (2.22)	41 (1.79)	0.2144
Diagnosis year			0.2116
2015	3429 (57.36)	1281 (55.84)	
2016	2549 (42.64)	1013 (44.16)	
Provider type at dx			<.0001
Emergency	588 (9.84)	345 (15.04)	
General	1100 (18.40)	444 (19.35)	
Hospital	1686 (28.20)	488 (21.27)	
Cardiologist/EP	1800 (30.11)	849 (37.01)	
Other specialist	352 (5.89)	54 (2.35)	
Other, unknown, or LTC	452 (7.56)	114 (4.97)	

Table 35. (A6.3) Adjusted odds of initiating OACs within 3-months of diagnosis (2008-2014)

CHADS₂ score	Any OAC	NOACs	Warfarin
	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	Ref	Ref	Ref
1	1.326 (1.198, 1.468)	1.175 (1.014, 1.362)	1.345 (1.193, 1.517)
2	1.728 (1.564, 1.910)	1.220 (1.053, 1.414)	1.854 (1.650, 2.083)
3	1.538 (1.366, 1.732)	0.997 (0.829, 1.199)	1.771 (1.547, 2.028)

≥4	1.750 (1.544, 1.983)	0.899 (0.732, 1.104)	2.105 (1.828, 2.425)
Other characteristics or comorbidities			
Alzheimer's disease and related dementias	0.463 (0.392, 0.548)	0.426 (0.299, 0.608)	0.515 (0.430, 0.616)
Cardiomyopathy	0.513 (0.324, 0.812)	0.652 (0.302, 1.407)	0.505 (0.300, 0.847)
Chronic obstructive pulmonary disease	0.750 (0.654, 0.859)	0.724 (0.566, 0.925)	0.798 (0.688, 0.925)
Coagulation defect	0.863 (0.714, 1.044)	0.500 (0.327, 0.766)	1.019 (0.837, 1.241)
Female	0.902 (0.852, 0.955)	0.868 (0.794, 0.950)	0.934 (0.876, 0.995)
Hyperthyroidism	1.112 (0.849, 1.456)	1.175 (0.768, 1.796)	1.071 (0.796, 1.440)
Liver disease	0.594 (0.510, 0.692)	0.946 (0.750, 1.193)	0.541 (0.455, 0.643)
Major bleed composite	0.721 (0.659, 0.788)	0.586 (0.498, 0.690)	0.813 (0.738, 0.895)
Medication/alcohol excess	8.664 (7.947, 9.446)	1.542 (1.353, 1.757)	8.314 (7.649, 9.037)
Neurological disorders	0.715 (0.577, 0.885)	0.683 (0.454, 1.028)	0.772 (0.614, 0.971)
Obesity	1.210 (1.060, 1.383)	1.261 (1.025, 1.552)	1.137 (0.983, 1.317)
Renal disease	0.912 (0.835, 0.995)	0.923 (0.796, 1.070)	0.932 (0.848, 1.026)
Vascular disease	0.845 (0.779, 0.917)	0.890 (0.776, 1.021)	0.863 (0.789, 0.944)
Ventricular arrhythmia	0.595 (0.481, 0.735)	0.699 (0.488, 1.003)	0.610 (0.482, 0.772)
Provider type			
General	Ref	Ref	Ref
Emergency	1.225 (1.106, 1.357)	1.186 (1.014, 1.387)	1.240 (1.107, 1.389)
Hospital	0.844 (0.775, 0.920)	0.688 (0.597, 0.793)	0.958 (0.873, 1.052)
Cardiologist/EP	1.212 (1.119, 1.312)	1.403 (1.245, 1.580)	1.070 (0.978, 1.169)
Other specialty	0.759 (0.655, 0.880)	0.800 (0.633, 1.010)	0.796 (0.679, 0.933)
Unknown/other	0.633 (0.559, 0.717)	0.389 (0.302, 0.500)	0.808 (0.709, 0.921)

Major bleed composite includes history of hemorrhagic stroke, major upper, lower, or unspecified gastrointestinal bleed, major urogenital, or other major bleed; EP=electrophysiologist

Table 36. Table A6.4. Adjusted odds of initiating OAC within 3-months of diagnosis (2015-2016)

CHA ₂ DS ₂ -VASc score	Any OAC	NOACs	Warfarin
	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	Ref	Ref	Ref
1	0.912 (0.686, 1.211)	0.887 (0.658, 1.195)	0.796 (0.463, 1.367)
2	1.033 (0.793, 1.346)	0.819 (0.618, 1.085)	1.544 (0.957, 2.492)
3	1.171 (0.906, 1.515)	0.914 (0.697, 1.200)	1.733 (1.085, 2.766)
≥4	1.264 (0.985, 1.622)	0.858 (0.659, 1.117)	2.243 (1.421, 3.542)

Other characteristics or comorbidities			
Alzheimer's disease and related dementias	0.583 (0.455, 0.746)	0.572 (0.416, 0.787)	0.699 (0.509, 0.960)
Cardiomyopathy	1.077 (0.692, 1.677)	1.734 (1.097, 2.741)	0.391 (0.176, 0.867)
Chronic obstructive pulmonary disease	0.853 (0.674, 1.080)	0.840 (0.633, 1.116)	0.987 (0.728, 1.338)
Coagulation defect	0.678 (0.500, 0.920)	0.661 (0.451, 0.968)	0.865 (0.589, 1.272)
Hyperthyroidism	0.666 (0.415, 1.068)	0.831 (0.490, 1.408)	0.551 (0.263, 1.153)
Liver disease	0.685 (0.546, 0.858)	0.809 (0.625, 1.045)	0.658 (0.473, 0.916)
Major bleed composite	0.749 (0.651, 0.861)	0.735 (0.622, 0.868)	0.869 (0.722, 1.046)
Medication/alcohol excess	6.475 (5.499, 7.625)	2.722 (2.294, 3.230)	5.458 (4.588, 6.492)
Neurological disorders	0.753 (0.543, 1.044)	0.623 (0.407, 0.954)	0.938 (0.611, 1.440)
Obesity	1.469 (1.225, 1.761)	1.329 (1.081, 1.635)	1.292 (1.014, 1.646)
Renal disease	0.832 (0.728, 0.950)	0.703 (0.598, 0.827)	1.104 (0.928, 1.313)
Ventricular arrhythmia	0.804 (0.558, 1.157)	0.716 (0.462, 1.112)	1.081 (0.677, 1.727)
Provider type			
General	Ref	Ref	Ref
Emergency	1.634 (1.381, 1.933)	1.626 (1.347, 1.963)	1.316 (1.037, 1.670)
Hospital	0.810 (0.699, 0.938)	0.792 (0.667, 0.940)	0.870 (0.709, 1.068)
Cardiologist/EP	1.287 (1.124, 1.474)	1.394 (1.197, 1.623)	0.977 (0.807, 1.184)
Other specialty	0.427 (0.318, 0.573)	0.573 (0.413, 0.794)	0.347 (0.215, 0.561)
Unknown/other	0.555 (0.436, 0.705)	0.319 (0.224, 0.452)	1.114 (0.838, 1.481)
Major bleed composite includes history of hemorrhagic stroke, major upper, lower, or unspecified gastrointestinal bleed, major urogenital, or other major bleed; EP=electrophysiologist			

Table 37. Table A6.3 Odds of initiating OACs within 3-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

<i>CHADS₂</i> score	Adjusted Odds ratio (95% CI)	<i>CHA₂DS₂-VASc</i> score	Adjusted Odds ratio (95% CI)
0	Ref	0	Ref
1	1.326 (1.198, 1.468)	1	0.912 (0.686, 1.211)
2	1.728 (1.564, 1.910)	2	1.033 (0.793, 1.346)
3	1.538 (1.366, 1.732)	3	1.171 (0.906, 1.515)
≥4	1.750 (1.544, 1.983)	≥4	1.264 (0.985, 1.622)

Table 38. Table A6.4. Adjusted odds of initiating an OAC by RSS component within 3-months of diagnosis (2008-2014)

	Any OAC	NOACs	Warfarin
CHADS ₂ score components	OR (95% CI)	OR (95% CI)	OR (95% CI)
Congestive heart failure	0.889 (0.799, 0.990)	0.811 (0.672, 0.979)	0.939 (0.836, 1.055)
Hypertension	1.318 (1.222, 1.421)	1.416 (1.257, 1.595)	1.212 (1.113, 1.319)
Diabetes mellitus	1.145 (1.069, 1.228)	1.031 (0.924, 1.151)	1.172 (1.086, 1.265)
Stroke/TIA	1.138 (1.050, 1.235)	0.797 (0.692, 0.919)	1.276 (1.170, 1.391)
Age (years)			
<65	<i>Ref</i>	<i>Ref</i>	<i>Ref</i>

≥65 and <75	1.288 (1.188, 1.396)	1.143 (1.015, 1.286)	1.313 (1.198, 1.439)
≥75	1.277 (1.185, 1.376)	0.837 (0.746, 0.939)	1.490 (1.370, 1.621)

Adjusted for comorbidities not included in RSS and provider type

Table 39. Table A6.5. Adjusted odds of initiating an OAC by RSS component within 3-months of diagnosis (2015-2016)

	Any OAC	NOACs	Warfarin
CHA2DS2-VASc components	OR (95% CI)	OR (95% CI)	OR (95% CI)
Congestive heart failure	0.792 (0.664, 0.944)	0.723 (0.583, 0.897)	0.936 (0.744, 1.179)
Hypertension	1.516 (1.334, 1.724)	1.543 (1.334, 1.786)	1.217 (1.005, 1.474)
Diabetes mellitus	1.145 (1.023, 1.283)	1.030 (0.904, 1.174)	1.225 (1.048, 1.432)
Stroke/TIA	1.052 (0.919, 1.204)	0.844 (0.718, 0.993)	1.376 (1.156, 1.638)
Vascular disease	0.962 (0.843, 1.099)	0.893 (0.763, 1.046)	1.094 (0.916, 1.306)
Female	1.001 (0.909, 1.103)	1.010 (0.905, 1.128)	0.970 (0.846, 1.113)
Age (years)			
<65	Ref	Ref	Ref
≥65 and <75	1.049 (0.914, 1.205)	0.872 (0.749, 1.015)	1.528 (1.228, 1.901)
≥75	1.052 (0.924, 1.199)	0.800 (0.693, 0.925)	1.798 (1.463, 2.211)

Adjusted for comorbidities not included in RSS and provider type

Table 40. Table A6.6. Odds of initiating OACs within 3-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

<i>CHADS₂</i> score	Adjusted Odds ratio (95% CI)	<i>CHA₂DS₂-VASc</i> score	Adjusted Odds ratio (95% CI)
0 or 1	Ref	0 or 1	Ref
≥2	1.382 (1.299, 1.470)	≥2	1.261 (1.092, 1.455)

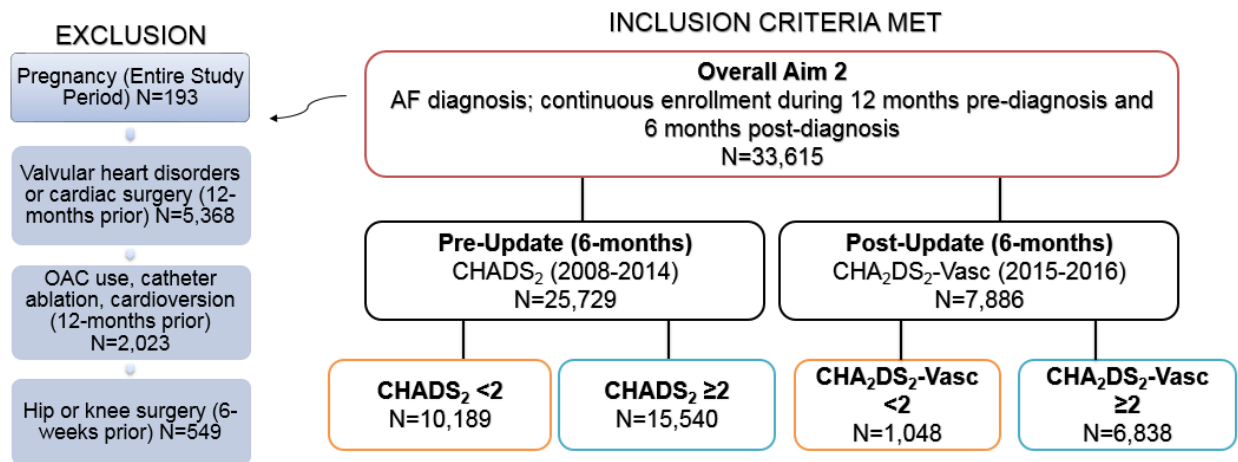


Figure 13. A6.1. Study cohorts (6-month follow-up)

Table 41. Table A6.7. Proportion of Patients Receiving an OAC within 6-months of diagnosis
Pre-Update *Post-update*

	CHADS₂ <2	CHADS₂ ≥2	CHA₂DS₂-VASc <2	CHA₂DS₂-VASc ≥2
<i>All patients</i>	26.9%	33.6%	27.1%	30.8%
<i>Female</i>	23.6%	32.6%	18.4%	30.5%
<i>Male</i>	29.2%	34.6%	28.6%	31.1%
<i>Age <65</i>	22.5%	35.5%	28.0%	32.1%
<i>Age 65-74 years</i>	31.7%	33.8%	23.9%	31.5%
<i>Age ≥75</i>	28.3%	33.2%	¥	30.1%

Table 42. Table A6.8. Odds of initiating OACs within 6-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

CHADS₂ score	Adjusted Odds ratio (95% CI)	CHA₂DS₂-VASc score	Adjusted Odds ratio (95% CI)

<i>0</i>	Ref	<i>0</i>	Ref
<i>1</i>	1.310 (1.184, 1.451)	<i>1</i>	1.036 (0.761, 1.410)
≥ 2	1.691 (1.535, 1.862)	<i>2</i>	1.263 (0.968, 1.648)

Table 43. Table A6.9. Odds of initiating OACs within 6-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

<i>CHADS₂ score</i>	Adjusted Odds ratio (95% CI)	<i>CHA₂DS₂-VASc score</i>	Adjusted Odds ratio (95% CI)
<i>0 or 1</i>	Ref	<i>0</i>	Ref
≥ 2	1.396 (1.311, 1.487)	<i>2</i>	1.232 (1.057, 1.436)

Table 44. Table A6.10. Odds of initiating OACs within 6-months of diagnosis based on RSS scores
Pre-Update *Post-Update*

<i>CHADS₂ score</i>	Adjusted Odds ratio (95% CI)	<i>CHA₂DS₂-VASc score</i>	Adjusted Odds ratio (95% CI)
<i>0</i>	Ref	<i>0</i>	Ref
<i>1</i>	1.310 (1.183, 1.450)	<i>1</i>	1.037 (0.762, 1.411)
<i>2</i>	1.749 (1.583, 1.934)	<i>2</i>	1.108 (0.831, 1.479)
<i>3</i>	1.488 (1.320, 1.677)	<i>3</i>	1.260 (0.952, 1.668)
≥ 4	1.756 (1.547, 1.993)	≥ 4	1.344 (1.024, 1.765)

Adjusted for: ADRD, coagulation defect, cardiomyopathy, COPD, hyperthyroidism, neurological disorders, obesity, ventricular arrhythmia, provider type, major bleeding, liver disease, renal disease, and prior medication use (NSAIDs)

Table 45. Table A6.11 Pre-Update co-morbid condition medication utilization (CHADS2 ≥2)

	Pre-update	Pre-update
	OAC non-initiators (11,802)	OAC-initiators (n=5,091)
% with co-morbid hypertension	96.2% (n=11,357)	96.8% (n=4,929)
<i>RX* pre- and post-dx</i>	62.3% (9,587)	84.1% (5391)
<i>No pre-dx RX, RX post-dx</i>	5.4% (827)	6.6% (423)
<i>RX pre-dx, no RX post-dx</i>	11.1% (1,709)	6.0% (381)
<i>No RX in pre- or post-dx</i>	21.3% (3,273)	3.3% (212)
% with co-morbid diabetes	41.1% (n=4,986)	38.3% (n=1,948)
<i>RX* pre- and post-dx</i>	50.3% (2,500)	69.0% (1,363)
<i>No pre-dx RX, RX post-dx</i>	2.4% (118)	1.9% (37)
<i>RX pre-dx, no RX post-dx</i>	13.6% (677)	10.7% (211)
<i>No RX in pre- or post-dx</i>	33.8% (1679)	18.5% (365)
	<i>Post-update</i>	<i>Post-update</i>
	<i>OAC non-initiators (n=5,978)</i>	<i>OAC-initiators (n=2,294)</i>
% with co-morbid hypertension	84.7% (n=5,061)	89.3% (n=2,049)
<i>RX pre- and post-dx</i>	57.3% (3,074)	84.2% (1,833)
<i>No pre-dx RX, RX post-dx</i>	4.5% (239)	7.5% (163)
<i>RX pre-dx, no RX post-dx</i>	9.5 (508)	4.7% (102)
<i>No RX in pre- or post-dx</i>	28.8% (1,544)	3.6% (79)

% with co-morbid diabetes	30.9% (n=1,847)	33.3% (n=763)
<i>RX pre- and post-dx</i>	48.5% (899)	67.4% (517)
<i>No pre-dx RX, RX post-dx</i>	1.3% (24)	2.5% (19)
<i>RX pre-dx, no RX post-dx</i>	12.5% (232)	11.0% (84)
<i>No RX in pre- or post-dx</i>	37.7% (700)	19.2 (147)

*hypertension RXs include: CCB, ACEI, ARB, BB, thiazide diuretics, and direct antihypertensive agents

*diabetes RXs include: insulin and oral antidiabetics

Table 46. Appendix A6.11. Odds of initiating OACs within 6-months of diagnosis among patients recommended to initiate OACs

	<i>Pre-Update</i> (<i>CHADS₂ ≥2</i>)	<i>Post-Update</i> (<i>CHA₂DS₂-VASc ≥2</i>)
RSS components		
Congestive heart failure	0.829 (0.739, 0.929)	0.758 (0.626, 0.917)
Diabetes mellitus	1.066 (0.979, 1.160)	1.134 (1.005, 1.281)
Hypertension	1.402 (1.131, 1.739)	1.550 (1.351, 1.778)
Stroke/TIA	1.049 (0.956, 1.151)	1.027 (0.888, 1.187)
Age <65	Ref	Ref
Age 65-74 years	1.066 (0.931, 1.220)	1.061 (0.914, 1.232)
Age ≥75	0.974 (0.860, 1.103)	1.091 (0.947, 1.256)
Female	0.992 (0.920, 1.070)	1.017 (0.917, 1.129)
Vascular disease	0.827 (0.754, 0.909)	0.915 (0.793, 1.056)
Other characteristics or comorbidities		
Alzheimer's disease and related dementias	0.446 (0.370, 0.538)	0.560 (0.424, 0.739)
Cardiomyopathy	0.522 (0.312, 0.873)	1.389 (0.807, 2.391)
Chronic obstructive pulmonary disease	0.775 (0.661, 0.909)	0.926 (0.721, 1.190)

Coagulation defect	0.942 (0.753, 1.178)	0.769 (0.559, 1.058)
Hyperthyroidism	1.193 (0.850, 1.673)	0.629 (0.381, 1.037)
Liver disease	0.604 (0.498, 0.732)	0.653 (0.509, 0.836)
Major bleed composite	0.710 (0.640, 0.789)	0.827 (0.711, 0.962)
Medication/alcohol excess	12.007 (10.707, 13.464)	7.107 (5.904, 8.554)
Neurological disorders	0.719 (0.564, 0.917)	0.694 (0.485, 0.991)
Obesity	1.223 (1.042, 1.436)	1.390 (1.134, 1.705)
Renal disease	0.923 (0.836, 1.019)	0.837 (0.723, 0.970)
Ventricular arrhythmia	0.759 (0.601, 0.958)	0.872 (0.591, 1.288)
Provider type		
General	Ref	Ref
Emergency	1.227 (1.069, 1.408)	1.678 (1.398, 2.015)
Hospital	0.912 (0.816, 1.019)	0.826 (0.705, 0.967)
Cardiologist/EP	1.257 (1.130, 1.398)	1.277 (1.105, 1.476)
Other specialty	0.826 (0.685, 0.994)	0.455 (0.336, 0.617)
Unknown/other	0.747 (0.639, 0.873)	0.573 (0.444, 0.740)

Appendix XIII. Aim 3: Supplementary Tables

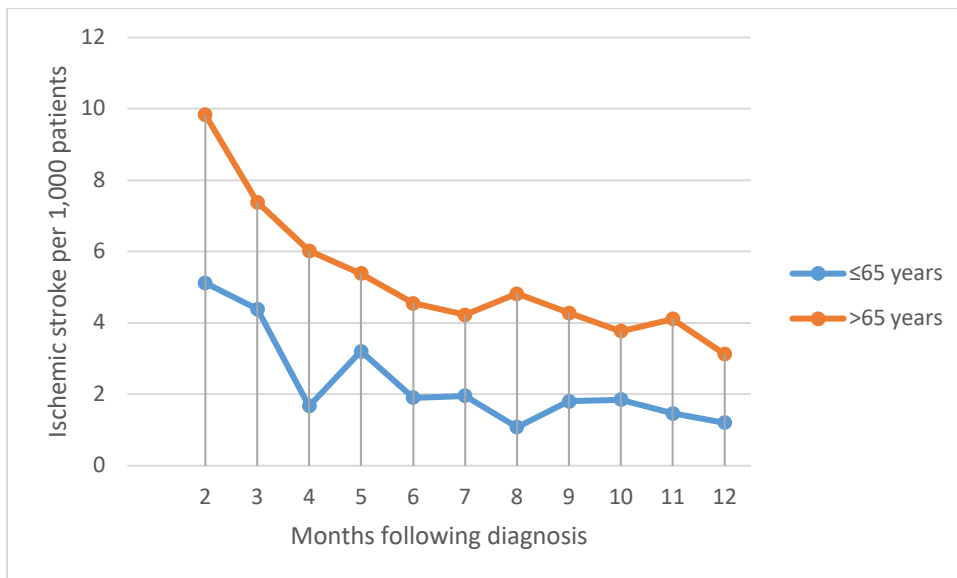


Figure 14. A7.1. Ischemic stroke per 1,000 patients by follow-up month in the overall population (age)

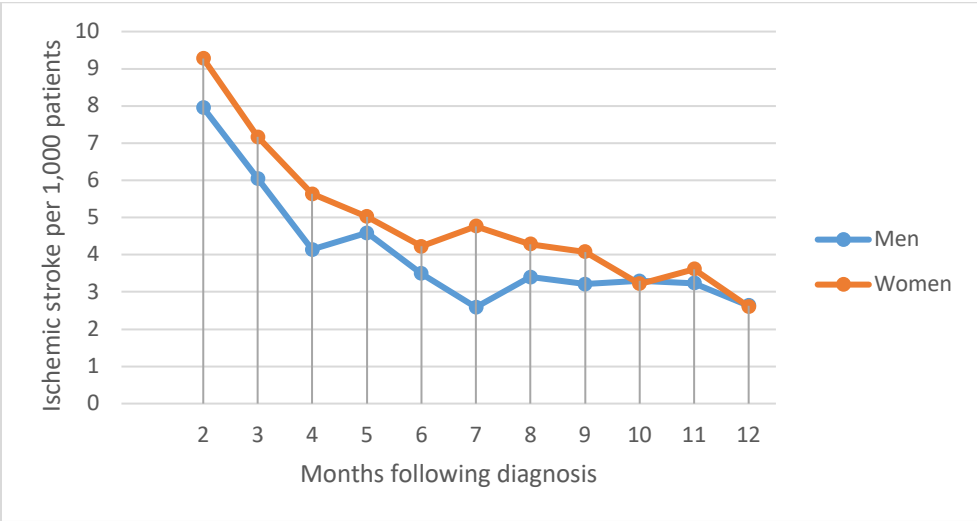


Figure 15. A7.2. Ischemic stroke per 1,000 patients by follow-up month in the overall population (sex)

Table 47. A7.1. Stroke within 12-months of AF diagnosis

	CHADS ₂ <2	CHADS ₂ ≥2
All patients	13,883	21,387
% experiencing stroke	1.66%	5.71%
Female	5,654	10,906
% experiencing stroke	2.00%	5.87%
Male	8,229	10,481
% experiencing stroke	1.43%	5.55%
Age <65	6,270	2,503
% experiencing stroke	0.97%	4.67%
Age 65-74 years	5,278	3,872
% experiencing stroke	1.99%	6.46%
Age ≥75	2,335	15,012
% experiencing stroke	2.78%	5.70%
Women age <65	2,176	898
% experiencing stroke	1.19%	4.57%
Men age <65	4,094	1,605
% experiencing stroke	0.85%	4.74%
Women age 65-74 years	2,363	1,653
% experiencing stroke	1.86%	6.78%
Men age 65-74 years	2,915	2,219
% experiencing stroke	2.09%	6.22%
Women age ≥75	1,115	8,355
% experiencing stroke	3.86%	5.83%
Men age ≥75	1,220	6,657
% experiencing stroke	1.80%	5.53%

Table 48. A7.2. Stroke within 12-months of AF diagnosis

	CHA2DS₂ -VASc <2	CHA2DS₂ - VASc ≥2
All patients	5,727	29,543
% experiencing stroke	0.93%	4.74%
Female	969	15,591
% experiencing stroke	0.41%	4.80%
Male	4,758	13,952
% experiencing stroke	1.03%	4.67%
Age <65	4,880	3,893
% experiencing stroke	0.74%	3.65%
Age 65-74 years	847	8,303
% experiencing stroke	2.01%	4.07%
Age ≥75	**	17,347
% experiencing stroke	**	5.30%
Women age <65	969	2,105
% experiencing stroke	0.41%	2.99%
Men age <65	3,911	1,788
% experiencing stroke	0.82%	4.42%
Women age 65-74 years	**	4,016
% experiencing stroke	**	3.88%
Men age 65-74 years	847	4,287
% experiencing stroke	2.01%	4.25%
Women age ≥75	**	9,470
% experiencing stroke	**	5.60%
Men age ≥75	**	7,877
% experiencing stroke	**	4.95%

Figure 16. (A7.3) Women's prognostic model development

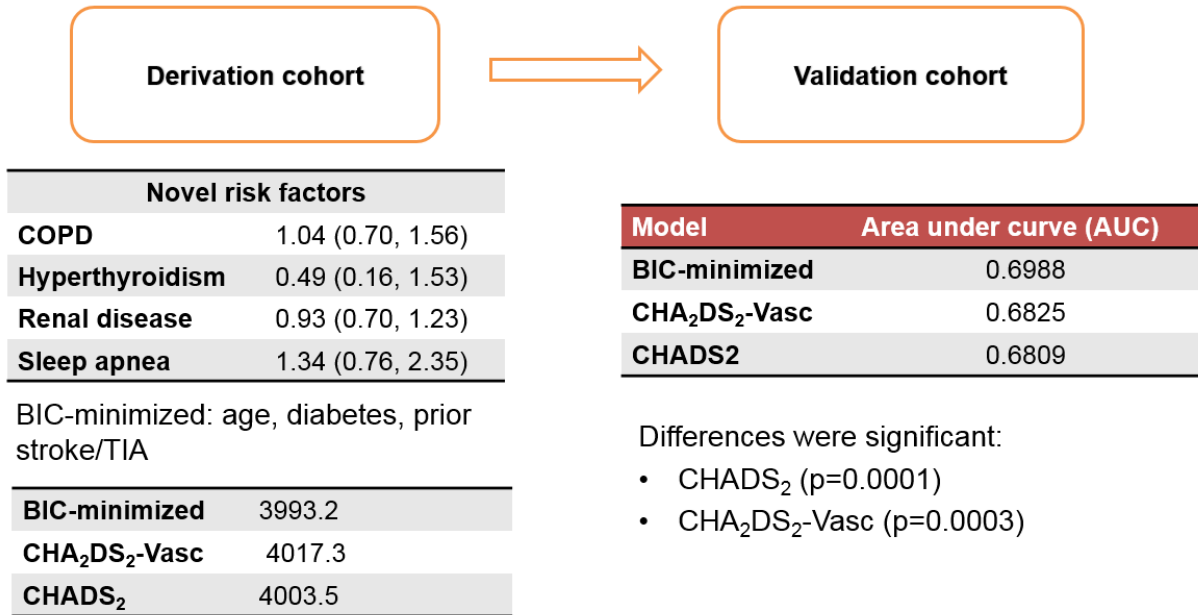
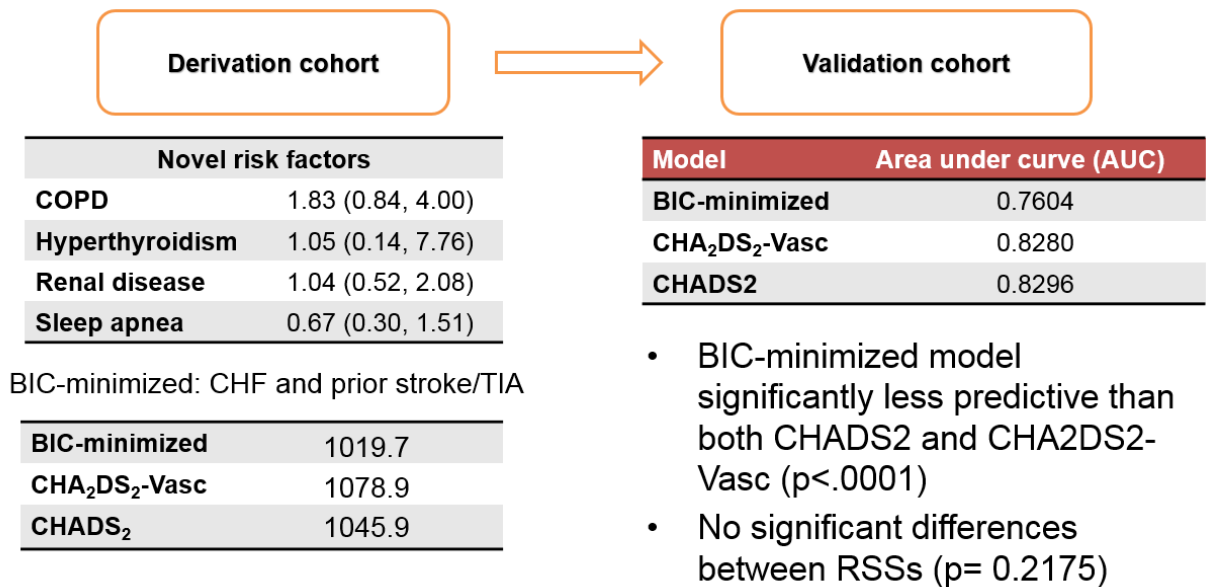


Figure 17. (A7.4) ≤65 years cohort's prognostic model development



References

1. Benjamin EJ, Chen P, Bild DE, et al. Prevention of atrial fibrillation: Report from an NHLBI workshop. *Circulation*. 2009;119(4):606-618. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2635942/>. doi: 10.1161/CIRCULATIONAHA.108.825380.
2. Leahy DM, Desmond D, Coughlan T, O'Neill D, Collins DR. Stroke in young women: An interpretative phenomenological analysis. *J Health Psychol*. 2016;21(5):669-678. doi: 10.1177/1359105314535125 [doi].
3. Smith JA., Flowers P., Larkin M. *Interpretative phenomenological analysis theory, method and research*. SAGE Publishing; 2009.
4. Reid K, Flower P, Larkin M. Exploring lived experience. *The Psychologist*. 2005;18 No. 1:20.
5. Lalmohamed A, Vestergaard P, Cooper C, et al. Timing of stroke in patients undergoing total hip replacement and matched controls: A nationwide cohort study. *Stroke*. 2012;43(12):3225-3229. doi: 10.1161/STROKEAHA.112.668509 [doi].
6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary A report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. *Journal of the American College of Cardiology*. 2014. doi: 10.1016/j.jacc.2014.03.021.
7. Katsi V, Georgiopoulos G, Marketou M, et al. Atrial fibrillation in pregnancy: A growing challenge. *Curr Med Res Opin*. 2017;33(8):1497-1504. <https://doi.org/10.1080/03007995.2017.1330257>. doi: 10.1080/03007995.2017.1330257.

8. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the european heart rhythm association and the heart rhythm society. *Circulation*. 2006;114(7):e257-354. doi: 114/7/e257 [pii].
9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the Management of patients With Atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. *J Am Coll Cardiol*. 2014;64(21):e1-e76. doi: <http://dx.doi.org/10.1016/j.jacc.2014.03.022>.
10. Deitelzweig SB, Pinsky B, Buysman E, et al. Bleeding as an outcome among patients with nonvalvular atrial fibrillation in a large managed care population. *Clin Ther*. 2013;35(10):1536-1545.e1. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.clinthera.2013.08.013>.
11. Wang SV, Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: New initiator cohort study. *BMJ*. 2016;353:i2607. doi: 10.1136/bmj.i2607 [doi].
12. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004;58(8):635-641. doi: 10.1136/jech.2003.008466.
13. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. doi: 10.1378/chest.09-1584 [doi].

14. Albrecht JS, Liu X, Baumgarten M, et al. Benefits and risks of anticoagulation resumption following traumatic brain injury. *JAMA Internal Medicine*. 2014;174(8):1244-1251. doi: 10.1001/jamainternmed.2014.2534.
15. Khokhar B, Simoni-Wastila L, Albrecht JS. Risk of stroke among older medicare antidepressant users with traumatic brain injury. *J Head Trauma Rehabil*. 2017;32(1):E42-E49. doi: 10.1097/HTR.000000000000231 [doi].
16. Austin PC. A tutorial on multilevel survival analysis: Methods, models and applications. *International Statistical Review*. 2017;85(2):185-203. <https://doi.org/10.1111/insr.12214>. doi: 10.1111/insr.12214.
17. Albrecht JS. Presentation on discrete time analysis. .
18. Ridker P, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds risk score. *JAMA*. 2007;297(6):611-619. doi: 10.1001/jama.297.6.611.
19. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Annals of Internal Medicine*. 2006;145(1):21-29. doi: 10.7326/0003-4819-145-1-200607040-00128.
20. Halabi S, Lin C, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *Journal of Clinical Oncology*. 2014;32(7):671-677. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3927736/>. doi: 10.1200/JCO.2013.52.3696.
21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics*. 1988;44(3):837-845.

22. Molodianovitch K, Faraggi D, Reiser R. Comparing the areas under two correlated ROC curves: Parametric and non-parametric approaches. *Biometrical Journal* [DOI 10.1002/bimj.200610223]. 2006;5, 745–757.
23. What is atrial fibrillation? - NHLBI, NIH. <http://www.nhlbi.nih.gov/health/health-topics/topics/af/>. Accessed 9/25/2014, 2014.
24. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in olmsted county, minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114(2):119-125. doi: CIRCULATIONAHA.105.595140 [pii].
25. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: Implications for thromboprophylaxis. *J Am Coll Cardiol*. 2010;56(11):827-837. doi: 10.1016/j.jacc.2010.05.028 [doi].
26. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. *Circulation*. 2014;129(8):837-847. doi: 10.1161/CIRCULATIONAHA.113.005119.
27. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112(8):1142-1147. doi: 10.1016/j.amjcard.2013.05.063 [doi].
28. National Heart, Lung, and Blood Institute. Who is at risk for atrial fibrillation? <https://www.nhlbi.nih.gov/health/health-topics/topics/af/atrisk>. Accessed 04/26, 2016.

29. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: Implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309. doi: S0735-1097(00)00886-X [pii].
30. Thrall G, Lane D, Carroll D, Lip GYH. Quality of life in patients with atrial fibrillation: A systematic review. *Am J Med*. 2006;119(5):448.e1-448.e19. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2005.10.057>.
31. Nabauer M, Gerth A, Limbourg T, et al. The registry of the german competence NETwork on atrial fibrillation: Patient characteristics and initial management. *Europace*. 2009;11(4):423-434. Accessed 25 September 2015.
32. National Heart, Lung, and Blood Institute. What are the signs and symptoms of atrial fibrillation? <https://www.nhlbi.nih.gov/health/health-topics/topics/af/signs>. Accessed 04/26, 2016.
33. National Heart, Lung, and Blood Institute. How is atrial fibrillation diagnosed? <https://www.nhlbi.nih.gov/health/health-topics/topics/af/diagnosis>. Accessed 04/26, 2016.
34. McCabe PJ, Schumacher K, Barnason SA. Living with atrial fibrillation: A qualitative study. *J Cardiovasc Nurs*. 2011;26(4):336-344. doi: 10.1097/JCN.0b013e31820019b9 [doi].
35. Deaton C, Dunbar SB, Moloney M, Sears SF, Ujhelyi MR. Patient experiences with atrial fibrillation and treatment with implantable atrial defibrillation therapy. *Heart Lung*. 2003;32(5):291-299. doi: S0147956303000748 [pii].
36. McCabe PJ, Rhudy LM, DeVon HA. Patients' experiences from symptom onset to initial treatment for atrial fibrillation. *J Clin Nurs*. 2015;24(5-6):786-796. doi: 10.1111/jocn.12708 [doi].

37. Evans W, Swann P. LONE AURICULAR FIBRILLATION. *British Heart Journal*. 1954;16(2):189-194. doi: 10.1136/hrt.16.2.189.
38. Potpara TS, Lip GY. Lone atrial fibrillation - an overview. *Int J Clin Pract*. 2014;68(4):418-433. doi: 10.1111/ijcp.12281 [doi].
39. Ceresnak SR, Liberman L, Silver ES, et al. Lone atrial fibrillation in the young - perhaps not so "lone"? *J Pediatr*. 2013;162(4):827-831. doi: 10.1016/j.jpeds.2012.09.016 [doi].
40. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: An update of the 2010 ESC guidelines for the management of atrial fibrillation--developed with the special contribution of the european heart rhythm association. *Europace*. 2012;14(10):1385-1413. doi: eus305 [pii].
41. Martins RP, Galand V, Colette E, et al. Defining nonvalvular atrial fibrillation: A quest for clarification. *American Heart Journal*. 2016;178:161-167. doi: <https://doi-org.proxy-hs.researchport.umd.edu/10.1016/j.ahj.2016.05.014>.
42. Haraphongse M, Haraphongse Y, Montague TJ. Nonrheumatic atrial fibrillation: A brief overview. *Can J Cardiol*. 1995;11(6):498-502.
43. Fauchier L, Philippart R, Clementy N, et al. How to define valvular atrial fibrillation? *Archives of Cardiovascular Diseases*. 2015;108(10):530-539. doi: <http://dx.doi.org/10.1016/j.acvd.2015.06.002>.
44. De Caterina R, Renda G, Carnicelli AP, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *Journal of the American College of Cardiology*. 2017;69(11):1372-1382. doi: <https://doi-org.proxy-hs.researchport.umd.edu/10.1016/j.jacc.2016.12.031>.

45. National Institute of Neurological Disorders and Stroke. NINDS atrial fibrillation and stroke information page.

http://www.ninds.nih.gov/disorders/atrial_fibrillation_and_stroke/atrial_fibrillation_and_stroke.htm.

Accessed August 16, 2016.

46. Senoo K, Lip GYH, Lane DA, Büller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. *Stroke*.

2015;46(9):2523-2528. doi: 10.1161/STROKEAHA.115.009487.

47. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The framingham study. *Stroke*. 1991;22(8):983-988.

48. Hughes M, Lip GYH. Stroke and thromboembolism in atrial fibrillation: A systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost*.

2008;99(2):295-304. <http://dx.doi.org/10.1160/TH07-08-0508>. doi: 10.1160/TH07-08-0508.

49. Moulton AW, Singer DE, Haas JS. Risk factors for stroke in patients with nonrheumatic atrial fibrillation: A case-control study. *Am J Med*. 1991;91(2):156-161. doi: 0002-9343(91)90008-L [pii].

50. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: The framingham heart study. *JAMA*. 2003;290(8):1049-1056. doi: 10.1001/jama.290.8.1049 [doi].

51. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: The atrial fibrillation investigators. *Stroke*. 2009;40(4):1410-1416. doi:

10.1161/STROKEAHA.108.526988 [doi].

52. Chan P, Lau C, Tse H, Chiang C, Siu C. CHA2DS2-VASc recalibration with an additional age category (50-64 years) enhances stroke risk stratification in chinese patients with atrial fibrillation. *Can J Cardiol.* . doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.cjca.2016.05.009>.
53. Hijazi Z, Lindback J, Alexander JH, et al. The ABC (age, biomarkers, clinical history) stroke risk score: A biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J.* 2016. doi: ehw054 [pii].
54. Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial FibrillationClinical perspective. *Circulation.* 2012;125(13):1605-1616. doi: 10.1161/CIRCULATIONAHA.111.038729.
55. Pastori D, Pignatelli P, Farcomeni A, et al. Urinary 11-dehydro-thromboxane B2 is associated with cardiovascular events and mortality in patients with atrial fibrillation. *Am Heart J.* 2015;170(3):490-7.e1. doi: 10.1016/j.ahj.2015.05.011 [doi].
56. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154(13):1449-1457.
57. Predictors of thromboembolism in atrial fibrillation: I. clinical features of patients at risk. the stroke prevention in atrial fibrillation investigators. *Ann Intern Med.* 1992;116(1):1-5.
58. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154(13):1449-1457.
59. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke prevention in atrial fibrillation iii study. *JAMA.* 1998;279(16):1273-1277. doi: 10.1001/jama.279.16.1273.

60. Petersen P, Kastrup J, Helweg-Larsen S, Boysen G, Godtfredsen J. Risk factors for thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK study. *Archives of Internal Medicine*. 1990;150(4):819-821. doi: 10.1001/archinte.1990.00390160077016.
61. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: Possible mechanisms. *Thromb Haemost*. 2014;111(3):385-391. doi: 10.1160/TH13-04-0347 [doi].
62. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation. *Circulation*. 2005;112(12):1687-1691. doi: 10.1161/CIRCULATIONAHA.105.553438.
63. Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behloul H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307(18):1952-1958. doi: 10.1001/jama.2012.3490.
64. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: Incidence and predictors during aspirin therapy. stroke prevention in atrial fibrillation investigators. *J Am Coll Cardiol*. 2000;35(1):183-187. doi: S0735109799004891 [pii].
65. Squizzato A, Gerdes VEA, Brandjes DPM, Büller HR, Stam J. Thyroid diseases and cerebrovascular disease. *Stroke*. 2005;36(10):2302-2310. doi: 10.1161/01.STR.0000181772.78492.07.
66. Bronnum Nielsen P, Larsen TB, Gorst-Rasmussen A, Skjoth F, Rasmussen LH, Lip GY. Intracranial hemorrhage and subsequent ischemic stroke in patients with atrial fibrillation: A nationwide cohort study. *Chest*. 2015;147(6):1651-1658. doi: 10.1378/chest.14-2099 [doi].

67. Sakr SA, El-Rasheedy WA, Ramadan MM, El-Menshawy I, Mahfouz E, Bayoumi M. Association between left atrial appendage morphology evaluated by trans-esophageal echocardiography and ischemic cerebral stroke in patients with atrial fibrillation. *Int Heart J.* 2015;56(3):329-334. doi: 10.1536/ihj.14-374 [doi].
68. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146(12):857-867. doi: 146/12/857 [pii].
69. Echocardiographic predictors of stroke in patients with atrial fibrillation: A prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med.* 1998;158(12):1316-1320.
70. Hamatani Y, Ogawa H, Uozumi R, et al. Low body weight is associated with the incidence of stroke in atrial fibrillation patients - insight from the fushimi AF registry. *Circ J.* 2015;79(5):1009-1017. doi: 10.1253/circj.CJ-14-1245 [doi].
71. Hamatani Y, Yamashita Y, Esato M, et al. Predictors for stroke and death in non-anticoagulated asian patients with atrial fibrillation: The fushimi AF registry. *PLoS One.* 2015;10(11):e0142394. doi:10.1371/journal.pone.0142394. doi: 10.1371/journal.pone.0142394 [doi].
72. Yaranov DM, Smyrlis A, Usatii N, et al. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. *Am J Cardiol.* 2015;115(4):461-465. doi: 10.1016/j.amjcard.2014.11.027 [doi].
73. Kabra R, Cram P, Girotra S, Sarrazin MV. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol.* 2015;116(2):230-235. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780330/>. doi: 10.1016/j.amjcard.2015.04.012.

74. Saliba W, Barnett-Griness O, Elias M, Rennert G. The association between red cell distribution width and stroke in patients with atrial fibrillation. *Am J Med.* 2015;128(2):192.e11-192.e18. doi: 10.1016/j.amjmed.2014.09.020 [doi].
75. Guo Y, Wang H, Zhao X, et al. Relation of renal dysfunction to the increased risk of stroke and death in female patients with atrial fibrillation. *Int J Cardiol.* 2013;168(2):1502-1508. doi: 10.1016/j.ijcard.2012.12.099 [doi].
76. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: The swedish atrial fibrillation cohort study. *Eur Heart J.* 2015;36(5):297-306. doi: 10.1093/eurheartj/ehu139 [doi].
77. Kwon Y, Norby FL, Jensen PN, et al. Association of smoking, alcohol, and obesity with cardiovascular death and ischemic stroke in atrial fibrillation: The atherosclerosis risk in communities (ARIC) study and cardiovascular health study (CHS). *PLoS One.* 2016;11(1):e0147065. doi:10.1371/journal.pone.0147065. doi: 10.1371/journal.pone.0147065 [doi].
78. Olesen JB, Lip GY, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: A nationwide cohort study. *Am J Med.* 2012;125(8):826.e13-826.e23. doi: 10.1016/j.amjmed.2011.11.024 [doi].
79. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The framingham heart study. *Circulation.* 1998;98(10):946-952.
80. American Heart Association. Atrial fibrillation medications. http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Atrial-Fibrillation-Medications_UCM_423781_Article.jsp#.Vq9suns1j8s. Accessed 02/01, 2016.

81. American Heart Association. Non-surgical procedures for atrial fibrillation (AFib or AF).
http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Non-surgical-Procedures-for-Atrial-Fibrillation-AFib-or-AF_UCM_423782_Article.jsp#.Vyzc6-RUVfY. Accessed 05/06, 2016.
82. American Heart Association. Surgical procedures for atrial fibrillation (AFib or AF).
http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Surgical-Procedures-for-Atrial-Fibrillation-AFib-or-AF_UCM_423783_Article.jsp#.Vyzc7eRUVfY. Accessed 04/05, 2016.
83. USC Cardiothoracic Surgery. MAZE procedure for treatment of atrial fibrillation.
<http://www.cts.usc.edu/mazeprocure.html>. Accessed August 23, 2016.
84. Verheugt FWA, Granger CB. Oral anticoagulants for stroke prevention in atrial fibrillation: Current status, special situations, and unmet needs. *The Lancet*. 2015;386(9990):303-310. doi:
[http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/S0140-6736\(15\)60245-8](http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/S0140-6736(15)60245-8).
85. UpToDate. Warfarin and other VKAs: Dosing and adverse effects.
<http://www.uptodate.com/contents/warfarin-and-other-vkas-dosing-and-adverse-effects>. Accessed March 14, 2017.
86. Matchar DB, Samsa GP, Cohen SJ, Oddone EZ, Jurgelski AE. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: Results of the managing anticoagulation services trial. *Am J Med*. 2002;113(1):42-51. doi: [http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/S0002-9343\(02\)01131-2](http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/S0002-9343(02)01131-2).
87. Rose AJ, Ozonoff A, Grant RW, Henault LE, Hylek EM. Epidemiology of subtherapeutic anticoagulation in the united states. *Circ Cardiovasc Qual Outcomes*. 2009;2(6):591-597. doi: 10.1161/CIRCOUTCOMES.109.862763.

88. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. <http://dx.doi.org/10.1056/NEJMoa1107039>. doi: 10.1056/NEJMoa1107039.
89. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962. doi: 10.1016/S0140-6736(13)62343-0 [doi].
90. Caldeira D, Rodrigues FB, Barra M, et al. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: A systematic review and meta-analysis. *Heart*. 2015;101(15):1204-1211. doi: 10.1136/heartjnl-2015-307489 [doi].
91. Lapner S, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: A systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(5):595-605.
92. Shah A, Shewale A, Hayes CJ, Martin BC. Cost-effectiveness of oral anticoagulants for ischemic stroke prophylaxis among nonvalvular atrial fibrillation patients. *Stroke*. 2016;47(6):1555-1561. doi: 10.1161/STROKEAHA.115.012325 [doi].
93. Lehto M, Niiranen J, Korhonen P, et al. Quality of warfarin therapy and risk of stroke, bleeding, and mortality among patients with atrial fibrillation: Results from the nationwide FinWAF registry. *Pharmacoepidemiol Drug Saf*. 2017. doi: 10.1002/pds.4194 [doi].
94. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):10.1161/JAHA.115.003074. doi: 10.1161/JAHA.115.003074 [doi].

95. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost*. 2015;114(4):826-834. doi: 10.1160/TH15-07-0565 [doi].
96. Lip GY, Lanitis T, Mardekian J, Kongnakorn T, Phatak H, Dorian P. Clinical and economic implications of apixaban versus aspirin in the low-risk nonvalvular atrial fibrillation patients. *Stroke*. 2015;46(10):2830-2837. doi: 10.1161/STROKEAHA.115.009995 [doi].
97. Argulian E, Conen D, Messerli FH. Misconceptions and facts about atrial fibrillation. *Am J Med*. 2015;128(9):938-942. doi: 10.1016/j.amjmed.2015.02.016 [doi].
98. Steinberg BA, Kim S, Piccini JP, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: Insights from the ORBIT-AF registry. *Circulation*. 2013;128(7):721-728. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3908483/>. doi: 10.1161/CIRCULATIONAHA.113.002927.
99. Kirchhof P, Benussi S, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. .
100. Cameron C, Coyle D, Richter T, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open*. 2014;4(6):e004301-2013-004301. doi: 10.1136/bmjopen-2013-004301 [doi].
101. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. *JAMA*. 2001;285(22):2864-2870. doi: 10.1001/jama.285.22.2864.

102. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e601S-36S. doi: 10.1378/chest.11-2302 [doi].
103. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;31(19):2369-2429. doi: 10.1093/eurheartj/ehq278.
104. Welles CC, Whooley MA, Na B, Ganz P, Schiller NB, Turakhia MP. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: Data from the heart and soul study. *Am Heart J*. 2011;162(3):555-561. doi: 10.1016/j.ahj.2011.05.023 [doi].
105. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation-
-friend or foe? *Thromb Haemost*. 2010;104(1):45-48. doi: 10.1160/TH09-11-0757 [doi].
106. Giralt-Steinhauer E, Cuadrado-Godia E, Ois A, et al. Comparison between CHADS2 and CHA2
DS2 -VASc score in a stroke cohort with atrial fibrillation. *Eur J Neurol*. 2013;20(4):623-628. doi:
10.1111/j.1468-1331.2012.03807.x [doi].
107. Aspberg S, Chang Y, Atterman A, Bottai M, Go AS, Singer DE. Comparison of the ATRIA,
CHADS2, and CHA2DS2-VASc stroke risk scores in predicting ischaemic stroke in a large swedish
cohort of patients with atrial fibrillation. *Eur Heart J*. 2016. doi: ehw077 [pii].
108. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and
bleeding in 182 678 patients with atrial fibrillation: The swedish atrial fibrillation cohort study. *Eur Heart
J*. 2012;33(12):1500-1510. doi: 10.1093/eurheartj/ehr488 [doi].

109. Crawford M. A new risk score for stroke in atrial fibrillation.
<https://www.ahcmmedia.com/articles/139982-a-new-risk-score-for-stroke-in-atrial-fibrillation>. Accessed May 15, 2017.
110. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest*. 2010;138(5):1093-1100. doi: [http://dx.doi.org.proxy-
hs.researchport.umd.edu/10.1378/chest.10-0134](http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1378/chest.10-0134).
111. O'Brien E,C., Simon D,N., Thomas L,E., et al. The ORBIT bleeding score: A simple bedside score to assess bleeding risk in atrial fibrillation. *European Heart Journal*. 2015;36(46):3258-3264. doi: 10.1093/eurheartj/ehv476 [doi].
112. Uppsala Clinical Research Center. ABC risk calculators. <http://www.ucr.uu.se/en/services/abc-risk-calculators>. Accessed May 15, 2017.
113. Lip GYH. HAS-BLED tool – what is the real risk of bleeding in anticoagulation? HAS-BLED tool – what is the real risk of bleeding in anticoagulation? - see more at: <Http://Www.acc.org/latest-in-cardiology/articles/2014/07/18/15/13/has-bled-tool-what-is-the-real-risk-of-bleeding-in-anticoagulation#sthash.7BLKsyQS.dpuf> HAS-BLED tool – what is the real risk of bleeding in anticoagulation? - see more at: <Http://Www.acc.org/latest-in-cardiology/articles/2014/07/18/15/13/has-bled-tool-what-is-the-real-risk-of-bleeding-in-anticoagulation#sthash.7BLKsyQS.dpuf>. HAS-BLED Tool – What is the Real Risk of Bleeding in Anticoagulation? - See more at: <http://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/13/has-bled-tool-what-is-the-real-risk-of-bleeding-in-anticoagulation#sthash.7BLKsyQS.dpuf>. Accessed May 15, 2017.

114. Senoo K, Proietti M, Lane DA, Lip GYH. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. *Am J Med.* . doi: <http://dx.doi.org/10.1016/j.amjmed.2015.10.001>.
115. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2014;45(5):1545-1588. doi: 10.1161/01.str.0000442009.06663.48 [doi].
116. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the Management of patients with atrial fibrillation: Executive SummaryA report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. *Journal of the American College of Cardiology.* 2014;64(21):2246-2280. doi: 10.1016/j.jacc.2014.03.021.
117. Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: A commercial insurer perspective. *J Manag Care Pharm.* 2013;19(4):302-316. doi: 2013(19)4: 302-316 [pii].
118. Zimetbaum PJ, Thosani A, Yu H, et al. Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? *Am J Med.* 2010;123(5):446-453. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2009.11.015>.
119. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: A systematic review. *Am J Med.* 2010;123(7):638-645.e4. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2009.11.025>.
120. Pechlaner C. Anticoagulation for atrial fibrillation: Underuse? *Am J Med.* 2011;124(7):e11. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2010.07.030>.

121. Johansson C, Hagg L, Johansson L, Jansson JH. Characterization of patients with atrial fibrillation not treated with oral anticoagulants. *Scand J Prim Health Care*. 2014;32(4):226-231. doi: 10.3109/02813432.2014.984952 [doi].
122. Dreischulte T, Barnett K, Madhok V, Guthrie B. Use of oral anticoagulants in atrial fibrillation is highly variable and only weakly associated with estimated stroke risk: Cross-sectional population database study. *Eur J Gen Pract*. 2014;20(3):181-189. doi: 10.3109/13814788.2013.852535 [doi].
123. Pandya EY, Bajorek B. Factors affecting patients perception on, and adherence to, anticoagulant therapy: Anticipating the role of direct oral anticoagulants. *The Patient - Patient-Centered Outcomes Research*. 2016:1-23. <http://dx.doi.org/10.1007/s40271-016-0180-1>. doi: 10.1007/s40271-016-0180-1.
124. Decker C, Garavalia L, Garavalia B, et al. Exploring barriers to optimal anticoagulation for atrial fibrillation: Interviews with clinicians. *J Multidiscip Healthc*. 2012;5:129-135. doi: 10.2147/JMDH.S33045 [doi].
125. Naderi S, Wang Y, Miller AL, et al. The impact of age on the epidemiology of atrial fibrillation hospitalizations. *Am J Med*. 2014;127(2):158.e1-158.e7. doi: <http://dx.doi.org/10.1016/j.amjmed.2013.10.005>.
126. Chao TF, Wang KL, Liu CJ, et al. Age threshold for increased stroke risk among patients with atrial fibrillation: A nationwide cohort study from taiwan. *J Am Coll Cardiol*. 2015;66(12):1339-1347. doi: 10.1016/j.jacc.2015.07.026 [doi].
127. Huang D, Anguo L, Yue WS, Yin L, Tse HF, Siu CW. Refinement of ischemic stroke risk in patients with atrial fibrillation and CHA2 DS2 -VASc score of 1. *Pacing Clin Electrophysiol*. 2014;37(11):1442-1447. doi: 10.1111/pace.12445 [doi].

128. Piccini JP, Simon DN, Steinberg BA, et al. Differences in clinical and functional outcomes of atrial fibrillation in women and men: Two-year results from the ORBIT-AF registry. *JAMA Cardiol.* 2016;1(3):282-291. doi: 10.1001/jamacardio.2016.0529 [doi].
129. Shantsila E, Wolff A, Lip GY, Lane DA. Gender differences in stroke prevention in atrial fibrillation in general practice: Using the GRASP-AF audit tool. *Int J Clin Pract.* 2015;69(8):840-845. doi: 10.1111/ijcp.12625 [doi].
130. Sandhu RK, Bakal JA, Ezekowitz JA, McAlister FA. Risk stratification schemes, anticoagulation use and outcomes: The risk-treatment paradox in patients with newly diagnosed non-valvular atrial fibrillation. *Heart.* 2011;97(24):2046-2050. doi: 10.1136/heartjnl-2011-300901.
131. Groenwold RHH, Moons KGM, Pajouheshnia R, et al. Explicit inclusion of treatment in prognostic modeling was recommended in observational and randomized settings. *J Clin Epidemiol.* . doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.jclinepi.2016.03.017>.
132. Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: The ATRIA study stroke risk score. *J Am Heart Assoc.* 2013;2(3):e000250. doi: 10.1161/JAHA.113.000250 [doi].
133. Andersen RM. Revisiting the behavioral model and access to medical care: Does it matter? *J Health Soc Behav.* 1995;36(1):1-10.
134. 2013 SYR accepted poster abstracts. *Int J Yoga Therap.* 2013;23 Suppl:32-53. doi: 725531PU2R110135 [pii].

135. McCabe PJ, Barnason SA. Illness perceptions, coping strategies, and symptoms contribute to psychological distress in patients with recurrent symptomatic atrial fibrillation. *J Cardiovasc Nurs*. 2012;27(5):431-444. doi: 10.1097/JCN.0b013e31821e7ab1 [doi].
136. McCabe PJ, Schumacher K, Barnason SA. Living with atrial fibrillation: A qualitative study. *J Cardiovasc Nurs*. 2011;26(4):336-344. doi: 10.1097/JCN.0b013e31820019b9 [doi].
137. McCabe PJ, Rhudy LM, DeVon HA. Patients' experiences from symptom onset to initial treatment for atrial fibrillation. *J Clin Nurs*. 2015;24(5-6):786-796. doi: 10.1111/jocn.12708 [doi].
138. Glotzer TV, Ziegler PD. Silent atrial fibrillation as a stroke risk factor and anticoagulation indication. *Canadian Journal of Cardiology*. 2013;29(7, Supplement):S14-S23. doi: <https://doi.org/10.1016/j.cjca.2013.03.023>.
139. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost*. 2013;110(2):213-222. doi: 10.1160/TH13-02-0165 [doi].
140. Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM. Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev*. 2013;(4):CD009586. doi(4):CD009586. doi: 10.1002/14651858.CD009586.pub2 [doi].
141. Turakhia MP, Shafrin J, Bognar K, et al. Economic burden of undiagnosed nonvalvular atrial fibrillation in the united states. *Am J Cardiol*. 2015;116(5):733-739. doi: 10.1016/j.amjcard.2015.05.045 [doi].
142. Lindsberg PJ, Toivonen L, Diener H. The atrial fibrillation epidemic is approaching the physician's door: Will mobile technology improve detection? *BMC Medicine*. 2014;12:180. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180533/>. doi: 10.1186/s12916-014-0180-8.

143. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old Population Clinical perspective. *Circulation*. 2013;127(8):930-937. doi: 10.1161/CIRCULATIONAHA.112.126656.
144. Hickey KT, Hauser NR, Valente LE, et al. A single-center randomized, controlled trial investigating the efficacy of a mHealth ECG technology intervention to improve the detection of atrial fibrillation: The iHEART study protocol. *BMC Cardiovascular Disorders*. 2016;16:152. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4947299/>. doi: 10.1186/s12872-016-0327-y.
145. American Heart Association. AFib resources for patients & professionals. http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/AFib-Resources-For-Patients-Professionals_UCM_423786_Article.jsp#.Wdu8xTtrxph. Accessed October 9, 2017.
146. StopAfib. AfibTown - my afib experience. <https://myafibexperience.org/home>. Accessed October 9, 2017.
147. Fosbol EL, Holmes DN, Piccini JP, et al. Provider specialty and atrial fibrillation treatment strategies in united states community practice: Findings from the ORBIT-AF registry. *J Am Heart Assoc*. 2013;2(4):e000110. doi: 10.1161/JAHA.113.000110 [doi].
148. Caldeira D, Costa J, Fernandes RM, Pinto FJ, Ferreira JJ. Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES in patients with atrial fibrillation: A systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2014;40(3):277-284. doi: 10.1007/s10840-014-9930-y [doi].
149. Floria M, Drug VL. Atrial fibrillation and gastroesophageal reflux disease: From the cardiologist perspective. *World Journal of Gastroenterology : WJG*. 2014;21(10):3154-3156. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4356942/>. doi: 10.3748/wjg.v21.i10.3154.

150. Mandyam MC, Vedantham V, Scheinman MM, et al. Alcohol and vagal tone as triggers for paroxysmal atrial fibrillation. *Am J Cardiol*. 2012;110(3):364-368. doi: 10.1016/j.amjcard.2012.03.033 [doi].
151. Nguyen JL, Link MS, Luttmann-Gibson H, et al. Drier air, lower temperatures, and triggering of paroxysmal atrial fibrillation. *Epidemiology*. 2015;26(3):374-380. doi: 10.1097/EDE.0000000000000284 [doi].
152. Rose AJ, Miller DR, Ozonoff A, et al. Gaps in monitoring during oral anticoagulation: Insights into care transitions, monitoring barriers, and medication nonadherence. *Chest*. 2013;143(3):751-757. doi: 10.1378/chest.12-1119 [doi].
153. Kakkar AK, Mueller I, Bassand J, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: Perspectives from the international, observational, prospective GARFIELD registry. *PLoS ONE*. 2013;8(5):e63479. <http://dx.doi.org/10.1371/journal.pone.0063479>.
154. Nieuwlaat R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: A report from the euro heart survey on atrial fibrillation. *Eur Heart J*. 2006;27(24):3018-3026. doi: ehl015 [pii].
155. Thompson LE, Maddox TM, Lei L, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: A report from the national cardiovascular data registry (NCDR((R))) PINNACLE registry. *J Am Heart Assoc*. 2017;6(7):10.1161/JAHA.117.005801. doi: e005801 [pii].
156. Tavassoli N, Perrin A, Berard E, et al. Factors associated with undertreatment of atrial fibrillation in geriatric outpatients with alzheimer disease. *Am J Cardiovasc Drugs*. 2013;13(6):425-433. doi: 10.1007/s40256-013-0040-5 [doi].

157. Durham TA, Hassmiller Lich K, Viera AJ, et al. Utilization of standard and target-specific oral anticoagulants among adults in the united kingdom with incident atrial fibrillation. *The American Journal of Cardiology*. 2017;120(10):1820-1829. doi: <https://doi.org/10.1016/j.amjcard.2017.07.091>.
158. Food and Drug Administration. Drug approval package: Pradaxa (dabigatran etexilate mesylate). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000TOC.cfm. Accessed March 5, 2018.
159. Sapra S. A regression error specification test (RESET) for generalized linear models. *Economics Bulletin*. 2005;3:1-6.
160. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: A systematic review. *Am J Med*. 2010;123(7):638-645.e4. doi: 10.1016/j.amjmed.2009.11.025 [doi].
161. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *Journal of the American College of Cardiology*. 2005;46(9):1729-1736. doi: <https://doi.org/10.1016/j.jacc.2005.06.077>.
162. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *J Am Heart Assoc*. 2015;4(1):e001486. doi: 10.1161/JAHA.114.001486 [doi].
163. O'Brien EC, Holmes DN, Ansell JE, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: Findings from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) registry. *Am Heart J*. 2014;167(4):601-609.e1. doi: <http://dx.doi.org/10.1016/j.ahj.2013.12.014>.

164. Hess PL, Mirro MJ, Diener HC, et al. Addressing barriers to optimal oral anticoagulation use and persistence among patients with atrial fibrillation: Proceedings, Washington, DC, December 3-4, 2012. *Am Heart J*. 2014;168(3):239-247.e1. doi: 10.1016/j.ahj.2014.04.007 [doi].
165. Lip GYH. Can we predict stroke in atrial fibrillation? *Clin Cardiol*. 2012;35(S1):S21-S27. doi: 10.1002/clc.20969.
166. Lewis WR, Piccini JP, Turakhia MP, et al. Get with the guidelines AFIB: Novel quality improvement registry for hospitalized patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2014;7(5):770-777. doi: 10.1161/CIRCOUTCOMES.114.001263 [doi].
167. Lip GYH. Assessing bleeding risk with the HAS-BLED score: Balancing simplicity, practicality, and predictive value in bleeding-risk assessment. *Clin Cardiol*. 2015;38(9):562-564. doi: 10.1002/clc.22436.
168. An J, Niu F, Lang DT, et al. Stroke and bleeding risk associated with antithrombotic therapy for patients with nonvalvular atrial fibrillation in clinical practice. *J Am Heart Assoc*. 2015;4(7):10.1161/JAHA.115.001921. doi: 10.1161/JAHA.115.001921 [doi].
169. Donze J, Clair C, Hug B, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med*. 2012;125(8):773-778. doi: 10.1016/j.amjmed.2012.01.033 [doi].
170. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*. 1999;159(7):677-685.
171. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham atrial fibrillation treatment of the aged

study, BAFTA): A randomised controlled trial. *Lancet*. 2007;370(9586):493-503. doi: S0140-6736(07)61233-1 [pii].

172. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: A predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol*. 2012;11(3):225-231. doi: 10.1016/S1474-4422(12)70017-0 [doi].

173. Heidenreich PA, Solis P, Estes NA, 3rd, et al. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: A report of the american college of cardiology/american heart association task force on performance measures. *J Am Coll Cardiol*. 2016;68(5):525-568. doi: 10.1016/j.jacc.2016.03.521 [doi].

174. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and african-americans: The atherosclerosis risk in communities (ARIC) study. *Am Heart J*. 2009;158(1):111-117. doi: 10.1016/j.ahj.2009.05.010 [doi].

175. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the united states: A systematic review and meta-analysis. *BMC Fam Pract*. 2012;13:5-2296-13-5. doi: 10.1186/1471-2296-13-5 [doi].

176. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. *JAMA*. 2001;285(22):2864-2870. doi: 10.1001/jama.285.22.2864.

177. Zirlik A, Bode C. Vitamin K antagonists: Relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. *J Thromb Thrombolysis*. 2017;43(3):365-379. doi: 10.1007/s11239-016-1446-0 [doi].

178. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074. doi:10.1002/(ISSN)2047-9980 10.1161/JAHA.115.003074. doi: 10.1161/JAHA.115.003074 [doi].
179. Kuruville M, Gurk-Turner C. A review of warfarin dosing and monitoring. *Proceedings (Baylor University Medical Center)*. 2001;14(3):305-306.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1305837/>.
180. Steinberg BA, Greiner MA, Hammill BG, et al. Contraindications to anticoagulation therapy and eligibility for novel anticoagulants in older patients with atrial fibrillation. *Cardiovascular therapeutics*. 2015;33(4):177-183. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4497930/>. doi: 10.1111/1755-5922.12129.
181. Lip GY. The CHA2DS2-VASc score for stroke risk stratification in patients with atrial fibrillation: A brief history. *Eur Heart J*. 2015. doi: ehv431 [pii].
182. Cheng EY, Kong MH. Gender differences of thromboembolic events in atrial fibrillation. *The American Journal of Cardiology*. 2016;117(6):1021-1027. doi:
<https://doi.org/10.1016/j.amjcard.2015.12.040>.
183. Hijazi Z, Oldgren J, Lindback J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: A derivation and validation study. *Lancet*. 2016;387(10035):2302-2311. doi: 10.1016/S0140-6736(16)00741-8 [doi].
184. Hsu JC, Maddox TM, Kennedy K, et al. Aspirin instead of oral anticoagulant prescription in atrial fibrillation Patients at Risk for stroke. *Journal of the American College of Cardiology*. 2016;67(25):2913-2923. doi: <https://doi.org/10.1016/j.jacc.2016.03.581>.

185. Pauly NJ, Brown JD. Prevalence of low-cost generic program use in a nationally representative cohort of privately insured adults. *J Manag Care Spec Pharm*. 2015;21(12):1162-1170. doi: 2015(21)12:1162-1170 [pii].
186. An J, Niu F, Lang DT, et al. Stroke and bleeding risk associated with antithrombotic therapy for patients with nonvalvular atrial fibrillation in clinical practice. *J Am Heart Assoc*. 2015;4(7):10.1161/JAHA.115.001921. doi: 10.1161/JAHA.115.001921 [doi].
187. Michtalik HJ, Carolan HT, Haut ER, et al. Use of provider-level dashboards and pay-for-performance in venous thromboembolism prophylaxis. *J Hosp Med*. 2015;10(3):172-178. doi: 10.1002/jhm.2303 [doi].
188. Clarkesmith DE, Lip GYH, Lane DA. Patients' experiences of atrial fibrillation and non-vitamin K antagonist oral anticoagulants (NOACs), and their educational needs: A qualitative study. *Thromb Res*. 2017;153:19-27. doi: S0049-3848(17)30219-0 [pii].
189. Schoof N, Schnee J, Schneider G, et al. Characteristics of patients with non-valvular atrial fibrillation using dabigatran or warfarin in the US. *Curr Med Res Opin*. 2014;30(5):795-804. doi: 10.1185/03007995.2013.879529 [doi].
190. the pharma letter. Atrial fibrillation market value to plummet post 2020 as patents expire, report predicts. <https://www.thepharmaletter.com/article/atrial-fibrillation-market-value-to-plummet-post-2022-as-patents-expire-report-predicts>. Accessed April 20, 2018.
191. Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS, Davidson PM. Education and practice gaps on atrial fibrillation and anticoagulation: A survey of cardiovascular nurses. *BMC Med Educ*. 2016;16:9-015-0504-1. doi: 10.1186/s12909-015-0504-1 [doi].

192. Brais C, Larochelle J, Turgeon MH, et al. Predictors of direct oral anticoagulants utilization for thromboembolism prevention in atrial fibrillation. *J Pharm Pharm Sci.* 2017;20:8-14. doi: 10.18433/J30W4F [doi].
193. Hess PL, Kim S, Fonarow GC, et al. Absence of oral anticoagulation and subsequent outcomes among outpatients with atrial fibrillation. *Am J Med.* 2017;130(4):449-456. doi: <https://doi-org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2016.11.001>.
194. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: The example of COX2 inhibitors and myocardial infarction. *Epidemiology.* 2005;16(1):17-24. doi: 00001648-200501000-00004 [pii].
195. Edwards JD, Kapral MK, Fang J, Saposnik G, Gladstone DJ. Underutilization of ambulatory ECG monitoring after stroke and transient ischemic attack. *Stroke.* 2016;47(8):1982-1989. doi: 10.1161/STROKEAHA.115.012195.
196. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the framingham heart study: A cohort study. *Lancet.* 2015;386(9989):154-162. doi: 10.1016/S0140-6736(14)61774-8 [doi].
197. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the framingham heart study: A cohort study. *Lancet.* 2015;386(9989):154-162. doi: 10.1016/S0140-6736(14)61774-8 [doi].
198. Nunes AP, Loughlin AM, Qiao Q, et al. Tolerability and effectiveness of exenatide once weekly relative to basal insulin among type 2 diabetes patients of different races in routine care. *Diabetes Therapy.* 2017;8(6):1349-1364. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5688980/>. doi: 10.1007/s13300-017-0314-z.

199. Rodriguez CJ, Soliman EZ, Alonso A, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: The multi-ethnic study of atherosclerosis. *Ann Epidemiol.* 2015;25(2):71-6, 76.e1. doi: 10.1016/j.annepidem.2014.11.024 [doi].
200. Siouta E, Hellstrom Muhli U, Hedberg B, Brostrom A, Fossum B, Karlgren K. Patients' experiences of communication and involvement in decision-making about atrial fibrillation treatment in consultations with nurses and physicians. *Scand J Caring Sci.* 2015. doi: 10.1111/scs.12276 [doi].
201. Thukkani AK, Agrawal K, Prince L, et al. Long-term outcomes in patients with diabetes mellitus related to prolonging clopidogrel more than 12 months After Coronary stenting. *J Am Coll Cardiol.* 2015;66(10):1091-1101. doi: [http://dx.doi.org.proxy-
hs.researchport.umd.edu/10.1016/j.jacc.2015.06.1339](http://dx.doi.org.proxy-
hs.researchport.umd.edu/10.1016/j.jacc.2015.06.1339).
202. Yasaitis LC, Berkman LF, Chandra A. Comparison of self-reported and medicare claims-identified acute myocardial infarction. *Circulation.* 2015;131(17):1477-85; discussion 1485. doi: 10.1161/CIRCULATIONAHA.114.013829 [doi].
203. CMS. MDC 20 alcohol/drug use & alcohol/drug induced organic mental disorders. <https://www.cms.gov/icd10manual/version30-fullcode-cms/P0023.html>. Accessed 02/03, 2016.
204. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: A retrospective observational pharmacy claims analysis. *Diabetes Care.* 2010;33(11):2349-2354. doi: 10.2337/dc10-0482 [doi].
205. Huang T, Wei Y, Moyo P, Harris I, Lucas JA, Simoni-Wastila L. Treated behavioral symptoms and mortality in medicare beneficiaries in nursing homes with alzheimer's disease and related dementias. *J Am Geriatr Soc.* 2015;63(9):1757-1765. doi: 10.1111/jgs.13606.

206. Will JC, Loustalot F, Hong Y. National trends in visits to physician offices and outpatient clinics for angina 1995 to 2010. *Circulation. Cardiovascular quality and outcomes*. 2014;7(1):110-117.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4363730/>. doi: 10.1161/CIRCOUTCOMES.113.000450.
207. 2012 ICD-9-CM diagnosis code 440.0: Atherosclerosis of aorta.
<http://www.icd9data.com/2012/Volume1/390-459/440-449/440/440.0.htm>. Accessed 02/03, 2016.
208. Xie L, Liu X, Phatak H, et al. Warfarin discontinuation in patients with unprovoked venous thromboembolism: A large US insurance database analysis. *Am J Ther*. 2015. doi: 10.1097/MJT.000000000000167 [doi].
209. Allen LaPointe NM, Dai D, Thomas L, Piccini JP, Peterson ED, Al-Khatib SM. Antiarrhythmic drug use in patients <65 Years with atrial fibrillation and without structural heart disease. *Am J Cardiol*. 2015;115(3):316-322. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjcard.2014.11.005>.
210. Epstein AJ, Yang L, Yang F, Groeneveld PW. A comparison of clinical outcomes from carotid artery stenting among US hospitals. *Circ Cardiovasc Qual Outcomes*. 2014;7(4):574-580. doi: 10.1161/CIRCOUTCOMES.113.000819 [doi].
211. Brodovicz KG, Chen Y, Liu Z, Ritchey ME, Liao J, Engel SS. Characterization of sitagliptin use in patients with type 2 diabetes and chronic kidney disease by cross-sectional analysis of a medical insurance claims database. *Diabetes Therapy*. 2015;6(4):627-634.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4674473/>. doi: 10.1007/s13300-015-0133-z.
212. Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singal AG. Use of administrative claims data for identifying patients with cirrhosis. *J Clin Gastroenterol*. 2013;47(5):e50-4. doi: 10.1097/MCG.0b013e3182688d2f [doi].

213. Lang K, Patel AA, Munsell M, et al. Recurrent hospitalization and healthcare resource use among patients with deep vein thrombosis and pulmonary embolism: Findings from a multi-payer analysis. *J Thromb Thrombolysis*. 2014;39(4):434-442. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4379443/>. doi: 10.1007/s11239-014-1108-z.
214. Henk HJ, Paoli CJ, Gandra SR. A retrospective study to examine healthcare costs related to cardiovascular events in individuals with hyperlipidemia. *Adv Ther*. 2015;32(11):1104-1116. doi: 10.1007/s12325-015-0264-7 [doi].
215. van Deen WK, van Oijen MG, Myers KD, et al. A nationwide 2010-2012 analysis of U.S. health care utilization in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2014;20(10):1747-1753. doi: 10.1097/MIB.000000000000139 [doi].
216. 2012 ICD-9-CM diagnosis code 286.6: Defibrination syndrome. <http://www.icd9data.com/2012/Volume1/280-289/286/286.6.htm>. Accessed 02/03, 2016.
217. 2013 ICD-9-CM diagnosis code 424.0: Mitral valve disorders. <http://www.icd9data.com/2013/Volume1/390-459/420-429/424/424.0.htm>. Accessed 02/03, 2016.
218. Lloyd JT, Blackwell SA, Wei II, Howell BL, Shrank WH. Validity of a claims-based diagnosis of obesity among medicare beneficiaries. *Eval Health Prof*. 2015;38(4):508-517. doi: 10.1177/0163278714553661 [doi].
219. 2014 ICD-9-CM diagnosis code 327.23: Obstructive sleep apnea (adult)(pediatric). <http://www.icd9data.com/2014/Volume1/320-389/320-327/327/327.23.htm>. Accessed 02/03, 2016.
220. 2012 ICD-9-CM diagnosis code 459.9: Unspecified circulatory system disorder. <http://www.icd9data.com/2012/Volume1/390-459/451-459/459/459.9.htm>.

221. 2014 ICD-9-CM diagnosis code 443.9: Peripheral vascular disease, unspecified.
<http://www.icd9data.com/2014/Volume1/390-459/440-449/443/443.9.htm>. Accessed 02/02, 2016.
222. Kim SC, Solomon DH, Liu J, Franklin JM, Glynn RJ, Schneeweiss S. Risk of venous thromboembolism in patients with rheumatoid arthritis: Initiating disease-modifying antirheumatic drugs. *Am J Med*. 2015;128(5):539.e7-539.e17. doi: <http://dx.doi.org.proxy-hs.researchport.umd.edu/10.1016/j.amjmed.2014.11.025>.
223. 2013 ICD-9-CM diagnosis code 780.50: Sleep disturbance, unspecified.
<http://www.icd9data.com/2013/Volume1/780-799/780-789/780/780.50.htm>. Accessed 02/03, 2016.
224. ICD9Data. Thyrotoxicosis without mention of goiter or other cause.
<http://www.icd9data.com/2013/Volume1/240-279/240-246/242/242.9.htm>. Accessed 3/4, 2016.
225. O'Brien EC, Zhao X, Fonarow GC, et al. Quality of care and ischemic stroke risk after hospitalization for transient ischemic attack: Findings from get with the guidelines-stroke. *Circ Cardiovasc Qual Outcomes*. 2015;8(6 Suppl 3):S117-24. doi: 10.1161/CIRCOUTCOMES.115.002048 [doi].