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Warfarin Treatment and All-Cause Mortality in Community-Dwelling Older Adults with Atrial Fibrillation: A Retrospective Observational Study

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Abstract

OBJECTIVES: To investigate the relationship between warfarin treatment and different strata of all-cause mortality risk assessed using the Multidimensional Prognostic Index (MPI) based on information collected using the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA) in community-dwelling older adults with atrial fibrillation (AF).

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Author Contributions: Pilotto, Gallina, Panza, Pilotto, Ferrucci: study concept and design, interpretation of data, writing the manuscript, directing the study. Panza, Marcato, Mello, Simonato, Logroscino, Padovani: literature search, interpretation of data, manuscript preparation. Copetti, Marcato: study design, data interpretation, statistical analysis; had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All members of the MPI_AGE Project Steering Committee participated in interpretation of the data and performed the internal review process.

Conflict of Interest:

The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Sponsor's Role: The funding agency had no role in design or conduct of the study.

APPENDIX: EC FUNDED MPI_AGE PROJECT INVESTIGATORS

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

DESIGN: Retrospective observational study.

SETTING: Older community-dwelling adults who underwent a SVaMA evaluation establishing accessibility to homecare services and nursing home admission from 2005 to 2013 in the Padova Health District, Italy.

PARTICIPANTS: Community-dwelling individuals with AF aged 65 and older (N = 1,827).

MEASUREMENTS: Participants were classified as being at mild (MPI-SVaMA-1), moderate (MPI-SVaMA-2), or severe (MPI-SVaMA-3) risk of mortality using the MPI-SVaMA, a validated prognostic tool based on age, sex, comorbidity, cognitive status, mobility and functional disability, pressure sore risk, and social support. The association between warfarin treatment and mortality was tested using multivariate- and propensity score-adjusted Cox regression models, controlling for age, sex, all SVaMA domains, concomitant diseases, and drug treatments.

RESULTS: Higher MPI-SVaMA scores were associated with lower rates of warfarin treatment and higher 3-year mortality. After adjustment for propensity score quintiles, warfarin treatment was significantly associated with lower 2-year mortality in individuals with MPI-SVaMA-1 (hazard ratio (HR) = 0.64, 95% confidence interval (CI) = 0.50–0.82), MPI-SVaMA-2 (HR = 0.68,95% CI = 0.55–0.85), and MPI-SVaMA-3 (HR = 0.55, 95% CI = 0.44–0.67). Heterogeneity analyses confirmed that the effect of warfarin treatment was not different between MPI-SVaMA groups (*P* for heterogeneity = .48).

CONCLUSION: Community-dwelling older adults with AF benefitted from anticoagulation in terms of lower all-cause mortality over a mean follow-up of 2 years, regardless of poor health and functional condition. Although this benefit can be ascribed to the treatment, it may also reflect better overall care. **J Am Geriatr Soc 64:1416–1424, 2016**.

Keywords

atrial fibrillation; all-cause mortality; warfarin; aging; frailty; multidimensional prognostic index

Atrial fibrillation (AF), the most common cardiac arrhythmia,[1] is associated with twice the risk mortality[2] and five times the risk of stroke.[3] Randomized controlled trials have shown that treatment with a vitamin K antagonist, traditionally warfarin, and new oral anticoagulants decreases the risk of cerebrovascular events.[4–9] Current guidelines generally recommend that oral anticoagulation treatment for individuals with AF should be customized to their individual risk of stroke and bleeding.[10,11] According to Congestive Heart Failure, Hypertension, Age category, Diabetes, Stroke, Vascular disease, Sex category (CHA2DS2-VASc), all individuals with AF aged 75 and older should be anticoagulated, and according to Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes, Stroke (CHADS2), anticoagulation should be considered for all people aged 75 and older, and is recommended in the presence of an additional risk factor,[12] but warfarin prescription was unrelated to CHADS2 score, and warfarin use did not differ according to risk stratum.[13,14] Nonetheless, clinical decisions about anticoagulant prescription in older adults with AF only seldom take mortality risk stratification into account,[13–16] resulting in many hospitalized or community-dwelling older adults not receiving anticoagulation therapy.[17–19] Thus, although

anticoagulation treatment seems to be effective in older adults,[4,13,20] many of them are not treated.[13,17–20]

Frailty is a multidimensional state of vulnerability,[21] and frail older adults with AF were less likely than their nonfrail counterparts to receive a prescription for an antithrombotic and had greater risk of embolic stroke and greater mortality.[22] Frailty was also associated with not receiving all guideline-recommended therapies for cardiovascular comorbid conditions and risk factors.[23] Previous studies investigating barriers to warfarin prescription in older age have found that many frailty-related factors such as high risk of falls, history of bleeding, poor adherence to prescribed medications, impaired cognitive status, and comorbidities are inversely correlated with warfarin prescription.[24] In the absence of clear indications in frail older adults with AF for anticoagulation treatment, the decision of whether to provide an anticoagulant should take risk of severe complications and expected future survival time into account.[25,26]

Mortality risk stratification in older adults should be based on information about comorbidity and functional status[27] using a multidimensional Comprehensive Geriatric Assessment (CGA) and integrating information from several domains of health and function.[21,28] A Multidimensional Prognostic Index (MPI) derived from a standardized CGA has been developed and validated for mortality risk assessment in several independent cohorts of hospitalized[29] and community-dwelling[30] older adults with acute or chronic disease. A balance between risk of stroke and risk of bleeding in older age has been difficult to find, and physicians are often uncertain about antithrombotic therapy, with an overall trend toward underuse of anticoagulant drugs.[31] Therefore, mortality risk stratification is strictly linked to anticoagulation treatment and older age, given that, in approximately 66% of individuals aged 80 and older, a stroke will result in death or disability.[32] The aim of the present study was to investigate the relationship between warfarin treatment and different strata of allcause mortality risk in community-dwelling older adults with AF over a mean follow-up of 2 years.

METHODS

Study Population

This was a retrospective observational study conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[33] All community-dwelling individuals aged 65 and older who underwent a CGA-based multidimensional assessment according to the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (Scheda per la Valutazione Multidimensionale delle persone adulte e Anziane (SVaMA))[29] from January 1, 2005 to December 31, 2013, were screened for inclusion in the study. Inclusion criteria were previous hospitalization with a discharge diagnosis of AF, aged 65 and older at time of the hospitalization, and SVaMA evaluation within 2 months of the date of first registration of AF diagnosis. The institutional review board of the Social and Health-Care Local Unit 16, Padova, Italy, approved this retrospective observational study. Individuals who underwent SVaMA evaluation or their proxies provided informed consent for their clinical records to be used in clinical studies. For warfarin users, enrollment was defined as the first warfarin prescription after AF diagnosis. For warfarin nonusers,

enrollment was defined as the date of SVaMA completion after the first registered AF diagnosis. Subjects with a date of SVaMA completion preceding the date of AF diagnosis registration but with an interval between these dates of less than 2 months were also included. Subjects were followed for a mean of 2.0 ± 1.9 years. Vital status was assessed by consulting the registry offices of the cities where the individuals resided at the time of the evaluation. Dates of death were identified from death certificates.

MPI Based on the SVaMA

The Veneto Regional Health System introduced the SVaMA, the officially recommended multidimensional assessment schedule that the health personnel of the National Healthcare System use to perform multidimensional assessments of community-dwelling older persons, in 2000 to establish accessibility to some healthcare resources (homecare services or nursing home admission).[30] The SVaMA domains of age; sex; main diagnosis; nursing care needs evaluated according to a validated numeric scale including 11 items; cognitive status, evaluated using the Short Portable Mental Status Questionnaire (SPMSQ); pressure sore risk, evaluated using the Exton-Smith Scale; activities of daily living (ADLs); mobility, evaluated using the Barthel Index; and social support, evaluated using a numeric scale of 16 items that explores the presence of a support network during the day and the night were used to calculate the MPI. The SVaMA instrument (Italian version) is available on-line (http://www.uneba.org/regione-veneto-nuova-svama-e-nuova-svamdi/).

To calculate the MPI from the SVaMA, a weighted sum of each domain (D_i) was computed (raw formula), and then weights (S_i) were estimated from a multivariate Cox proportional hazards model for 1-year mortality prediction. Each weighted sum ($R = \Sigma(S_i . D_i)$) was then normalized into a range from 0 (lowest risk) to 1 (highest risk), subtracting the observed raw minimum score and then dividing the difference by the observed range (minimum to maximum span). The MPI-SVaMA was expressed as a continuous score ranging from 0 (low risk) to 1 (high risk of mortality). The Recursive Partition and Amalgamation algorithm[34] was used to identify subgroups of individuals at different risk of mortality.[30] Cut-off scores were estimated for the normalized MPI-SVaMA 1-year mortality prediction (0–0.33 = MPI-SVaMA-1 (mild risk), 0.34–0.47 = MPI-SVaMA-2 (moderate risk), 0.48–1.0 = MPI-SVaMA-3 (severe risk)). To calculate MPI-SVaMA, software for Windows may be downloaded (for free from http://www.mpiage.eu (English version)). Information on the reliability, accuracy, calibration, and validation of the MPI based on the SVaMA can be found elsewhere.[30]

Thromboembolic Risk Evaluation

At baseline, the risk of thromboembolism was evaluated according to CHA2DS2-VASc score[35] calculated by assigning 1 point each for congestive heart failure, hypertension, aged 65 to 74, diabetes mellitus, vascular disease, and female sex and 2 points each for previous thromboembolism and aged 75 and older. Participants were divided into three classes of risk (0 = low risk, 1 = intermediate risk, ≥2 = high risk, as previously reported).[35]

Drug Treatment Assessment

The cohort was linked to the Pharmaceutical Prescription database of the Azienda ULSS 16 Padova to extract information on individual medication use. Warfarin and other drug prescriptions were determined according to Anatomical Therapeutic Chemical codes. Individuals were considered warfarin users if they had received a warfarin prescription after their first registered AF diagnosis. Warfarin nonusers were defined as those who had never received a warfarin prescription. The mean monthly past treatment rate, defined as number of all medications used before enrollment divided by number of months between first prescription and enrollment, was used as a proxy for polypharmacy.

Statistical Analysis

Baseline characteristics for men and women were reported as percentages and as means and standard deviations and were compared using Pearson chi-square tests for categorical variables and Mann-Whitney *U*-tests for continuous variables. Linear trends among MPI scores (the presence of a constant increasing or decreasing trend of mean values or frequencies across the ordinal MPI groups) were evaluated using Spearman correlation coefficients for continuous variables and Mantel-Haenszel chi-square tests for categorical variables. Mortality incidence rates were expressed as the number of new events per 100 person-years and compared using a Poisson regression model. Propensity score methodology was used to reduce the selection bias between treatment comparisons found in observational studies.[36] Propensity score logistic regression models were built to predict the probability of receiving warfarin according to all variables used for the calculation of MPI-SVaMA at treatment assignment (age; sex; nursing care needs; cognitive status; pressure sore risk; ADLs; mobility; social support; fractures; cancer; dementia; stroke; hypokinetic syndrome; cardiovascular, respiratory, neurological, or other diseases; CHA2DS2-VASc score; tertiles of past treatment rate). Overlapping of propensity scores between treatment and control groups was also checked, and subjects with nonoverlapping propensity scores were excluded from the analyses. Separate propensity score logistic models were run for the overall sample and MPI-SVaMA score subgroups. Multivariate and propensity score quintile-adjusted Cox regression models were used to assess the effect of warfarin use on 1-, 2-, and 3-year mortality, and results were expressed as hazard ratios (HRs) and 95% confidence intervals (95% CIs). A 5 to 1 greedy 1:1 propensity score matching algorithm[37] was used to check the robustness of the findings. Propensity score 1:1 matching identified a unique matched control for each treated individual according to their propensity scores. Adequacy of covariate balance in the matched sample was eventually assessed using the McNemar or Wilcoxon signed rank test. For the overall sample and for specific MPI-SVaMA score subgroups, adjusted HRs of warfarin use for each endpoint (1-, 2-, 3-year mortality) were reported along with total number of events, total subjects per group, and mortality. Multivariate models included treatment, age, sex, main diagnoses, all SVaMA domains, CHA2DS2-VASc score, and past treatment rate. Because the propensity score-matched sample did not consist of independent observations, a marginal survival model with robust standard errors was used. *P*-values assessing the presence of a heterogeneous effect of warfarin treatment between MPI-SVaMA risk subgroups on mortality risk were calculated and reported.[38] Two-sided $P < .05$ was considered significant. All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the Study Population

The study population included 1,827 individuals (653 men (35.7%), 1,174 women (64.3%)) with a mean age of 84.4 ± 7.1. Men were younger (82.2 ± 7.5 vs 85.6 ± 6.5, $P < .001$) and had higher mean MPI scores (0.5 ± 0.2 vs 0.4 ± 0.2, $P < .001$) and nursing care needs (8.3 ± 8.2 vs 7.3 ± 8.3, $P < .001$) and significantly higher mortality incidence rates at 1 (62.4% vs 43.7%, $P < .001$), 2 (55.7% vs 38.7%, $P < .001$), and 3 (51.4% vs 35.9%, $P < .001$) years of follow-up than women. Women were significantly more cognitively impaired (SPMSQ score 5.7 ± 3.6 vs 5.1 ± 3.7, $P < .001$) and had higher mean CHA2DS2-VASc scores (4.2 ± 0.7 vs 3.0 ± 0.8, $P < .001$) than men. Overall, 99.0% of participants had a high-risk CHA2DS2-VASc profile (CHA2DS2-VASc ≥2: women 100%, men 97.1%, $P < .001$). No significant differences between sexes were observed in past treatment rate or rate of participants starting warfarin treatment (men 45.5%, women 42.7%, $P = .25$) (see also Table S1).

Table 1 shows the characteristics of participants divided according to MPI-SVaMA score; 705 participants (38.6%) had mild risk of mortality, 634 (34.7%) had moderate risk, and 488 (26.7%) had severe risk. As expected, participants with higher MPI-SVaMA scores were more likely to be male ($P < .001$) and older ($P < .001$) and had significantly worse ADL, cognitive status, nursing care needs, pressure sore risk, mobility, and social support scores (all $P < .01$). Three-year mortality incidence was 22.2% for MPI-SVaMA-1, 43.3% for MPI-SVaMA-2, and 91.4% for MPI-SVaMA-3 (P for trend <.001). Participants included in the MPI-SVaMA-3 class had significantly lower total CHA2DS2-VASc scores (continuous score, $P < .001$), even though 98.0% of participants in the MPI-SVaMA-3 class were classified as being at high risk. Moreover, to determine the presence of residual confounding, overall mortality was estimated at 1, 2, and 3 years of follow-up according to CHA2DS2-VASc score group, and P-values from type 3 effects were highly nonsignificant ($P = .63$ at 1 year, $P = .34$ at 2 years, $P = .54$ at 3 years), reflecting the absence of any survival bias.

Characteristics of Participants According to Warfarin Treatment

Overall, 798 participants with AF (43.7% of the total study population with AF) were treated with warfarin. Treated participants were younger ($P < .001$) and had better cognitive status, ADL, and mobility scores and less pressure sore risk ($P < .001$ in all domains) and better MPI-SVaMA scores ($P < .001$) than untreated participants (Table 2). Moreover, treated participants were more frequently in the MPI-SVaMA-1 group (47.6% vs 31.6%, $P < .001$) and in the high-risk past-treatment rate group (3rd tertile, 39.5% vs 29.7%, $P < .001$) than untreated participants. Treated participants also had higher prevalence of cardiovascular disease but similar previous stroke history and $CHAD_2DS_2$-VASc scores. Untreated participants were more frequently in the MPI-SVaMA-2 group (37.8% vs 30.7%, $P < .001$), in the MPI-SVaMA-3 group (30.6% vs 21.7%, $P < .001$), and in the low-risk past-treatment rate group (1st tertile, 39.8% vs 34.0%, $P = .01$) and had greater prevalence of dementia and cancer than treated participants.

Warfarin Treatment and Mortality in Participants Divided According to MPI-SVaMA Score

Multivariate analysis demonstrated that, in the overall study population, warfarin treatment was associated with lower mortality after 1, 2, and 3 years of follow-up (Table 3). Warfarin treatment was significantly associated with lower mortality after 1, 2, and 3 years of follow-up in MPI-SVaMA-1 mild-risk participants, MPI-SVaMA-2 moderate-risk participants, and MPI-SVaMA 3 severe-risk participants (Table 3). The assessment of heterogeneity suggested that the effect of warfarin treatment was not different in the three groups of participants (P = .08 for 1 year, P = .21 for 2 years, P = .21 for 3 years).

Adjustment for propensity score quintiles confirmed a significant association between warfarin treatment and lower mortality in the overall population after 1, 2, and 3 years of follow-up. Similarly, warfarin treatment was significantly associated with lower mortality after 1, 2, and 3 years of follow-up in MPI-SVaMA-1 mild-risk participants, MPI-SVaMA-2 moderate-risk participants, and MPI-SVaMA 3 severe-risk participants. Moreover, the presence of an interaction between MPI-SVaMA groups and CHA2DS2-VASc scores was tested for, and P-values for such interaction terms were all highly nonsignificant (P = .29 for 1 year of follow-up, P = .47 for 2 years, P = .29 for 3 years), which led to the conclusion that there was no statistical evidence that mortality risk in participants with low, medium, and high MPI-SVaMA grades was different on the basis of CHA2DS2-VASc score. The analyses for heterogeneity suggested that the effect of warfarin treatment was not different in the three groups of participants (P = .42 for 1 year, P = .76 for 2 years, P = .48 for 3 years). The propensity score-based greedy matching algorithm successfully matched 671 of 798 treated participants. Adequacy of covariate balance in the matched sample is shown in Table S2. Results of warfarin treatment effects from marginal univariate Cox regression models, with robust standard errors, were fully overlapping with those reported in Table 3 (Table S3).

DISCUSSION

The present retrospective observational study demonstrated that, in the overall study population of community-dwelling older adults with AF, warfarin treatment was associated with lower all-cause mortality over a mean follow-up of 2 years. Anticoagulation treatment was associated with a highly significantly lower mortality in participants at lower and higher risk of dying (all MPI-SVaMA groups). Therefore, these findings demonstrate that severely compromised health and functional status was not associated with lack of effect of warfarin treatment on mortality in older adults with AF. Although many studies have evaluated warfarin efficacy in stroke prevention, only a few have suggested lower mortality in older adults with AF treated with anticoagulants than in those not treated.[39] Nevertheless, no study had explored whether different individual mortality risk could be associated with different efficacy of anticoagulation treatment in older adults with AF.

In agreement with other recent studies,[12–16,18,19,39–41] the current study found that anticoagulation treatment was underused in this older population (prevalence of warfarin use in participants with AF 43.7%), but the individuals included in this study were selected from a population of older adults with poor health and functional condition who underwent a CGA-based multidimensional assessment according to the SVaMA to determine need for homecare services or nursing home admission. Therefore, it cannot be excluded that the

observed low prevalence of anticoagulation treatment may reflect the reluctance of physicians to treat older adults with clinical, functional, and social impairments. Warfarin-treated participants were significantly younger and had fewer functional, cognitive, and clinical impairments and significantly lower mortality risk than untreated participants. To minimize this selection bias, propensity score methods were used to define two cohorts in which the two groups of participants differed only in terms of treatment with warfarin. Propensity score-adjusted models and the analyses within the propensity score-matched cohorts confirmed that warfarin efficacy was evident in low- and high-risk participants after 1, 2, and 3 years of follow-up. The subgroup analyses for heterogeneity, moreover, showed that the association between warfarin treatment and lower mortality was not significantly different in participants with different mortality risk.

Therefore, poor health and functional conditions are probably not per se a contraindication to warfarin in older adults with AF. In a previous prospective study in a hospital-based cohort of 220 individual aged 70 and older with AF, those who were frail were significantly less likely to receive warfarin than those who were not on admission and discharge from a tertiary referral hospital.[22] In Portuguese community-dwelling frail older adults, the number of drugs consumed per day was independently associated with physical frailty.[42] In particular, the consumption of antihypertensives and anticoagulants explained part of the variance of total and physical frailty,[42] providing further evidence of the association between this geriatric syndrome and cardiovascular risk. Furthermore, many frailty-related factors may contribute to nonprescription of warfarin.[24]

This may suggest that multidimensional impairment with poor health and functional condition may deter a physician from prescribing warfarin. Nevertheless, according to the present findings, many of the factors that are purported to be barriers to anticoagulation treatment in older persons with AF, including predisposition to falling and old age per se, do not increase the chance of anticoagulation-related major bleeding[43] and should probably not influence the choice of stroke prophylaxis in these individuals.

Nonetheless, clinical decision-making about anticoagulant prescription in older adults with AF does not often consider mortality risk stratification.[13–16] In particular, in a cohort of 3,020 men and 3,749 women aged 75 and older diagnosed with AF selected from 75 primary care centers in Sweden, longer survival was associated with anticoagulants than with no treatment or with antiplatelets.[16] A recent population-based study found that warfarin use in older age was associated not only with lower stroke risk, but also with longer life expectancy.[13] In the present study, to evaluate mortality risk in an older population, the MPI based on the SVaMA,[30] a well-calibrated, highly accurate predictor of mortality in this age group, was adopted.[27,44,45] As expected, the MPI-SVaMA was effective in predicting mortality. A large multicenter study performed in more than 2,000 hospitalized older adults demonstrated that MPI had significantly greater predictive power for all-cause mortality than three other instruments measuring frailty specifically.[46] A recent article on thromboembolic prevention in frail older adults with AF has proposed a multidimensional decision-making algorithm for the use of oral anticoagulants with a standard ischemic and bleeding risk assessment and an additional anticoagulation-focused frailty assessment including the MPI to assess life expectancy in these individuals.[26] As expected in the present older population,

CHA2DS2-VASc score was not associated with anticoagulation treatment, and its use showed an important ceiling effect. More than 99% of participants had high-risk CHA2DS2-VASc scores because of older age and common vascular risk factors, supporting the limited applicability of the CHA2DS2-VASc and CHADS2 risk stratification tools in clinical decision-making in older adult with AF.[15,18,41]

This study had limitations. First, the efficacy of warfarin was considered only in terms of lower all-cause mortality, not taking into account minor events not leading to death or the final cause-specific deaths (fatal and nonfatal stroke, coronary death, nonfatal myocardial infarction, cardiovascular death). Nevertheless, considering the net clinical benefit of lower mortality, it may be relevant in older adults with shorter life expectancy. Second, a bleeding risk stratification with a score focused on individuals with AF (Hypertension, Abnormal liver or renal function, Stroke, Bleeding, Labile international normalized ratio (INR), Elderly, Drugs or alcohol)[47] was not used because laboratory data on INR and renal and liver function were not available. In agreement with recent findings from the General Practice Research Database,[15] the same ceiling effect observed for the CHA2DS2-VASc score could be expected in the current study's older cohort. Furthermore, the present findings were observational and noninterventional. In an observational study, there would be confounding by indication that arises from the fact that individuals who are prescribed a medication or who take a given medication are inherently different from those who do not take the drug, but few individuals aged 80 and older were enrolled in the early randomized controlled trials of oral anticoagulation vs placebo, with only 20% of the study population being aged 75 and older.[17] Therefore, observational studies in frail older individuals are needed to determine the effectiveness of anticoagulation treatment in this subgroup. A recent Cochrane review assessing the effect of study design on healthcare outcomes that demonstrated no significant differences between observational studies and randomized controlled trials, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions, supports this.[48] Moreover, another potential confounder arises from the fact that warfarin use could simply be a marker of better medical care quality, potentially influencing the effect of anticoagulation on all-cause mortality in these older adults. Lastly, follow-up of these participants was limited to 3 years, with mean follow-up of 2 years; it cannot be excluded that significant differences in effectiveness between individuals with different mortality risk could emerge with longer follow-up.

In community-dwelling older adults with AF, the present findings strongly suggest that severe multidimensional impairment per se was not an impediment to the prescription of warfarin. Regardless of poor health and functional condition, these individuals can benefit from anticoagulation in terms of lower mortality. Although this benefit can be ascribed to treatment, it may also reflect better overall care. The longer survival associated with warfarin use in these community-dwelling older adults with AF may suggest a significant effect of anticoagulation treatment also on individuals requiring homecare services or nursing home admission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–2375. [PubMed: 11343485]
2. Miyasaka Y, Barnes ME, Bailey KR et al. Mortality trends in patients diagnosed with first atrial fibrillation: A 21-year community-based study. J Am Coll Cardiol 2007;49:986–992. [PubMed: 17336723]
3. Lip GYH, Lim HS. AF and stroke prevention. Lancet 2007;6:981–993. [PubMed: 17945152]
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–867. [PubMed: 17577005]
5. Singer DE, Chang Y, Fang MC et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009;151:297–305. [PubMed: 19721017]
6. Connolly SJ, Ezekowitz MD, Yusuf S et al.; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–1151. [PubMed: 19717844]
7. Granger CB, Alexander JH, McMurray JJ et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992. [PubMed: 21870978]
8. Patel MR, Mahaffey KW, Garg J et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–891. [PubMed: 21830957]
9. Giugliano RP, Ruff CT, Braunwald E et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–2104. [PubMed: 24251359]
10. Camm AJ, Lip GYH, De Caterina R et al.; ESC Committee for Practice Guidelines. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719–2747. [PubMed: 22922413]
11. Anderson JL, Halperin JL, Albert NM et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations). A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:1935–1944. [PubMed: 23558044]
12. Lip GYH, Nieuwlaat R, Pisters R et al. Refining clinical risk stratification for predicting stroke and thromboembolism in AF using a novel risk factor-based approach. The Euro Heart Survey on AF. Chest 2010;137:263–272. [PubMed: 19762550]
13. Sandhu R, Bakal AB, Ezekowitz JA et al. Risk stratification schemes, anticoagulation use and outcomes: The risk-treatment paradox in patients with newly diagnosed non-valvular atrial fibrillation. Heart 2011;97:2046–2050. [PubMed: 22076011]
14. Carlsson AC, Wandell P, Sundquist K et al. Differences and time trends in drug treatment of atrial fibrillation in men and women and doctors' adherence to warfarin therapy recommendations: A Swedish study of prescribed drugs in primary care in 2002 and 2007. Eur J Clin Pharmacol 2013;69:245–253. [PubMed: 22684091]

15. Scowcroft AC, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in the UK: An analysis using the General Practice Research Database (GPRD) 2000–2009. Heart 2013;99:127–132. [PubMed: 23086966]
16. Wändell PE, Carlsson AC, Sundquist J et al. Pharmacotherapy and mortality in atrial fibrillation-a cohort of men and women 75 years or older in Sweden. Age Ageing 2015;44:232–238. [PubMed: 25324331]
17. Hylek EM, D'Antonio J, Evans-Molina C et al. Translating the results of randomized trials into clinical practice: The challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006;37:1075–1080. [PubMed: 16527999]
18. Chan PS, Maddox TM, Tang F et al. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). Am J Cardiol 2011;108:1136–1140. [PubMed: 21798501]
19. Sinnaeve PR, Brueckmann M, Clemens A et al. Stroke prevention in elderly patients with atrial fibrillation: Challenges for anticoagulation. J Intern Med 2012;271:15–24. [PubMed: 21995885]
20. Mant J, Hobbs FD, Fletcher K et al.; BAFTA investigators; Midland Research Practices Network. 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;370:493–503. [PubMed: 17693178]
21. Clegg A, Young J, Iliffe S et al. Frailty in elderly people. Lancet 2013;381:752–762. [PubMed: 23395245]
22. Perera V, Bajorek BV, Matthews S et al. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing 2009;38:156–162. [PubMed: 19151165]
23. Hess PL, Kim S, Piccini JP et al. Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation. Am J Med 2013;126:625–632. [PubMed: 23787195]
24. Bajorek BV, Krass I, Ogle SJ et al. Optimizing the use of antithrombotic therapy for atrial fibrillation in older people: A pharmacist-led multidisciplinary intervention. J Am Geriatr Soc 2005;53:1912–1920. [PubMed: 16274372]
25. Gill TM. The central role of prognosis in clinical decision making. JAMA 2012;307:199–200. [PubMed: 22235093]
26. Granziera S, Cohen AT, Nante G et al. Thromboembolic prevention in frail elderly patients with atrial fibrillation: A practical algorithm. J Am Med Dir Assoc 2015;16:358–364. [PubMed: 25680239]
27. Yourman LC, Lee SJ, Schonberg MA et al. Prognostic indices for older adults: A systematic review. JAMA 2012;307:182–192. [PubMed: 22235089]
28. Wieland D, Ferrucci L. Multidimensional geriatric assessment: Back to the future. J Gerontol A Biol Sci Med Sci 2008;63A:272–274.
29. Pilotto A, Ferrucci L, Franceschi M et al. Development and validation of a multidimensional prognostic index for 1-year mortality from the comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res 2008;11:151–161. [PubMed: 18173367]
30. Pilotto A, Gallina P, Fontana A et al. Development and validation of a Multidimensional Prognostic Index for mortality based on a Standardized Multidimensional Assessment Schedule (MPI-SVaMA) in community-dwelling older subjects. J Am Med Dir Assoc 2013;14:287–292. [PubMed: 23402948]
31. Ogilvie IM, Newton N, Welner SA et al. Underuse of oral anticoagulants in atrial fibrillation: A systematic review. Am J Med 2010;123:638–645. [PubMed: 20609686]
32. Saposnik G, Black SE, Hakim A et al. Age disparities in stroke quality of care and delivery of health services. Stroke 2009;40:3328–3335. [PubMed: 19696418]
33. Von Elm E, Altman DG, Egger M et al.; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. BMJ 2007;335:806–808. [PubMed: 17947786]
34. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: Model specific population value and confidence interval estimation. Stat Med 2004;23:2109–2123. [PubMed: 15211606]

35. Olesen JB, Lip GYH, Hansen ML et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. BMJ 2011;342:d124. [PubMed: 21282258]
36. Yanovitzky I, Zanutto E, Hornik R. Estimating causal effects of public health education campaigns using propensity score methodology. Eval Progr Plann 2005;28:209–220.
37. Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. Proceedings of the Twenty-Sixth Annual SAS users Group International Conference Cary, NC: SAS Institute, Inc., 2004.
38. Wang R, Lagakos SW, Ware JH et al. Statistics in medicine. Reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189–2194. [PubMed: 18032770]
39. Asberg S, Eriksson M, Henriksson KM et al. Reduced risk of death with warfarin—Results of an observational nationwide study of 20,442 patients with atrial fibrillation and ischaemic stroke. Int J Stroke 2013;8:689–695. [PubMed: 22928583]
40. Cowan C, Healicon R, Robson I et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart 2013;99:1166–1172. [PubMed: 23393083]
41. Wolff A, Shantsila E, Lip GY et al. Impact of advanced age on management and prognosis in atrial fibrillation: Insights from a population-based study in general practice. Age Ageing 2015;44:874–878. [PubMed: 26082176]
42. Coelho T, PaÚl C, Gobbens RJ et al. Determinants of frailty: The added value of assessing medication. Front Aging Neurosci 2015;7:56. [PubMed: 25954195]
43. Man-Son-Hing M, Laupacis A. Anticoagulant-related bleeding in older persons with atrial fibrillation: Physicians' fears often unfounded. Arch Intern Med 2003;163:1580–1586. [PubMed: 12860581]
44. Siontis GC, Tzoulaki I, Ioannidis JP. Predicting death: An empirical evaluation of predictive tools for mortality. Arch Intern Med 2011;171:1721–1726. [PubMed: 21788535]
45. Pilotto A, Panza F, Ferrucci L. A multidimensional prognostic index in common conditions leading to death in older patients. Arch Intern Med 2012;172:594–595. [PubMed: 22493470]
46. Pilotto A, Rengo F, Marchionni N et al.; FIRI-SIGG Study Group. Comparing the prognostic accuracy for all-cause mortality of the frailty instruments: A multicentre 1-year follow-up in hospitalized older patients. PLoS ONE 2012;7:e29090. [PubMed: 22247767]
47. Pisters R, Lane DA, Nieuwlaat R et al. A novel user-friendly score (HAS-BLED) to assess one-year risk of bleeding in AF patients: The Euro Heart Survey. Chest 2010;138:1093–1100. [PubMed: 20299623]
48. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014;4:MR000034.

Table 1.

Baseline Characteristics of Community-Dwelling Older Adults with Atrial Fibrillation Divided According to Multidimensional Prognostic Index (MPI) Score Based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA)

Characteristic	All, N = 1,827, 100%	MPI-SVaMA-1 (Mild Risk), n = 705, 38.6%	MPI-SVaMA-2 (Moderate Risk), n = 634, 34.7%	MPI-SVaMA-3 (Severe Risk), n = 488, 26.7%	*P* for Trend
Age, mean ± SD	84.4 ± 7.1	83.8 ± 7.1	85.0 ± 6.4	83.2 ± 7.5	.74
Male, n (%)	653 (35.7)	164 (23.3)	218 (34.4)	271 (55.5)	<.001
Activities of Daily Living, mean ± SD	43.5 ± 18.4	31.6 ± 18.5	52.7 ± 11.1	48.9 ± 16.3	<.001
Cognitive Status, mean ± SD	5.5 ± 3.6	4.6 ± 3.4	6.7 ± 3.3	5.3 ± 3.9	<.001
Nursing Care Needs, mean ± SD	7.6 ± 8.2	2.9 ± 4.8	7.9 ± 6.6	14.1 ± 9.5	<.001
Mobility, mean ± SD	30.0 ± 11.7	23.2 ± 12.5	36.8 ± 5.9	34.5 ± 9.8	<.001
Pressure Sore Risk, mean ± SD	5.2 ± 6.1	0.9 ± 2.0	7.6 ± 5.2	8.4 ± 6.8	<.001
Social Support, mean ± SD	156.5 ± 70.1	156.0 ± 70.4	165.2 ± 68.5	144.4 ± 69.8	.01
Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke,Vascular disease, Age,Sex score					
Continuous, mean ± SD	3.8 ± 0.1	3.9 ± 0.9	3.8 ± 0.9	3.5 ± 1.0	<.001
Low risk (0), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Intermediate risk (1), n (%)	18 (0.1)	5 (0.7)	3 (0.5)	10 (2.4)	.04
High risk (2–9), n (%)	1,809 (99.0)	700 (99.3)	631 (99.5)	478 (98.0)	.04
Past treatment rate, mean ± SD[a]	7.4 ± 27.6	8.7 ± 40.4	6.3 ± 12.0	7.1 ± 17.5	.44
Participants starting warfarin, n (%)	798 (43.7)	380 (53.9)	245 (38.6)	173 (35.5)	<.001
Main diagnoses, n (%)					
Fracture	32 (1.8)	27 (3.8)	5 (0.8)	0 (0.0)	<.001
Cancer	278 (15.2)	0 (0.0)	6(0.1)	272 (55.7)	<.001
Dementia	455 (24.9)	231 (32.8)	199 (31.4)	25 (5.1)	<.001
Stroke	174 (9.5)	62 (8.8)	85 (13.4)	27 (5.5)	.15
Cardiovascular disease	282 (15.4)	133 (18.9)	102 (16.1)	47 (9.6)	<.001
Respiratory disease	63 (3.5)	28 (4.0)	21 (3.3)	14 (2.9)	.30
Neurological disease	86 (4.7)	61 (8.7)	21 (3.3)	4 (0.8)	<.001
Hypokinetic syndrome	259 (14.2)	74 (10.5)	128 (20.2)	57 (11.7)	.25
Other diseases	198 (10.8)	89 (12.6)	67 (10.6)	42 (8.6)	.03
Main drug classes, n (%)					
Alpha adrenergic blocker	248 (13.6)	91 (12.9)	87 (13.7)	70 (14.3)	.47
Nonloop diuretic	1,350 (73.9)	509 (72.2)	487 (76.8)	354 (72.5)	.72
Vasodilator	4 (0.2)	0 (0.0)	4 (0.6)	0 (0.0)	.77
Beta-blocker	562 (30.8)	209 (29.7)	187 (29.5)	166 (34.0)	.13
Statin	427 (23.4)	169 (24.0)	127 (20.0)	131 (26.8)	.38
Renin-angiotensin system inhibitor	1,167 (63.9)	461 (65.4)	411 (64.8)	295 (60.5)	.10
Calcium channel blocker	559 (30.6)	213 (30.2)	187 (29.5)	159 (32.6)	.43
Antiplatelet drug	1,098 (60.1)	429 (60.9)	387 (61.0)	282 (57.8)	.32
Amiodarone	152 (8.3)	62 (8.8)	40 (6.3)	50 (10.3)	.52
Digoxin	747 (40.9)	303 (43.0)	266 (42.0)	178 (36.5)	.03

Characteristic	All, N = 1,827, 100%	MPI-SVaMA-1 (Mild Risk), n = 705, 38.6%	MPI-SVaMA-2 (Moderate Risk), n = 634, 34.7%	MPI-SVaMA-3 (Severe Risk), n = 488, 26.7%	*P* for Trend
Insulin	391 (21.4)	151 (21.4)	129 (20.4)	111 (22.8)	.65
Follow-up time, years, mean ± SD	2.0 ± 1.9	2.7 ± 2.2	1.8 ± 1.8	1.1 ± 1.3	<.001
Mortality (events/person-year, incidence rate[b])					
At 1 year	682/1,366 (49.9)	141/606 (23.3)	240/472 (50.8)	301/288 (104.6)	<.001
At 2 years	983/2,223 (44.2)	240/1,051 (22.8)	347/762 (45.5)	396/410 (96.7)	<.001
At 3 years	1,125/2,755 (40.8)	303/1,365 (22.2)	404/932 (43.3)	418/458 (91.4)	<.001

[a]Number of all medications per month before enrollment.

[b]Number of events per 100 person-years.

SD = standard deviation.

Table 2.

Baseline Characteristics of Community-Dwelling Older Adults with Atrial Fibrillation According to Warfarin Treatment

Characteristic	Not Treated, n = 1,029, 56.3%	Treated, n = 798, 43.7%	*P*-Value	Standardized Mean Difference
Age, mean ± SD	85.4 ± 7.5	83.1 ± 6.3	<.001	−33.6
Male, n (%)	356 (34.6)	297 (37.2)	.25	5.5
Activities of daily living, mean ± SD	46.4 ± 17.3	39.9 ± 19.1	<.001	−35.5
Cognitive status, mean ± SD	6.1 ± 3.6	4.7 ± 3.5	<.001	−37.8
Nursing care needs, mean ± SD	7.9 ± 8.6	7.3 ± 7.8	.34	−7.5
Mobility, mean ± SD	31.9 ± 11.4	29.7 ± 11.9	<.001	−18.6
Pressure sore risk, mean ± SD	5.9 ± 6.1	4.3 ± 5.9	<.001	−26.9
Social support, mean ± SD	160.6 ± 70.4	151.1 ± 69.3	.01	−13.6
Multidimensional Prognostic Index based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons				
Continuous, mean ± SD	0.4 ± 0.2	0.4 ± 0.2	<.001	−24.9
1 (mild risk), n (%)	325 (31.6)	380 (47.6)	<.001	33.2
2 (moderate risk), n (%)	389 (37.8)	245 (30.7)	.06	−15.0
3 (severe risk), n (%)	315 (30.6)	173 (21.7)	<.001	−20.4
Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Age, Sex score, mean ± SD	3.8 ± 1.0	3.8 ± 0.9	.09	1.4
Past treatment rate tertile, n (%)[a]				
First (low)	410 (39.8)	272 (34.1)	.01	−12.0
Second (medium)	313 (30.4)	211 (26.4)	.06	−8.8
Third (high)	306 (29.7)	315 (39.5)	<.001	20.6
Fractures, n (%)	13 (1.3)	19 (2.4)	.07	8.4
Cancer, n (%)	175 (17.0)	103 (12.9)	.02	−11.5
Dementia, n (%)	286 (27.8)	169 (21.2)	.00	−15.4
Stroke, n (%)	105 (10.2)	69 (8.7)	.26	−5.3
Cardiovascular disease, n (%)	109 (10.6)	173 (21.7)	<.001	30.5
Respiratory disease, n (%)	33 (3.2)	30 (3.8)	.52	3.0
Neurologic disease, n (%)	47 (4.6)	39 (4.9)	.75	1.5
Hypokinetic syndrome, n (%)	161 (15.7)	98 (12.3)	.04	−9.7
Other diseases, n (%)	100 (9.7)	98 (12.3)	.08	8.2

[a]Number of all medications per month taken before enrollment.

SD = standard deviation.

Table 3.

Overall and Subgroup Analyses for Community-Dwelling Older Adults with Atrial Fibrillation According to Warfarin Use: Multivariate and Propensity Score Quintile-Adjusted Models

	n		Mortality (Events per 100 Person-Years)				Hazard Ratio (95% Confidence Interval) *P*-Value	
			Warfarin Use					
MPI Based on the SVaMA Risk	Events	Participants	All	No	Yes	Change[b]	Multivariable[a]	Adjusted for Propensity Score Quintile
1 year								
1 (mild)	141	705	23.3	33.7	15.4	−18.3	0.5 (0.3–0.7) <.001	0.5 (0.4–0.7) <.001
2 (moderate)	240	634	50.8	65.5	31.7	−33.8	0.5 (0.4–0.7) <.001	0.5 (0.4–0.7) <.001
3 (severe)	301	488	104.6	147.2	54.9	−92.3	0.4 (0.3–0.5) <.001	0.4 (0.3–0.5) <.001
All	682	1,827	49.9	71.8	28.0	−43.8	0.4 (0.4–0.5) <.001	0.5 (0.4–0.6) <.001
2 years								
1 (mild)	240	705	22.8	31.5	16.5	−15.0	0.6 (0.4–0.8) <.001	0.6 (0.4–0.8) <.001
2 (moderate)	347	634	45.5	56.1	32.2	−23.9	0.6 (0.5–0.8) <.001	0.7 (0.5–0.8) <.001
3 (severe)	396	488	96.7	126.9	64.6	−62.3	0.5 (0.4–0.6) <.001	0.5 (0.4–0.7) <.001
All	983	1,827	44.2	59.8	29.5	−30.3	0.6 (0.5–0.6) <.001	0.6 (0.5–0.7) <.001
3 years								
1 (mild)	303	705	22.2	29.2	17.2	−12.0	0.6 (0.5–0.8) <.001	0.6 (0.5–0.8) <.001
2 (moderate)	404	634	43.3	52.8	31.9	−20.9	0.7 (0.5–0.8) <.001	0.7 (0.6–0.9) <.001
3 (severe)	418	488	91.4	119.6	61.8	−57.8	0.5 (0.4–0.6) <.001	0.6 (0.4–0.7) <.001
All	1,125	1,827	40.8	54.5	28.4	−26.1	0.6 (0.5–0.7) <.001	0.6 (0.6–0.7) <.001

[a]Models were adjusted for age at Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA) evaluation; sex; nursing care needs; cognitive status; pressure sore risk; activities of daily living; mobility; social support (all Multidimensional Prognostic Index (MPI)-SVaMA domains); Congestive Heart Failure, Hypertension, Age, Diabetes mellitus, Stroke, Vascular disease, Age, Sex category score; main diagnoses of fracture, cancer, dementia, stroke, hypokinetic syndrome, and cardiovascular, respiratory neurological, or other diseases, and number of all medications prescribed within 1 year before enrollment (tertiles).

[b]Absolute difference of mortality rates between warfarin users vs nonusers.