Benefit of Warfarin Compared With Aspirin in Patients With Heart Failure in Sinus Rhythm:

A Subgroup Analysis of WARCEF, a Randomized Controlled Trial

Shunichi Homma, MD[*], **John L.P. Thompson, PhD**[*], **Alexandra R. Sanford, MS**, **Douglas L. Mann, MD**, **Ralph L. Sacco, MD, MS**, **Bruce Levin, PhD**, **Patrick M. Pullicino, MD**, **Ronald S. Freudenberger, MD**, **John R. Teerlink, MD**, **Susan Graham, MD**, **J.P. Mohr, MD**, **Barry M. Massie, MD**, **Arthur J. Labovitz, MD**, **Marco R. Di Tullio, MD**, **André P. Gabriel, MD**, **Gregory Y.H. Lip, MD**, **Conrado J. Estol, MD, PhD**, **Dirk J. Lok, MD**, **Piotr Ponikowski, MD, PhD**, **Stefan D. Anker, MD, PhD**, and **for the WARCEF Investigators**

Division of Cardiology, Department of Medicine (S.H., M.R.D.T., A.P.G.), and Department of Neurology (J.P.M.), Columbia University Medical Center, New York, NY; Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY (J.L.P.T., A.R.S., B.L.); Department of Medicine, Washington University, St Louis, MO (D.L.M.); Department of Neurology, University of Miami Miller School of Medicine, FL (R.L.S.); Kent Institute of Medicine and Health Sciences, University of Kent, Canterbury, United Kingdom (P.M.P.); Division of Cardiology, Department of Medicine, Lehigh Valley Hospital, Allentown, PA (R.S.F.); Section of Cardiology, Department of Medicine, San Francisco VA Medical Center, University of California, CA (J.R.T., B.M.M.); Division of Cardiology, Department of Medicine, SUNY Upstate Medical University, Buffalo, NY (S.G.); Department of Cardiovascular Medicine, University of South Florida, Tampa, FL (A.J.L.); University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.); Centro Neurológico de Tratamiento y Rehabilitación, Buenos Aires, Argentina (C.J.E.); Department of Cardiology, Deventer Hospital, The Netherlands (D.J.L.); Department of Heart Diseases, Wroclaw Medical University, Military Hospital, Poland (P.P.); and Department of Cardiology, Charité Universitätsmedicin, Campus Virchow-Klinikum, Berlin, Germany (S.D.A.)

Abstract

Background—The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial found no difference in the primary outcome between warfarin and aspirin in 2305 patients with reduced left ventricular ejection fraction in sinus rhythm. However, it is unknown whether any subgroups benefit from warfarin or aspirin.

Methods and Results—We used a Cox model stepwise selection procedure to identify subgroups that may benefit from warfarin or aspirin on the WARCEF primary outcome. A secondary analysis added major hemorrhage to the outcome. The primary efficacy outcome was time to the first to occur of ischemic stroke, intracerebral hemorrhage, or death. Only age group was a significant treatment effect modifier (P for interaction, 0.003). Younger patients benefited from warfarin over aspirin on the primary outcome (4.81 versus 6.76 events per 100 patient-years: hazard ratio, 0.63; 95% confidence interval, 0.48–0.84; P=0.001). In older patients, therapies did not differ (9.91 versus 9.01 events per 100 patient-years: hazard ratio, 1.09; 95% confidence interval, 0.88–1.35; P=0.44). With major hemorrhage added, in younger patients the event rate remained lower for warfarin than aspirin (5.41 versus 7.25 per 100 patient-years: hazard ratio, 0.68; 95% confidence interval, 0.52–0.89; P=0.005), but in older patients it became significantly higher for warfarin (11.80 versus 9.35 per 100 patient-years: hazard ratio, 1.25; 95% confidence interval, 1.02–1.53; P=0.03).

Conclusions—In patients <60 years, warfarin improved outcomes over aspirin with or without inclusion of major hemorrhage. In patients   60 years, there was no treatment difference, but the aspirin group had significantly better outcomes when major hemorrhage was included.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00041938.

Chronic heart failure (HF) is a major cause of mortality and morbidity. HF is associated with a hypercoagulable state, left ventricular thrombus formation, and cerebral embolism.[1,2] It is also associated with both sudden death and death resulting from progressive HF that may be caused by unrecognized atherothrombotic events.[3] This provides a rationale for the use of oral anticoagulants to treat patients with chronic HF.

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial found no significant difference between warfarin and aspirin among patients with HF for the primary end point of first to occur of ischemic stroke, intracerebral hemorrhage (ICH), or death, although there was a large reduction in ischemic stroke in the warfarin group.[4] Patients with HF are diverse in terms of demographics, etiology of HF, symptomatology, and many other factors.[4–6] Patients in various groups may respond differently to warfarin or aspirin, and there is a great interest in this issue.[7,8] As such, we sought to explore whether there are readily identifiable subgroups for whom warfarin or aspirin is preferable, without compromise from increased risk of major bleeding. We chose to consider multiple baseline clinical factors, both individually and in combination because many of them are closely interrelated and cannot be considered in isolation. To our knowledge, this is the first study able to assess this issue with a large and comprehensive database.

Methods

Patients

In the randomized, double-blind WARCEF trial, patients with left ventricular ejection fraction 35% in sinus rhythm were randomly assigned to warfarin (target International Normalized Ratio [INR] 2.75, with acceptable target range of 2.0–3.5) or aspirin (325 mg/d). Patients were enrolled at 168 centers in 11 countries between October 2002 and January 2010. The study was approved by institutional review boards at the coordinating centers of all sites, and all subjects gave informed consent. The median follow-up time was 3.4 years (Q1, 2.0; Q3, 5.0). Left ventricular ejection fraction was assessed by quantitative echocardiography (or a wall-motion index of 1.2) or radionuclide contrast ventriculography within 3 months before randomization. Patients who had a clear indication for warfarin or aspirin were not eligible. Additional eligibility criteria were a modified Rankin score of 4 (on a scale of 0–6, with higher scores indicating more severe disability) and planned treatment with a β-blocker, an angiotensin-converting enzyme inhibitor (or, if the side-effect profile with angiotensin-converting enzyme inhibitors was unacceptable, with an angiotensin-receptor blocker), or hydralazine and nitrates. Patients were ineligible if they had a condition that conferred a high risk of cardiac embolism, such as atrial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus.

Randomization and Outcome Events

Patients were randomly assigned (1:1) to warfarin or aspirin by a 24-hour central computerized system. Randomization was stratified according to whether or not patients had an ischemic stroke or transient ischemic attack within 12 months before randomization, New York Heart Association classification (I versus II, III, or IV), and clinical site. Participants, investigators, and the sponsor were masked to individual participant treatment assignments. The Statistical Analysis Center fabricated clinically plausible INR results for patients in the aspirin group and provided these results to the sites, along with the actual INR results for the patients in the warfarin group. All patients were treated as if they were receiving active warfarin.

The primary efficacy outcome was time to the first to occur of ischemic stroke, ICH, or death. Ischemic stroke was defined as a clinically relevant new lesion detected by computer tomography or MRI or, in the absence of new lesion, clinical findings consistent with the occurrence of clinical stroke that lasted for >24 hours. A total of 622 events occurred: 302 in warfarin and 320 in aspirin arm. The primary safety outcome was major hemorrhage, defined as intracerebral, epidural, subdural, subarachnoid, spinal intramedullary, retinal hemorrhage, or any other bleeding with >2 g hemoglobin decline in 48 hours, requiring 2 units of transfusion or requiring hospitalization or surgical intervention. Minor hemorrhage included all other hemorrhages. An independent end point adjudication committee unaware of the treatment assignments adjudicated all efficacy outcomes and major hemorrhages.

Statistical Analysis

Subgroup Candidates—We purposefully included both prespecified and other variables known to affect HF patient outcome.[9,10] Prespecified criteria were sex, race ethnicity, left

ventricular ejection fraction, New York Heart Association class, and etiology of HF. Other variables were age, body mass index, education, country, diabetes mellitus, hypertension, smoking, alcohol use, 6-minute walk distance, prior stroke or transient ischemic attack, systolic blood pressure, diastolic blood pressure, atrial fibrillation, myocardial infarction, defibrillator or pacemaker use, coronary artery disease, peripheral vascular disease, statin use, prerandomization use of warfarin, prerandomization use of aspirin or other antiplatelets, mini-mental status examination, blood urea nitrogen, estimated glomerular filtration rate, white blood cell count, serum sodium, hematocrit, and hemoglobin. We used a 2-stage approach, with no adjustments for multiple testing because the analyses were exploratory.

In stage 1, we created 32 individual stratified Cox models, each assessing the impact of 1 candidate variable on the treatment effect for the WARCEF primary outcome, without taking account of the impact of the other candidates. Each of these models included terms for treatment (warfarin or aspirin), 1 candidate variable, and the interaction of that candidate variable with treatment. The candidate variable was considered to be an effect modifier if its interaction with treatment was significant at level α=0.05 2-sided. In this stage we dichotomized age at <60 versus ≥60 years because 60 was the closest age to the sample mean and median for age in 5-year increments. Body mass index was scored low (<25 kg/m^2), medium (25–30 kg/m^2), or high (>30 kg/m^2).[11] Ejection fraction was scored low (≤20%), medium (>20% and <30%), or high (≥30%). Other continuous variables were dichotomized at the median. Countries with low event rates were combined.

Stage 2 used a stepwise selection procedure to develop a multivariable Cox model identifying the subgroups likely to benefit from 1 of the 2 treatments, when accounting for the impact of all other selected variables. All candidate variables were eligible for selection. In this stage, age and body mass index were retained as categorical variables but other continuous variables were not dichotomized. An interaction term was included in the final model only if its *P* values and the corresponding main effect term both met the 0.05 selection criterion or if the combination of the main effect and the interaction term was jointly significant at that level using a type 3 test. Treatment was forced into the final model. All statistical analyses were performed with SAS (version 9.2).

Results

In the stage 1 models, which considered each candidate variable separately, only age and country interacted significantly with treatment (*P*=0.001 and 0.02, respectively; Table 1). Among younger patients (<60 years), the rate of the primary end point was 4.81 events per 100 patient-years in the warfarin group and significantly higher in the aspirin group at 6.76 events per 100 patient-years (unadjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.49–0.86; *P*=0.002). Among older patients (≥60 years), the primary end point rates did not differ by treatment (9.91 events per 100 patient-years in the warfarin group compared with 9.01 events per 100 patient-years in the aspirin group; unadjusted HR for warfarin versus aspirin 1.16; 95% CI, 0.94–1.43; *P*=0.16). In Poland there was a statistically significant benefit for warfarin. The rate of primary end point was 7.70 events per 100 patient-years in the warfarin group, compared with 12.38 events per 100 patient-years in the aspirin group (unadjusted HR 0.61; 95% CI, 0.40–0.95; *P*=0.03). There were nonsignificant

trends toward a benefit for warfarin in the United States (*P*=0.07) and for aspirin in Canada (*P*=0.06; Table 1).

Primary Outcome

The final stage 2 multiple regression model included terms for treatment, sex, blood urea nitrogen, left ventricular ejection fraction, 6-minute walk, diabetes mellitus, hemoglobin, peripheral vascular disease, diastolic blood pressure, body mass index category, age group, and age group-by-treatment interaction, all of which affected the prognosis (Table I in the online-only Data Supplement). After adjustment for other predictors of outcome, only age group was a significant warfarin or aspirin treatment effect modifier with respect to the primary composite end point (*P* for interaction, 0.003; Table 2). Among younger patients, there was a statistically significant benefit for warfarin (adjusted HR for warfarin versus aspirin 0.63; 95% CI, 0.48–0.84; *P*=0.001). However, among older patients, there was no difference between warfarin and aspirin (adjusted HR, 1.09; 95% CI, 0.88–1.35; *P*=0.44; Table 2). Figure 1A shows the unstratified cumulative incidence curves for the primary end point for the younger and older age groups, respectively.

We evaluated our age cutoff (<60 years) by modeling age as a continuous variable and by comparing warfarin and aspirin by age quintile. There was a significant interaction between treatment and continuous age as a linear effect on the log HR (*P*=0.04 when adjusting for covariates from the final selected model; table not presented). According to this model, there was a significant benefit for warfarin among younger patients. The upper limit of the 95% CI crossed 1.0 at 59.4 years, and there was no significant treatment effect among patients >60 years. When warfarin and aspirin were compared in age quintiles, there was a statistically significant interaction between treatment and age quintile (*P*=0.04). Figure 2A presents the HRs for treatment effect by quintile and supports 60 years as a reasonable cutoff.

Components of the Primary Outcome

The ischemic stroke rates in younger and older patients were similar, and in both age groups those assigned to warfarin achieved a substantial reduction in ischemic stroke compared with aspirin (HR, 0.51; 95% CI, 0.32–0.81; *P* for HR, 0.005; *P* for interaction, 0.64; Table 2). Warfarin reduced death in the younger group (4.08 per 100 patient-years for warfarin versus 5.40 for aspirin; adjusted HR, 0.65; 95% CI, 0.48–0.89; *P*=0.007), but not in the older group, whose death rate was higher (8.96 per 100 patient-years for warfarin versus 7.54 for aspirin; adjusted HR, 1.18; 95% CI, 0.94–1.49; *P*=0.16). Because few patients experienced ICH, it was not possible to test for a differential treatment effect by age group. There was no significant difference overall between warfarin and aspirin with respect to ICH (adjusted HR, 2.35; 95% CI, 0.44–12.48; *P*=0.32; Table 2).

Hemorrhage

In the younger age group, there was no significant difference between warfarin and aspirin in the rate of major hemorrhages (odds ratio, 1.30; 95% CI, 0.56–3.07; *P*=0.64). However, in the older age group, significantly more major hemorrhages occurred in those receiving warfarin (odds ratio, 2.73; 95% CI, 1.56–4.97; *P*<0.001; Table 3). When the time to first to

occur of primary outcome or major hemorrhage was analyzed, there was a statistically significant treatment-by-age group interaction with respect to this composite outcome (*P*<0.001; Table 4). Among the younger patients, those randomized to warfarin had a lower rate of combined events compared with aspirin patients (5.41 versus 7.25% per 100 patient-years; adjusted HR, 0.68; 95% CI, 0.52–0.89; *P*=0.005), whereas older patients in the warfarin arm experienced a significantly higher rate of events than those in the aspirin arm (11.8 versus 9.35% per 100 patient-years; adjusted HR, 1.25; 95% CI, 1.02–1.53; *P*=0.03; Table 4). Figure 1B presents the unstratified cumulative incidence curves and Figure 2B the HRs by age quintile, both by treatment, when major hemorrhage is included in the outcome.

Patient Characteristics by Age

Because randomization was not stratified by age group, we compared the warfarin and aspirin arms in each age group in terms of baseline characteristics. Among the younger patients, only education level was significantly different between the warfarin and aspirin groups (*P*=0.03; Table IIA in the online-only Data Supplement). Among the older patients, the differences between warfarin and aspirin were significant for 6-minute walk distance (*P*=0.02) and nitrate use (*P*=0.01; Table IIB in the online-only Data Supplement). Adjusting the analyses of time to primary composite end point and time to primary composite end point plus major hemorrhage for education and nitrate use did not materially change the results.

The younger warfarin patients had statistically significantly lower mean INR values than the older warfarin patients (2.36±0.63 versus 2.51±0.56, respectively; *P*<0.001, with patients weighted equally. When patients were weighted by total INR days of follow-up, the mean INR values in the 2 age groups were statistically different in same direction; *P*<0.001). At the same time, mean percentage of time in therapeutic range (TTR) in younger patients was significantly lower than in older patients (52.8±28.5% versus 60.4±28.0%; *P*<0.001). Compared with older patients, younger patients had a significantly longer time spent with INR below the therapeutic range (37.4±29.8% versus 28.4±27.6%; *P*<0.0001). However, the time with INR above the therapeutic range was similar between the 2 groups (9.7±12.5% versus 11.2±13.2%; *P*>0.06). The 2 age groups did not differ in terms of the mean proportion of follow-up time spent on interruption of study therapy (28.7% for younger versus 30.3% for older; *P*=0.30).

Discussion

WARCEF, with >4× the number of patient-years of follow-up compared with the next largest trial, was the largest trial to compare the efficacy of warfarin and aspirin in patients with HF in sinus rhythm.[12] It found no significant difference between them on the composite primary end point of ischemic stroke, ICH, or death.[4] However, the primary aim of WARCEF was to compare warfarin and aspirin in the general HF population, and not among different subgroups. The causes of HF are multifactorial, and warfarin or aspirin may benefit some specific groups but not others.[7,13] We sought to identify such groups using an automated stepwise selection procedure to adjust for subgroup variability in baseline

characteristics and identify treatment-by-variable interactions for multiple variables that may covary.

Country of recruitment significantly affected the efficacy of warfarin or aspirin, but this was because of country differences in age distribution. After adjustment for all factors considered, age group was the only modifier of treatment effect. Warfarin patients <60 years experienced a significant reduction in the rate of composite primary end point, and also in its separate components of ischemic stroke and death, without an increase in major bleeding. Older patients, in contrast, experienced no difference between warfarin and aspirin in the composite primary end point. Warfarin did reduce their ischemic stroke risk, but it was also associated with a nonsignificant increase in death; and when major bleeding was added to the composite outcome, the overall risk of a poor outcome became significantly greater for the older warfarin patients. The reduced benefit of warfarin in older patients compared with younger patients is not attributable to lower INRs or a lower TTR. In fact, the older group demonstrated significantly higher TTR and less time spent above therapeutic INR while having similar time duration spent in interruption of study therapy compared with the younger group.

There are ≈5.7 million patients with HF in the United States and 25% are aged <60 years.[14,15] Of this group, 60% or 855 000 are thought to have systolic rather than diastolic HF.[16,17] Among this group, since the prevalence of atrial fibrillation is smaller in younger patients with HF, 90% or 769 500 patients are in sinus rhythm.[18] In our study, in the younger population, the absolute yearly risk reduction was 1.95% (relative risk reduction of 28.8%), which would mean that ≈15 005 net events (5617 strokes and 10 157 deaths at a cost of 769 ICHs) may possibly be avoided by the use of warfarin in younger patients. However, in the older population, because warfarin resulted in increased bleeding risk while not affecting the primary end point, unnecessary bleeding may be avoided by the use of aspirin. We saw a longer time on interruption of study therapy among older patients assigned to warfarin. This may have blunted any possible benefit of warfarin and points to difficulty of warfarin use in older patients.[19,20] Although our findings may have a large public health impact, they require confirmation in a future trial. Also, given the possible benefit of warfarin in the younger population, the role of new anticoagulants needs to be established. Younger patients may benefit from the ease of use of these agents, and older patients may have a lower bleeding risk while maintaining the benefit for stroke reduction.[21,22]

In WARCEF, patients were double-blindly randomized, lost to follow-up rate was low, and core echocardiography laboratory and centralized adjudication process were used to achieve high data quality. However, there are important limitations. First, candidate variables included those that were not prespecified, although they are well known or thought to affect the outcome in patients with HF. Second, no correction for the number of variables examined was made. However, under a simple Bonferroni correction for the 32 variables considered in stage 1, the effect modification for age was significant. Third, no placebo group was included. Therefore, the comparison is strictly between those receiving warfarin and aspirin. Finally, although we can point to potential mechanisms, we have no clear biological explanation for our results.

Conclusions

In our exploratory analysis, patients with HF in sinus rhythm aged <60 years benefited from warfarin compared with aspirin on the combined outcome of ischemic stroke, ICH, or death, whereas older patients did not. When major hemorrhages are also considered, the warfarin benefit for the younger patients persisted, but older patients on warfarin had more adverse outcomes than those on aspirin. A pivotal trial to confirm the possible benefit of warfarin for younger patients is warranted given the potentially large impact on treatment of patients with HF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. Neurology. 2000; 54:288–294. [PubMed: 10668685]

2. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. J Am Coll Cardiol. 1999; 33:1424–1426. [PubMed: 10193748]

3. Uretsky BF, Thygesen K, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, Poole-Wilson PA, Ryden L. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. Circulation. 2000; 102:611–616. [PubMed: 10931799]

4. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R. WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012; 366:1859–1869. [PubMed: 22551105]

5. Velagaleti, RS.; Vasan, RS. Epidemiology of heart failure. In: Mann, DL., editor. Heart Failure, a Companion to Braunwald's Heart Disease. 2nd ed.. St. Louis, MO: Elsevier Saunders; 2011. p. 339-350.

6. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev. 2000; 5:167–173. [PubMed: 16228142]

8. Shah S, Parra D, Rosenstein R. Warfarin versus aspirin in heart failure and sinus rhythm [letter]. N Engl J Med. 2012; 367:771. [PubMed: 22913690]

9. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006; 113:1424–1433. [PubMed: 16534009]

10. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013; 34:1404–1413. [PubMed: 23095984]

11. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010; 121:586–613. [PubMed: 20089546]

12. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR. WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009; 119:1616–1624. [PubMed: 19289640]

13. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002; 347:969–974. [PubMed: 12324552]

14. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012; 125:e2–e220. [PubMed: 22179539]

15. Howden, L.; Meyer, J. [Accessed October 8, 2012] United States Census Bureau: 2010 Census Summary Files. http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf.

16. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004; 43:317–327. [PubMed: 15013109]

17. Chatterjee K, Massie B. Systolic and Diastolic Heart Failure. J Card Fail. 2007; 13:569–576. [PubMed: 17826648]

18. De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L, Devecchi P, Molon G, Revera M, Curnis A, Sarzi Braga S, Accardi F, Salerno-Uriarte JA. ALPHA Study Group. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. Eur J Heart Fail. 2007; 9:502–509. [PubMed: 17174599]

19. Torn M, Bollen WL, van Meerder FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med. 2005; 165:1527–1532. [PubMed: 16009869]

20. Froom P, Miron E, Barak M. Oral anticoagulants in the elderly. Br J Haematol. 2003; 120:526–528. [PubMed: 12580973]

21. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. ROCKET

AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365:883–891. [PubMed: 21830957]

22. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365:981–992. [PubMed: 21870978]

CLINICAL PERSPECTIVE

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial found no difference between warfarin and aspirin for the primary end point of ischemic stroke, intracerebral hemorrhage, or death in patients with heart failure and reduced systolic function. There was a benefit for warfarin over aspirin for ischemic stroke alone, but it was offset by a higher rate of major hemorrhages in the warfarin patients. This study asks whether there are easily identifiable groups of patients who may benefit from warfarin without increased risk of bleeding. We found that, among patients <60 years, compared with the aspirin patients, the warfarin patients had a significant reduction in the overall primary end point without a higher risk of bleeding. The same was true when we considered ischemic stroke and death separately. In patients >60 years, however, although the ischemic stroke rate was lower for the warfarin patients, the risk of bleeding was significantly higher than among the aspirin patients. In summary, this post hoc analysis found that, compared with aspirin, warfarin may be beneficial for younger patients with heart failure in sinus rhythm, but not for older patients.

A

Number at risk

≥ 60 years							
Warfarin	634	578	449	326	249	175	54
Aspirin	641	589	458	327	235	165	48
< 60 years							
Warfarin	508	471	403	327	276	188	61
Aspirin	522	484	402	331	273	164	46

B

Number at risk

≥ 60 years							
Warfarin	634	563	432	312	234	160	45
Aspirin	641	586	455	323	230	160	45
< 60 years							
Warfarin	508	468	397	320	268	181	60
Aspirin	522	482	398	325	268	161	46
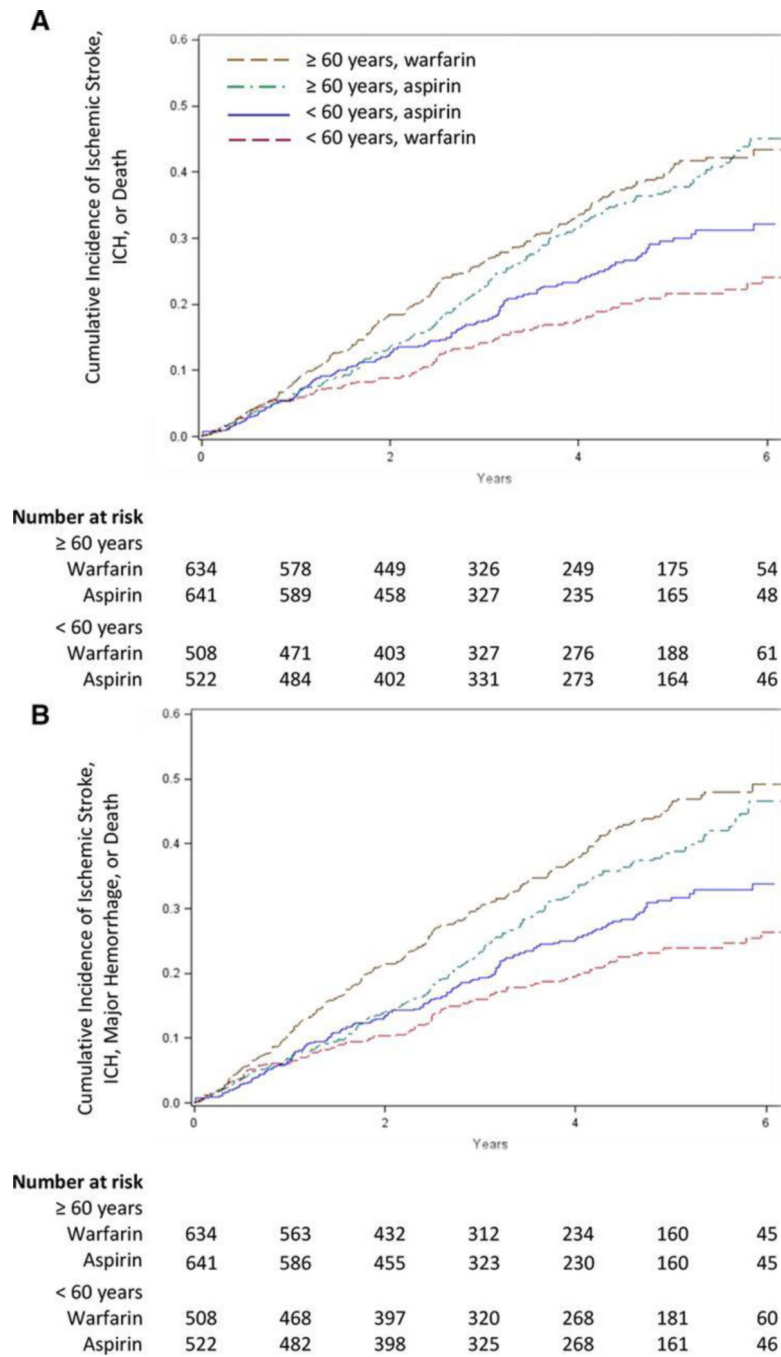
Figure 1.
Kaplan–Meier estimates in patients ≥60 and <60 years for the primary end point (**A**) and the primary end point or major hemorrhage (**B**). Plots show the Kaplan–Meier estimated probability of an event. ICH indicates intracerebral hemorrhage.
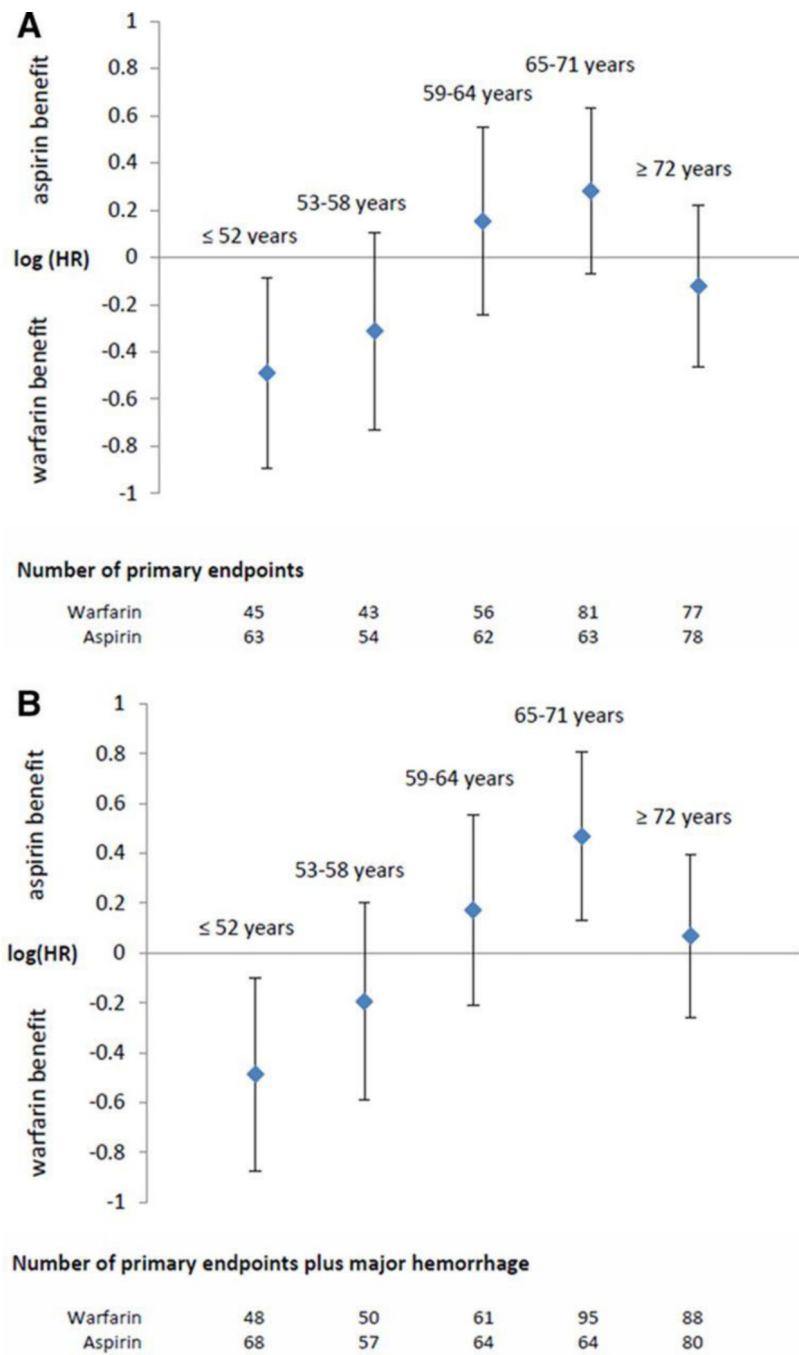
Figure 2.
Natural logarithm of the hazard ratio (HR) by quintile of age for the comparison of warfarin versus aspirin on the primary end point (**A**) and the primary end point or major hemorrhage (**B**).

Table 1

Hazard Ratios for the Primary End Point for Individual Cox Models[*]

	Warfarin		Aspirin		Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events/Patients	Rate[†]	Events/Patients	Rate[†]		For HR[‡]	For Interaction[§]
Age group, y							
<60	93/508	4.81	130/522	6.76	0.65 (0.49–0.86)	0.002	0.001
60	209/634	9.91	190/641	9.01	1.16 (0.94–1.43)	0.16	
Country							
Poland	34/129	7.70	50/134	12.38	0.61 (0.40–0.95)	0.03	
Ukraine	20/57	9.68	28/58	13.75	0.78 (0.43–1.43)	0.43	
United States	115/463	6.06	130/440	7.55	0.79 (0.61–1.02)	0.07	0.02
Argentina and other European	68/308	7.75	67/348	6.57	1.18 (0.84–1.67)	0.34	
Hungary	30/75	13.06	22/77	9.34	1.29 (0.73–2.28)	0.38	
Canada	35/110	8.90	23/106	5.12	1.69 (0.98–2.90)	0.06	
Sex							
Men	240/906	7.55	281/939	8.71	0.88 (0.73–1.05)	0.16	0.07
Women	62/236	7.17	39/224	4.83	1.34 (0.88–2.03)	0.17	
Smoking							
Current	46/213	5.96	63/195	9.30	0.62 (0.41–0.92)	0.02	
Former	173/585	8.29	178/604	8.50	0.98 (0.78–1.22)	0.84	0.08
Never	83/344	6.99	79/364	6.26	1.10 (0.80–1.53)	0.55	
NYHA class							
NYHA 3 or 4	116/368	9.12	131/347	11.72	0.78 (0.60–1.01)	0.06	0.11
NYHA 1 or 2	186/774	6.71	189/816	6.48	1.03 (0.83–1.26)	0.82	
Prior stroke or TIA	45/155	8.39	56/139	12.56	0.72 (0.47–1.11)	0.14	0.21
No prior stroke or TIA	257/987	7.33	264/1024	7.36	0.98 (0.82–1.17)	0.79	
Statin							
No	21/137	6.80	29/147	9.42	0.77 (0.42–1.39)	0.39	
Unknown	92/315	6.79	112/312	8.58	0.78 (0.59–1.04)	0.09	0.22
Yes	189/690	7.94	179/704	7.40	1.06 (0.85–1.31)	0.61	
Hemoglobin							

	Warfarin		Aspirin		Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events/Patients	Rate†	Events/Patients	Rate†		For HR‡	For Interaction§
Low	180/613	8.31	184/586	9.25	0.84 (0.67–1.04)	0.11	0.23
High	122/529	6.50	136/577	6.65	1.03 (0.80–1.33)	0.81	
6-minute walk, m							
High	97/499	5.49	126/550	6.60	0.81 (0.61–1.06)	0.12	0.24
Low	205/643	9.00	194/613	9.14	0.99 (0.81–1.22)	0.94	
Diabetes mellitus							
No	177/771	6.37	201/812	7.06	0.86 (0.70–1.06)	0.16	0.25
Yes	125/371	9.86	119/351	10.05	1.06 (0.81–1.39)	0.67	
Aspirin or other antiplatelet, prior use							
Unknown	88/304	6.77	99/288	8.34	0.75 (0.55–1.02)	0.06	0.25
No	38/221	7.67	36/233	6.97	1.01 (0.63–1.62)	0.96	
Yes	176/617	7.83	185/642	7.94	1.03 (0.83–1.27)	0.82	
BUN							
Low	126/555	6.03	151/598	6.95	0.83 (0.65–1.07)	0.15	0.26
High	176/587	9.00	169/565	9.08	1.01 (0.81–1.26)	0.93	
BMI category							
>30	89/415	5.75	106/428	6.95	0.82 (0.61–1.10)	0.18	0.27
<25	91/294	9.08	92/265	10.52	0.84 (0.61–1.14)	0.26	
25–30	122/433	8.17	122/470	7.47	1.10 (0.84–1.44)	0.47	
Warfarin, prior use							
Yes	26/90	7.72	27/89	8.62	0.69 (0.38–1.23)	0.21	0.29
No	276/1052	7.44	293/1074	7.88	0.96 (0.81–1.13)	0.60	
Device							
No	236/870	7.61	268/911	8.35	0.89 (0.75–1.07)	0.23	0.32
Yes	66/272	7.00	52/252	6.33	1.11 (0.76, 1.63)	0.59	
eGFR							
High	115/549	5.71	141/591	6.62	0.83 (0.65–1.08)	0.17	0.36
Low	187/593	9.22	179/572	9.41	0.98 (0.79–1.22)	0.84	
WBC							
High	144/590	6.76	166/596	8.28	0.87 (0.69–1.10)	0.23	0.40

	Warfarin		Aspirin		Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events/Patients	Rate[†]	Events/Patients	Rate[†]		For HR[‡]	For Interaction[§]
Low	158/552	8.25	154/567	7.59	1.00 (0.79–1.27)	0.98	
Myocardial infarction							
No	144/593	6.73	155/600	7.30	0.87 (0.69–1.11)	0.26	0.43
Yes	158/549	8.30	165/563	8.64	1.00 (0.79–1.26)	0.998	
Education							
College grad	32/163	4.96	52/193	6.99	0.72 (0.45–1.14)	0.16	
High School grad	134/487	7.36	130/460	8.04	0.92 (0.71–1.19)	0.52	0.45
Less than High School	136/492	8.62	138/510	8.25	1.01 (0.79–1.29)	0.96	
Alcohol use							
Current	63/279	6.23	67/293	6.73	0.80 (0.56–1.15)	0.23	
Former	73/250	7.85	87/256	9.31	0.87 (0.62–1.22)	0.42	0.49
Never	166/613	7.89	166/614	7.89	1.02 (0.82–1.28)	0.85	
Sodium							
High	160/611	7.30	167/608	7.82	0.89 (0.71–1.12)	0.32	0.55
Low	142/531	7.66	153/555	8.06	0.99 (0.78–1.25)	0.92	
Mini-mental status examination							
Low	121/397	8.91	127/415	8.93	0.88 (0.67–1.14)	0.33	0.58
High	181/745	6.74	193/748	7.40	0.97 (0.78–1.19)	0.75	
Coronary artery disease							
No	109/491	5.96	112/480	6.39	0.88 (0.67–1.18)	0.41	0.62
Yes	193/651	8.71	208/683	9.13	0.97 (0.79–1.20)	0.80	
Atrial fibrillation							
Yes	14/44	8.91	13/42	9.93	0.78 (0.33–1.80)	0.55	0.67
No	288/1098	7.41	307/1121	7.87	0.94 (0.79–1.11)	0.45	
Diastolic blood pressure							
High	133/577	6.38	142/587	6.92	0.89 (0.70–1.14)	0.38	0.67
Low	169/565	8.62	178/576	8.98	0.96 (0.77–1.20)	0.74	
PVD							
No	158/560	7.87	171/575	8.54	0.92 (0.76–1.09)	0.33	0.68
Yes	144/582	7.07	149/588	7.34	1.01 (0.67–1.52)	0.97	

	Warfarin		Aspirin		Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events/Patients	Rate[†]	Events/Patients	Rate[†]		For HR[‡]	For Interaction[§]
Ischemic cardiomyopathy							
No	147/654	6.01	155/660	6.39	0.91 (0.72–1.15)	0.43	0.70
Yes	155/488	9.68	165/503	10.28	0.97 (0.77–1.23)	0.82	
Race/ethnicity							
Hispanic	17/85	6.62	18/81	8.42	0.67 (0.33–1.33)	0.25	
Black	48/166	7.37	47/166	7.63	0.92 (0.59–1.41)	0.69	0.79
White	229/859	7.56	245/879	7.98	0.96 (0.80–1.16)	0.67	
Other	8/32	7.51	10/37	7.44	0.98 (0.37–2.61)	0.97	
Hypertension							
Unknown	12/38	7.75	13/35	9.52	0.82 (0.34–1.95)	0.65	
Yes	167/671	7.15	190/696	8.06	0.90 (0.72–1.12)	0.33	0.83
No	123/433	7.91	117/432	7.60	0.99 (0.76–1.29)	0.93	
Hematocrit							
High	128/552	6.6	143/577	7.07	0.87 (0.52–1.47)	0.61	0.83
Low	174/590	8.27	177/586	8.80	0.91 (0.73–1.13)	0.38	
Systolic blood pressure							
Low	158/560	7.87	171/575	8.54	0.92 (0.73–1.16)	0.48	0.88
High	144/582	7.07	149/588	7.34	0.94 (0.74–1.20)	0.64	
Ejection fraction							
Middle	83/283	8.04	76/269	8.00	0.90 (0.71–1.15)	0.41	
High	59/261	6.09	81/272	8.26	0.93 (0.65–1.33)	0.70	0.97
Low	100/305	9.48	89/298	8.80	0.95 (0.70–1.28)	0.72	

BMI indicates body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; PVD, peripheral vascular disease; TIA, transient ischemic attack; and WBC, white blood cell.

[*]Each model includes terms for treatment, baseline variable, and treatment×baseline variable interaction. Variables are presented in increasing order of P value for the interaction term. Within variables, subgroups are in increasing order of the HR.

[†]Rates are per 100 patient-years.

[‡]P value for the HR.

[§]P value for the test for treatment×baseline variable interaction in a Cox model stratified by site, prior stroke status, and NYHA classification.

Table 2

Adjusted Hazard Ratios for the Primary End Point and Its Components for Final Cox Regression Model

	Warfarin		Aspirin		Adjusted Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events, %	Rate[*]	Events, %	Rate[*]		For HR[†]	For Interaction
<60 y	n=508	1935.0 pt-years	n=522	1924.2 pt-years			
Primary composite	93 (18.3)	4.81	130 (24.9)	6.76	0.63 (0.48–0.84)	0.001	0.003
Ischemic stroke	12 (2.4)	0.62	26 (5.0)	1.35	0.51 (0.32–0.81)	0.005	0.64[‡]
Intracerebral hemorrhage	2 (0.4)	0.10	0 (0.0)	0.00	2.35 (0.44–12.48)	0.32	…[§]
Death	79 (15.6)	4.08	104 (19.9)	5.40	0.65 (0.48–0.89)	0.007	0.003
60 y	n=634	2109.7 pt-years	n=641	2108.6 pt-years			
Primary composite	209 (33.0)	9.91	190 (29.6)	9.01	1.09 (0.88–1.35)	0.44	0.003
Ischemic stroke	17 (2.7)	0.81	29 (4.5)	1.38	0.51 (0.32–0.81)	0.005	0.64[‡]
Intracerebral hemorrhage	3 (0.5)	0.14	2 (0.3)	0.09	2.35 (0.44–12.48)	0.32	…[§]
Death	189 (29.8)	8.96	159 (24.8)	7.54	1.18 (0.94–1.49)	0.16	0.003

6MW indicates 6-minute walk; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage; NYHA, New York Heart Association; and PVD, peripheral vascular disease.

[*] Rates are per 100 patient-years.

[†] From Cox models stratified by site, prior stroke status, and NYHA classification. HRs for composite end point, death, and stroke are adjusted for age category, sex, diabetes mellitus, PVD, BMI, BUN, ejection fraction, DBP, 6MW, and hemoglobin. HRs for ICH adjusted for age category. Treatment-by-age category interaction terms are included as applicable.

[‡] Hazard ratios are from models without treatment×age category interaction term for ischemic stroke, given no evidence of treatment×age category interaction.

[§] Not enough events to test for interaction. HR is from the model without a treatment×age category term.

Table 3

Odds Ratios for Major and Minor Hemorrhage

	Warfarin		Aspirin		Odds Ratio (95% CI)[‡] for Warfarin vs Aspirin	P Value
	Patients, %	Events[*] (Rate[†])	Patients, %	Events[*] (Rate[†])		
<60 y	n=508	1935.0 pt-years	n=522	1924.2pt-years		
Major hemorrhage	15 (3.0)	16 (0.83)	12 (2.3)	14 (0.73)	1.30 (0.56–3.07)	0.64
Minor hemorrhage	129 (25.4)	201 (10.39)	79 (15.1)	129 (6.70)	1.95 (1.41–2.71)	<0.001
60 y	n=634	2109.7 pt-years	n=641	2108.6 pt-years		
Major hemorrhage	51 (8.0)	56 (2.65)	19 (3.0)	21 (1.00)	2.73 (1.56–4.97)	<0.001
Minor hemorrhage	151 (23.8)	267 (12.66)	110 (17.2)	167 (7.92)	1.43 (1.07–1.92)	0.014

CI indicates confidence interval.

[*] Numbers of events refect multiple hemorrhages in some patients.

[†] Rates are per 100 patient-years.

[‡] Odds ratios were calculated by the exact test of 2 independent proportions, stratified by continent.

Table 4

Adjusted Hazard Ratios for Primary End point or Major Hemorrhage and Components, According to Age Subgroup

	Warfarin		Aspirin		Adjusted Hazard Ratio (95% CI) for Warfarin vs Aspirin	P Value	
	Events, %	Rate*	Events, %	Rate*		For HR[†]	For Interaction[‡]
<60 y	n=508	1903.7 pt-years	n=522	1904.1 pt-years			
Primary plus hemorrhage	103 (20.3)	5.41	138 (26.4)	7.25	0.68 (0.52–0.89)	0.005	<0.001
Major hemorrhage	13 (2.6)	0.68	12 (2.3)	0.63	0.98 (0.42–2.27)	0.96	0.06
Ischemic stroke	12 (2.4)	0.63	25 (4.8)	1.31	0.50 (0.31–0.81)	0.005	0.68[§]
Intracerebral hemorrhage	2 (0.4)	0.11	0 (0.0)	0.00	2.05 (0.36–11.52)	0.42	...//
Death	76 (15.0)	3.99	101 (19.3)	5.30	0.66 (0.48–0.90)	0.009	0.002
60 y	n=634	2026.2 pt-years	n=641	2085.9 pt-years			
Primary plus hemorrhage	239 (37.7)	11.8	195 (30.4)	9.35	1.25 (1.02–1.53)	0.03	<0.001
Major hemorrhage	48 (7.6)	2.37	17 (2.7)	0.82	2.67 (1.48–4.81)	0.001	0.06
Ischemic stroke	16 (2.5)	0.79	29 (4.5)	1.39	0.50 (0.31–0.81)	0.005	0.68[§]
Intracerebral hemorrhage	2 (0.3)	0.10	2 (0.3)	0.10	2.05 (0.36–11.52)	0.42	...//
Death	173 (27.3)	8.54	147 (22.9)	7.05	1.22 (0.96–1.56)	0.009	0.002

6MW indicates 6-minute walk; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage; NYHA, New York Heart Association; and PVD, peripheral vascular disease.

*
Rates are per 100 patient-years.

[†]
From Cox models stratified by site, prior stroke status, and NYHA classification. HRs for composite end point, death, stroke, and hemorrhage are adjusted for age category, sex, diabetes mellitus, PVD, BMI, BUN, ejection fraction, DBP, 6MW, and hemoglobin. HRs for ICH are adjusted for age category.

[‡]
Treatment-by-age category interaction terms are included as applicable.

[§]
Hazard ratios presented are from models without treatment×age category interaction term for ischemic stroke, because there was no evidence of treatment×age category interaction.

//
Not enough information to test for interaction. The HR presented is from the model without a treatment×age category term.