Circulation

ORIGINAL RESEARCH ARTICLE

Early Risks of Death, Stroke/Systemic Embolism, and Major Bleeding in Patients With Newly Diagnosed Atrial Fibrillation

Results From the GARFIELD-AF Registry

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BACKGROUND: Atrial fibrillation is associated with increased risks of death, stroke/systemic embolism, and bleeding (incurred by antithrombotic therapy), which may occur early after diagnosis.

METHODS: We assessed the risk of early events (death, stroke/systemic embolism, and major bleeding) over 12 months and their relation to the time after diagnosis of atrial fibrillation in 52 014 patients prospectively enrolled in the GARFIELD-AF registry (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) between March 2010 and August 2016.

RESULTS: Over 12 months, 2140 patients died (mortality rate, 4.3; 95% CI, 4.2–4.5 per 100 person-years), of whom 288 (13.5%) died in the first month (6.8; 95% CI, 6.1–7.6). Over 12 months, 657 patients had a stroke/systemic embolism (1.3; 95% CI, 1.2–1.4) and 411 had a major bleeding (0.8; 95% CI, 0.8–0.9). During the first month, the rates (per 100 person-years) of stroke/systemic embolism and major bleed were 2.3 (95% CI, 1.9–2.8) and 1.5 (95% CI, 1.2–1.9), respectively. The elevated 1-month mortality rate was mostly attributable to cardiovascular mortality (3.5; 95% CI, 3.0–4.1), in particular, heart failure, sudden death, and acute coronary syndromes (1.0 [95% CI, 0.8–1.4], 0.6 [95% CI, 0.4–0.8], and 0.5 [95% CI, 0.3–0.8], respectively). Age, heart failure, prior stroke, history of cirrhosis, vascular disease, moderate-to-severe kidney disease, diabetes mellitus, and living in North or Latin America were independent predictors of a higher risk of early death, whereas anticoagulation and living in Europe or Asia were independent predictors of a lower risk of early death. A predictive model developed for the 1-month risk of death had a C-statistic of 0.81 (95% CI, 0.78–0.83).

CONCLUSIONS: The increased hazard of early events, in particular, cardiovascular mortality, in newly diagnosed atrial fibrillation points to the importance of comprehensive care for such patients and should alert clinicians to detect warning signs of possible early mortality.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01090362.

*A complete list of investigators is given in the online-only Data Supplement.

Key Words: atrial fibrillation ■ death ■ hemorrhage ■ stroke

Sources of Funding, see page 797

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Clinical Perspective

What Is New?

- In newly diagnosed atrial fibrillation, the rates of all 3 major clinical events (death, stroke/systemic embolism, and major bleeding) were significantly higher during the first month than in subsequent periods of follow-up at 2 to 4, 5 to 8, and 9 to 12 months.
- The leading causes of early death were heart failure, sudden/unwitnessed death, acute coronary syndromes, infection/sepsis, and respiratory failure.
- Ischemic stroke modestly contributed to the excess of early mortality.
- The GARFIELD-AF registry (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) model had good predictive accuracy for assessing the risk of early mortality in this population.

What Are the Clinical Implications?

- The causality link between newly diagnosed atrial fibrillation and higher risk of death and other events during the first month of evolution cannot be established.
- Newly diagnosed atrial fibrillation may occur as a complication of preexisting, or acutely occurring, severe cardiovascular or noncardiovascular conditions, such as heart failure, acute coronary syndrome, respiratory failure, and infection/sepsis, and may worsen the situation of such patients.
- This points to the importance of comprehensive care of newly diagnosed atrial fibrillation and should alert clinicians to detect the warning signs of possible early mortality.
- The GARFIELD-AF predictive model may help to identify the most vulnerable patients.

Atrial fibrillation (AF) is associated with higher risks of death, stroke/systemic embolism (SE), and bleeding (associated with antithrombotic therapy). The rate of adverse events is higher early after AF onset or diagnosis and the initiation of treatment, particularly during the first 4 months of follow-up.[1–5] The aims of this study were (1) to assess the risks of death, stroke/SE, and major bleeding soon after AF diagnosis, in particular, during the first month of evolution and at the 1-year time point; (2) to determine the temporal trend of occurrence of these complications over the first year of follow-up; and (3) to assess the causes and predictors of early deaths. The analyses were based on data from the ongoing Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) registry in which patients were enrolled an average of 2 weeks (and not >6 weeks) after the diagnosis of AF.[6]

METHODS

The data, analytic methods, and study materials will not be made available to other researchers because considerably more confidential information is still to be analyzed.

The design of the GARFIELD-AF registry was reported previously.[6,7] In brief, men and women ≥18 years of age with AF diagnosed according to standard local procedures within the previous 6 weeks, and with at least 1 nonprespecified risk factor for stroke (as judged by the local investigator), were eligible for inclusion.[6]

Patients were enrolled prospectively and consecutively. Investigator sites were selected randomly (apart from 18 sites, out of >1000) and represent the different care settings in each participating country (office-based practice; hospital departments including neurology, cardiology, geriatrics, internal medicine, and emergency; anticoagulation clinics; and general or family practice).[6,7]

Ethics Statement

Independent ethics committee and hospital-based institutional review board approvals were obtained. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonization–Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all patients recruited into this registry are maintained.

Procedures and Outcome Measures

Baseline characteristics collected at inclusion in the registry included medical history, care setting, type of AF, date and method of diagnosis, symptoms, antithrombotic treatment (vitamin K antagonists [VKAs], non–vitamin K antagonist oral anticoagulants [NOACs], and antiplatelet treatment), and all cardiovascular drugs, as well. Race was classified by the investigator in agreement with the patient.[6] Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were collected. HAS-BLED scores were calculated excluding fluctuations in international normalized ratio.

Collection of follow-up data occurred at 4-month intervals up to 12 months.[6,7] Standardized definitions for clinical events have been reported previously.[6,7] In brief, baseline characteristics and treatments, and the incidences of death (cardiovascular and noncardiovascular), stroke/SE, and bleeding, were recorded. Submitted data were examined for completeness and accuracy by the coordinating center (Thrombosis Research Institute, London, UK), and data queries were sent to study sites. GARFIELD-AF data are captured by using an electronic case report form. In accordance with the study protocol, 20% of all electronic case report forms were monitored against source documentation.[8] Data for the analysis in this report were extracted from the study database on October 18, 2017.

Definitions

Vascular disease included coronary artery disease with or without a history of acute coronary syndromes and/or peripheral artery disease. Chronic kidney disease (CKD) was classified according to National Kidney Foundation guidelines into

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moderate-to-severe (stages 3–5), mild (stages 1 and 2), or none. Congestive heart failure (CHF) was defined as current/prior history of CHF or left ventricular ejection fraction of <40%.

Statistical Analysis

Continuous variables were expressed as median (interquartile range), and categorical variables were expressed as frequency and percentage. The occurrence of major clinical outcomes was expressed as person-time event rates (per 100 person-years) and 95% CIs, estimated by using a Poisson model with the number of events as the dependent variable and the log of time as an offset, ie, a covariate with a known coefficient of 1. Comparisons of events within prespecified time periods are illustrated as event rates within each period. Only the first occurrence of each event was taken into account.

To examine the hypothesis of an excess of mortality in specific time intervals, a piecewise exponential model was applied, thus comparing the hazard in a series of prespecified time periods (ie, 0–1, 2–4, 5–8 months) with the hazard in the last 4 months of follow-up. This method assumes that the hazard is constant within each interval but can vary across intervals, thus allowing comparisons between time periods. The assumption of constant hazards within the prespecified time intervals was verified through visual examination of the nonparametric kernel-smoothed hazard function.

In addition to testing for early hazard excess, a multivariable model was developed to identify factors associated with early death. The stepwise variable selection approach with Cox proportional hazard modeling was adopted to generate a model for early mortality. The results from this process were applied using a *P* value of 0.15 to enter and 0.15 to stay in the model. Variables considered in the full model were sex, age, race (white, Hispanic/Latino, Asian [not Chinese], Chinese, other race—including Afro-Caribbean and mixed/other), geographical region, type of AF at diagnosis (unclassified, paroxysmal, persistent, permanent), baseline use of NOAC or VKA, the composite of nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, systolic and diastolic blood pressures, heart rate, body mass index, diabetes mellitus, current smoking, hypertension, stent placement, previous stroke, history of coronary artery bypass surgery, vascular disease, carotid disease, moderate-to-severe renal disease, systemic embolism, history of bleeding, cirrhosis, current/prior history of CHF or an ejection fraction of <40%, sleep apnea, and heavy alcohol consumption.

Hazard ratios and 95% CIs were estimated using a proportional hazards Cox model. Comparison of the early mortality model with the GARFIELD-AF risk model[9] was performed by calculating the C-statistic with 95% CIs. Multiple imputation was applied to the final model of 1-month mortality. Combined hazard ratio estimates based on 5 imputed data sets are presented. The stepwise selection and C-statistic calculation were performed by using one of the imputed data sets. Data analyses were performed with SAS version 9.4 (SAS Institute Inc).

RESULTS

Study Population

This analysis involved all 5 cohorts of the GARFIELD-AF registry, totaling 52 014 patients recruited between March 2010 and August 2016 and followed prospectively for a minimum of 1 year. The median age of the population was 71.0 years, and 44.2% were women. Over a fifth of the patients had CHF (22.6%) or coronary artery disease (21.6%), and the majority had a history of hypertension (76.3%). In addition, prior stroke/transient ischemic attack was present in 11.4% of patients, history of bleeding in 2.5%, diabetes mellitus in 22.2%, and moderate-to-severe CKD in 11.7%. At enrollment, 66.9% of patients were prescribed anticoagulant therapy, with or without antiplatelet therapy (VKA 39.4%, factor Xa inhibitors 20.5%, direct thrombin inhibitors 7.1%); 21.0% were on antiplatelet therapy only; and 12.1% received no antithrombotic therapy (Table 1). Initial AF management strategy, available only for patients enrolled from the third cohort onward, included rate control, 14 021 (42.0%) patients; rhythm control, 9341 (28.0%) patients; or both, 5640 (16.9%) patients (as declared by the investigators). Rate control drugs (class 2, 4, and 5) were used in 21 988 (63.1%) patients. Rhythm control drugs (class 1a, 1c, and 3) were used in 4337 (12.4%) patients. In the 9341 patients declared to have been allocated to rhythm strategy, 2238 (24.0%) received class 1a or 1c or class 3 drugs. Cardioversion was attempted in 4047 (12.1%) patients. Other cardiovascular drugs involved CHF/hypertension drugs, antidiabetics, and α-blockers (Table 2). Pulmonary vein exclusion intervention was reported in <0.5% of patients (data not shown).

Early Risk of Mortality

Overall, 2140 patients died during the 12-month observation period (mortality rate, 4.3; 95% CI, 4.2–4.5 per 100 person-years), of whom 288 (13.5%) died within 1 month (6.8; 95% CI, 6.1–7.6 per 100 person-years). Six hundred twenty-three (29.1%) died during the 2- to 4-month time interval (4.9; 95% CI, 4.5–5.3 per 100 person-years), 621 (29.0%) died during the 5- to 8-month time interval, and 608 (28.4%) died during the 9- to 12-month time interval (3.8; 95% CI, 3.5–4.1 per 100 person-years) (Table 3 and Figure 1A). The hazard ratios in comparison with the 9- to 12-month interval were 1.78 (95% CI, 1.55–2.05) at 1 month; 1.29 (95% CI, 1.15–1.44) in the 2- to 4-month time interval; and 0.99 (95% CI, 0.88–1.11) in the 5- to 8-month time interval (Table I in the online-only Data Supplement).

Patients who died in the first 12 months after diagnosis of AF tended to be older and have a higher prevalence of comorbidities than those who survived the first 12 months. There were no major differences in the baseline characteristics of patients who died within the first month in comparison with those who died in the 2- to 12-month time interval. However, left ventricular ejection fraction <40% and CHF were more prevalent in the early-death subgroup and in the subgroup

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Table 1. Baseline Characteristics of All Patients

Variable	N=52 014	(%)
Female, n/N	22 987/52 013	(44.2)
Age, median (IQR), y	71.0 (63.0–78.0)	
Age group, n/N		
<65 y	15 693/52 014	(30.2)
65–74 y	16 948/52 014	(32.6)
75–84 y	15 239/52 014	(29.3)
≥85 y	4134/52 014	(7.9)
Race, n/N		
Afro-Caribbean	243/52 014	(0.5)
Asian (not Chinese)	11 555/52 014	(22.2)
Chinese	2742/52 014	(5.3)
White	31 958/52 014	(61.4)
Hispanic/Latino	3395/52 014	(6.5)
Mixed/other	838/52 014	(1.6)
Unwilling to declare/not recorded	1283/52 014	(2.5)
Body mass index, median (IQR), kg/m^2	27.0 (24.0–31.0)	
Pulse, median (IQR), bpm	84.0 (70.0–105.0)	
Systolic blood pressure, median (IQR), mm Hg	130.0 (120.0–145.0)	
Diastolic blood pressure, median (IQR), mm Hg	80.0 (70.0–88.0)	
LVEF <40%, n/N	3062/30 392	(10.1)
Type of atrial fibrillation, n/N		
Unclassified	23 288/52 009	(44.8)
Paroxysmal	14 316/52 009	(27.5)
Persistent	7765/52 009	(14.9)
Permanent	6640/52 009	(12.8)
Medical history, n/N		
Congestive heart failure	11 738 /52 007	(22.6)
Coronary artery disease	11 232/52 007	(21.6)
Acute coronary syndromes	4895/51 758	(9.5)
Carotid occlusive disease	1543/51 279	(3.0)
Pulmonary embolism/deep vein thrombosis	1356/51 702	(2.6)
Coronary artery bypass graft	1621/51 333	(3.2)
Stroke/transient ischemic attack	5954/52 007	(11.4)
Systemic embolism	337/51 697	(0.7)
History of bleeding	1317/51 782	(2.5)
History of hypertension	39 585/51 863	(76.3)
Hypercholesterolemia	20 940/50 369	(41.6)
Diabetes mellitus (type 1 or 2)	11 540/52 007	(22.2)
Cirrhosis	296/51 243	(0.6)
Chronic renal disease, n/N		
None or mild (stages 1 and 2)	40 427/45 800	(88.3)
Moderate to severe (stages 3 to 5)	5373/45 800	(11.7)
Dementia	764/51 729	(1.5)
Alcohol consumption, n/N		
Abstinent/light	38 793/44 015	(88.1)
Moderate	4192/44 015	(9.5)
Heavy	1030/44 015	(2.3)
Current/previous smoker, n/N	16 398/47 405	(34.6)
Antithrombotic treatment, n/N		
Vitamin K antagonists	15 365/51 291	(30.0)
Vitamin K antagonists + antiplatelet	4817/51 291	(9.4)
Factor Xa inhibitors	8592/51 291	(16.8)
Factor Xa inhibitors + antiplatelet	1889/51 291	(3.7)
Direct thrombin inhibitors	3023/51 291	(5.9)
Direct thrombin inhibitors + antiplatelet	626/51 291	(1.2)
Antiplatelet only	10 756/51 291	(21.0)
None	6223/51 291	(12.1)
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0–4.0)	
CHA_2DS_2-VASc score categories, n/N		
0	1417/50 629	(2.8)
1	6194/50 629	(12.2)
2	10 137/50 629	(20.0)
3	12 180/50 629	(24.1)
4	11 057/50 629	(21.8)
5	5761/50 629	(11.4)
6–9	3883/50 629	(7.7)
HAS-BLED score, median (IQR)*	1.0 (1.0–2.0)	
HAS-BLED score categories, n/N*		
0	5475/37 494	(14.6)
1	16 130/37 494	(43.1)
2	11 675/37 494	(31.1)
3	3567/37 494	(9.5)
4	588/37 494	(1.6)
5	56/37 494	(0.2)
6–8	3/37 494	(0.01)
Care setting specialty at diagnosis, n/N		
Cardiology	34 165/52 009	(63.6)
Geriatrics	202/52 009	(0.4)
Internal medicine	9356/52 009	(18.0)
Neurology	876/52 009	(1.7)
Primary care/general practice	7410/52 009	(14.2)

GARFIELD-AF indicates Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; IQR, interquartile range; and LVEF, left ventricular ejection fraction.

*The risk factor labile international normalized ratio is not included in the HAS-BLED score because it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points, not 9.

with no antithrombotic or antiplatelet-only treatment, as well (Table 4).

Cause of Death

Rates by cause of death at different time intervals are shown in Figure 2 and Table 5. The elevated all-cause

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Table 2. Baseline Treatment at Diagnosis (GARFIELD-AF Cohorts 3–5, n=34 854)

Variable	n (%)
AF treatment strategy initiated	
Rhythm	9341 (28.0)
Rate	14 021 (42.0)
Both	5640 (16.9)
Unknown	4416 (13.2)
Cardioversion	
No	29 537 (87.9)
Yes	4047 (12.1)
Antiarrhythmic drugs*	
Class Ia	177 (0.5)
Class Ic	1314 (3.8)
Class II (β-blockers)	13 153 (37.7)
Class III	2846 (8.2)
Class IV (calcium channel blocker)	5576 (16.0)
Class V (digoxin and other digitalis)	3259 (9.4)
Other cardiac medication maintained after AF diagnosis)*	
Heart failure /hypertension drugs	
ACEi/ARBs	18 334 (52.6)
β-Blockers	4899 (14.1)
Loop and other diuretics	11 225 (32.2)
MRA	2387 (6.9)
Other drugs of interest	
Oral antidiabetics	3853 (11.1)
Insulin	1184 (3.4)
α-Blockers	1033 (3.0)

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; and MRA, mineralocorticoid receptor antagonist.

*Categories are not mutually exclusive.

mortality rate in the first month was mostly attributable to cardiovascular mortality (3.5; 95% CI, 3.0–4.1 per 100 person-years), in particular, CHF, acute coronary syndromes, and sudden death. The rate of early death from ischemic stroke was low in comparison with other causes of death (0.3; 95% CI, 0.2–0.6 per 100 person-years) (Table 5). In comparison with subsequent time periods, a modestly higher rate of noncardiovascular mortality was also observed during the first month and the 2- to 4-month time period, linked to a higher rate of death from respiratory failure and infection/sepsis.

Early Risks of Stroke/SE and of Major Bleeding

A total of 657 stroke/SE (1.3; 95% CI, 1.2–1.4 per 100 person-years) and 411 major bleeding episodes (0.8; 95% CI, 0.8–0.9 per 100 person-years) occurred during the 12-month observation period, of which 98 stroke/SE (2.3; 95% CI, 1.9–2.8 per 100 person-years) and 63 major bleeding events (1.5; 95% CI, 1.2–1.9 per 100 person-years) occurred during the first month. The rate of stroke/SE was higher during the first month (2.3; 95% CI, 1.9–2.8 per 100 person-years) and during the 2- to 4-month observation period (1.5; 95% CI, 1.3–1.7 per 100 person-years) than during the subsequent time periods (Table 3 and Figure 1B and 1C).

Table 3. All-Cause Mortality Rates, Stroke/SE, and Major Bleeding (per 100 Person-Years) Assessed at Different Intervals During Follow-Up (GARFIELD-AF Cohorts 1–5)

Event	Time Interval, mo	No. of Events	Person-Years	Event Rate (95% CI)
Death	0–1	288	4233.9	6.8 (6.1–7.6)
	2–4	623	12 671.4	4.9 (4.5–5.3)
	5–8	621	16 482.4	3.8 (3.5–4.1)
	9–12	608	15 950.8	3.8 (3.5–4.1)
	0–12	2140	49 338.5	4.3 (4.2–4.5)
Stroke/SE	0–1	98	4230.1	2.3 (1.9–2.8)
	2–4	184	12 632.3	1.5 (1.3–1.7)
	5–8	210	16 383.5	1.3 (1.1–1.5)
	9–12	165	15 820.2	1.0 (0.9–1.2)
	0–12	657	49 066.0	1.3 (1.2–1.4)
Major bleeding	0–1	63	4231.7	1.5 (1.2–1.9)
	2–4	126	12 646.2	1.0 (0.8–1.2)
	5–8	116	16 420.8	0.7 (0.6–0.8)
	9–12	106	15 865.5	0.7 (0.6–0.8)
	0–12	411	49 164.2	0.8 (0.8–0.9)

GARFIELD-AF indicates Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; and SE, systemic embolism.

Predictors of Early Mortality

The impact of patients' characteristics on all-cause mortality rates at different time intervals is shown in Table II in the online-only Data Supplement. The higher rate of early death was a feature of patients of all ages, sex, and comorbidities (including prior myocardial infarction, moderate to severe CKD, previous stroke, CHF) and especially those with a CHA_2DS_2-VASc score of ≥3. In contrast, an increase in early mortality in comparison with subsequent time periods was less pronounced in patients with CHA_2DS_2-VASc score of 0 to 2, ie, without any comorbidities (Table II in the online-only Data Supplement and Figure I in the online-only Data Supplement).

Multivariate Analysis of Predictors of Early Mortality and Predictive Model

Stepwise regression analysis identified age, body mass index, heart rate, diastolic blood pressure, region of the world, heart failure, prior stroke, history of cirrhosis, vascular disease, moderate-to-severe CKD, and diabe-

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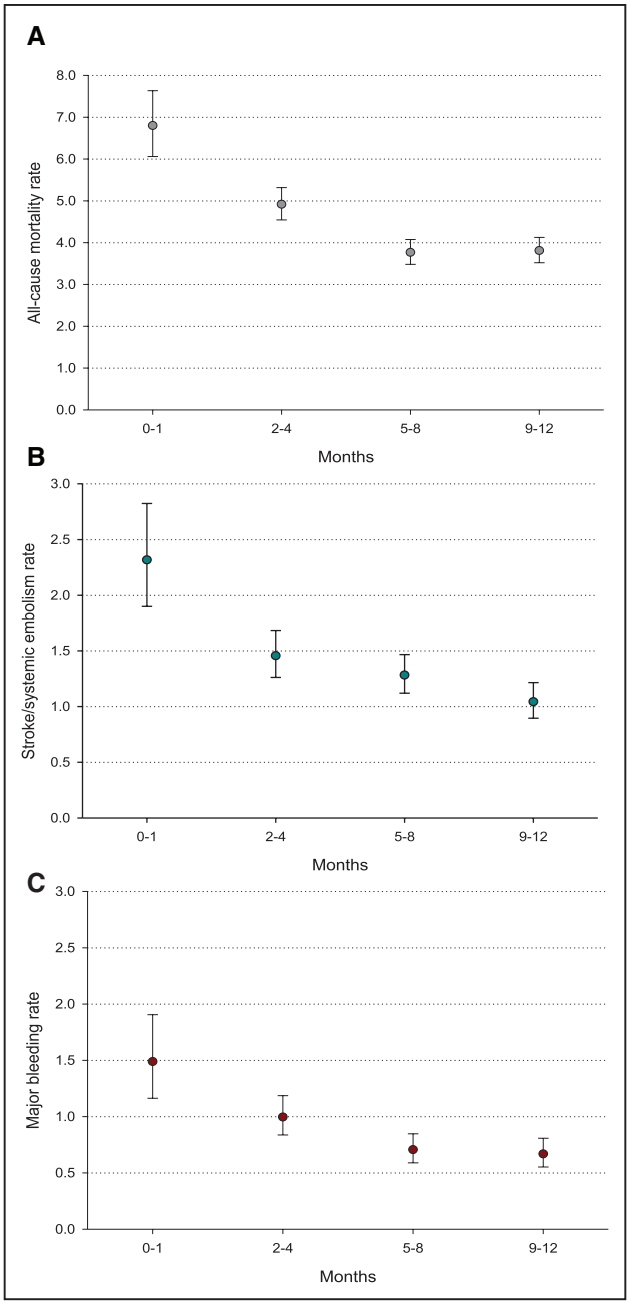


Figure 1. Event rates over 1-year follow-up.
All-cause mortality (**A**), stroke/systemic embolism (**B**), and major bleeding (**C**; per 100 person-years) at different intervals during follow-up. GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) cohorts 1 to 5. Only the first occurrence of each event was taken into account.

tes mellitus as independent predictors of a higher risk of death within 1 month of AF diagnosis. In comparison with living in Europe, living in Latin or North America also conferred a higher risk of early death, whereas the risk was lower for patients living in Asia. Baseline VKA or NOAC use were both independent predictors of a lower risk of early death (Table 6). The predictive model developed for the 1-month risk of death had a high predictive value, with a C-statistic of 0.81 (95% CI, 0.78–0.83).

DISCUSSION

This report confirms previous observations that show the risk of death in patients with newly diagnosed AF is at its highest during the first month of follow-up.[1,2,4] Of all deaths recorded during the first year of follow-up, 13% occurred during the first month. The rate of death remained slightly elevated for the time interval between 2 and 4 months, but not later. Deaths in the first month were mostly linked to cardiovascular causes. CHF was the leading cause of cardiovascular death followed by sudden/unwitnessed death, acute coronary syndromes, and ischemic stroke. The higher rate of early death was a feature of patients of all ages, sex, and comorbidities (including prior myocardial infarction, moderate to severe CKD, previous stroke, CHF) and patients with a CHA_2DS_2-VASc score of ≥3. There was an imbalance in the risk of early death between regions with higher risk in Latin and North America in comparison with Europe and Asia. Lower risk of death in Asia in comparison with other regions is a common observation.[10,11] In previous reports from GARFIELD-AF in smaller cohorts, but with longer follow-up, the risk of death was 34% lower in Asians, the risk of stroke was identical, but the risk of bleeding was also lower than in other ethnic groups.[3,5] A lower risk of death in Europe may be linked to the highly protective healthcare system and easier access to medications and to cardiologists than in other regions.

The causality link between newly diagnosed AF and higher risk of death during the first month cannot be established. AF may occur as a complication of preexisting or acutely occurring severe cardiovascular or noncardiovascular condition such as myocardial infarction, sepsis, or respiratory failure. In these cases, AF may worsen the situation of such patients and be considered a precipitating factor of early death. AF may also be the causal factor of CHF, in cases of prolonged high ventricular rate, even in patients without prior left ventricular dysfunction.[12] It is interesting to note that, in patients without additional comorbidities, ie, with CH_2ADS_2-VASc 0 to 2, no increased risk of early death was observed, suggesting that AF may not be in itself a causal factor of early mortality. However, in the Framingham Heart Study, a >2-fold higher risk of death in patients with AF than in patients without AF was observed during the first weeks after the diagnosis of AF, including in patients who had AF without any comorbidities. This led to the conclusion that AF may have a causal effect in death.[1] Our observations are not contradictory, because they only show that AF is not associated with an excess of early death in low-risk patients, but in any case, newly diagnosed AF should be considered as a marker of the risk of death.

These findings have to be put in perspective with treatment allocation. Anticoagulation at baseline is associated with a reduced risk of death as shown in

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Table 4. Baseline Characteristics Stratified by Follow-Up Status* (GARFIELD-AF Cohorts 1–5)

Variable	Deceased Within 1 mo (n=288)	Deceased in Period 2–12 mo (n=1852)	Alive at 12 mo (n=45 848)
Sex, n (%)			
Male	150 (52.1)	1002 (54.1)	25 062 (55.8)
Female	138 (47.9)	850 (45.9)	20 245 (44.2)
Age, median (IQR), y	78.0 (70.0–84.0)	78.0 (71.0–84.0)	71.0 (62.0–78.0)
Age group, n (%)			
<65 y	38 (13.1)	225 (12.2)	14 088 (30.7)
65–74 y	66 (22.9)	475 (25.7)	15 188 (33.1)
75–84 y	115 (39.9)	705 (37.9)	13 303 (29.0)
≥85 y	69 (24.0)	450 (24.3)	3269 (7.1)
Race, n (%)			
Afro-Caribbean	2 (0.7)	11 (0.6)	193 (0.4)
Asian (not Chinese)	50 (17.4)	270 (14.6)	9933 (21.7)
Chinese	12 (4.2)	77 (4.2)	2364 (5.2)
White	191 (66.3)	1251 (67.8)	28 508 (62.2)
Hispanic/Latino	22 (7.6)	149 (8.1)	2988 (6.5)
Mixed/other	7 (2.4)	37 (2.0)	722 (1.6)
Unwilling to declare/not recorded	4 (1.4)	57 (3.1)	1140 (2.5)
Body mass index, median (IQR), kg/m^2	25.0 (22.0–29.0)	26.0 (23.0–30.0)	27.0 (24.0–31.0)
Pulse, median (IQR), bpm	90.0 (77.0–116.0)	90.0 (74.0–111.0)	84.0 (70.0–105.0)
Systolic blood pressure, median (IQR), mm Hg	130.0 (115.0–148.0)	130.0 (118.0–141.0)	131.0 (120.0–145.0)
Diastolic blood pressure, median (IQR), mm Hg	79.0 (70.0–90.0)	78.0 (70.0–85.0)	80.0 (70.0–89.0)
Left ventricular ejection fraction, n (%)			
<40%	51 (27.4)	220 (21.4)	2555 (9.8)
≥40%	135 (72.6)	810 (78.6)	24 203 (90.2)
Type of atrial fibrillation, n (%)			
Permanent	45 (15.6)	314 (16.7)	5728 (12.5)
Persistent	39 (13.5)	238 (12.9)	6825 (14.9)
Paroxysmal	56 (19.4)	345 (18.6)	12 722 (27.8)
Unclassified	148 (51.4)	955 (51.6)	20 571 (44.9)
Medical history, n (%)			
Congestive heart failure	140 (48.6)	759 (41.0)	9966 (21.7)
Coronary artery disease	108 (37.5)	588 (31.8)	9746 (21.3)
Acute coronary syndromes	51 (18.1)	283 (15.4)	4246 (9.3)
Carotid occlusive disease	8 (2.8)	85 (4.7)	1320 (2.9)
Pulmonary embolism/deep vein thrombosis	14 (4.9)	59 (3.2)	1188 (2.6)
Coronary artery bypass graft	12 (4.3)	97 (5.3)	1422 (3.1)
Stroke/transient ischemic attack	53 (18.4)	296 (16.0)	5112 (11.2)
Systemic embolism	1 (0.4)	21 (1.2)	284 (0.6)
History of bleeding	14 (4.9)	110 (6.0)	1110 (2.4)
History of hypertension	219 (76.3)	1413 (76.5)	35 049 (76.7)
Hypercholesterolemia	96 (35.3)	696 (39.4)	18 738 (42.1)
Diabetes mellitus	86 (29.9)	493 (26.6)	10 067 (22.0)
Cirrhosis	6 (2.2)	26 (1.4)	233 (0.5)
Dementia	18 (6.3)	101 (5.5)	570 (1.3)

(*Continued*)

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Table 4. Continued

Variable	Deceased Within 1 mo (n=288)	Deceased in Period 2–12 mo (n=1852)	Alive at 12 mo (n=45 848)
Chronic renal disease, n (%)			
None or mild (grades I and II)	185 (72.8)	1201 (73.1)	35 807 (88.9)
Moderate to severe (grades III to V)	69 (27.2)	441 (26.9)	4477 (11.1)
Alcohol consumption, n (%)			
Abstinent/light	230 (92.7)	1429 (91.7)	34 168 (88.0)
Moderate	12 (4.8)	96 (6.2)	3744 (9.7)
Heavy	6 (2.4)	33 (2.1)	897 (2.3)
Smoking status, n (%)			
Current/previous smoker	95 (36.8)	664 (39.5)	14 329 (34.3)
Nonsmoker	163 (63.2)	1016 (60.5)	27 492 (65.7)
Antithrombotic treatment, n (%)			
Vitamin K antagonists	52 (18.4)	503 (27.6)	13 853 (30.7)
Vitamin K antagonists + antiplatelet	44 (15.6)	44 (15.6)	4197 (9.3)
Factor Xa inhibitors	26 (9.2)	229 (12.6)	7476 (16.5)
Factor Xa inhibitors + antiplatelet	8 (2.8)	60 (3.3)	1632 (3.6)
Direct thrombin inhibitors	4 (1.4)	71 (3.9)	2705 (6.0)
Direct thrombin inhibitors + antiplatelet	1 (0.4)	25 (1.4)	572 (1.3)
Antiplatelet only	88 (31.1)	449 (24.6)	9398 (20.8)
None	60 (21.2)	250 (13.7)	5365 (11.9)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	3.0 (2.0–4.0)
CHA_2DS_2-VASc score categories, n (%)			
0	0 (0.0)	16 (0.9)	1237 (2.8)
1	8 (2.8)	68 (3.8)	5593 (12.5)
2	29 (10.3)	206 (11.4)	9120 (20.4)
3	57 (20.2)	378 (20.9)	10 867 (24.3)
4	79 (28.0)	487 (27.0)	9701 (21.7)
5	49 (17.4)	322 (17.8)	4942 (11.1)
6–9	60 (21.3)	328 (18.2)	3194 (7.2)
HAS-BLED score, median (IQR)†	2.0 (1.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
HAS-BLED score category, n (%)			
0	9 (4.0)	71 (5.3)	4905 (14.9)
1	67 (29.8)	415 (31.0)	14 365 (43.6)
2	78 (34.7)	518 (38.7)	10 163 (30.8)
3	56 (24.9)	275 (20.6)	3000 (9.1)
4	13 (5.8)	55 (4.1)	484 (1.5)
5	2 (0.9)	4 (0.3)	44 (0.1)
6–8	0 (0.0)	0 (0.0)	2 (0.01)
Care setting specialty at diagnosis, n (%)			
Cardiology	185 (64.2)	1102 (59.5)	30 101 (65.7)
Geriatrics	3 (1.0)	24 (1.3)	164 (0.4)
Internal medicine	63 (21.9)	434 (23.4)	8180 (17.8)
Neurology	15 (5.2)	33 (1.8)	748 (1.6)
Primary care/general practice	22 (7.6)	259 (14.0)	6653 (14.5)

GARFIELD-AF indicates Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; INR, international normalized ratio; and IQR, interquartile range.

*Frequencies do not add up to the total because of the presence of patients lost to follow-up (n=3841) or with missing follow-up information (n=185).

†The risk factor Labile INRs is not included in the HAS-BLED score because it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).

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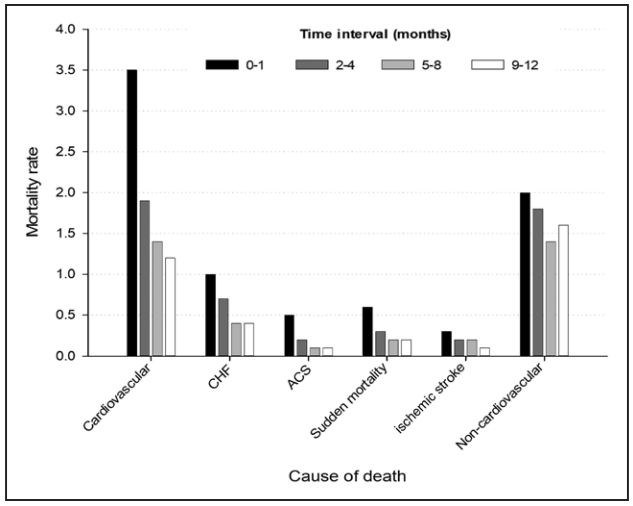


Figure 2. Mortality rate (per 100 person-years) according to cause of death assessed at different intervals during follow-up.
GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) cohorts 1 to 5. ACS indicates acute coronary syndrome; and CHF, congestive heart failure.

this and in previous reports.[2–5,13] The impact of AF management is more difficult to assess. In this report, a minority of patients were assigned to rhythm control, but cardioversion was attempted in less than half of the patients allocated to rhythm or rhythm/rate control strategies, and pulmonary vein exclusion was very rarely reported. Rhythm control drugs were prescribed in only half of the patients assigned to a rhythm control strategy. The vast majority of patients were assigned to either rate or both rhythm and rate control strategies. The discrepancies between intended strategies and the use of cardioversion and rhythm or rate control drugs reflect the complexity of the clinical decision making in routine practice, changes in strategy over time, and, to some extent, the inexperience of investigators who were not cardiologists in >30% of cases.

A predictive model for early (1 month) mortality risk was developed with a C-statistic of 0.81. It is interesting to note that the predictive ability of the 1-year mortality model, when tested for 1-month mortality, was equally good with a C-statistic of 0.79. We did not have a sufficient number of patients with stroke/SE and major bleeding at 1 month to run a robust multivariate analysis and develop a 1-month predictive model for these end points.

The increased rate/incidence of events was not confined to the risk of death. The risk of both nonfatal stroke/SE and nonfatal major bleeding was significantly increased during the first month. Wide variations of international normalized ratio after the initiation of VKAs may result in an increase in stroke/SE, major bleeding, and death.[14–16] Other factors may play a role, such as hypercoagulability at the onset of AF, and a transient hypercoagulable state attributable to differential deple-

Table 5. All-Cause Mortality Rates (per 100 Person-Years) According to Cause of Death Assessed at Different Intervals During Follow-Up (GARFIELD-AF Cohorts 1–5)

Cause of Death	Time Interval, mo	Deaths	Mortality Rate (95% CI)
Cardiovascular	0–1	147	3.5 (3.0–4.1)
	2–4	238	1.9 (1.7–2.1)
	5–8	225	1.4 (1.2–1.6)
	9–12	189	1.2 (1.0–1.4)
	0–12	799	1.6 (1.5–1.7)
CHF	0–1	44	1.0 (0.8–1.4)
	2–4	87	0.7 (0.6–0.8)
	5–8	70	0.4 (0.3–0.5)
	9–12	67	0.4 (0.3–0.5)
	0–12	268	0.5 (0.5–0.6)
ACS	0–1	22	0.5 (0.3–0.8)
	2–4	29	0.2 (0.2–0.3)
	5–8	19	0.1 (0.1–0.2)
	9–12	20	0.1 (0.1–0.2)
	0–12	90	0.2 (0.1–0.2)
Sudden mortality	0–1	24	0.6 (0.4–0.8)
	2–4	40	0.3 (0.2–0.4)
	5–8	38	0.2 (0.2–0.3)
	9–12	26	0.2 (0.1–0.2)
	0–12	128	0.3 (0.2–0.3)
Ischemic stroke	0–1	14	0.3 (0.2–0.6)
	2–4	23	0.2 (0.1–0.3)
	5–8	31	0.2 (0.1–0.3)
	9–12	19	0.1 (0.1–0.2)
	0–12	87	0.2 (0.1–0.2)
Noncardiovascular	0–1	84	2.0 (1.6–2.5)
	2–4	225	1.8 (1.6–2.0)
	5–8	236	1.4 (1.3–1.6)
	9–12	248	1.6 (1.4–1.8)
	0–12	793	1.6 (1.5–1.7)
Malignancy	0–1	17	0.4 (0.2–0.6)
	2–4	65	0.5 (0.4–0.7)
	5–8	71	0.4 (0.3–0.5)
	9–12	85	0.5 (0.4–0.7)
	0–12	238	0.5 (0.4–0.5)
Respiratory failure	0–1	18	0.4 (0.3–0.7)
	2–4	41	0.3 (0.2–0.4)
	5–8	43	0.3 (0.2–0.4)
	9–12	42	0.3 (0.2–0.4)
	0–12	144	0.3 (0.2–0.3)
Infection/sepsis	0–1	27	0.6 (0.4–0.9)
	2–4	44	0.3 (0.3–0.5)
	5–8	47	0.3 (0.2–0.4)
	9–12	43	0.3 (0.2–0.4)
	0–12	161	0.3 (0.3–0.4)

ACS indicates acute coronary syndromes; CHF, congestive heart failure; and GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.

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Table 6. Multivariate Analysis of Predictors of 1-Month All-Cause Mortality Using Stepwise Selection (GARFIELD-AF Cohorts 1–5)

Parameter	Hazard Ratio (95% CI)	*P* Value
CHF		
No	1*	
Yes	2.80 (2.21–3.55)	<0.001
Age at AF diagnosis (5-y increase)	1.28 (1.20–1.36)	<0.001
Baseline NOAC use		
No	1*	
Yes	0.31 (0.22–0.44)	<0.001
Baseline VKA use		
No	1*	
Yes	0.51 (0.39–0.66)	<0.001
Heart rate right-truncated at 80 (5-point increase)	1.24 (1.13–1.37)	<0.001
History of stroke		
No	1*	
Yes	1.84 (1.32–2.55)	<0.001
Moderate-to-severe CKD		
No	1*	
Yes	1.59 (1.18–2.13)	0.002
Body mass index (1-point increase)	0.95 (0.92–0.98)	0.001
DBP, right-truncated at 80 mm Hg (5-point increase)	0.89 (0.82–0.96)	0.002
DBP, left-truncated at 80 mm Hg (5-point increase)	1.09 (1.02–1.17)	0.012
Diabetes mellitus		
No	1*	
Yes	1.43 (1.10–1.87)	0.008
Vascular disease		
No	1*	
Yes	1.41 (1.08–1.87)	0.012
Cirrhosis		
No	1*	
Yes	2.91 (1.26–6.72)	0.012
Current smoker		
No	1*	
Yes	1.46 (0.97–2.19)	0.066
Region		
Europe	1*	
North America	1.67 (0.96–2.91)	0.069
Latin America	1.70 (1.18–2.44)	0.004
Asia	0.64 (0.46–0.90)	0.011
Rest of the world	2.37 (1.60–3.50)	<0.001

AF indicates atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; DBP, diastolic blood pressure; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; NOAC, non–vitamin K antagonist oral anticoagulant; and VKA, vitamin K antagonist.

*Reference category.

tion of certain vitamin K–dependent coagulation factors, as well, as suggested by Azoulay et al.[17]

Differences between VKAs and NOACs may exist in terms of their early risk-benefits as suggested by the hazard ratios for death derived from multivariate analysis (Table 6). Fluctuations in anticoagulation levels and drug interactions (with the depletion of VKA-dependent coagulation factors) at the initiation of anticoagulant therapy are unlikely to occur with NOACs. Therefore, patients taking NOACs may be less susceptible to an excess of early events.

Clinical Implications

Newly diagnosed AF should alert clinicians to the increased risk of early death, stroke/SE, and major bleeding. Among the independent predictors of early death, CHF, diabetes mellitus, vascular disease, and, to a lesser extent, CKD, are modifiable risk factors that should be targeted for early intervention, particularly CHF. The recently developed GARFIELD-AF 1-year predictive model[9] can predict the risk of death at 1 month as accurately as at 1 year and should be implemented to assess the early risk of events in clinical practice.

Limitations

The current analysis of 3 major outcome measures is based on the baseline characteristics and treatment allocation initially decided by the investigators at inclusion in the registry. A more detailed analysis taking into account management strategies and treatment changes over the follow-up period would make it possible to refine the picture. This kind of analysis was not in the scope of this article and will be the topic of further analysis.

CONCLUSIONS

A significant higher rate of early death is observed during the first month in patients with newly diagnosed AF. This is mostly linked to an increased cardiovascular mortality, including CHF, sudden death, acute coronary syndromes, and stroke/SE and, to a lesser extent, to noncardiovascular causes such as respiratory failure and sepsis. Anticoagulation decreases the risk of early death. An increased risk of stroke/SE and bleeding is also observed during the first month of follow-up. These data emphasize the importance of the comprehensive care of patients with newly diagnosed AF and should alert clinicians to detect warning signs of possible early mortality, in particular, CHF. Clinicians can potentially target more vulnerable patients by using the GARFIELD-AF predictive model, which is equally good at predicting all-cause mortality at 1 month as it is at 1 year.

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ARTICLE INFORMATION

Received March 22, 2018; accepted October 4, 2018.

Guest Editor for this article was Clyde W. Yancy, MD, MSc.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.118.035012.

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Acknowledgments

We thank the physicians, nurses, and patients involved in the GARFIELD-AF registry. Editorial support was provided by Emily Chu and Rae Hobbs (Thrombosis Research Institute, London, UK).

Sources of Funding

The GARFIELD-AF registry is sponsored by the Thrombosis Research Institute, London, UK, and is supported by an unrestricted research grant from Bayer AG, Berlin, Germany.

Disclosures

Dr Goldhaber reports grants from BiO2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb, BTG EKOS, Daiichi Sankyo, the National Heart, Lung, and Blood Institute of the National Institutes of Health, Janssen, and the Thrombosis Research Group; and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, and Portola. Dr Camm reports personal fees from Bayer, Boehringer Ingelheim, Pfzer/Bristol-Myers Squibb, and Daiichi Sankyo. Dr Fitzmaurice reports personal fees from Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bayer. Dr Fox reports grants from Bayer, Johnson and Johnson, and AstraZeneca; and personal fees from Bayer, Johnson and Johnson, Lilly, AstraZeneca, and Sanofi/Regeneron. Dr Goto reports personal fees from the Thrombosis Research Institute, Harvard University, the American Heart Association, Boehringer Ingelheim, Armethrom, Bayer, and AstraZeneca; and grants from the Japanese Society for Promotion of Science, RIKEN, Sanofi, and Pfizer. Dr Haas reports personal fees from Aspen, Bayer Healthcare, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and Sanofi. Dr Hacke reports personal fees from Bayer AG. Dr Mantovani reports grants and personal fees from Bayer AG and Pfizer, grants from Boehringer Ingelheim, and personal fees from Daiichi Sankyo. Dr Misselwitz is an employee of Bayer AG. Dr Turpie reports personal fees from Bayer Healthcare, Janssen Pharmaceutical Research & Development LLC, Astellas, Portola, and Takeda. Dr van Eickels is an employee of Bayer AG. Dr Verheugt reports educational and research grants from Bayer Healthcare; and personal fees from Bayer Healthcare, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and Boehringer Ingelheim. Dr Kakkar reports research support from Bayer AG; and personal fees from Bayer AG, Boehringer Ingelheim Pharma, Daiichi Sankyo Europe, Janssen Pharma, and Sanofi SA. Drs Virdone, Pieper, Kayani, and Bassand report no conflicts.

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