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Analysis of Outcomes in Ischemic vs Nonischemic Cardiomyopathy in Patients With Atrial Fibrillation
A Report From the GARFIELD-AF Registry

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IMPORTANCE Congestive heart failure (CHF) is commonly associated with nonvalvular atrial fibrillation (AF), and their combination may affect treatment strategies and outcomes.

OBJECTIVE To assess the treatment strategies and 1-year clinical outcomes of antithrombotic and CHF therapies for patients with newly diagnosed AF with concomitant CHF stratified by etiology (ischemic cardiomyopathy [ICM] vs nonischemic cardiomyopathy [NICM]).

DESIGN, SETTING, AND PARTICIPANTS The GARFIELD-AF registry is a prospective, noninterventional registry. A total of 52 014 patients with AF were enrolled between March 2010 and August 2016. A total of 11 738 patients 18 years and older with newly diagnosed AF (≤6 weeks' duration) and at least 1 investigator-determined stroke risk factor were included. Data were analyzed from December 2017 to September 2018.

EXPOSURES One-year follow-up rates of death, stroke/systemic embolism, and major bleeding were assessed.

MAIN OUTCOMES AND MEASURES Event rates per 100 person-years were estimated from the Poisson model and Cox hazard ratios (HRs) and 95% confidence intervals.

RESULTS The median age of the population was 71.0 years, 22 987 of 52 013 were women (44.2%) and 31 958 of 52 014 were white (61.4%). Of 11 738 patients with CHF, 4717 (40.2%) had ICM and 7021 (59.8%) had NICM. Prescription of oral anticoagulant and antiplatelet drugs was not balanced between groups. Oral anticoagulants with or without antiplatelet drugs were used in 2753 patients with ICM (60.1%) and 5082 patients with NICM (73.7%). Antiplatelets were prescribed alone in 1576 patients with ICM (34.4%) and 1071 patients with NICM (15.5%). Compared with patients with NICM, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (72.6% [3439] vs 60.3% [4236]) and of β blockers (63.3% [2988] vs 53.2% [3737]) was higher in patients with ICM. Rates of all-cause and cardiovascular death per 100 patient-years were significantly higher in the ICM group (all-cause death: ICM, 10.2; 95% CI, 9.2-11.1; NICM, 7.0; 95% CI, 6.4-7.6; cardiovascular death: ICM, 5.1; 95% CI, 4.5-5.9; NICM, 2.9; 95% CI, 2.5-3.4). Stroke/systemic embolism rates tended to be higher in ICM groups compared with NICM groups (ICM, 2.0; 95% CI, 1.6-2.5; NICM, 1.5; 95% CI, 1.3-1.9). Major bleeding rates were significantly higher in the ICM group (1.1; 95% CI, 0.8-1.4) compared with the NICM group (0.7; 95% CI, 0.5-0.9).

CONCLUSIONS AND RELEVANCE Patients with ICM received oral anticoagulants with or without antiplatelet drugs less frequently and antiplatelets alone more frequently than patients with NICM, but they received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers more often than patients with NICM. All-cause and cardiovascular death rates were higher in patients with ICM than patients with NICM.

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Supplemental content

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Congestive heart failure (CHF) is commonly associated with atrial fibrillation (AF), and their combined presentation confers a worse prognosis than either condition alone.[1] Treatment of both conditions implies use of specific drugs for CHF plus antithrombotic agents for stroke prevention. In addition, management strategies and outcomes may be affected by the etiology of CHF, namely ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM) because the prescription of antithrombotic therapies might be different and could affect prognosis in terms of death, stroke/systemic embolism (SE), and bleeding.[2,3] The aim of our study was to assess the treatment strategies in terms of antithrombotic and CHF therapies and 1-year clinical outcomes in patients with newly diagnosed AF and concomitant CHF stratified by etiology (ICM vs NICM) enrolled in the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) registry.

Key Points

Question What are the management strategies and outcomes of patients with nonvalvular atrial fibrillation and concomitant congestive heart failure (ischemic or nonischemic cardiomyopathy)?

Findings In this cohort study of a registry that included 52 014 patients, patients with ischemic cardiomyopathy were less likely to receive oral anticoagulants with or without antiplatelet drugs and more likely to receive antiplatelet drugs alone than patients with nonischemic cardiomyopathy and had a worse outcome in terms of all-cause and cardiovascular death.

Meaning There is a need for physicians to opt for improved adherence to guidelines-directed treatment of both atrial fibrillation and concomitant congestive heart failure, particularly in patients with ischemic cardiomyopathy.

Methods

The design of the GARFIELD-AF registry was reported previously.[4,5] Briefly, men and women 18 years and older 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 and no valvular disease were eligible for inclusion.[5] Patients were enrolled prospectively and consecutively in 35 countries. When random site selection did not generate the required number of sites in a given country, the national lead investigator was asked to recommend sites to make up the numbers (18 of 1317 sites). The sites 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).[4,5] Except for Egypt and South Africa, there were no other participant countries from Africa.

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 (ie, vitamin K antagonists, nonvitamin K antagonist oral anticoagulants, and antiplatelets [AP]), and all cardiovascular drugs. Race/ethnicity was classified by the investigator in agreement with the patient.[5] Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were collected. The HAS-BLED scores were calculated excluding fluctuations in international normalized ratio.

Collection of follow-up data was performed every 4 months up to 12 months.[4,5] Standardized definitions for clinical events have been reported previously.[4,5] 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, England), and data queries were sent to study sites. The GARFIELD-AF data are captured using an electronic case report form. In accordance with the study protocol, 20% of all electronic case report forms were monitored against source documentation.[6] Data for the analysis in this report were extracted from the study database on October 18, 2017.

Definitions

Heart failure was defined as current/prior history of CHF or left ventricular ejection fraction (LVEF) of less than 40%. Congestive heart failure was diagnosed according to clinical criteria at entry and classified according to the New York Heart Association (NYHA) functional class. Information about LVEF assessed by 2-dimensional echocardiography was available in 73% of patients with CHF and was stratified as preserved LVEF when this was 40% or higher and as reduced LVEF when less than 40%. Ischemic cardiomyopathy was defined as patients with a history of coronary artery disease, including known chronic angina pectoris, previous myocardial infarction or unstable angina, coronary artery bypass grafting, or previous percutaneous coronary intervention with or without stenting. Nonischemic cardiomyopathy was the default diagnosis. Worsening HF was defined as progressive or acute decompensation of previously stable CHF. Vascular disease included coronary artery disease with a history of acute coronary syndromes and/or peripheral artery disease. Chronic kidney disease (CKD) was classified according to National Kidney Foundation guidelines into moderate-to-severe (stages 3-5), mild (stages 1 and 2), or none.

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQR) and categorical variables as frequencies

and percentages. Because studies with large sample sizes are prone to producing statistically significant findings in the presence of clinically irrelevant differences, no formal statistical tests are performed for the baseline tables. Instead, clinical interpretations are applied, and statistical tests are reserved for hypotheses of differences in outcomes.

All cohorts of patients had been followed up for a minimum of 1 year. Thus, events and time to events are censored at 365 days. Occurrence of major clinical outcomes was expressed as person-time event rates (per 100 person-years) and 95% confidence intervals. Person-year rates for the first occurrence of the event of interest were estimated 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.

Evaluation of 1-year outcomes by patients with ischemic vs nonischemic HF were performed both as unadjusted and adjusted analyses using Cox proportional hazards models. In addition to the unadjusted person-time event rates, the hazard ratios with 95% confidence intervals are provided for both unadjusted and adjusted results. Adjustment factors, as determined in previous models of the key outcomes, were age with spline knots at 48, 65, 79, and 88 years; sex; race/ethnicity; smoking status; diabetes; hypertension; history of bleeding; moderate-to-severe CKD; use of oral anticoagulation therapy (OAC) at baseline; type of AF; and heavy use of alcohol.

The association of type of HF with outcomes in patients who used AP therapy was also of interest. The inclusion of the main effect of AP alone vs AP therapy plus OAC and the interaction of ischemic vs NICM by AP alone vs AP plus OAC was evaluated in unadjusted and adjusted analyses. The adjustment factors included those listed previously, except OAC use, which appears in the treatment of interest. The test for interaction specifies whether the association between patients with ICM and NICM varies according to treatment received. Hazard ratios with 95% confidence intervals of the difference outcomes for patients with ICM vs NICM within each of the 2 treatment strategies are derived from this model. All statistical analyses were performed using SAS, version 9.4 (SAS Institute), while forest plots were created using SigmaPlot, version 12.5 (Microsoft). The log-rank test was used to compare the survival distribution rates between ICM and NICM groups. A *P* value of less than .05 was considered statistically significant.

Results

Baseline Characteristics

The population of this study included all 5 cohorts of the GARFIELD-AF registry (eFigure 1 in the Supplement), totaling 52 014 patients recruited between March 2010 and August 2016 and followed up prospectively for a minimum of 1 year. Detailed baseline characteristics of the population are reported in eTable 1 in the Supplement. The median age of the population was 71.0 years, and 22 987 of 52 013 (44.2%) were women. Concomitant CHF was present in 11 738 of 52 007 patients (22.5%), coronary artery disease in 11 232 of 52 007 (21.6%), and history of hypertension in 38 585 of 51 863 (73.4%). Prior stroke/transient ischemic attack was present in 5954 of 52 007 patients (11.4%), history of bleeding in 1317 (2.5%), diabetes in 11 540 (22.2%), and moderate-to-severe CKD in 5373 (11.7%). At enrollment, 4717 patients (9.1%) had ICM and 7021 (13.5%) had NICM (eTable 1 in the Supplement).

Compared with patients with NICM, patients with ICM were more frequently white (74.5% [3465 of 4651] vs 55.8% [3848 of 6897]) and less frequently non-Chinese Asian (12.8% [596] vs 29.5% [2035]), had a higher mean body weight (80.7 kg vs 77.2 kg), had a similar mean LVEF (45.9% vs 46.9%), had a higher rate of depressed LVEF (32.4% [1170 of 3606] vs 37.8% [1892 of 5005]), were less likely to have permanent or persistent AF (30.4% [1434 of 4717] vs 37.3% [2619 of 7021]), and more frequently had NYHA class III/IV CHF (37.0% [1468 of 3964] vs 28.8% [1589 of 5533]). In addition, compared with patients with NICM, patients with ICM were more likely to have carotid occlusive disease (4.3% [199 of 4608] vs 2.4% [169 of 6932]), history of stroke/transient ischemic attack (12.6% [596 of 4717] vs 9.7% [684 of 7021]), hypertension (84.6% [3985 of 4710] vs 73.1% [5121 of 7004]), hypercholesterolemia (55.7% [2530 of 4545] vs 34.0% [2303 of 6782]), type 2 diabetes (28.3% [1335 of 4717] vs 20.2% [1415 of 7021]), and moderate-to-severe CKD (16.2% [764 of 4717] vs 13.7% [960 of 7020]), had a higher mean CHA_2DS_2-VASc score (4.4 vs 3.8), and were treated more frequently in cardiology (74.5% [3514 of 4717] vs 68.5% [4812 of 7021]) (**Table 1**).

Antithrombotic Therapies

Oral anticoagulants alone or in combination with AP were prescribed in fewer patients with ICM than patients with NICM (alone: ICM, 31.5% [1443 of 4579]; NICM, 61.2% [4225 of 6898]; combined: ICM, 60.1% [2753 of 4579]; NICM, 73.7% [5082 of 6898]). Patients with ICM were more likely to receive AP alone than patients with NICM (34.4% [1576 of 4579] vs 15.5% [1071 of 6898]). Dual AP therapy was given in 580 of 4681 patients with ICM (12.4%) and in 103 of 6961 with NICM (1.5%). No antithrombotic drugs were prescribed in 250 of 4579 patients with ICM (5.5%) and 745 of 6898 with NICM (10.8%) (**Table 2**). The prescription patterns were remarkably similar across the various categories of risk of stroke as defined by CHA_2DS_2-VASc score (0-1, 2-4, and >4), with OAC with or without AP rates approximately 60% in patients with ICM vs 70% in patients with NICM and AP only rates approximately 30% in patients with ICM vs 15% in patients with NICM (**Figure 1**). The prescription patterns were also mostly similar in cardiology, internal medicine, and primary care settings; the rates of AC with or without AP were approximately 60% for patients with ICM and 74% for patients with NICM, and rates of AP were approximately 35% and 15%, respectively. There were too few patients in neurology and geriatrics settings to have a reliable picture of the prescription patterns (eFigure 2 in the Supplement). Lastly, in emergency departments, hospitals, and office settings, rates of AC with or without AP were approximately 60% in patients with ICM and 70% in patients with NICM, and rates of AP were approximately 30% and 15%, respectively. In anticoagulation clinics, most patients received AC with or without AP, primarily in the form of vitamin K antagonists (eFigure 3 in the Supplement).

Table 1. Baseline Characteristics of Patients With Ischemic and Nonischemic Cardiomyopathy

Characteristic	No. (%)	
	Ischemic Cardiomyopathy (n = 4717)	Nonischemic Cardiomyopathy (n = 7021)
Sex		
Male	2814 (59.7)	3892 (55.4)
Female	1903 (40.3)	3128 (44.6)
Age at diagnosis, y		
Mean (SD)	70.2 (10.6)	70.0 (12.3)
Median (IQR)	71.0 (63.0-78.0)	71.0 (62.0-79.0)
Race/ethnicity		
White	3465 (74.5)	3848 (55.8)
Hispanic/Latino	150 (3.2)	557 (8.1)
Afro-Caribbean	11 (0.2)	46 (0.7)
Asian (not Chinese)	596 (12.8)	2035 (29.5)
Chinese	337 (7.2)	267 (3.9)
Mixed/other	92 (2.0)	144 (2.1)
Height, cm		
Mean (SD)	167.7 (9.6)	165.5 (11.0)
Median (IQR)	168.0 (160.0-175.0)	165.0 (158.0-173.0)
Weight, kg		
Mean (SD)	80.7 (18.7)	77.2 (21.4)
Median (IQR)	80.0 (68.0-92.0)	75.0 (62.0-90.0)
BMI		
Mean (SD)	28.6 (5.8)	28.0 (6.4)
Median (IQR)	28.0 (25.0-32.0)	27.0 (24.0-31.0)
Pulse, bpm		
Mean (SD)	88.6 (25.1)	95.2 (27.6)
Median (IQR)	82.0 (70.0-100.0)	90.0 (75.0-112.0)
Systolic BP, mm Hg		
Mean (SD)	132.0 (19.7)	132.0 (20.9)
Median (IQR)	130.0 (120.0-142.0)	130.0 (120.0-144.0)
Diastolic BP, mm Hg		
Mean (SD)	79.8 (12.7)	80.2 (14.1)
Median (IQR)	80.0 (70.0-90.0)	80.0 (70.0-90.0)
LVEF, %		
Mean (SD)	46.9 (14.1)	45.9 (15.3)
Median (IQR)	48.0 (35.0-58.0)	45.0 (34.0-59.0)
LVEF category		
<40%	1170 (32.4)	1892 (37.8)
≥40%	2436 (67.6)	3113 (62.2)
Care setting specialty at diagnosis		
Internal medicine	794 (16.8)	1363(19.4)
Cardiology	3514 (74.5)	4812 (68.5)
Neurology	27 (0.6)	60 (0.9)
Geriatrics	9 (0.2)	43 (0.6)
Primary care/general practice	373 (7.9)	743 (10.6)
Type of AF diagnosed		
Permanent	710 (15.1)	1126 (16.0)
Persistent	724 (15.3)	1493 (21.3)
Paroxysmal	1025 (21.7)	1395 (19.9)
New onset (unclassified)	2258 (47.9)	3007 (42.8)

(continued)

Table 1. Baseline Characteristics of Patients With Ischemic and Nonischemic Cardiomyopathy (continued)

Characteristic	No. (%)	
	Ischemic Cardiomyopathy (n = 4717)	Nonischemic Cardiomyopathy (n = 7021)
Congestive heart failure NYHA class		
I	544 (13.7)	1281 (23.2)
II	1952 (49.2)	2663 (48.1)
III	1285 (32.4)	1348 (24.4)
IV	183 (4.6)	241 (4.4)
Unknown, No.	294	606
Coronary artery disease	4365 (92.5)	NA
Acute coronary syndrome	1695 (36.7)	NA
Vascular disease	2200 (47.3)	327 (4.7)
Coronary artery bypass graft	490 (10.8)	NA
PCI with stenting	1041 (22.1)	NA
Carotid occlusive disease	199 (4.2)	169 (2.4)
Stroke/TIA	596 (12.6)	684 (9.7)
Systemic embolization	26 (0.6)	45 (0.6)
History of bleeding	160 (3.4)	193 (2.8)
History of hypertension	3985 (84.6)	5121 (73.1)
Hypercholesterolaemia	2530 (55.7)	2303 (34.0)
Diabetes		
Type 1	52 (1.1)	62 (0.9)
Type 2	1335 (28.3)	1415 (20.2)
Alcohol consumption		
Abstinent	2284 (55.3)	3411 (55.8)
Light	1456 (35.3)	1822 (29.8)
Moderate	317 (7.7)	667 (10.9)
Heavy	70 (1.7)	216 (3.5)
Unknown, No.	590	905
Smoker		
No	2727 (62.0)	4229 (65.4)
Former smoker	1155 (26.3)	1473 (22.8)
Current smoker	518 (11.8)	769 (11.9)
Chronic renal disease		
I	816 (20.0)	1545 (24.9)
II	639 (15.6)	882 (14.2)
III	635 (15.5)	793 (12.8)
IV	95 (2.3)	129 (2.1)
V	34 (0.8)	38 (0.6)
None	1868 (45.7)	2821 (45.4)
Moderate-to-severe CKD	764 (16.2)	930 (13.7)
CHA_2DS_2-VASc score		
Mean (SD)	4.4 (1.6)	3.8 (1.5)
Median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)
HAS-BLED score		
Mean (SD)	1.8 (0.9)	1.4 (0.9)
Median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-2.0)

Abbreviations: AF, atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CKD, chronic kidney disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Table 2. Baseline Treatments (GARFIELD-AF Cohorts 1 to 5) and AF Management at Diagnosis (GARFIELD-AF Cohorts 3 to 5)

Treatment	No. (%)	
	Ischemic Cardiomyopathy	Nonischemic Cardiomyopathy
Cohorts 1 to 5		
No.	4717	7021
Antithrombotic drugs		
AC	1443 (31.5)	4225 (61.2)
AC with or without AP	2753 (60.1)	5082 (73.7)
VKA	880 (19.2)	2440 (35.4)
VKA+AP	887 (19.4)	627 (9.1)
FXA	391 (8.5)	1342 (19.5)
FXA+AP	318 (6.9)	173 (2.5)
DTI	172 (3.8)	443 (6.4)
DTI+AP	105 (2.3)	57 (0.8)
AP only	1576 (34.4)	1071 (15.5)
None	250 (5.5)	745 (10.8)
Unknown, No.	138	123
Heart failure/hypertension drugs		
ACEi/ARBs	3439 (72.9)	4236 (60.3)
β-Blockers	2988 (63.3)	3737 (53.2)
Loop and other diuretics	2753 (58.4)	3897 (55.5)
MRA	979 (20.8)	1225 (17.4)
Digoxin and other digitalis	471 (10.0)	662 (9.4)
Other drugs of interest		
Oral antidiabetics	461 (13.8)	416 (9.3)
Insulin	241 (7.2)	153 (3.4)
α-Blockers	98 (2.9)	131 (2.9)
Cohorts 3 to 5		
No.	3332	4459
AF treatment/strategy initiated		
None declared	194 (6.0)	398 (9.2)
Rhythm control	1111 (34.5)	939 (21.7)
Rate control	1262 (39.2)	2197 (51.0)
Both	651 (20.2)	777 (18.0)
Unknown, No.	114	148
Cardioversion		
No	2815 (86.5)	3787 (88.4)
Yes	440 (13.5)	498 (11.6)
Current[a]	124 (33.8)	234 (62.4)
Pharmacological[a]	242 (66.1)	141 (37.6)
Antiarrhythmic drugs		
Class Ia	22 (0.7)	22 (0.5)
Class Ic	59 (1.8)	113 (2.5)
Class II (β-blockers)	1492 (44.8)	1842 (41.3)
Class III	568 (17.1)	358 (8.0)
Class IV (calcium-channel blocker)	395 (11.9)	608 (13.6)
Class V (digoxin and other digitalis)	624 (18.7)	939 (21.1)

Abbreviations: AC, anticoagulants; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; AP, antiplatelets; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; MRA, mineralocorticoid receptor antagonist; VKA, vitamin K antagonist.

[a] Patients submitted to cardioversion during the first month after inclusion in GARFIELD-AF. Patients who underwent both current and pharmacologic cardioversion are not reported here.

Treatment of AF

Complete information about treatment and drug therapies of AF were available for the last 3 cohorts of 34 854 patients (Table 2), of whom 3332 had ICM and 4459 had NICM. Rate control was attempted more frequently than rhythm control in both groups. The uptake of antiarrhythmic drugs was mostly similar in both groups, except that class 3 drugs were more frequently used in patients with ICM. Cardioversion was attempted in a minority of patients, at a similar rate in both groups. Patients with NICM were more likely to receive electric cardioversion than patients with ICM.

HF Drugs

The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was higher in patients with ICM vs patients with NICM (72.9% [3439 of 4717] vs 60.3% [4236 of 7021]). The same was observed for β-blocker use (63.3% [2988 of 4717] vs 53.2% [3737 of 7021], respectively). The use of mineralocorticoid receptor antagonists, loop diuretics, and digoxin and other digitalis was similar between the 2 groups (Table 2).

Clinical Outcomes at 1-Year Follow-up

Incidence rates per 100 person-years of all-cause and cardiovascular death were significantly higher in patients with ICM compared with NICM (all-cause death: ICM, 10.2; 95% CI, 9.2-11.1; NICM, 7.0; 95% CI, 6.4-7.6; $P<.001$; cardiovascular death: ICM, 5.1; 95% CI, 4.5-5.9; NICM, 2.9; 95% CI, 2.5-3.4; $P<.001$) (**Table 3** and **Figure 2**A). Rates of noncardiovascular death were similar in both cardiomyopathy groups.

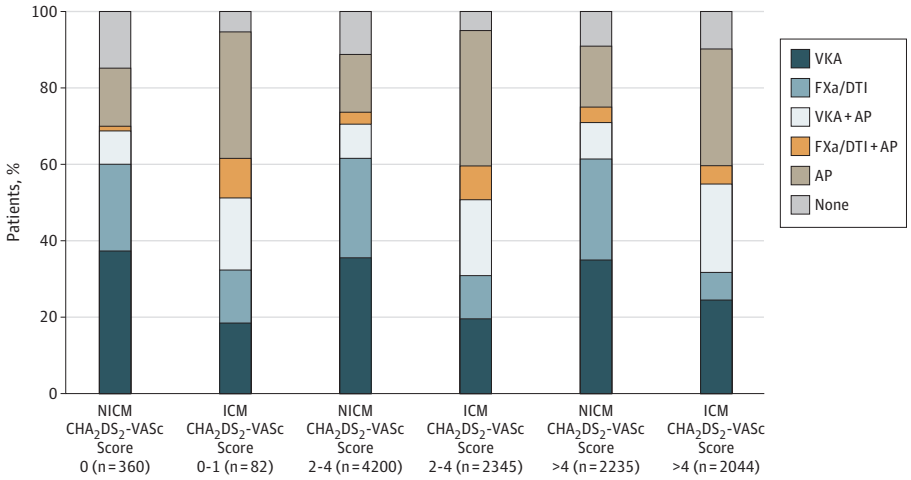
Incidence rates of stroke/SE tended to be higher in the ICM group (2.0; 95% CI, 1.6-2.5) compared with the NICM group (1.5; 95% CI, 1.3-1.9). Incidence rates of major bleeding were significantly higher in the ICM group than in the NICM group. New acute coronary syndromes occurred at a significantly higher rate in the ICM group (1.9; 95% CI, 1.5-2.3) compared with the NICM group (0.7; 95% CI, 0.6-1.0). Worsening CHF occurred at similar rates in both ICM and NICM groups.

The most frequent classified causes of cardiovascular death were CHF, unwitnessed/sudden death, and myocardial infarction, which tended to be balanced in the 2 CHF groups. The causes of deaths classified as noncardiovascular were also balanced between the ICM and NICM groups and were mostly linked to malignancy, respiratory failure, and infection/sepsis. Nevertheless, there was some imbalance in the rates of other and undetermined causes of death between the 2 groups; in particular, the rate of undetermined cause of death was substantially higher in ICM group (eTable 2 in the Supplement).

AP Therapy and 1-Year Clinical Outcomes

The adjusted hazard ratios for ICM vs NICM in patients who received AP therapy and in patients who did not receive AP therapy at enrollment are presented for mortality, stroke/SE, and major bleeding in Figure 2B. Ischemic cardiomyopathy was significantly associated with higher rates of all-cause death, cardiovascular death, and major bleeding in patients who did not receive AP therapy at enrollment. No such excess of risk in ICM vs NICM was observed among patients who received AP therapy.

Figure 1. Percentage of Prescription of Anticoagulants and Antiplatelets (AP) and Their Combination in Ischemic Cardiomyopathy (ICM) and Nonischemic Cardiomyopathy (NICM) According to CHA_2DS_2-VASc Score



DTI indicates direct thrombin inhibitor; FXA, factor Xa inhibitor; VKA, vitamin K anticoagulation.

Table 3. Incidence Rates per 100 Person-Years of Clinical Outcomes at 1-Year Follow-up

Variable	Ischemic Cardiomyopathy (n = 4717)	Nonischemic Cardiomyopathy (n = 7021)	*P* Value[a]
All-cause mortality			
No. (%)	443 (9.4)	456 (6.5)	NA
Incidence rate (95% CI)	10.2 (9.2-11.1)	7.0 (6.4-7.6)	<.001
Cardiovascular mortality			
No. (%)	224 (4.7)	191 (2.7)	NA
Incidence rate (95% CI)	5.1 (4.5-5.9)	2.9 (2.5-3.4)	<.001
Noncardiovascular mortality			
No. (%)	102 (2.2)	157 (2.2)	NA
Incidence rate (95% CI)	2.3 (1.9-2.9)	2.4 (2.1-2.8)	.84
Undetermined cause of mortality			
No. (%)	117 (2.5)	108 (1.5)	NA
Incidence rate (95% CI)	2.7 (2.2-3.2)	1.7 (1.4-2.0)	<.001
Stroke/SE			
No. (%)	87 (1.8)	99 (1.4)	NA
Incidence rate (95% CI)	2.0 (1.6-2.5)	1.5 (1.3-1.9)	.06
Major bleeding			
No. (%)	46 (1.0)	44 (0.6)	NA
Incidence rate (95% CI)	1.1 (0.8-1.4)	0.7 (0.5-0.9)	.03
New ACS			
No. (%)	81 (1.7)	48 (0.7)	NA
Incidence rate (95% CI)	1.9 (1.5-2.3)	0.7 (0.6-1.0)	<.001
Worsening CHF			
No. (%)	265 (5.6)	444 (6.3)	NA
Incidence rate (95% CI)	6.3 (5.6-7.1)	7.1 (6.5-7.8)	.79

Abbreviations: ACS, acute coronary syndrome; CHF, chronic heart failure; NA, not applicable; SE, systemic embolism.

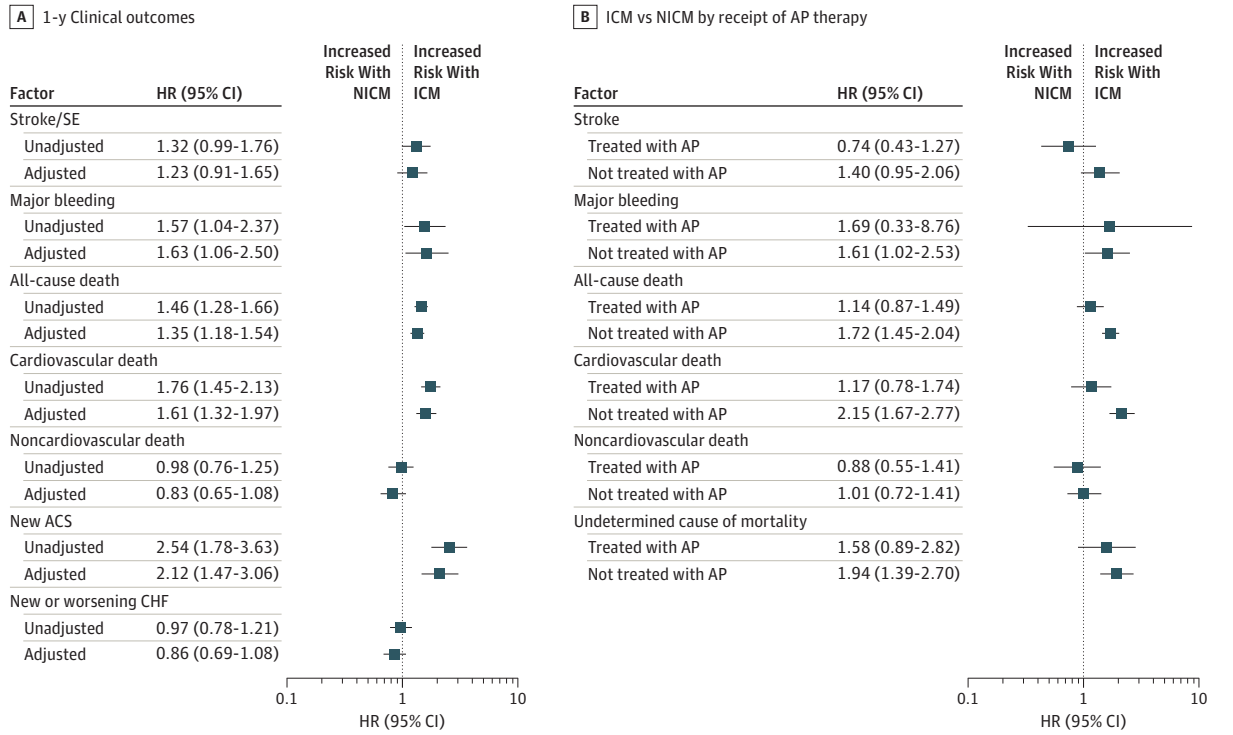
[a] *P* value is log-rank test.

Discussion

The main findings of this study are that patients with ICM and patients with NICM and concomitant AF substantially differ in terms of baseline characteristics, functional impairment, LV function impairment, and treatments that may be significantly associated with outcomes. They also significantly differ in terms of outcome, with higher rates of death, major bleeding, and new acute coronary syndromes. The known causes of cardiovascular death were proportionally mostly similar in both groups, including death from ischemic stroke (eTable 2 in the Supplement).

In patients without AF, a higher risk of death in patients with ICM compared with patients with NICM was inconsistently reported in observational studies, in retrospective analy-

Figure 2. Unadjusted and Adjusted Hazard Ratios (HRs) for 1-Year Outcomes



A, Unadjusted and adjusted HRs for clinical outcomes at 1 year. Rates were adjusted for age, sex, race/ethnicity, smoking, diabetes, hypertension, history of bleeding, moderate-to-severe kidney disease, type of medication, type of atrial fibrillation, and heavy alcohol use. B, Adjusted HRs for patients with ischemic cardiomyopathy (ICM) vs patients with nonischemic cardiomyopathy (NICM) according to antiplatelet (AP) treatment. Rates were adjusted for age, sex, race/ethnicity, smoking, diabetes, hypertension, history of bleeding, moderate-to-severe kidney disease, type of atrial fibrillation, and heavy alcohol use. ACS indicates acute coronary syndrome; CHF, congestive heart failure; SE, systemic embolism.

ses of hospital records, and in reviews of randomized clinical trials.[7-13] The discrepancies between reports were thought to be associated with inconsistency in diagnosing ischemic CHF in the absence of rigorous discriminant definitions of ischemic and nonischemic CHF, with patient selection, or with imbalance in baseline characteristics, with more severe comorbidities in ischemic vs nonischemic CHF.[10] The poorer prognosis of ICM was attributed to differences in structural alterations between the 2 entities, with more regional wall motion abnormalities, asynchrony of LV contraction, extensive scar tissue, and poorer LV compliance in addition to a greater extent of coronary artery disease and residual ischemia in ICM vs NICM.[14]

A limited number of reports addressed the outcome of patients with CHF and concomitant AF. They showed that concomitant AF was associated with a higher risk of death in ICM only.[2,3] Atrial fibrillation in patients with ischemic heart disease may contribute to impaired myocardial perfusion, coronary vasoconstriction, and further deterioration of diastolic function. In addition, impaired myocardial perfusion is associated with electrical instability and a higher risk of sudden death.[15,16]

In this report, patients with ICM had more advanced deterioration of their cardiac condition, as shown by a higher NYHA functional class, a higher rate of depressed LV function (about two-thirds of patients with CHF had preserved LVEF, but patients with ICM had higher rates of reduced LVEF), and higher rates of comorbidities, particularly coronary artery disease and CKD, which might have contributed to a worse prognosis. Treatment strategy of AF and use of antiarrhythmic drugs were mostly similar in both groups, but there was some imbalance between the 2 groups regarding rate or rhythm control and use of class 3 antiarrhythmic drugs. Antithrombotic therapy was suboptimal in the ICM group compared with the NICM group, as shown by a much lower rate of anticoagulation with or without AP therapy and, consequently, a high rate of AP alone prescription even in patients without indication for AP therapy, as already reported[17] (Table 2). This may have had a detrimental effect on the risk of death because anticoagulation was shown to be associated with a substantial reduction of the risk of death in previous reports.[18,19] In the Reduction of Atherothrombosis for Continued Health Registry (REACH) trial,[20] where the incidence of AF in patients with coronary artery disease was 12.5%, it was shown that only 53% of these patients were given anticoagulation therapy whereas 40% were receiving AP agents alone. Additionally, there were higher rates of heart failure and cardiovascular death in the AF population than in the non-AF population.

The reasons for inadequate antithrombotic treatment in the ICM group remain to be determined. These patients, often el-

derly, need treatments for stroke prevention, heart failure, and coronary disease, resulting in an extensive list of drugs, which may deter the physician from prescribing them all and deter the patient from complying with the prescription.[21] Physicians' adherence to guideline recommendations remains a matter of debate.[22,23] In a previous report of the GARFIELD registry,[19] physicians' decision was the most common reason for not prescribing OACs in patients with AF. Lack of adherence may have played a role because the implementation of guidelines was shown to have a favorable association with outcomes in other settings.[24,25] In this context, an intriguing fact needs to be mentioned. In patients who did not receive AP therapy, the risks of all-cause and cardiovascular death as well as the risk of major bleeding were significantly higher in those with ICM than in those with NICM; in contrast, in patients who did receive AP therapy, there was no excess of events in those with ICM (Figure 2B). This tends to confirm that AP therapy is associated with a more positive outcome in patients with ischemic heart disease. However, these data were generated from a nonprespecified subgroup analysis. As such, no firm conclusions can be derived, and these data are only hypothesis generating.

There was a substantial but not significant excess of stroke/SE and a significant excess of major bleeding risks in patients with ICM compared with patients with NICM (Table 3 and Figure 2A). Congestive heart failure without AF is associated with a higher risk of stroke, and the combination of CHF and AF further increases this risk irrespective of LV function (preserved or depressed) or of etiology (ischemic or nonischemic).[26-28] A higher mean CHA_2DS_2-VASc score and a higher incidence of carotid artery disease in the ICM group may also explain the excess of stroke/SE. Furthermore, as already mentioned, stroke prophylaxis was suboptimal in the ICM group, where twice as many patients received AP therapy alone compared with the NICM group. In addition, prescribing rates of OAC alone or in combination with AP therapy were substantially lower in patients with ICM than in those with NICM (Table 2). These prescription patterns were observed irrespective of CHA_2DS_2-VASc score, medical specialty, and care setting. Combination therapy is known to increase the risk of bleeding,[29,30] and AP therapy alone does not confer any protection against stroke/SE but increases bleeding risk.[31,32] This may explain the higher risk of major bleeding in patients with ICM in this study.

Finally, to our knowledge, this study is the first to assess the outcomes of ICM and NICM in patients with AF from an unselected prospective registry population representative of real life. Ischemic cardiomyopathy carried a poorer prognosis than NICM in terms of all-cause and cardiovascular death. It was also associated with a substantial but not significant excess of stroke/SE and significantly higher risk of bleeding. In addition, patients with ICM were suboptimally treated with regards to stroke prophylaxis, which may have affected outcomes. Polypharmacy and/or poor adherence to guideline-recommended therapies may explain the inadequacy of treatment in ischemic CHF.

Limitations

Our study had limitations. Ischemic cardiomyopathy was not defined by the investigator but retrospectively based on the history of coronary artery disease (ie, known chronic angina pectoris, previous myocardial infarction or unstable angina, coronary artery bypass grafting, or previous percutaneous coronary intervention with or without stenting), low LVEF, and signs/symptoms of CHF. Nevertheless, we cannot rule out that some patients in the NICM group had ischemic heart disease. The population included in this analysis is mostly made of white and Asian individuals, so the results may not be relevant for other racial/ethnic groups.

Conclusions

More than 22% of the population of patients with newly diagnosed AF included in the GARFIELD-AF registry had concomitant CHF, of whom around 40% had ICM. They were suboptimally given anticoagulation therapy and more often received AP therapy alone or in combination with anticoagulants. These patients had worse outcomes than patients with NICM in terms of all-cause and cardiovascular death despite the fact that they were more likely to receive angiotensin-converting enzyme inhibitors/angiotensin receptor blockers than patients with NICM. These findings should prompt physicians to opt for active treatment of both AF and CHF, particularly in patients with ICM.

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Murakami Kinshiro Cardiovascular Internal Clinic, Sasebo-shi, Japan: Kinshiro Murakami; Wakasa Medical Clinic, Kanazawa-shi, Japan: Yutaka Wakasa; Yamasawa Naika, Koriyama-shi, Japan: Masanori Yamasawa; Maekawa Medical Clinic, Yokohama-shi, Japan: Hiromitsu Maekawa; Kokankai Kokan Clinic, Kawasaki-shi, Japan: Sumihisa Abe; Kikokai Kihara Cardiovascular Internal Medicine Clinic, Asahikawa-shi, Japan: Hajime Kihara; Close To You Est Clinic, Hirosaki-shi, Japan: Satoru Tsunoda; Seiwakai Nishiarai Heart Center Hospital, Adachi-ku, Japan: Katsumi Saito; Tachibana-Iiyama Hospital, Kagoshima-shi, Japan: Hiroki Tachibana; Showakai Imakiire General Hospital, Kagoshima-shi, Japan: Ichiro Oba; Yushikai Kuwahata Clinic, Kagoshima-shi, Japan: Takashi Kuwahata; Hakuaikai Makiminato Central Hospital, Urasoe-shi, Japan: Satoshi Higa; Doshinkai Gushiken Junkanki Naika, Urasoe-shi, Japan: Masamichi Gushiken; Eto Clinic, Nichinan-shi, Japan: Takuma Eto; Shonankai Shonan Hospital, Okinawa-shi, Japan: Hidetoshi Chibana; Fujisawa Clinic, Itoshima-shi, Japan: Kazuaki Fujisawa; Seishinkai Inoue Hospital, Itoshima-shi, Japan: Yuhei Shiga; Sumi Junkankinaika Clinic, Oita-shi, Japan: Hirokuni Sumi; Chojukai Nagatomo Naika Junkankinaika Clinic, Kitakyushu-shi, Japan: Toshihisa Nagatomo; Tenyokai Chuo Clinic, Kagoshima-shi, Japan: Yoshihiko Atsuchi; Nagoshi Naika, Miyazaki-shi, Japan: Toshiro Nagoshi; Ojukai Sanno Naika, Aira-shi, Japan: Kazuhisa Sanno; Karinkai Murakamikarindoh Hospital, Fukuoka-shi, Japan: Fumihiro Hoshino; Yokota Naika, Miyazaki-shi, Japan: Naoto Yokota; Kanoya Medical Center Citizens' Health Plaza, Kanoya-shi, Japan: Masahiro Kameko; Tabuchi Naika Junkankika, Kikuchi-gun, Japan: Toshifumi Tabuchi; Ishizawa Junkankinaika, Ebino-shi, Japan: Munesumi Ishizawa; Hojunkai Fujiura Junkankinaika Clinic, Nichinan-shi, Japan: Yoshitake Fujiura; Seijinkai Ikeda Hospital, Kanoya-shi, Japan: Daisuke Ikeda; Seto Junkankinaika Clinic, Fukuoka-shi, Japan: Taku Seto; Oita Red Cross Hospital, Oita-shi, Japan: Tetsu Iwao; Kieikai Fukuoka Kieikai Hospital, Fukuoka-shi, Japan: Norio Ishioka; Omotokai Ohama Daiichi Hospital, Naha-shi, Japan: Koichi Oshiro; Tsuchida Clinic of Internal and Cardiovascular Medicine, Nagaoka-shi, Japan: Keizo Tsuchida; Hatori Clinic, Kawasaki-shi, Japan: Yutaka Hatori; Takeuchi Clinic, Kobe-shi, Japan: Motoshi Takeuchi; Takezawa Clinic (Nagoya), Nagoya-shi, Japan: Hiroto Takezawa; Jiaikai Imamura General Hospital, Kagoshima-shi, Japan: Shinjiro Nagano; Matsushirokai Hayato Spa Hospital, Kirishima-shi, Japan: Masaaki Iwaki; Nakamura Cardiovascular Clinic, Itoshima-shi, Japan: Yuichiro Nakamura; Sanyukai Saino Clinic, Tokorozawa-shi, Japan: Naomasa Miyamoto; Taguchi Junkankikanaika Clinic, Miyakonojo-shi, Japan: Toshifumi Taguchi; Ashida Medical Clinic, Tamba-shi, Japan: Ko Ashida; Yoshizawa Heart Clinic, Setagaya-ku, Japan: Naoto Yoshizawa; Agata Clinic, Obihiro-shi, Japan: Jun Agata; Matsukawa Heart Clinic, Edogawa-ku, Japan: Seishiro Matsukawa; Yuaikai Tomishiro Chuo Hospital, Tomigusuku-shi, Japan: Osamu Arasaki and Tetsuji Shinjo; Fukuoka Clinic, Nichinan-shi, Japan: Shuji Fukuoka; South Tokyo Heart Clinic, Machida-shi, Japan: Hirofumi Murakami; Mishima Naika Clinic, Kitamorokata-gun, Japan: Kazuya Mishima; Naha City Hospital, Naha-shi, Japan: Mamoru Manita; Kenshinkai Minamino Cardiovascular Hospital, Hachioji-shi, Japan: Yoshiki Hata; Caress Sapporo Hokko Memorial Clinic, Sapporo-shi, Japan: Ichiro Sakuma; Tokyobay Urayasu Ichikawa Medical Center, Urayasu-shi, Japan: Kotaro Obunai; Takamura Naika Iin, Otaru-shi, Japan: Ichiro Takamura; Akutsu Naika Iin, Otaru-shi, Japan: Mitsuyuki Akutsu; Unoki Junkankinaika Iin, Miyakonojo-shi, Japan: Toshihide Unoki; Kochikukai Go Neurosurgical Clinic, Chikushi-gun, Japan: Yoshinori Go; Shinseikai Ikemura Internal Medicine Clinic, Miyakojima-shi, Japan: Makoto Ikemura; Miike Junkankika Naika Iin, Kusu-gun, Japan: Shoji Morii; Tokachi Heart Clinic, Kato-gun, Japan: Shigeru Marusaki; Doi Naika Junkankika, Miyazaki-shi, Japan: Hideo, Doi; Tanaka Junkankinaika Clinic, Kobayashi-shi, Japan: Mitsuru Tanaka; 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Murata Clinic, Sanyoonoda-shi, Japan: Kazuya Murata; Shimoyama Clinic, Yonago-shi, Japan: Masaki Shimoyama; Jisshokai Nakatsuka Naika, Hofu-shi, Japan: Masami Nakatsuka; Asakurashinryojo Asakura Clinic, Imabari-shi, Japan: Yutaka Kitami; Soyokaze Cardiovascular Medicine and Diabetes Care, Matsuyama-shi, Japan: Yoichi Nakamura; Shogen Naika Clinic, Sendai-shi, Japan: Hiroshi Oda; Tojukai Ito Naika Iin, Shimonoseki-shi, Japan: Rikimaru Oyama; Ageta Naika Clinic, Nichinan-shi, Japan: Masato Ageta; Mita Medical-Cardiovascular Clinic, Sapporo-shi, Japan: Teruaki Mita; Nagao Naika Junkanki Clinic, Sapporo-shi, Japan: Kazuhiko Nagao; Mito Naika Junkanki Clinic, Sapporo-shi, Japan: Takafumi Mito; Saito Naika Clinic, Hakodate-shi, Japan: Tsutomu Saito; Juntenkai Teshima Clinic, Kure-shi, Japan: Junichi Minami; Yotsuba Circulation Clinic, Matsuyama-shi, Japan: Mitsunori Abe; Fujii Heart Clinic, Kurashiki-shi, Japan: Masako Fujii; Okawa Naika, Kochi-shi, Japan: Makoto Okawa; Kawaguchi Heart Clinic, Kawaguchi-shi, Japan: Tsuneo Fujito; Aishin Clinic, Yachiyo-shi, Japan: Toshiya Taniguchi; Gyokushinkai Kashima Heart Clinic, Kamisu-shi, Japan: Tenei Ko; Hakushinkai Hiro Clinic, Takasaki-shi, Japan: Hiroshi Kubo; Chiba Heart Clinic, Chiba-shi, Japan: Mizuho Imamaki; Heart Clinic, Tatebayashi-shi, Japan: Masahiro Akiyama; Ueda Heart Clinic, Tatsuno-shi, Japan: Takashi Ueda; Dobashi Naika Iin, Sendai-shi, Japan: Hironori Odakura; Inagaki Clinic, Itami-shi, Japan: Masahiko Inagaki; Katsube Clinic, Nishinomiya-shi, Japan: Yoshiki Katsube; Nakata Naika Clinic, Nishinomiya-shi, Japan: Atsuyuki, Nakata; Tojo Clinic, Kato-shi, Japan: Shinobu Tomimoto; Juzenkai Tateyama Junkankinaika Geka, Tateyama-shi, Japan: Mitsuhiro Shibuya; Kaiseikai Nakano Hospital, Shibukawa-shi, Japan: Masayuki Nakano; Ito Cardiovascular Clinic, Saiki-shi, Japan: Kenichiro Ito; Matsuta Heart Clinic, Yamatokoriyama-shi, Japan: Masahiro Matsuta; Yi Yuan Hui Ishiguro Clinic, Gifu-shi, Japan: Motoyuki Ishiguro; Minagawa Clinic, Gifu-shi, Japan: Taro Minagawa; Wada Clinic (Gunma), Tomioka-shi, Japan: Masamichi Wada; Mukawa Heart Clinic, Ogaki-shi, Japan: Hiroaki Mukawa; Mizuguchi Clinic, Suzuka-shi, Japan: Masato Mizuguchi; Kosumosukai Okuda Clinic, Ube-shi, Japan: Fumio Okuda; Meihokai Meiho Clinic, Tsuruga-shi, Japan: Teruaki Kimura; Keiyukai Taga Naika Junkankika Iin, Fukui-shi, Japan: Kuniaki Taga; Techigawara Clinic, Koriyama-shi, Japan: Masaaki Techigawara; Asunarokai Igarashi Clinic, Shirakawa-shi, Japan: Morio Igarashi; HAL Clinic, Niigata-shi, Japan: Hiroshi Watanabe; Seo Naika Clinic, Osaka-shi, Japan: Toshihiko Seo; Hiramitsu Heart Clinic, Nagoya-shi, Japan: Shinya Hiramitsu; Yuaikai Higashi Junkanki Clinic, Toyohashi-shi, Japan: Hiroaki Hosokawa; Hoshiai Clinic, Owariasahi-shi, Japan: Mitsumoto Hoshiai; Hibino Naika Clinic, Toyota-shi, Japan: Michitaka Hibino; Miyagawa Clinic, Nisshin-shi, Japan: Koichi Miyagawa; Heart Naika Clinic, Yatomi-shi, Japan: Hideki Horie; Wakeikai Sugishita Iin, Gujo-shi, Japan: Nobuyoshi Sugishita; Meisei Shiga Clinic, Obu-shi, Japan: Yukio Shiga; Heart Clinic Kokoro, Koka-shi, Japan: Akira Soma; Neya Naika Clinic, Itabashi-ku, Japan: Kazuo Neya; Onga Hospital, Onga-gun, Japan: Tetsuro Yoshida; Akahane Clinic, Nagano-shi, Japan: Kunio Akahane; Shofukai Naito Hospital, Kurume-shi, Japan: Sen Adachi; Takanaka Clinic, Hamamatsu-shi, Japan: Chiei Takanaka; Ueda Neurosurgery, Miyazaki-shi, Japan: Takashi Ueda; Matsui Clinic, Hamamatsu-shi, Japan: Saori Matsui; Heart Clinic Kanda, Okazaki-shi, Japan: Hirofumi Kanda; Kaneko Naika Junkankika Clinic, Hamamatsu-shi, Japan: Masanori Kaneko; Nagasaka Heart Clinic, Hamamatsu-shi, Japan: Shiro Nagasaka; Taguchi Naika Junkankika Iin, Hamamatsu-shi, Japan: Atsushi Taguchi; Nitobe Memorial Nakano General Hospital, Nakano-ku, Japan: Shuta Toru and Kazuyuki Saito and Akiko Miyashita and Hiroki Sasaguri; Osaka General Hospital of West Japan Railway Company, Osaka-shi, Japan: Jin Nariyama and Hiroyuki Miyamoto and Yusuke Nishida and Tatsuya Suga and Hiroki Nagata; Hatsuno Clinic, Iruma-gun, Japan: Taketo Hatsuno; Iwase Internal Medicine Cardiology Clinic, Shibuya-ku, Japan: Takash Iwase; Itsukikai Heart Clinic, Katsushika-ku, Japan: Kazuki Sato; Chikamorikai Chikamori Hospital, Kochi-shi, Japan: Kazuya Kawai; Jinikai Makita General Hospital, Ota-ku, Japan: Tomobumi Kotani; Tsuji Clinic, Toyonaka-shi, Japan: Tsuyoshi Tsuji; Sakai Medical Clinic, Higashiosaka-shi, Japan: Hirosumi Sakai; Nishino Clinic, Kochi-shi, Japan: Kiyoshi Nishino; Tachikawa IM Clinic, Tachikawa-shi, Japan: Kenichi Ikeda; Maeda Naika Iin, Niigata-shi, Japan: Kazuo Maeda; Murao Shinryojo, Neyagawa-shi, Japan: Tomohiro Shinozuka; Inoue Cardiovascular Clinic, Oita-shi, Japan: Takeshi Inoue; Kawakami Clinic, Ota-shi, Japan: Koichi Kawakami; Kitazumi Clinic, Itabashi-ku, Japan: Hiromichi Kitazumi; Takagi Cardiology Clinic, Kyoto-shi, Japan: Tsutomu Takagi; Hamaoka Clinic, Nishinomiya-shi, Japan: Mamoru Hamaoka; Kojima Clinic, Odawara-shi, Japan: Jisho Kojima; Sasaki Heart Clinic, Shizuoka-shi, Japan: Akitoshi Sasaki; Ohashi Cardiovascular & Internal Medicine Clinic, Fukuoka-shi, Japan: Yoshihiro Tsuchiya; Tokyo Tenshi Hospital, Hachioji-shi, Japan: Tetsuo Betsuyaku; Hiratsuka Kyosai Hospital, Hiratsuka-shi, Japan: Koji Higuchi; Honda Clinic, Izumo-shi, Japan: Masaaki Honda; Hasegawa Outpatients Clinic for Cardiovascular Disease, Takamatsu-shi, Japan: Koichi Hasegawa; Baba Clinic, Nishitokyo-shi, Japan: Takao Baba; Mineoi Clinic, Matsuyama-shi, Japan: Kazuaki Mineoi; Saien Cardiovascular Medicine Clinic, Morioka-shi, Japan: Toshihiko Koeda; Hirasawa Cardiovascular Medicine Clinic, Asahikawa-shi, Japan: Kunihiko Hirasawa; Sunomata Clinic, Ogaki-shi, Japan: Toshihide Kumazaki; Nakagomi Medical Clinic, Akita-shi, Japan: Akira Nakagomi; Otaki Cardiology Clinic, Bunkyo-ku, Japan: Eiji Otaki; Shindo Clinic, Amagasaki-shi, Japan: Takashi Shindo; Chiyo Clinic, Kitakyushu-shi, Japan: Hiroyoshi Hirayama; Toyoda Heart Clinic, Iwata-shi, Japan: Chikako Sugimoto; Yamagishi Medical Clinic, Yamaguchi-shi, Japan: Takashi Yamagishi; Orange Clinic, Yokohama-shi, Japan: Ichiro Mizuguchi; Nico Nico Heart Clinic, Higashimatsuyama-shi, Japan: Kazunori Sezaki; Niwa Medical Clinic, Kyoto-shi, Japan: Isamu Niwa; Takenaka Clinic, Kyoto-shi, Japan: Ken Takenaka; Nakatani Clinic, Yao-shi, Japan: Osamu Iiji; Taya Clinic, Tsuchiura-shi, Japan: Koichi Taya; Tachikawa General Hospital, Nagaoka-shi, Japan: Hitoshi Kitazawa; Okinawa Tokushukai Chiba Tokushukai Hospital, Funabashi-shi, Japan: Osamu Ueda; Kakuda Clinic, Kahoku-shi, Japan: Hirokazu Kakuda; Ono Medical Clinic, Koto-ku, Japan: Takuya Ono; Oriso Internal Medicine Cardiology Clinic, Ninohe-shi, Japan: Seizo Oriso; Odori Kamata Medicine Clinic, Morioka-shi, Japan: Junya Kamata; Gakuen Heart Clinic, Machida-shi, Japan: Toshihiko Nanke; Miyanomori Memorial Hospital, Sapporo-shi, Japan: Itaru Maeda and Takashi Kawamoto; Sakaemachi Clinic, Tottori-shi, Japan: Yoshifusa Matsuura; JR Hiroshima Hospital, Hiroshima-shi, Japan: Hiroki Teragawa and Yuichi Fujii and Shuichi Nomura and Tomohiro Ueda; Kosekai Iwatsuki-minami Hospital, Saitama-shi, Japan: Yasuyuki Maruyama; Takei Medical Clinic, Odawara-shi, Japan: Kazuo Takei; Horie Clinic, Omihachiman-shi, Japan: Hajime Horie; Clinic Kakehashi, Nagoya-shi, Japan: Tetsutaro Kito; Asuka Clinic, Nakano-ku, Japan: Hiroshi Asano; Matsushita Medical Clinic, Toyonaka-shi, Japan: Koji Matsushita; Nakamura Medical Clinic, Suita-shi, Japan: Masaichi Nakamura; Washizuka Clinic, Kamo-shi, Japan: Takashi Washizuka; Yoshida Heart Clinic, Hiroshima-shi, Japan: Tomoki Yoshida; Sawano Clinic, Yokohama-shi, Japan: Masato Sawano and Koji Matsushita; Arima Shinichi Clinic, Kagoshima-shi, Japan: Shinichi Arima; Kanoya Heart Center, Kanoya-shi, Japan: Hidekazu Arai; Iwamoto Medical Clinic, Zentsuji-shi, Japan: Hisanori Shinohara; Takai Clinic, Kawachinagano-shi, Japan: Hiroyuki Takai; Furukawa Medical Clinic, Nakatsu-shi, Japan: Nobufusa Furukawa; Ota Shinryojo, Awa-shi, Japan: Akira Ota; Yamamoto Naika, Sakai-shi, Japan: Kentaro Yamamoto; Ebetsu City Hospital, Ebetsu-shi, Japan: Kenji Aoki and Masahiko Abe and Rikiya Shinohe; Yamamoto Clinic (Shiga), Moriyama-shi, Japan: Taku Yamamoto; Kasai Naika Junkanki Clinic, Nerima-ku, Japan: Takeaki Kasai; Suzuki Medical Clinic, Minamiawaji-shi, Japan: Shunji Suzuki; KKR Tohoku Kosai Hospital, Sendai-shi, Japan: Kikuyo Takahashi and Shu Suzuki; Sakakibarakosekai Shinjuku Mitsui Building Clinic, Shinjuku-ku, Japan: Nitaro Shibata; Omori Internal Medicine Cardiology Clinic, Fukushima-shi, Japan: Masayuki Watanabe St Luke's International Hospital, Chuo-ku, Japan: Hiroyuki Niinuma and Yasuhiro Yokoyama and Hirotsugu Mitsuhashi and Ryo Nakazato and Takeaki Shirai and Yumi Shiina and Atsushi Mizuno and Toru Adachi and Taku Asano and Ikki Komatsu and Masahiro Yamazoe and Yosuke Nishihata and Yosuke Nishihata and Yutaro Nishi; Yamaichi Building Medical Clinic, Adachi-ku, Japan: Toru Arino; Okuyama Clinic, Murayama-shi, Japan: Masaki Okuyama; Wakiyama Clinic, Karatsu-shi, Japan: Tetsushi Wakiyama; Juntendo University Hospital, Bunkyo-ku, Japan: Tomoko, Kato; Sasagawa Clinic, Shibata-shi, Japan: Yasuo Sasagawa; Shuri Jokamachi Clinic Daiichi, Naha-shi, Japan: Takeshi Tana and Ayano Ishihara; Internal Medicine Cardiology Hayashi Clinic, Asahikawa-shi, Japan: Yoshihito Hayashi; Ueki Hospital, Kumamoto-shi, Japan: Shinichi Hirota; Abe Clinic, Fukushima-shi, Japan: Yukihiko Abe; Hidamari no Mori Clinic, Japan: Yoshihiro Saito; Uchiyama Clinic, Japan: Hirohide Uchiyama; Takeda Heart Clinic, Japan: Hiroshi Takeda; Sakanoue Family Clinic, Japan: Hiroshi Ono; Hoden Clinic, Japan: Shuichi Tohyo; Clinic Hanazono Naika Iin, Japan: Naoto Hanazono; Miyajima Junkanki Naika, Japan: Seiichi Miyajima; Shimono Clinic, Japan: Hisashi Shimono; Koseikai Kizawa Memorial Hospital, Japan: Takuma Aoyama and Shusaku Miyata Shigekiyo Takahashi and Takahisa Ido and Makoto Yamaura and Keita Suzuki and Yuto Kumai and Gen Tanabe and Takehiro Yamada and Yuka Kawada; Shozawa Clinic, Japan: Yasunobu Shozawa; Kanetsu Chuo Hospital, Japan: Yawara Niijima; Sekishinkai Kawasaki Saiwai Hospital, Japan: Osamu Murai; Sekishinkai Kawasaki Saiwai Clinic, Japan: Osamu Murai; Teikyo University School of Medicine University Hospital, Mizonokuchi, Japan: Hideko Inaba; Nomura Medical Clinic, Japan: Katsumasa Nomura; Saiseikai Fukuoka General Hospital, Japan: Masatsugu Nozoe; Kenkokan Suzuki Clinic, Japan: Kazuo Suzuki; St Marianna University School of Medicine Hospital, Japan: Toshiyuki

Furukawa; Shiraiwa Medical Clinic, Japan: Toshihiko Shiraiwa; Grace Medical Clinic, Japan: Nobuhisa Ito; Nagai Clinic, Japan: Shunichi Nagai; Sendai Ekihigashi Clinic, Japan: Kiyoharu Sato; Dokkyo Medical University Koshigaya Hospital, Japan: Shiro Nakahara; Risshokoseikai Kosei General Hospital, Japan: Yujin Shimoyama; Kojinkai Tsuruhashi Clinic, Japan: Naoko Ohara; Omotecho Family Clinic, Japan: Teruhiko Kozuka; Okita Internal Medicine Clinic, Japan: Hideaki Okita; Endo Clinic (Miyagi), Japan: Masato Endo; Goto Iin, Japan: Tsutomu Goto; Hirose Clinic, Japan: Makoto Hirose; Harada Naika Clinic, Japan: Emiko Nagata; Kogakai Nakanishi Clinic, Japan: Noriyuki Nakanishi; Mori Clinic (Osaka), Japan: Toshizumi Mori; Seki Iin, Japan: Shuichi Seki; Okamoto Naika Iin, Japan: Katsuhiro Okamoto; Moriai Naika Clinic, Japan: Osamu Moriai; Emura Clinic, Japan: Yoko Emura; Fukuda Clinic (Tondabayashi), Japan: Tsuyoshi Fukuda; Date Clinic, Japan: Haruhiko Date; Meikikai Uchimura Kawakami Naika, Japan: Shuichi Kawakami; Ebino Sentoro Clinic, Japan: Sho Nagai; Ueyama Clinic, Japan: Yuya Ueyama; Fudo Clinic, Osaka-shi, Japan: Tetsuro Fudo; Ichikawa Iin, Japan: Mitsuru Imaizumi; Ogawa Naika Clinic, Japan: Takuo Ogawa; Hakujinkai Take Naika Clinic, Japan: Shunsuke Take; Ikeda Naika Hifuka Clinic, Japan: Hideo Ikeda; Nishioka Family Clinic, Japan: Hiroaki Nishioka; Ebisu Clinic, Japan: Norihiko Sakamoto; Ikeoka Clinic, Japan: Kiyomitsu Ikeoka; Wakaki Clinic, Japan: Nobuo Wakaki; Abe Junkanki Clinic, Japan: Masatake Abe; Kazahaya Clinic, Japan: Junji Doiuchi; Kira Cardiovascular Clinic, Japan: Tetsuya Kira; Tada Naika (Hakodate), Japan: Masato Tada; Eiseikai Tsuzaki Cardiovascular Anesthesiology Clinic, Japan: Ken Tsuzaki; Miura Clinic (Sapporo), Japan: Naoya Miura; Fujisawa Cardio-Vascular Clinic, Japan: Yasuaki Fujisawa; Furumoto Clinic, Japan: Wataru Furumoto; Rumoi Central Clinic, Japan: Susumu Suzuki; Honbetsu Cardiovascular Medicine Clinic, Japan: Akinori Fujisawa; Nakamurakai Nakamura Clinic, Japan: Ryosai Nakamura; Soseikai Komatsu Iin, Japan: Hiroyasu Komatsu; Seiwakai Fujiki Clinic, Japan: Rei Fujiki; Keiwakai Kawano Iin, Japan: Shuichi Kawano; Nishizawa Clinic, Japan: Keijiro Nishizawa; Kato Medical Clinic, Japan: Yoji Kato; Tsurugaoka Azuma Clinic, Japan: Junya Azuma; Koseikai Yotsubashi Clinic, Japan: Kiyoshi Yasui; Amano Naika, Japan: Toshio Amano; Yuwakai Sekine Iin, Japan, Yasuhiro Sekine; Honzawa Medical Center, Japan: Tatsuo Honzawa; Koshibu Clinic, Japan: Yuichiro Koshibu; SYU Cardiovascular Clinic, Japan: Yasuhide Sakamoto; Seta Clinic, Japan: Yukihiro Seta; Miyaguchi Clinic, Japan: Shingo Miyaguchi; Morishita Naika Iin, Japan: Kojuro Morishita; Yoshikawa Medical Clinic, Japan: Yasuko Samejima; Ishizawa Iin, Japan: Toyoshi Sasaki; Iseki Junkanki Naika, Japan: Fumiko Iseki; Clinica de Kobayashi, Japan: Toshiyuki Kobayashi; Kano Clinic, Japan: Hiroshi Kano; Akiyama Heart Clinic, Japan: Jaeyoung Kim; Hiroshi Yamaguchi Clinic, Japan: Hiroshi Yamaguchi; Takagi Naika Junkankika, Japan: Yoichi Takagi; Galatea Pearce Clinic, Japan: Yoko Onuki Pearce; Medical Clinic Suzuki, Japan: Yasuyuki Suzuki; Fukui Clinic, Japan: Takayuki Fukui; Nakayama Clinic (Kochi), Japan: Toru Nakayama; Kanai Clinic, Japan: Hideaki Kanai; Tenshindo Hetsugi Hospital, Japan: Yoshiyuki Kawano; Souseikai Fukuoka Mirai Hospital, Japan: Tetsuji Ino; Miyoshi Junkanki Clinic, Japan: Hironori Miyoshi; Jonan Koen Clinic, Japan: Yasufumi Miyamoto; Shigekiyo Naika Geka, Japan: Masahito Shigekiyo; Marugame Ono Clinic, Japan: Shimato Ono; Tenshindo Hetsugi Clinic, Japan: Yoshiyuki Kawano; Okamoto Iin, Japan: Yutaka Okamoto; Nijumarukai Ubukata Heart Clinic, Japan: Satoshi Ubukata; Juzenkai Kisarazu Heart Clinic, Japan: Kojiro Kodera; Shinseikai Oriuchi Clinic, Japan: Tatsuo Oriuchi; Sanikai Tsurukawa Kinen Hospital, Japan: Naoki Matsumoto; Inagaki Heart Clinic, Japan: Koichi Inagaki; Iseki Clinic, Japan: Atsushi Iseki; Yoshida Clinic Internal & Cardiology, Japan: Tomohiro Yoshida; Aishinkan Aishin Circulatory Organ Clinic, Japan: Toshihiro Goda; Katsuki Naika Clinic, Japan: Tsukasa Katsuki; Sato Naika Shonika Toriage Iin, Japan: Atsushi Sato; Chihaya Heart Clinic, Japan: Etsuo Mori; Tsubokura Clinic, Japan: Toshio Tsubokura; Hiro Clinic, Japan: Hiroshi Shudo; Hakuyokai Fujimoto Clinic, Japan: Shunichi Fujimoto; Katsuya Clinic, Japan: Tomohiro Katsuya; Furukawa Naika Clinic, Japan: Yoshiyuki Furukawa; Ichibangai Sogo Clinic, Japan: Hiroshi Hosokawa; Narumiyakai Narumiya Heart Clinic, Japan: Jun Narumi; Shozankai Yamamoto Naika Junkankika Iin, Japan: Kiichiro Yamamoto; Owari Cardiovascular & Diabetes Clinic, Japan: Masaki Owari; Keiaikai Inakura Clinic, Japan: Takuya Inakura; Anno Clinic, Japan: Takafumi Anno; Shirakawa Clinic, Japan: Kazuyuki Shirakawa.

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