Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes

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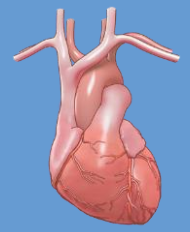
on behalf of G.L. Bakris, B. Pitt, R. Agarwal, P. Rossing, L.M. Ruilope, J. Butler, C.S.P. Lam, P. Kolkhof, L. Roberts, C. Tasto, A. Joseph, S.D. Anker, and the FIDELIO-DKD investigators

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

Disclosures

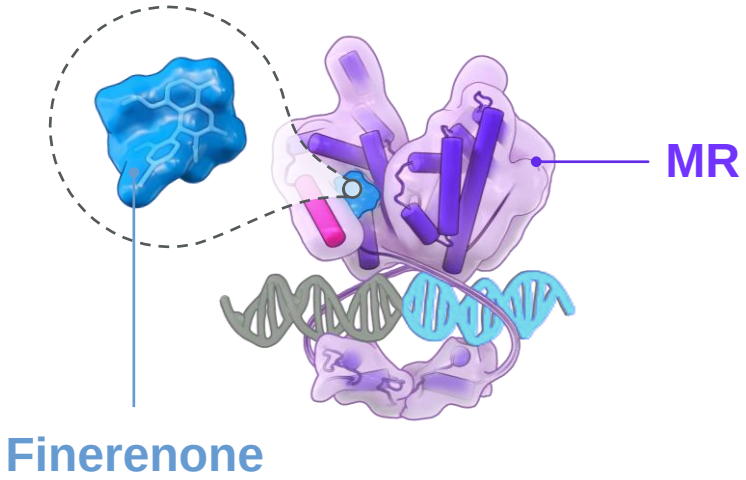
- **Lecture Fees and/or Committee Member:** of trials/registries sponsored by Boehringer Ingelheim, Bayer, Vifor, Novartis, Medtronic, Servier, Amgen
- **Research Grants:** European Union
- **Senior Consulting Editor:** *JACC – Heart Failure*
- **Past President:** Heart Failure Association of the ESC

MR-Induced Structural Cardiac Remodeling is a Potential Contributing Factor to Atrial Fibrillation



Patients with **CKD** and **T2D** are at **increased risk of AF**[1–4]

- **Atrial structural** or **electrical remodeling**, known to be induced in both patient populations, may be a contributing factor[1–4]



Preclinical evidence suggests that **MR overactivation** is associated with **structural cardiac remodeling** and **inhibition with MRAs reduces chronic inflammation and fibrosis**[5–7]

Finerenone is a novel, nonsteroidal, selective MRA shown to reduce the risk of CVD and CKD progression in patients with CKD and T2D[8,9]

AF, atrial fibrillation or flutter; CKD, chronic kidney disease; CVD, cardiovascular disease; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes

1. Alonso A, *et al*. *Circulation* 2011;123:2946–2953; 2. Seyed Ahmadi S, *et al*. *Cardiovasc Diabetol* 2020;19:9; 3. Qiu H, *et al*. *Front Physiol* 2018;9:1726; 4. Bohne LJ, *et al*. *Front Physiol* 2019;10:135; 5. Reil JC, *et al*. *Eur Heart J* 2012;33:2098–2108; 6. Lavall D, *et al*. *J Biol Chem* 2014;289:6656–6668; 7. Tsai CT, *et al*. *J Am Coll Cardiol* 2010;55:758–770; 8. Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229; 9. Filippatos G, *et al*. *Circulation* 2021;143:540–552

Finerenone May Be Effective in Lowering New-Onset AF in Patients With CKD and T2D

FIDELIO-DKD Trial Design

13,911 patients enrolled

48 countries

5,734 patients randomized

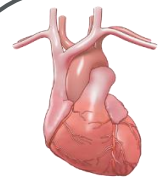
Run-in (4–16 weeks) → Screening → R

- **Finerenone 10 or 20 mg od*** → Post-treatment follow-up
- **Placebo** → Post-treatment follow-up

2.6 years' median follow-up

Key outcomes

- Kidney composite: Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death
- **CV composite**: **Time to CV death, nonfatal MI, nonfatal stroke or hospitalization for HF**



1. **New-onset AF** was evaluated as a **prespecified outcome**
2. **Kidney** and **CV composite outcomes** were analysed in **patients with** and **without history of AF**

*10 mg if screening eGFR 25 to <60 mL/min/1.73 m^2; 20 mg if ≥60 mL/min/1.73 m^2, up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/L and eGFR stable

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; od, once daily

Bakris GL, et al. *N Engl J Med* 2020;383:2219–2229

FIDELIO-DKD Was a Global Trial Including Patients With and Without a History of AF

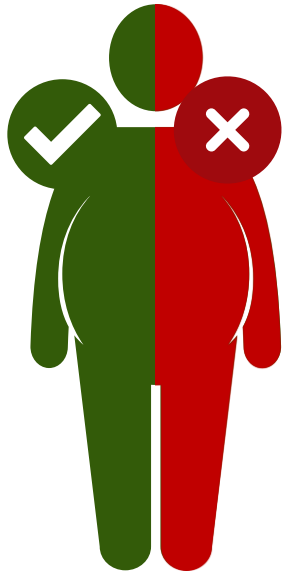
Aged ≥18 years with T2D

eGFR of ≥25 to <75 mL/min/1.73 m^2

On maximum tolerated dose of ACEi or ARB for ≥4 weeks

Moderately*/severely elevated albuminuria

Serum [K+] ≤4.8 mmol/L



HFrEF with NYHA class II-IV

Uncontrolled arterial hypertension#

HbA1c >12%

Other kidney disease‡

Among patients in the trial, 461 (8.1%) were defined by the investigators as having a history of AF at baseline

*Patients with moderately elevated albuminuria were required to also have diabetic retinopathy; #mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit, or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit; ‡known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; Serum [K+], serum potassium level

Bakris GL, et al. *N Engl J Med* 2020;383:2219–2229

Baseline Characteristics were Similar Between Patients With and Without a History of AF

Characteristic*	Without history of AF (n = 5,213)	With history of AF (n = 461)
Age, years	65	70
Male, %	69	80
Mean systolic blood pressure, mm Hg	138#	138
BMI, kg/m^2	31#	32#
Duration of diabetes, years	17#	17
HbA1c, %	8#	7
Serum [K+], mmol/L	4#	4
eGFR, mL/min/1.73m^2	44#	44
Waist circumference, cm	106#	112
CRP, mg/L	5#	6#
Heart rate, bpm	72#	70
History of CVD, %		
Yes	45	62
No	56	38

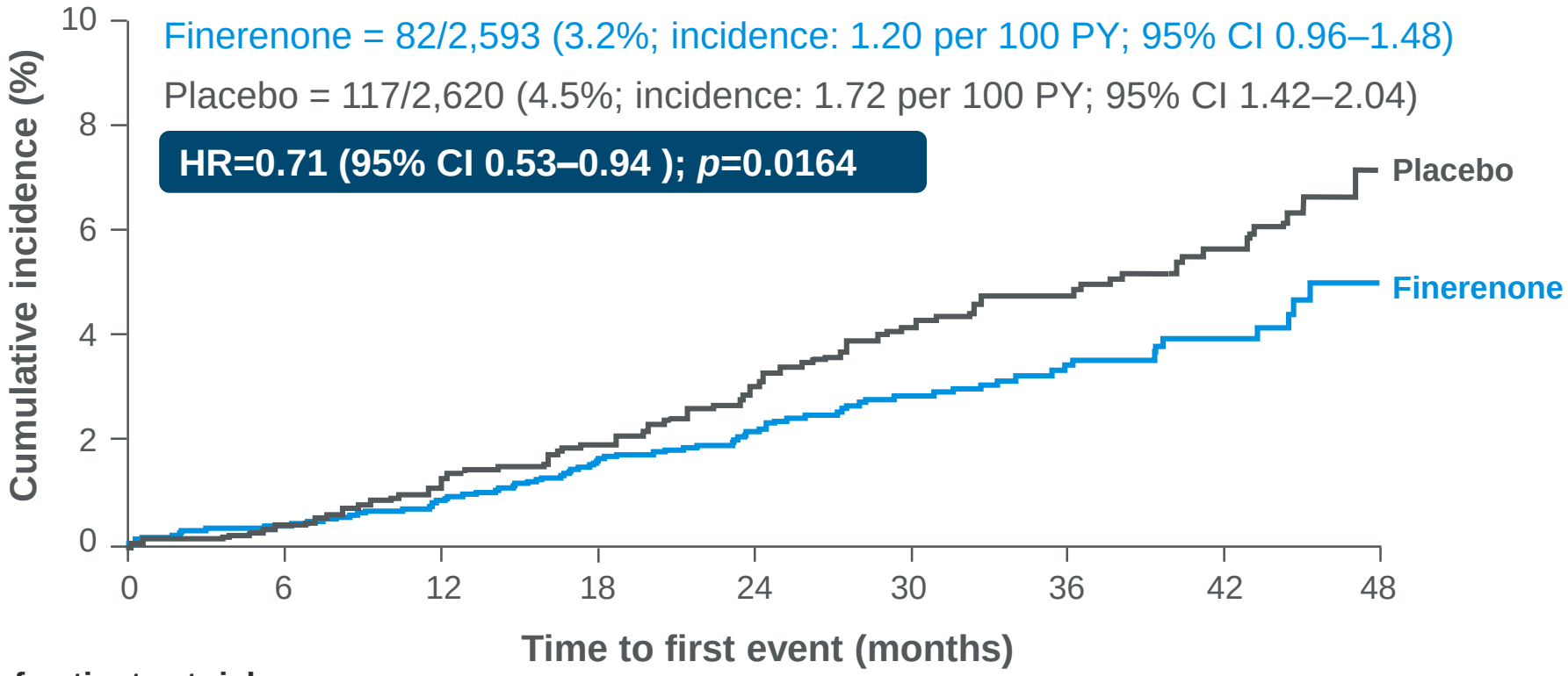
*Data expressed as means unless otherwise stated; #missing data for n≤14 patients
BMI, body mass index; bpm, beat per minute; CRP, C-reactive protein; SD, standard deviation

At Baseline, the Use of Beta-blocker, Loop Diuretics and Antithrombotic Medications were Different Between Patients With and Without a History of AF

Medication, %	Without history of AF (n = 5,213)	With history of AF (n = 461)
Angiotensin-converting enzyme inhibitors	33	43
Angiotensin receptor blockers	67	56
Beta blockers	50	78
Diuretics	55	71
Loop diuretics	27	46
Thiazide diuretics	24	25
Statins	74	76
Potassium supplements	3	9
Potassium-lowering agents	3	2
Glucose-lowering therapies	97	97
SGLT-2 inhibitor	5	5
Antithrombotic medication		
Antithrombotic agents	60	92
Aspirin	51	28
Antiplatelet therapy	59	37
NOACs	1	35

NOACs, nonvitamin K antagonist oral anticoagulant; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Finerenone Significantly Lowered the Incidence of New-Onset AF*



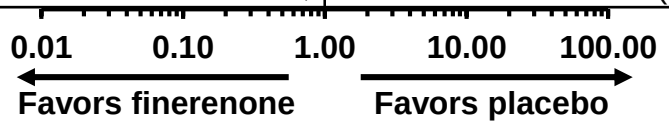
Number of patients at risk

Finerenone	2593	2563	2524	2459	1939	1444	961	539	109
Placebo	2620	2580	2532	2463	1914	1446	945	552	112

*New-onset AF was evaluated in patients without a history of AF as a prespecified outcome adjudicated by an independent cardiologist committee
CI, confidence interval; HR, hazard ratio; PY, patient-years

The Effect of Finerenone on New-Onset AF Was Not Modified by Age, Sex or Kidney Characteristics at Screening

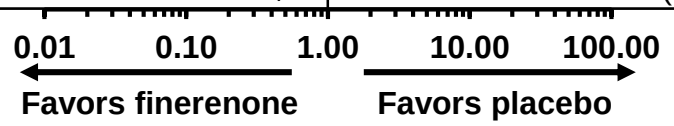
Subgroup	Finerenone n/N	Placebo n/N	Hazard ratio (95% CI)	*p*-value for interaction
All patients	**82/2,593**	**117/2,620**	**0.71 (0.53–0.94)**	
Age at run-in visit				0.48
<65 years	21/1,149	25/1,135	0.85 (0.47–1.52)	
≥65 years	61/1,444	92/1,485	0.67 (0.48–0.92)	
Sex				0.37
Male	59/1,767	91/1,848	0.66 (0.47–0.91)	
Female	23/826	26/772	0.89 (0.51–1.57)	
Region				0.17
Europe	51/1,038	64/1,051	0.80 (0.55–1.16)	
North America	16/423	21/438	0.79 (0.41–1.52)	
Latin America	4/287	2/290	1.94 (0.36–10.60)	
Asia	8/755	26/753	0.30 (0.14–0.66)	
Other	3/90	4/88	0.72 (0.16–3.24)	
Screening eGFR				0.11
25 to <45 mL/min/1.73 m^2	52/1,422	56/1,425	0.93 (0.64–1.36)	
45 to <60 mL/min/1.73 m^2	26/977	52/990	0.51 (0.32–0.81)	
≥60 mL/min/1.73 m^2	4/194	9/205	0.47 (0.14–1.52)	
Screening UACR				0.23
>30 to ≤300 mg/g	4/188	11/200	0.36 (0.11–1.13)	
>300 mg/g	78/2,405	106/2,420	0.74 (0.55–1.00)	



UACR, urine albumin-to-creatinine ratio

The Effect of Finerenone on New-Onset AF Was Not Modified by Baseline Serum Potassium Levels, Systolic Blood Pressure, BMI, HbA1c, or the Use of Glucose-Lowering Therapies

Subgroup	Finerenone n/N	Placebo n/N	Hazard ratio (95% CI)	*p*-value for interaction
All patients	**82/2,593**	**117/2,620**	**0.71 (0.53–0.94)**	
Baseline serum [K+]				0.12
≤4.4 mmol/L (median)	43/1,480	73/1,475	0.58 (0.40–0.85)	
>4.4 mmol/L (median)	39/1,112	44/1,144	0.92 (0.60–1.42)	
Baseline SBP				0.19
≤138.3 mmHg (median)	28/1,263	51/1,299	0.56 (0.35–0.88)	
>138.3 mmHg (median)	54/1,327	66/1,319	0.83 (0.58–1.18)	
Baseline BMI				0.13
<30 kg/m^2	25/1,234	49/1,255	0.53 (0.33–0.86)	
≥30 kg/m^2	57/1,348	68/1,360	0.84 (0.59–1.19)	
Baseline HbA1c				0.32
≤7.5%	34/1,316	57/1,360	0.60 (0.39–0.92)	
>7.5%	48/1,270	60/1,256	0.81 (0.55–1.18)	
SGLT-2i at baseline				0.49
No	80/2,485	111/2,493	0.72 (0.54–0.96)	
Yes	2/108	6/127	0.41 (0.08–2.03)	
GLP-1RA at baseline				0.39
No	77/2,421	106/2,430	0.73 (0.55–0.99)	
Yes	5/172	11/190	0.45 (0.16–1.31)	

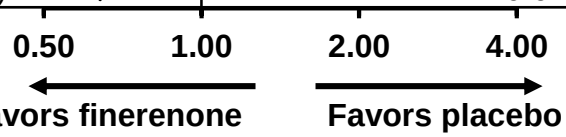


GLP-1RA, glucagon-like peptide-1 receptor agonist

The Effect of Finerenone on Kidney and CV Outcomes Was Consistent Independent of History of AF

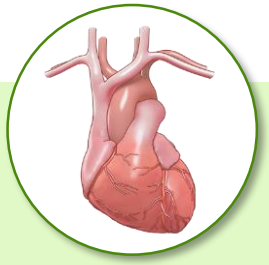
Primary outcome: Kidney failure*, sustained ≥40% decrease in eGFR from baseline, or renal death
Secondary outcome: CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF

Outcome	Finerenone n/N	Placebo n/N	Hazard ratio (95% CI)	*p*-value for interaction
Primary composite kidney outcome				
All patients	504/2,833	600/2,841	0.82 (0.73–0.93)	
Medical history of AF				0.16
No	466/2,593	565/2,620	0.81 (0.71–0.91)	
Yes	38/240	35/221	1.13 (0.71–1.79)	
Key secondary composite CV outcome				
All patients	367/2,833	420/2,841	0.86 (0.75–0.99)	
Medical history of AF				0.85
No	303/2,593	354/2,620	0.85 (0.73–0.99)	
Yes	64/240	66/221	0.88 (0.62–1.24)	
	n (gmean)	**n (gmean)**	**Ratio of LS-mean (95% CI)**	***p*-value for interaction**
UACR at month 4 compared to baseline				
All patients	2,711 (0.66)	2,705 (0.95)	0.69 (0.66–0.72)	
Medical history of AF				0.22
No	2,482 (0.66)	2,494 (0.96)	0.69 (0.67–0.72)	
Yes	229 (0.58)	211 (0.91)	0.64 (0.55–0.73)	

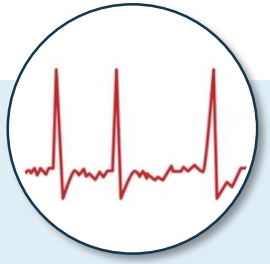


*End-stage kidney disease or an eGFR <15 mL/min/1.73 m^2
gmean, geometric mean; HF, heart failure; LS-mean, least-squares mean; MI, myocardial infarction

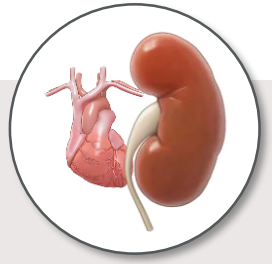
Finerenone Reduced the Risk of New-Onset AF in Patients With CKD and T2D



Finerenone significantly lowered the incidence of new-onset AF at month 6 and risk was reduced throughout the trial



Lower incidence of new-onset AF was generally consistent across prespecified patient subgroups



Finerenone demonstrated cardiorenal protection in patients with CKD and T2D irrespective of history of AF

Thank You

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

The FIDELIO-DKD team would like to thank all participating investigators, the centers, the sponsor study team, and the patients and their families

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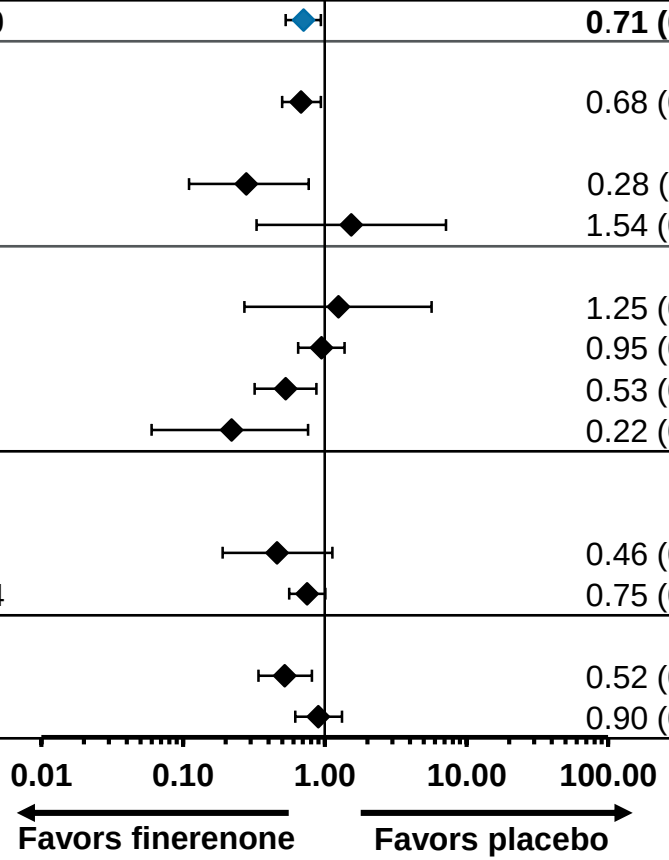
48 countries, 913 sites, 13,911* participants

*Number of patients who provided informed consent

Additional Slides

The Effect of Finerenone on New-Onset AF Was Not Modified by Race and Baseline Kidney Characteristics in Patients Without a History of AF

Subgroup	Finerenone n/N	Placebo n/N	Hazard ratio (95% CI)	*p*-value for interaction
All patients	**82/2,593**	**117/2,620**	**0.71 (0.53–0.94)**	
Race				–
White	66/1,575	96/1,621	0.68 (0.50–0.94)	
Black/African American	7/136	0/120	–	
Asian	5/693	18/705	0.28 (0.11–0.77)	
Other	4/189	3/174	1.54 (0.33–7.16)	
Baseline eGFR				0.06
<25 mL/min/1.73 m^2	4/58	3/63	1.25 (0.27–5.66)	
25 to <45 mL/min/1.73 m^2	51/1,349	56/1,381	0.95 (0.65–1.38)	
45 to <60 mL/min/1.73 m^2	24/895	43/859	0.53 (0.32–0.87)	
≥60 mL/min/1.73 m^2	3/290	15/316	0.22 (0.06–0.76)	
Baseline UACR				–
<30 mg/g	0/10	0/12	–	
30 to <300 mg/g	7/318	15/313	0.46 (0.19–1.13)	
≥300 mg/g	75/2,263	102/2,294	0.75 (0.56–1.01)	
Baseline UACR				0.06
≤851.9 mg/g (median)	31/1,305	59/1,291	0.52 (0.34–0.81)	
>851.9 mg/g (median)	51/1,286	58/1,328	0.90 (0.62–1.32)	



The Effects of Finerenone on Other Outcomes Were Consistent in Patients With and Without a History of AF

Outcome	Finerenone n/N	Placebo n/N	Hazard ratio (95% CI)	*p*-value for interaction
Secondary composite kidney outcome				
All patients	252/2,833	326/2,841	0.76 (0.65–0.90)	
Medical history of AF				0.85
No	240/2,593	308/2,620	0.76 (0.65–0.91)	
Yes	12/240	18/221	0.71 (0.34–1.48)	
All-cause mortality				
All patients	219/2,833	244/2,841	0.90 (0.75–1.07)	
Medical history of AF				0.88
No	183/2,593	205/2,620	0.90 (0.73–1.09)	
Yes	36/240	39/221	0.86 (0.55–1.36)	
All-cause hospitalization				
All patients	1,263/2,833	1,321/2,841	0.95 (0.88–1.02)	
Medical history of AF				0.87
No	1,126/2,593	1,190/2,620	0.94 (0.87–1.02)	
Yes	137/240	131/221	0.96 (0.76–1.22)