SUPPLEMENTARY MATERIAL

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation : nationwide cohort study

Daehoon Kim, MD; Pil-Sung Yang, MD; Seng Chan You, MD, MS; Jung-Hoon Sung, MD; Eunsun Jang, MS; Hee Tae Yu, MD; Tae-Hoon Kim, MD; Hui-Nam Pak, MD; Moon-Hyoung Lee, MD; Gregory Y.H. Lip, MD; Boyoung Joung, MD

Supplementary Table 1. Summary of strategies for emulating target trial.

Components	Target trial (EAST-AFNET4)	This study
Inclusion period	28 July 2011 – 30 December 2016	28 July 2011 – 31 December 2015
Eligibility criteria	1) Adults (≥18 years of age) who were older than 75 years of age, had had a previous transient ischaemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, and left ventricular hypertrophy 2) Early AF (diagnosed ≤12 months before enrolment)	1) Selected adults (≥18 years of age) that received a rhythm-control or rate-control treatments and have no prior history of prescriptions and no records of ablation in the database who were older than 75 years of age, had a previous transient ischaemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, myocardial infarction, and chronic kidney disease 2) Early AF (defined as AF diagnosed ≤12 months before enrolment) and late AF (diagnosed >12 months before enrolment) 3) Undergoing oral anticoagulation (>90 days of supply within 180 days after their first recorded prescription of rhythm- or rate-control medications or ablation procedure)
Exposed group	Rhythm control: AADs, AF ablation, cardioversion of persistent AF, to be initiated early after randomization	Rhythm control: a prescription of more than a 90-day supply of any rhythm-control drugs in the 180-day period since the first prescription or the performance of an ablation procedure for AF.
Unexposed group	Usual care: initially treated with rate-control therapy without rhythm-control therapy	Rate control: a prescription of more than a 90-day supply of any rate-control drugs in the 180-day period since the first prescription and with no prescription of rhythm-control drug and no ablation within this period. Patients prescribed rhythm-control drugs for more than 90 days or who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified as intention-to-treat with rhythm control.
Primary outcome	1) A composite of death from cardiovascular causes, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome 2) The number of nights spent in the hospital per year.	1) A composite of death from cardiovascular causes, ischaemic stroke, hospitalisation for heart failure, or acute myocardial infarction 2) The number of nights spent in the hospital per year.
Secondary outcome	Each component of the primary outcome, rhythm, left ventricular function, quality of life, AF-related symptom	Each component of the primary outcome
Safety outcome	A composite of death from any cause, stroke, or pre-specified serious adverse events of special interest capturing	A composite of death from any cause, intracranial or gastrointestinal bleeding requiring hospitalisation, or pre-specified

	complications of rhythm-control therapy	serious adverse events of special interest capturing complications of rhythm-control therapy
Follow-up	From randomization until the end of the trial, death, or withdrawal from the trial.	From 180 days after their first recorded prescription or procedure to avoid immortal time bias until the end of follow-up of the database (31 December 2016) or death.

Supplementary Table 2. Definitions and codes used for defining medical conditions, comorbidities, and drug treatments and procedures for atrial fibrillation.

	Definitions	Codes or conditions
Medical conditions		
Atrial fibrillation	Defined from diagnosis*	I48
Heart failure	Defined from diagnosis*	ICD-10: I11.0, I50, I97.1
Heart failure admission history	Defined from principal or first secondary admission diagnoses of heart failure	ICD-10: I11.0, I50, I97.1
Hypertension	Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control	ICD-10: I10, I11, I12, I13, I15 Treatment: prescription for at least one of all kinds of antihypertensive medication
Diabetes mellitus	Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control	ICD-10: E10, E11, E12, E13, E14 Treatment: prescription for at least one of all kinds of oral antidiabetics or insulin
Dyslipidaemia	Defined from diagnosis*	ICD-10: E78
Ischaemic stroke	Defined from diagnosis*	ICD-10: I63, I64
Transient ischaemic attack	Defined from diagnosis*	ICD-10: G45
Intracranial bleeding	Defined from diagnosis*	ICD-10: I60, I61, I62
Myocardial infarction	Defined from diagnosis*	ICD-10: I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis*	ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9
Valvular heart disease	Defined from diagnoses* mitral stenosis or claims for heart valve surgery	ICD-10: I05.0, I05.2, I34.2, Z95.2-4 Claim for valve replacement or valvuloplasty: O1781, O1782, O1783, O1791, O1792, O1793, O1797, O1794, O1795, O1796, O1798
Chronic kidney disease	Defined from eGFR or diagnosis* (if laboratory value was not available, diagnosis code was used)	eGFR <60mL/min per 1.73 m^2 ICD-10: N18, N19
Proteinuria	Defined from laboratory data (if laboratory value was not available, diagnosis code* was used)	Urine dipstick proteinuria 1+ or higher (ICD-10: N06, N391, N392, R80)
Hyperthyroidism	Defined from diagnosis*	ICD-10: E05
Hypothyroidism	Defined from diagnosis*	ICD-10: E03
Malignancy	Defined from diagnoses* of cancer (non-benign)	ICD-10: C00-C97
Chronic obstructive pulmonary disease	Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control	ICD-10: J42, J43(except J43.0), J44 Treatment: SABA, SAMA, LABA, LAMA, ICS, ICS+LABA, or methylxanthine (>1 months).
Chronic liver disease	Defined from diagnosis* of chronic liver disease, cirrhosis, and hepatitis	ICD-10: B18, K70, K71, K72, K73, K74, K76.1
Hypertrophic	Defined from at least one	ICD-10: I42.1, I42.2

cardiomyopathy	records of either inpatient or outpatient diagnoses	
Osteoporosis	Defined from diagnosis*	ICD-10: M80, M81, M82 (except M82.0)
Sleep apnea	Defined from diagnosis*	ICD-10: G47.3
Drug treatment for atrial fibrillation (available in South Korea)		
Anti-arrhythmic drug		
Class Ic		flecainide, pilsicainide, propafenone
Class III		amiodarone, dronedarone, sotalol
Rate control drugs		
Beta-blocker		atenolol, bisoprolol, carvedilol, metoprol, nebivolol, propranolol, labetalol
Calcium channel blocker		diltiazem, verapamil
Cardiac glycosides		digoxin
Procedures for atrial fibrillation		
Catheter ablation for AF	Defined from admission diagnosis of AF plus claims for ablation procedures	ICD-10: I48 Claim codes: M6542 (Conventional Radiofrequency Ablation of Atrial fibrillation) or M6547 (Radiofrequency Ablation of Atrial fibrillation Through Intracardiac Electrophysiologic 3-Dimensional Mapping)
Cardioversion	Defined from diagnosis of AF plus claims for cardioversion	ICD-10: I48 Claim codes:M5880

*For greater accuracy, either one diagnosis during hospitalisation or more than twice at outpatient clinics was requited for the diagnosis.

Supplementary Table 3. Definitions and codes used for study outcomes.

Outcomes	Definitions	Codes or conditions	PPV
Primary composite outcomes			
Ischaemic stroke	Defined from admission diagnosis with concomitant imaging studies of the brain or related death	ICD-10: I63, I64	90.6%* (2347/2591)
Hospitalisation owing to heart failure	Defined from principal or first secondary admission diagnoses of heart failure	ICD-10: I11.0, I50, I97.1	82.1%* (110/134)
Acute myocardial infarction	Defined from admission diagnosis of acute myocardial infarction concurrently with coronary angiography or related death	ICD-10: I21, I22	86.5%† (4054/4688)
Safety outcomes			
Intracranial bleeding	Defined from admission diagnosis with concomitant imaging studies of the brain or related death	ICD-10: I60-I62	87.5%* (286/327)
Gastrointestinal bleeding	Defined from admission diagnosis or related death	ICD-10: K25-28 (subcodes 0-2 and 4-6 only), K62.5, K92.0, K92.1, K92.2, I85.0, I98.3	92.0%‡ (184/200)
Serious adverse events related to rhythm control			
Cardiac tamponade	Defined from claims for pericardiocentesis	Claim codes:C8060, C8061	-
Syncope	Defined from either one diagnosis during hospitalisation or more than twice at outpatient clinics	ICD-10: R55.x	-
Sick sinus syndrome	Defined from either one diagnosis during hospitalisation or more than twice at outpatient clinics	ICD-10: I495.	91.1%* (307/337)
Atrioventricular block	Defined from either one diagnosis during hospitalisation or more than twice at outpatient clinics	ICD-10: I44.1, I44.2, I44.3, I45.3, I45.8, I45.9	95.7%* (264/276)
Pacemaker implantation	Defined from claims for pacemaker implantation	Claim codes: O2003, O2004, O0203, O0204, O0205, O0206, O0207	-
Sudden cardiac arrest	Defined from admission diagnosis or related death§	ICD-10: I46, I49.0	80.2%⁑ (586/731)

PPV was represented as % (number of true positive cases / number of examined cases).

*We conducted a validation study using hospital administrative data from two tertiary hospitals.

†Validated in a study by Lee, HY. et al. (Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. *Sci Rep* 2017;7(1):12716).

‡Validated in a study by Park, J. et al. (Validation of diagnostic codes of major clinical outcomes in a National Health Insurance database. *Int J Arrhythm* 2019;20:5).

§To avoid erroneous inclusion of the patients with non-cardiac arrest, we excluded the patient with sudden arrest diagnosis accompanied by respiratory arrest (R09.0, R09.2), gastrointestinal bleeding (I85.0, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K92.0-K92.2), brain haemorrhage (I60.x-I62.x, S06.4-S06.6), septic shock (A41.9, R57.2), pregnancy and delivery (O00-O99), diabetic ketoacidosis (E14.1), anaphylaxis (T78.2), and accidents including suicide (T71, T75.1, T36-T65, V80-V89, W76.x, X60-X84).

⁑Validated in a study by Kim, IJ. et al. (Relationship Between Anemia and the Risk of Sudden Cardiac Arrest - A Nationwide Cohort Study in South Korea. Circ J 2018;82(12):2962-9).

ICD-10, International Classification of Diseases-10th Revision; PPV, positive predictive value.

Supplementary Table 4. Baseline characteristics after propensity score matching.

	After propensity score matching					
	Early AF treatment (≤1 year since AF diagnosis)			Late AF treatment (>1 year since AF diagnosis)		
Variables	Rhythm Control (N=3973)	Rate Control (N=3973)	ASD	Rhythm Control (N=1351)	Rate Control (N=1351)	ASD
Sociodemographic						
Age, years	70 (62-77)	71 (62-77)	1.1%	71 (64-77)	71 (63-77)	4.1%
<65 years	1180 (29.7)	1160 (29.2)	1.1%	363 (26.9)	382 (28.3)	3.1%
65-74 year	1455 (36.6)	1480 (37.3)	1.3%	506 (37.5)	516 (38.2)	1.5%
≥75 years	1338 (33.7)	1333 (33.6)	0.3%	482 (35.7)	453 (33.5)	4.5%
Male	2127 (53.5)	2091 (52.6)	1.8%	773 (57.2)	795 (58.8)	3.3%
AF duration, months	0.0 (0.0-0.8)	0.0 (0.0-0.4)	0.1%	56.2 (29.5-97.2)	58.5 (28.7-96.9)	1.2%
Enroll year						
2011	246 (6.2)	231 (5.8)	1.6%	92 (6.8)	94 (7.0)	0.6%
2012	672 (16.9)	678 (17.1)	0.4%	274 (20.3)	274 (20.3)	<0.1%
2013	837 (21.1)	876 (22.0)	2.4%	292 (21.6)	295 (21.8)	0.5%
2014	917 (23.1)	891 (22.4)	1.6%	313 (23.2)	313 (23.2)	<0.1%
2015	1301 (32.7)	1297 (32.6)	0.2%	380 (28.1)	375 (27.8)	0.8%
High tertile of income	1748 (44.0)	1757 (44.2)	0.5%	614 (45.4)	615 (45.5)	0.1%
Number of OPD visits ≥12/year	3185 (80.2)	3224 (81.1)	2.5%	1120 (82.9)	1128 (83.5)	1.6%
Living in metropolitan areas	1774 (44.7)	1762 (44.3)	0.6%	587 (43.4)	594 (44.0)	1.0%
Level of care initiating treatment						
Tertiary	1926 (48.5)	1927 (48.5)	0.1%	648 (48.0)	656 (48.6)	1.2%
Secondary	1843 (46.4)	1836 (46.2)	0.4%	623 (46.1)	608 (45.0)	2.2%
Primary	204 (5.1)	210 (5.3)	0.7%	80 (5.9)	87 (6.4)	2.2%
Risk scores						
CHA$_2$DS$_2$-VASc score	4 (3-5)	4 (3-5)	0.7%	4 (3-6)	4 (3-6)	7.3%
mHAS-BLED score[*]	2 (2-3)	2 (2-3)	0.5%	3 (2-4)	3 (2-3)	3.1%
Charlson comorbidity index	3 (2-5)	3 (2-5)	2.1%	5 (3-7)	4 (3-6)	4.3%
Hospital Frailty Risk score	2.8 (0.3-6.7)	2.6 (0.0-6.6)	1.3%	4.1 (0.9-8.6)	3.9 (0.8-8.9)	1.9%
Medical history						
Heart failure	2067 (52.0)	2084 (52.5)	0.9%	823 (60.9)	788 (58.3)	5.3%
Previous hospitalisation for heart failure	565 (14.2)	579 (14.6)	1.0%	172 (12.7)	161 (11.9)	2.5%
Hypertension	3064 (77.1)	3034 (76.4)	1.8%	1204 (89.1)	1181 (87.4)	5.3%
Diabetes	1147 (28.9)	1150 (28.9)	0.2%	414 (30.6)	389 (28.8)	4.0%
Dyslipidaemia	3233 (81.4)	3232 (81.3)	0.1%	1189 (88.0)	1178 (87.2)	2.5%
Ischaemic stroke	1359 (34.2)	1330 (33.5)	1.5%	590 (43.7)	588 (43.5)	0.3%
Transient ischaemic attack	360 (9.1)	393 (9.9)	2.8%	174 (12.9)	159 (11.8)	3.4%
Intracranial bleeding	100 (2.5)	87 (2.2)	2.2%	62 (4.6)	63 (4.7)	0.4%
Myocardial infarction	271 (6.8)	279 (7.0)	0.8%	162 (12.0)	157 (11.6)	1.1%
Peripheral arterial disease	509 (12.8)	536 (13.5)	2.0%	239 (17.7)	243 (18.0)	0.8%
Valvular heart disease	376 (9.5)	375 (9.4)	0.1%	246 (18.2)	247 (18.3)	0.2%
Chronic kidney disease	232 (5.8)	220 (5.5)	1.3%	94 (7.0)	92 (6.8)	0.6%
Proteinuria	281 (7.1)	283 (7.1)	0.2%	127 (9.4)	117 (8.7)	2.6%
Hyperthyroidism	371 (9.3)	381 (9.6)	0.9%	165 (12.2)	161 (11.9)	0.9%
Hypothyroidism	466 (11.7)	441 (11.1)	2.0%	211 (15.6)	184 (13.6)	5.7%
Malignancy	890 (22.4)	915 (23.0)	1.5%	410 (30.3)	383 (28.3)	4.4%
COPD	1191 (30.0)	1211 (30.5)	1.1%	487 (36.0)	472 (34.9)	2.3%
Chronic liver disease	1603 (40.3)	1626 (40.9)	1.2%	571 (42.3)	607 (44.9)	5.4%
Hypertrophic cardiomyopathy.	56 (1.4)	55 (1.4)	0.2%	13 (1.0)	16 (1.2)	2.2%
Osteoporosis	1430 (36.0)	1420 (35.7)	0.5%	484 (35.8)	494 (36.6)	1.5%
Sleep apnea	20 (0.5)	19 (0.5)	0.4%	7 (0.5)	8 (0.6)	1.0%
Concurrent medication†						

Oral anticoagulant	3973 (100.0)	3973 (100.0)	<0.1%	1351 (100.0)	1351 (100.0)	<0.1%
Warfarin	3253 (81.9)	3240 (81.6)	0.8%	1168 (86.5)	1161 (85.9)	1.5%
NOAC	962 (24.2)	980 (24.7)	1.1%	242 (17.9)	255 (18.9)	2.5%
Beta-blocker	2911 (73.3)	2793 (70.3)	6.6%	946 (70.0)	921 (68.2)	4.0%
Non-DHP CCB	663 (16.7)	642 (16.2)	1.4%	201 (14.9)	208 (15.4)	1.4%
Digoxin	613 (15.4)	729 (18.3)	7.8%	286 (21.2)	287 (21.2)	0.2%
Aspirin	794 (20.0)	793 (20.0)	0.1%	273 (20.2)	252 (18.7)	3.9%
P2Y$_{12}$ inhibitor	397 (10.0)	386 (9.7)	0.9%	110 (8.1)	101 (7.5)	2.5%
Statin	1833 (46.1)	1807 (45.5)	1.3%	634 (46.9)	611 (45.2)	3.4%
DHP CCB	627 (15.8)	642 (16.2)	1.0%	214 (15.8)	226 (16.7)	2.4%
ACEI/ARB	2087 (52.5)	2107 (53.0)	1.0%	722 (53.4)	721 (53.4)	0.1%
Loop/thiazide diuretics	1863 (46.9)	1849 (46.5)	0.7%	655 (48.5)	640 (47.4)	2.2%
K$^+$ sparing diuretics	736 (18.5)	746 (18.8)	0.6%	278 (20.6)	262 (19.4)	3.0%
Alpha-blocker	69 (1.7)	72 (1.8)	0.6%	28 (2.1)	35 (2.6)	3.4%

Values are presented as median (interquartile range) or n (%).

*Modified HAS-BLED = hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalised ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point.

†Defined as a prescription fill of ≥90 days within 6 months after the index date.

AAD, antiarrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; NOAC, non-vitamin K antagonist oral anticoagulant.

Supplementary Table 5. Definitions of 35 falsification endpoints.

Falsification endpoints	Definitions	ICD-10 codes / other conditions
Major fracture	Defined from diagnosis on inpatient or emergency department record	S72, S72.0, S72.1, S72.2, S12.0, S12.1, S12.2, S12.7, S12.9, S22.0, S22.1, S32.0, S32
Fall accident	Defined from diagnosis on inpatient or emergency department record	W00-W19
Viral enteritis	Defined from diagnosis*	A08
Warts	Defined from diagnosis*	B07
Acute hepatitis A	Defined from diagnosis*	B15
Viral conjunctivitis	Defined from diagnosis*	B30
Stomach cancer	Defined from diagnosis*	C16
Bone malignancy	Defined from diagnosis*	C40, C41, C90, C795
Lymphoma	Defined from diagnosis*	C81, C82, C83, C84, C85
Pterygium	Defined from diagnosis*	H110
Otitis media	Defined from diagnosis*	H65, H66, H67
Meniere's disease	Defined from diagnosis*	H810
Benign paroxysmal positional vertigo	Defined from diagnosis*	H811
Varicose veins of lower extremities	Defined from diagnosis*	I83
Chronic sinusitis	Defined from diagnosis*	J32
Benign neoplasm of colon, rectum	Defined from diagnosis*	D12
Acute appendicitis	Defined from diagnosis on inpatient or emergency department record	K35
Inguinal hernia	Defined from diagnosis*	K40
Diverticulitis of intestine	Defined from diagnosis*	K57
Cholecystitis	Defined from diagnosis*	K81
Cellulitis	Defined from diagnosis*	L03
Allergic contact dermatitis	Defined from diagnosis*	L23
Urticaria	Defined from diagnosis*	L50
Ingrowing nail	Defined from diagnosis*	L600
Seropositive rheumatoid arthritis	Defined from diagnosis*	M05
Gout	Defined from diagnosis*	M10
Spinal stenosis	Defined from diagnosis*	M480
Frozen shoulder	Defined from diagnosis*	M750
Osteomyelitis	Defined from diagnosis*	M86
Nausea and vomiting	Defined from diagnosis*	R11
Dysuria	Defined from diagnosis*	R30
Voice disturbances	Defined from diagnosis*	R49
Seizure	Defined from diagnosis*	R56
Burns	Defined from diagnosis*	T20-T32
Anaphylaxis/Allergic reaction	Defined from diagnosis*	T78

*For greater accuracy, either one diagnosis during hospitalisation or more than twice at outpatient clinics was requited for the diagnosis.

ICD-10, International Classification of Diseases, Tenth Revision.

Supplementary Table 6. Baseline characteristics of patients undergoing early (≤1 year) and late (>1 year) AF treatment.

Variables	Early AF treatment (N=16323)	Late AF treatment (N=6312)	P value
Sociodemographic			
Age, years	70 (62-76)	69 (61-75)	<0.001
<65 years	5010 (30.7)	2119 (33.6)	<0.001
65-74 year	6050 (37.1)	2389 (37.8)	0.28
≥75 years	5263 (32.2)	1804 (28.6)	<0.001
Male	8567 (52.5)	3633 (57.6)	<0.001
AF duration, months	0.0 (0.0-0.8)	62.2 (31.5-105.3)	<0.001
Enroll year			
2011	1028 (6.3)	494 (7.8)	<0.001
2012	2832 (17.3)	1217 (19.3)	0.001
2013	3461 (21.2)	1372 (21.7)	0.39
2014	3849 (23.6)	1471 (23.3)	0.67
2015	5153 (31.6)	1758 (27.9)	<0.001
High tertile of income	7410 (45.4)	2993 (47.4)	0.006
Number of OPD visits ≥12/year	13363 (81.9)	5417 (85.8)	<0.001
Living in metropolitan areas	7425 (45.5)	2826 (44.8)	0.34
Level of care initiating treatment			
Tertiary	8486 (52.0)	3717 (58.9)	<0.001
Secondary	6984 (42.8)	2281 (36.1)	<0.001
Primary	853 (5.2)	314 (5.0)	0.46
Risk scores			
CHA_2DS_2-VASc score	4 (3-5)	4 (3-6)	<0.001
mHAS-BLED score[*]	2 (2-3)	3 (2-3)	<0.001
Charlson comorbidity index	3 (2-5)	5 (3-7)	<0.001
Hospital Frailty Risk score	2.5 (0.0-6.3)	3.7 (0.8-8.4)	<0.001
Medical history			
Heart failure	8419 (51.6)	3945 (62.5)	<0.001
Previous hospitalisation for heart failure	2250 (13.8)	953 (15.1)	0.01
Hypertension	12335 (75.6)	5682 (90.0)	<0.001
Diabetes	4673 (28.6)	1973 (31.3)	<0.001
Dyslipidaemia	13257 (81.2)	5667 (89.8)	<0.001
Ischaemic stroke	5241 (32.1)	2477 (39.2)	<0.001
Transient ischaemic attack	1610 (9.9)	818 (13.0)	<0.001
Intracranial bleeding	366 (2.2)	270 (4.3)	<0.001
Myocardial infarction	1217 (7.5)	898 (14.2)	<0.001
Peripheral arterial disease	2222 (13.6)	1217 (19.3)	<0.001
Valvular heart disease	1520 (9.3)	1095 (17.3)	<0.001
Chronic kidney disease	1001 (6.1)	540 (8.6)	<0.001
Proteinuria	1125 (6.9)	529 (8.4)	<0.001
Hyperthyroidism	1699 (10.4)	1126 (17.8)	<0.001
Hypothyroidism	1978 (12.1)	1104 (17.5)	<0.001
Malignancy	3761 (23.0)	1773 (28.1)	<0.001
COPD	4912 (30.1)	2335 (37.0)	<0.001
Liver disease	6652 (40.8)	3066 (48.6)	<0.001
Hypertrophic cardiomyopathy	262 (1.6)	143 (2.3)	0.001
Osteoporosis	5810 (35.6)	2274 (36.0)	0.55
Sleep apnea	83 (0.5)	50 (0.8)	0.02
Concurrent medication†			
Oral anticoagulant	16323 (100.0)	6312 (100.0)	-
Warfarin	13193 (80.8)	5282 (83.7)	<0.001

NOAC	4065 (24.9)	1354 (21.5)	<0.001
Beta-blocker	9646 (59.1)	3359 (53.2)	<0.001
Non-DHP CCB	2308 (14.1)	828 (13.1)	0.05
Digoxin	3076 (18.8)	957 (15.2)	<0.001
Aspirin	3344 (20.5)	1333 (21.1)	0.30
P2Y$_{12}$ inhibitor	1475 (9.0)	563 (8.9)	0.80
Statin	7281 (44.6)	2884 (45.7)	0.15
DHP CCB	2949 (18.1)	1118 (17.7)	0.55
ACEI/ARB	8810 (54.0)	3286 (52.1)	0.01
Loop/thiazide diuretics	7405 (45.4)	2846 (45.1)	0.72
K$^+$ sparing diuretics	2974 (18.2)	1101 (17.4)	0.18
Alpha-blocker	317 (1.9)	142 (2.2)	0.16

Values are presented as median (interquartile range) or n (%).

[*]Modified HAS-BLED = hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalised ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point.

[†]Defined as a prescription fill of ≥90 days within 6 months after the index date.

AAD, antiarrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; NOAC, non-vitamin K antagonist oral anticoagulant.

Supplementary Table 7. Baseline characteristics after overlap weighting.

Variables	After overlap weighting					
	Early AF treatment (≤1 year since AF diagnosis)			Late AF treatment (>1 year since AF diagnosis)		
	Rhythm Control (N=2666.2 [9246]*)	Rate Control (N=2666.2 [7077]*)	ASD	Rhythm Control (N=927.6 [4407]*)	Rate Control (N=927.6 [1905]*)	ASD
Sociodemographic						
Age, years	70 (62-76)	71 (62-77)	<0.1%	70 (63-76)	71 (63-77)	<0.1%
<65 years	791.9 (29.7)	791.9 (29.7)	<0.1%	271.7 (29.3)	271.7 (29.3)	<0.1%
65-74 year	987.9 (37.1)	987.9 (37.1)	<0.1%	348.1 (37.5)	348.1 (37.5)	<0.1%
≥75 years	886.5 (33.2)	886.5 (33.2)	<0.1%	307.7 (33.2)	307.7 (33.2)	<0.1%
Male	1426.5 (53.5)	1426.5 (53.5)	<0.1%	542.1 (58.4)	542.1 (58.4)	<0.1%
AF duration, months	0.0 (0.0-0.9)	0.0 (0.0-0.5)	<0.1%	57.9 (29.6-100.8)	59.5 (29.2-98.5)	<0.1%
Enroll year						
2011	160.0 (6.0)	160.0 (6.0)	<0.1%	66.6 (7.2)	66.6 (7.2)	<0.1%
2012	465.0 (17.4)	465.0 (17.4)	<0.1%	184.7 (19.9)	184.7 (19.9)	<0.1%
2013	567.8 (21.3)	567.8 (21.3)	<0.1%	203.0 (21.9)	203.0 (21.9)	<0.1%
2014	615.0 (23.1)	615.0 (23.1)	<0.1%	214.9 (23.2)	214.9 (23.2)	<0.1%
2015	858.4 (32.2)	858.4 (32.2)	<0.1%	258.4 (27.9)	258.4 (27.9)	<0.1%
High tertile of income	1187.0 (44.5)	1187.0 (44.5)	<0.1%	423.8 (45.7)	423.8 (45.7)	<0.1%
Number of OPD visits ≥12/year	2161.2 (81.1)	2161.2 (81.1)	<0.1%	776.9 (83.8)	776.9 (83.8)	<0.1%
Living in metropolitan areas	1203.9 (45.2)	1203.9 (45.2)	<0.1%	403.6 (43.5)	403.6 (43.5)	<0.1%
Level of care initiating treatment						
Tertiary	1325.4 (49.7)	1325.4 (49.7)	<0.1%	468.9 (50.6)	468.9 (50.6)	<0.1%
Secondary	1205.4 (45.2)	1205.4 (45.2)	<0.1%	402.3 (43.4)	402.3 (43.4)	<0.1%
Primary	135.4 (5.1)	135.4 (5.1)	<0.1%	56.3 (6.1)	56.3 (6.1)	<0.1%
Risk scores						
CHA_2DS_2-VASc score	4 (3-5)	4 (3-5)	<0.1%	4 (3-6)	4 (3-6)	<0.1%
mHAS-BLED score†	2 (2-3)	2 (2-3)	<0.1%	3 (2-3)	3 (2-3)	<0.1%
Charlson comorbidity index	3 (2-5)	3 (2-5)	<0.1%	5 (3-7)	5 (3-7)	<0.1%
Hospital Frailty Risk score	2.7 (0.1-6.6)	2.6 (0.0-6.6)	<0.1%	3.9 (0.8-8.5)	3.8 (0.8-8.9)	<0.1%
Medical history						
Heart failure	1398.2 (52.4)	1398.2 (52.4)	<0.1%	562.3 (60.6)	562.3 (60.6)	<0.1%
Previous hospitalisation for heart failure	387.6 (14.5)	387.6 (14.5)	<0.1%	119.3 (12.9)	119.3 (12.9)	<0.1%
Hypertension	2052.8 (77.0)	2052.8 (77.0)	<0.1%	830.0 (89.5)	830.0 (89.5)	<0.1%
Diabetes	778.3 (29.2)	778.3 (29.2)	<0.1%	282.9 (30.5)	282.9 (30.5)	<0.1%
Dyslipidaemia	2178.9 (81.7)	2178.9 (81.7)	<0.1%	817.2 (88.1)	817.2 (88.1)	<0.1%
Ischaemic stroke	897.4 (33.7)	897.4 (33.7)	<0.1%	394.7 (42.6)	394.7 (42.6)	<0.1%
Transient ischaemic attack	260.2 (9.8)	260.2 (9.8)	<0.1%	114.3 (12.3)	114.3 (12.3)	<0.1%
Intracranial bleeding	63.1 (2.4)	63.1 (2.4)	<0.1%	41.0 (4.4)	41.0 (4.4)	<0.1%
Myocardial infarction	194.1 (7.3)	194.1 (7.3)	<0.1%	116.1 (12.5)	116.1 (12.5)	<0.1%
Peripheral arterial disease	358.2 (13.4)	358.2 (13.4)	<0.1%	171.6 (18.5)	171.6 (18.5)	<0.1%
Valvular heart disease	249.0 (9.3)	249.0 (9.3)	<0.1%	163.0 (17.6)	163.0 (17.6)	<0.1%
Chronic kidney disease	159.3 (6.0)	159.3 (6.0)	<0.1%	66.5 (7.2)	66.5 (7.2)	<0.1%
Proteinuria	187.1 (7.0)	187.1 (7.0)	<0.1%	84.1 (9.1)	84.1 (9.1)	<0.1%
Hyperthyroidism	258.4 (9.7)	258.4 (9.7)	<0.1%	124.3 (13.4)	124.3 (13.4)	<0.1%
Hypothyroidism	310.1 (11.6)	310.1 (11.6)	<0.1%	134.8 (14.5)	134.8 (14.5)	<0.1%
Malignancy	618.9 (23.2)	618.9 (23.2)	<0.1%	272.7 (29.4)	272.7 (29.4)	<0.1%
COPD	819.9 (30.8)	819.9 (30.8)	<0.1%	338.2 (36.5)	338.2 (36.5)	<0.1%
Chronic liver disease	1085.4 (40.7)	1085.4 (40.7)	<0.1%	415.5 (44.8)	415.5 (44.8)	<0.1%
Hypertrophic cardiomyopathy	40.9 (1.5)	40.9 (1.5)	<0.1%	11.5 (1.2)	11.5 (1.2)	<0.1%
Osteoporosis	948.0 (35.6)	948.0 (35.6)	<0.1%	333.3 (35.9)	333.3 (35.9)	<0.1%
Sleep apnea	12.8 (0.5)	12.8 (0.5)	<0.1%	5.3 (0.6)	5.3 (0.6)	<0.1%

Concurrent medication‡						
Oral anticoagulant	2666.2 (100.0)	2666.2 (100.0)	<0.1%	927.6 (100.0)	927.6 (100.0)	<0.1%
Warfarin	2170.3 (81.4)	2170.3 (81.4)	<0.1%	791.1 (85.3)	791.1 (85.3)	<0.1%
NOAC	658.6 (24.7)	658.6 (24.7)	<0.1%	181.1 (19.5)	181.1 (19.5)	<0.1%
Beta-blocker	1860.8 (69.8)	1860.8 (69.8)	<0.1%	623.3 (67.2)	623.3 (67.2)	<0.1%
Non-DHP CCB	439.9 (16.5)	439.9 (16.5)	<0.1%	144.3 (15.6)	144.3 (15.6)	<0.1%
Digoxin	451.3 (16.9)	451.3 (16.9)	<0.1%	194.3 (20.9)	194.3 (20.9)	<0.1%
Aspirin	548.3 (20.6)	548.3 (20.6)	<0.1%	183.2 (19.8)	183.2 (19.8)	<0.1%
$P2Y_{12}$ inhibitor	262.2 (9.8)	262.2 (9.8)	<0.1%	76.1 (8.2)	76.1 (8.2)	<0.1%
Statin	1227.3 (46.0)	1227.3 (46.0)	<0.1%	426.2 (45.9)	426.2 (45.9)	<0.1%
DHP CCB	438.7 (16.5)	438.7 (16.5)	<0.1%	153.4 (16.5)	153.4 (16.5)	<0.1%
ACEI/ARB	1420.6 (53.3)	1420.6 (53.3)	<0.1%	493.5 (53.2)	493.5 (53.2)	<0.1%
Loop/thiazide diuretics	1236.3 (46.4)	1236.3 (46.4)	<0.1%	438.1 (47.2)	438.1 (47.2)	<0.1%
K^+ sparing diuretics	496.3 (18.6)	496.3 (18.6)	<0.1%	179.6 (19.4)	179.6 (19.4)	<0.1%
Alpha-blocker	49.5 (1.9)	49.5 (1.9)	<0.1%	21.2 (2.3)	21.2 (2.3)	<0.1%

Values are presented as median (interquartile range) or n (%).

*Weighted number of individuals [crude number of individuals]

†Modified HAS-BLED = hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalised ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point.

‡Defined as a prescription fill of ≥90 days within 6 months after the index date.

AAD, antiarrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; NOAC, non-vitamin K antagonist oral anticoagulant.

Supplementary Table 8. Biological interactions.

Interaction with treatment strategies (rate/rhythm control)	Early AF treatment	Late AF treatment
Sex		
RERI	0.09 (-0.05 to 0.22)	-0.18 (-0.47 to 0.11)
AP	0.12 (-0.06 to 0.29)	-0.18 (-0.46 to 0.10)
Age : ≥75 vs <75		
RERI	0.08 (-0.09 to 0.25)	0.15 (-0.13 to 0.44)
AP	0.07 (-0.08 to 0.22)	0.12 (-0.10 to 0.34)
Previous ischaemic stroke		
RERI	-0.23 (-0.44 to -0.01)	0.09 (-0.22 to 0.41)
AP	-0.19 (-0.37 to -0.01)	0.06 (-0.15 to 0.28)
Previous hospitalisation for heart failure		
RERI	0.30 (0.08 to 0.53)*	0.65 (0.29 to 1.02)*
AP	0.23 (0.07 to 0.38)*	0.42 (0.20 to 0.64)*
Previous myocardial infarction		
RERI	0.17 (-0.10 to 0.45)	-0.08 (-0.46 to 0.31)
AP	0.16 (-0.09 to 0.41)	-0.07 (-0.45 to 0.30)
Hypertension		
RERI	-0.18 (-0.39 to 0.04)	-0.08 (-0.56 to 0.40)
AP	-0.18 (-0.38 to 0.03)	-0.07 (-0.48 to 0.34)
Diabetes		
RERI	-0.04 (-0.19 to 0.12)	-0.04 (-0.30 to 0.23)
AP	-0.04 (-0.24 to 0.15)	-0.04 (-0.35 to 0.26)
Chronic kidney disease		
RERI	0.05 (-0.30 to 0.41)	0.52 (0.03 to 1.01)*
AP	0.05 (-0.29 to 0.39)	0.39 (0.06 to 0.71)*
Level or care : tertiary vs primary/secondary		
RERI	-0.09 (-0.22 to 0.05)	-0.35 (-0.63 to -0.06)
AP	-0.13 (-0.34 to 0.08)	-0.46 (-0.81 to -0.10)
CHA$_2$DS$_2$-VASc : 1-3 vs ≥4		
RERI	-0.24 (-0.50 to 0.01)	0.03 (-0.34 to 0.41)
AP	-0.35 (-0.71 to 0.02)	0.05 (-0.48 to 0.58)

Data are estimates (95% confidence interval).

*Statistically significant with RERI >0 and AP >0, indicating biological interaction.

AP, attributable proportion due to interaction; RERI, relative excess risk due to interaction.

Supplementary Table 9. Crossovers during follow-up.

	Early AF treatment		Late AF treatment	
	Rhythm control (N=9246)	**Rate control (N=7707)**	**Rhythm control (N=4407)**	**Rate control (N=1905)**
Crossover	To rate control	To rhythm control	To rate control	To rhythm control
N (%)	4078 (44.1)	557 (7.9)	1993 (45.2)	119 (6.2)
Median days to crossover (interquartile range)	263 (100-594)	180 (0-496)	163 (0-477)	312 (100-549)

Supplementary Table 10. Outcomes in weighted patients undergoing rhythm or rate control in on-treatment analyses in which patients were censored patients were censored at the time of crossover between treatment modalities or discontinuation of treatment.

	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference* (95% CI)	Weighted HR (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
	Rhythm control (N=9246)			Rate control (N=7077)					
Primary outcome	791	13872	7.03	1103	11940	9.11	-2.08 (-3.32 to -0.85)	0.77 (0.65 to 0.89)	<0.001
Components of primary outcome									
Cardiovascular death	119	14546	1.08	155	13002	1.06	0.02 (-0.41 to 0.46)	1.01 (0.67 to 1.52)	0.96
Ischaemic stroke	321	14259	2.62	469	12567	3.93	-1.31 (-2.08 to -0.54)	0.66 (0.52 to 0.84)	<0.001
Hospitalisation for HF	388	14167	3.43	603	12357	4.56	-1.13 (-1.99 to -0.28)	0.74 (0.60 to 0.92)	0.007
Acute MI	30	14515	0.24	46	12957	0.43	-0.19 (-0.43 to 0.05)	0.54 (0.25 to 1.18)	0.12
Late AF treatment (>1 year since the first diagnosis of AF)									
	Rhythm control (N=4407)			Rate control (N=1905)					
Primary outcome	438	6841	8.06	291	3152	8.56	-0.50 (-2.62 to 1.62)	0.93 (0.72 to 1.20)	0.58
Components of primary outcome									
Cardiovascular death	60	7242	1.28	44	3416	1.17	0.10 (-0.67 to 0.89)	1.08 (0.57 to 2.06)	0.81
Ischaemic stroke	156	7074	3.08	135	3301	3.70	-0.62 (-1.94 to 0.71)	0.82 (0.55 to 1.22)	0.32
Hospitalisation for HF	256	7002	4.19	142	3262	4.05	0.14 (-1.33 to 1.62)	1.02 (0.72 to 1.46)	0.92
Acute MI	17	7231	0.23	13	3405	0.36	-0.13 (-0.51 to 0.25)	0.63 (0.16 to 2.47)	0.51

*Weighted incidence rate (per 100 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied.

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Supplementary Table 11. Outcomes in weighted patients undergoing rhythm or rate control in time-varying regression analyses which treatment was treated as a time-dependent variable.

	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference* (95% CI)	Weighted HR (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
		Rhythm control			Rate control				
Primary outcome	864	14543	7.20	1499	17529	8.88	-1.68 (-2.79 to -0.56)	0.81 (0.71 to 0.94)	0.005
Components of primary outcome									
Cardiovascular death	162	15416	1.32	363	19198	2.00	-0.69 (-1.17 to -0.20)	0.65 (0.48 to 0.90)	0.008
Ischaemic stroke	341	15006	2.60	617	18472	3.63	-1.02 (-1.70 to -0.35)	0.73 (0.58 to 0.91)	0.006
Hospitalisation for HF	433	14887	3.60	756	18220	4.15	-0.55 (-1.31 to 0.22)	0.88 (0.72 to 1.07)	0.19
Acute MI	33	15380	0.25	68	19127	0.37	-0.12 (-0.33 to 0.09)	0.68 (0.33 to 1.39)	0.29
Late AF treatment (>1 year since the first diagnosis of AF)									
		Rhythm control			Rate control				
Primary outcome	452	6991	8.05	544	5912	8.95	-0.90 (-2.85 to 1.05)	0.90 (0.71 to 1.14)	0.37
Components of primary outcome									
Cardiovascular death	66	7428	1.40	180	6580	2.25	-0.85 (-1.69 to -1.39)	0.62 (0.38 to 1.03)	0.07
Ischaemic stroke	161	7241	3.01	225	6290	3.56	-0.54 (-1.72 to 0.64)	0.85 (0.59 to 1.24)	0.40
Hospitalisation for HF	266	7169	4.28	266	6186	4.14	0.14 (-1.22 to 1.50)	1.04 (0.76 to 1.44)	0.80
Acute MI	17	7416	0.21	22	6556	0.32	-0.11 (-0.43 to 0.22)	0.69 (0.19 to 2.56)	0.58

*Weighted incidence rate (per 100 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied.

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Supplementary Table 12. Outcomes in propensity score matched patients undergoing rhythm or rate control.

	Number of events	Person-years	Event rate	Number of events	Person-years	Event rate	Absolute rate difference per 100 person-years (95% CI)	Hazard ratio (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
	Rhythm control (N=3973)			Rate control (N=3973)					
Primary outcome	587	8197	7.16	712	7939	8.97	-1.81 (-2.68 to -0.93)	0.81 (0.72 to 0.90)	<0.001
Components of primary outcome									
Cardiovascular death	183	8824	2.07	202	8757	2.31	-0.23 (-0.67 to 0.20)	0.91 (0.74 to 1.11)	0.35
Ischaemic stroke	229	8537	2.68	307	8373	3.67	-0.98 (-1.52 to -0.47)	0.74 (0.62 to 0.88)	<0.001
Hospitalisation for HF	270	8476	3.19	335	8308	4.03	-0.85 (-1.42 to -0.27)	0.80 (0.68 to 0.94)	0.007
Acute MI	17	8807	0.19	35	8709	0.40	-0.21 (-0.37 to -0.05)	0.49 (0.27 to 0.87)	0.02
Late AF treatment (>1 year since the first diagnosis of AF)									
	Rhythm control (N=1351)			Rate control (N=1351)					
Primary outcome	261	2839	9.19	255	2839	8.98	0.21 (-1.36 to 1.78)	1.03 (0.86 to 1.22)	0.77
Components of primary outcome									
Cardiovascular death	79	3125	2.53	87	3110	2.80	-0.27 (-1.08 to 0.54)	0.91 (0.67 to 1.23)	0.52
Ischaemic stroke	101	2972	3.40	110	2990	3.68	-0.28 (-1.24 to 0.67)	0.92 (0.71 to 1.21)	0.56
Hospitalisation for HF	134	2974	4.51	108	2959	3.65	0.86 (-0.17 to 1.89)	1.25 (0.97 to 1.61)	0.09
Acute MI	7	3120	0.22	11	3095	0.36	-0.13 (-0.40 to 0.14)	1.25 (0.98 to 1.61)	0.08

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; MI, myocardial infarction.

Supplementary Table 13. Outcomes in weighted patients undergoing rhythm or rate control among those without prevalent heart failure, hypertension, or previous myocardial infarction.

	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference per 100 person-years* (95% CI)	Weighted HR (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
	Rhythm control (N=843)			Rate control (N=1114)					
Primary outcome	72	1816	4.65	173	2461	6.53	-1.88 (-3.48 to -0.28)	0.71 (0.53 to 0.96)	0.03
Components of primary outcome									
Cardiovascular death	26	1880	1.71	63	2636	2.18	-0.47 (-1.39 to 0.45)	0.79 (0.49 to 1.29)	0.34
Ischaemic stroke	42	1831	2.59	95	2510	3.53	-0.93 (-2.11 to 0.24)	0.74 (0.50 to 1.10)	0.13
Hospitalisation for HF	11	1867	0.84	48	2578	1.75	-0.91 (-1.66 to -0.16)	0.49 (0.25 to 0.93)	0.03
Acute MI	5	1875	0.19	0	2636	0.00	0.19 (-0.03 to 0.41)	-	0.99
Late AF treatment (>1 year since the first diagnosis of AF)									
	Rhythm control (N=169)			Rate control (N=179)					
Primary outcome	19	390	6.68	29	394	6.92	-0.23 (-4.63 to 4.15)	1.00 (0.52 to 1.91)	0.99
Components of primary outcome									
Cardiovascular death	4	416	1.31	13	423	2.67	-1.36 (-3.64 to 0.92)	0.51 (0.15 to 1.74)	0.28
Ischaemic stroke	12	397	4.00	16	405	4.04	-0.03 (-3.37 to 3.31)	1.03 (0.45 to 2.37)	0.94
Hospitalisation for HF	6	405	1.73	6	412	1.31	0.41 (-1.61 to 2.43)	1.38 (0.36 to 5.26)	0.64
Acute MI	0	416	0.00	1	422	0.18	-0.18 (-0.66 to 0.30)	-	-

*Weighted incidence rate (per 100 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied.

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Supplementary Table 14. Outcomes in weighted patients undergoing rhythm or rate control defined using a 30-day enroll period after the first prescription instead of the 180-day period in main analyses.

	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference per 100 person-years* (95% CI)	Weighted HR (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
	Rhythm control (N=10342)			Rate control (N=7890)					
Primary outcome	2136	24697	10.02	2231	18157	11.92	-1.90 (-2.92 to -0.88)	0.85 (0.77 to 0.93)	<0.001
Components of primary outcome									
Cardiovascular death	532	26687	2.49	573	20235	2.56	-0.07 (-0.54 to 0.39)	0.98 (0.82 to 1.18)	0.84
Ischaemic stroke	753	25513	3.32	882	18872	4.73	-1.41 (-2.02 to -0.80)	0.71 (0.61 to 0.83)	<0.001
Hospitalisation for HF	867	25242	3.88	961	18742	4.88	-1.00 (-1.64 to -0.37)	0.80 (0.69 to 0.93)	0.003
Acute MI	82	26567	0.32	67	20143	0.38	-0.06 (-0.23 to 0.12)	0.86 (0.52 to 1.42)	0.56
Late AF treatment (>1 year since the first diagnosis of AF)									
	Rhythm control (N=4826)			Rate control (N=2387)					
Primary outcome	1226	11747	11.51	709	5537	12.12	-0.62 (-2.34 to 1.11)	0.95 (0.82 to 1.10)	0.52
Components of primary outcome									
Cardiovascular death	343	12871	2.84	175	6272	2.61	0.23 (-0.56 to 1.01)	1.08 (0.81 to 1.45)	0.58
Ischaemic stroke	399	12235	3.66	272	5854	4.32	-0.66 (-1.64 to 0.32)	0.84 (0.66 to 1.07)	0.16
Hospitalisation for HF	607	11943	4.68	260	5861	4.36	0.32 (-0.73 to 1.37)	1.07 (0.85 to 1.35)	0.58
Acute MI	49	12819	0.35	23	6238	0.34	0.00 (-0.27 to 0.29)	1.01 (0.45 to 2.28)	0.98

*Weighted incidence rate (per 100 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied.

Rhythm control in this analysis was defined as a prescription of more than a 20-day supply of any rhythm-control drugs in the 30-day period since the first prescription or the performance of an ablation procedure for AF.

Rate control in this analysis was defined as a prescription of more than a 20-day supply of any rate-control drugs in the 30-day period since the first prescription and with no prescription of rhythm-control drug and no ablation within this period. Patients prescribed rhythm-control drugs for more than 20 days or who underwent ablation within the 30-day period since the initiation of rate-control drugs were classified as intention-to-treat with rhythm control.

AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Supplementary Table 15. Risk of composite outcome not including hospitalisation for heart failure in weighted patients undergoing rhythm or rate control.

Outcome	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference* (95% CI)	Weighted HR (95% CI)	P value
Early AF treatment (≤1 year since the first diagnosis of AF)									
	Rhythm control (N=9246)			Rate control (N=7077)					
The composite of cardiovascular death, ischaemic stroke, or acute myocardial infarction	776	20117	4.69	874	15175	5.77	-1.08 (-1.92 to -0.23)	0.82 (0.70 to 0.97)	0.02
Late AF treatment (≥1 year since the first diagnosis of AF)									
	Rhythm control (N=4407)			Rate control (N=1905)					
The composite of cardiovascular death, ischaemic stroke, or acute myocardial infarction	417	10043	5.35	268	4128	6.06	-0.71 (-2.17 to 0.76)	0.88 (0.68 to 1.14)	0.35

*Weighted incidence rate (per 100 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied.

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

Supplementary Table 16. Risk of 35 falsification endpoints in weighted patients undergoing rhythm control compared with rate control.

Endpoints	Early AF treatment (≤1 year since AF diagnosis)		Late AF treatment (>1 year since AF diagnosis)	
	HR (95% CI)	P value	HR (95% CI)	P value
Major fracture	1.16 (0.97 to 1.39)	0.111	1.02 (0.77 to 1.35)	0.887
Fall accident	1.49 (0.69 to 3.19)	0.310	0.41 (0.14 to 1.19)	0.100
Viral enteritis	1.24 (0.77 to 2.00)	0.384	1.57 (0.77 to 3.18)	0.215
Warts	1.07 (0.59 to 1.95)	0.818	0.38 (0.17 to 0.82)	0.015
Acute hepatitis A	1.01 (0.45 to 2.30)	0.975	0.77 (0.28 to 0.82)	0.599
Viral conjunctivitis	1.17 (0.78 to 1.75)	0.444	1.11 (0.61 to 2.03)	0.724
Stomach cancer	0.80 (0.61 to 1.05)	0.103	1.17 (0.76 to 1.80)	0.481
Bone malignancy	0.79 (0.52 to 1.21)	0.279	0.53 (0.24 to 1.16)	0.111
Lymphoma	0.91 (0.43 to 1.92)	0.802	0.34 (0.10 to 1.17)	0.087
Pterygium	1.05 (0.75 to 1.46)	0.777	1.64 (0.90 to 2.99)	0.106
Otitis media	1.02 (0.88 to 1.19)	0.770	1.14 (0.88 to 1.48)	0.319
Meniere's disease	1.02 (0.88 to 1.19)	0.856	1.32 (0.87 to 2.01)	0.192
Benign paroxysmal positional vertigo	0.91 (0.74 to 1.11)	0.356	1.63 (1.15 to 2.32)	0.006
Varicose veins of lower extremities	0.90 (0.61 to 1.34)	0.614	0.98 (0.57 to 1.70)	0.945
Chronic sinusitis	1.09 (0.95 to 1.25)	0.237	1.15 (0.93 to 1.42)	0.186
Benign neoplasm of colon, rectum	1.35 (1.07 to 1.70)	0.011	1.19 (0.85 to 1.66)	0.305
Acute appendicitis	1.30 (0.76 to 2.23)	0.336	1.64 (0.67 to 4.02)	0.279
Inguinal hernia	1.33 (0.87 to 2.03)	0.193	0.70 (0.36 to 1.37)	0.302
Diverticulitis of intestine	1.48 (0.89 to 2.45)	0.127	1.20 (0.53 to 2.71)	0.662
Cholecystitis	0.83 (0.59 to 1.16)	0.275	1.25 (0.71 to 2.21)	0.440
Cellulitis	1.14 (1.02 to 1.28)	0.027	0.95 (0.80 to 1.13)	0.591
Allergic contact dermatitis	1.08 (1.00 to 1.16)	0.049	1.04 (0.93 to 1.18)	0.471
Urticaria	1.03 (0.94 to 1.13)	0.495	1.16 (0.99 to 1.35)	0.060
Ingrowing nail	1.30 (0.91 to 1.86)	0.148	0.75 (0.43 to 1.32)	0.317
Seropositive rheumatoid arthritis	0.95 (0.64 to 1.41)	0.789	1.02 (0.53 to 1.97)	0.949
Gout	0.95 (0.64 to 1.41)	0.511	1.10 (0.90 to 1.35)	0.344
Spinal stenosis	1.05 (0.97 to 1.41)	0.244	1.13 (0.99 to 1.30)	0.067
Frozen shoulder	0.94 (0.83 to 1.06)	0.329	0.86 (0.70 to 1.05)	0.125
Osteomyelitis	1.07 (0.52 to 2.21)	0.859	1.00 (0.35 to 2.85)	0.998
Nausea and vomiting	1.06 (0.98 to 1.16)	0.135	1.20 (1.05 to 1.38)	0.007
Dysuria	0.92 (0.76 to 1.10)	0.360	0.99 (0.74 to 1.32)	0.932
Voice disturbance	1.49 (0.58 to 3.82)	0.407	1.18 (0.35 to 3.98)	0.793
Seizure	0.86 (0.68 to 1.11)	0.245	0.94 (0.64 to 1.39)	0.767
Burns	1.21 (0.93 to 1.59)	0.159	1.32 (0.83 to 2.08)	0.238
Anaphylaxis/Allergic reaction	0.92 (0.65 to 1.29)	0.617	1.17 (0.69 to 1.98)	0.558

CI, confidence interval; HR, hazard ratio.

Supplementary Table 17. Cumulative duration of treatment for patients initiating rhythm- or rate-control treatments.

Duration (days)	Early AF treatment		Late AF treatment	
	Rhythm control* (N=9101)	Rate control (N=7077)	Rhythm control* (N=3768)	Rate control (N=1905)
0-360	2383 (26.2)	1195 (16.9)	1202 (31.9)	373 (19.6)
361-720	3100 (34.1)	2400 (33.9)	1202 (31.9)	596 (31.3)
721-1080	1703 (18.7)	1405 (19.9	622 (16.5)	405 (21.3)
1080-	1915 (21.0)	2077 (29.3)	72 (19.7)	531 (27.9)

Numbers are n (%).

*Analysis conducted in rhythm-controlled patients not undergoing catheter ablation at baseline.

Supplementary Table 18. Primary composite outcome associated with cumulative exposure to antiarrhythmic drugs (AADs).

Duration (days)	Early rhythm control Hazard ratio (95% confidence interval)	Late rhythm control Hazard ratio (95% confidence interval)
0-360	1 (ref)	1 (ref)
361-720	0.97 (0.84 to 1.11)	1.13 (0.94 to 1.35)
721-1080	0.77 (0.64 to 0.92)	0.78 (0.60 to 1.02)
1081-	0.35 (0.27 to 0.44)	0.42 (0.30 to 0.59)
P value for trend	**<0.001**	**<0.001**

Analysis conducted in rhythm-controlled patients not undergoing catheter ablation.

Follow-up begins at the end of the last AAD prescription.

Supplementary Figure 1. Distributions of the propensity scores before and after overlap weighting in (A) early and (B) late treatment populations.
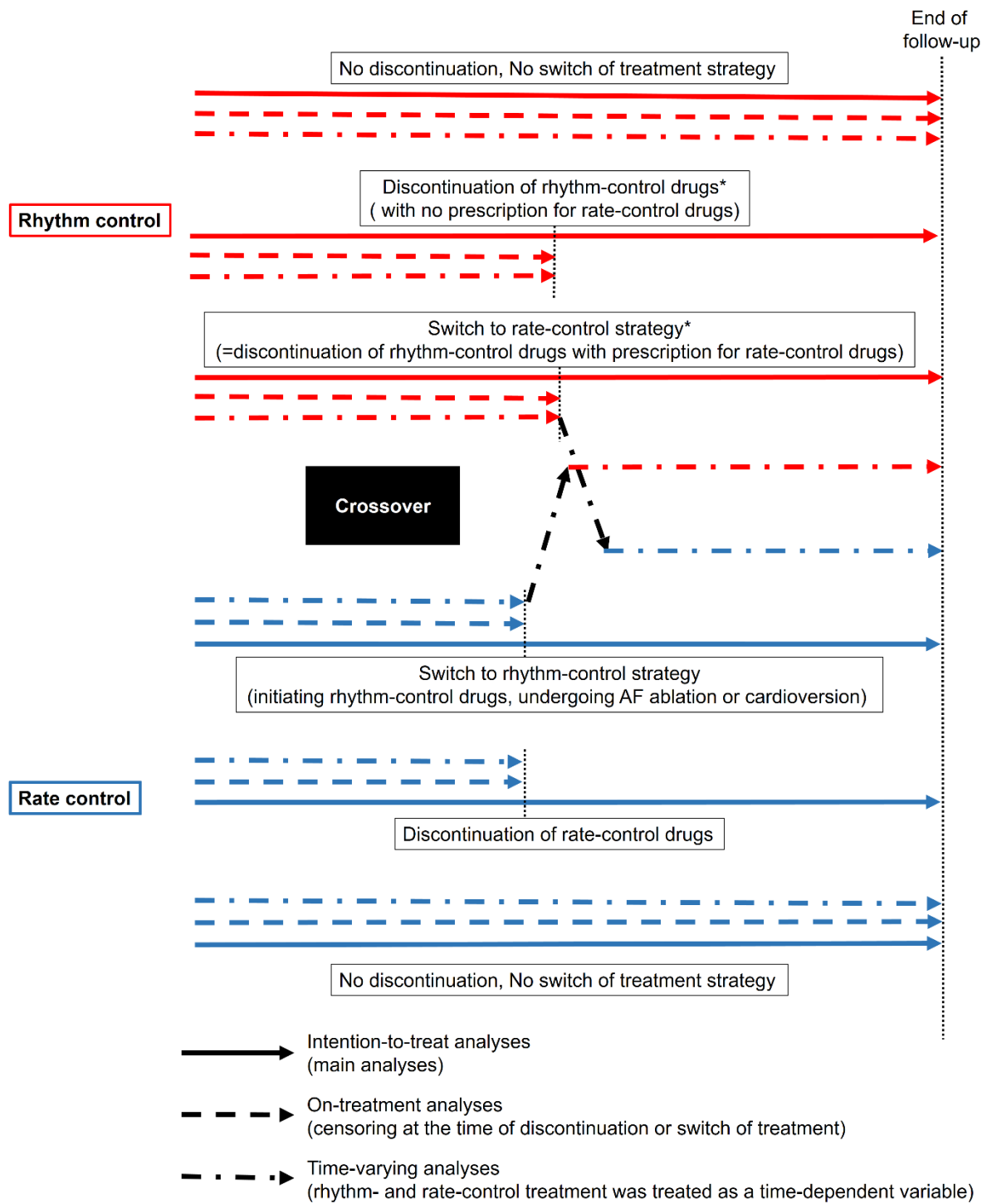
A. Early AF treatment (≤1 year since the first AF diagnosis)
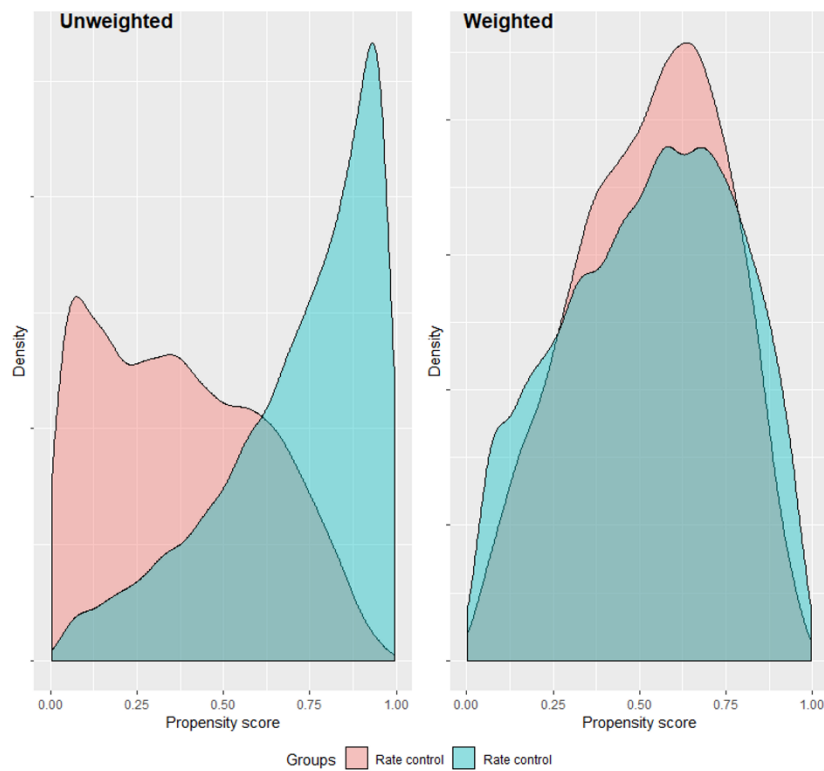
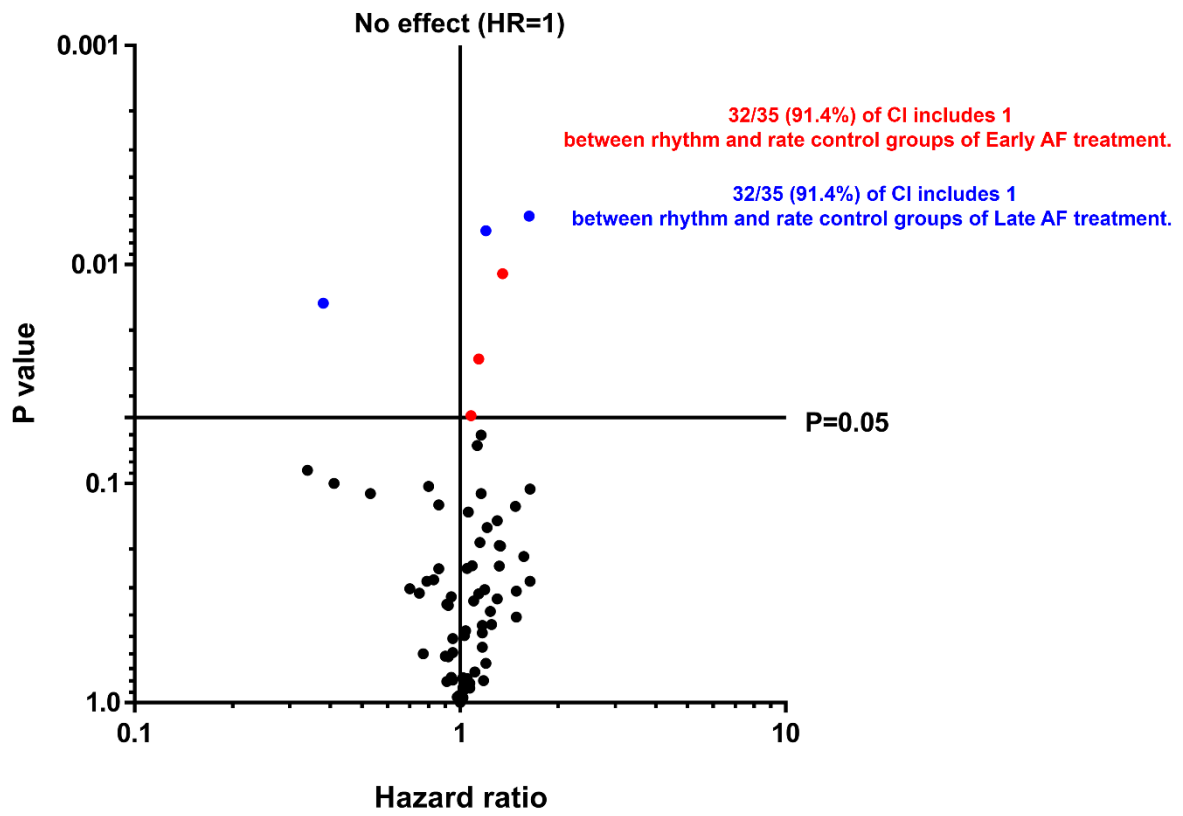## B. Late AF treatment (>1 year since the first AF diagnosis)
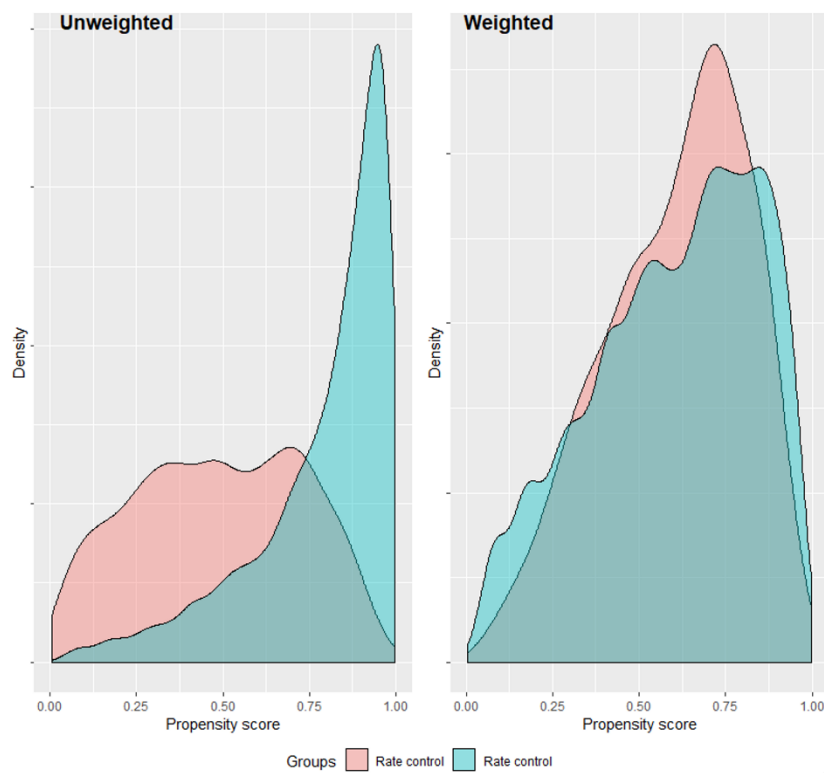
Supplementary Figure 2. Schematic diagram showing the analytical approach used in this study.

*No crossover was permitted in the rhythm-controlled patients who underwent ablation.

Supplementary Figure 3. Risk of 35 falsification endpoints in weighted patients undergoing rhythm or rate control.

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.