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Research article

Rate control or rhythm control in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention

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ABSTRACT

Background: Restoring and maintaining sinus rhythm in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) has been studied in clinical trials to reduce symptoms and improve quality of life. Limited data exist on the effectiveness of rate or rhythm control therapy in these patients.

Methods: Consecutive patients with AF and ACS or referred for PCI were prospectively recruited in Fuwai Hospital during 2017–2020. The primary endpoints were all-cause death and major adverse cardiovascular and cerebrovascular events (MACCEs), including cardiovascular mortality, myocardial infarction, ischemic stroke, non-central nervous system embolism and ischemia-driven revascularization. Kaplan–Meier curves and Cox regressions were performed to evaluate the association between rhythm/rate control and subsequent outcomes. For the primary endpoints, we used the Benjamini–Hochberg correction for multiple comparisons.

Results: A total of 1499 patients with AF and ACS or undergoing PCI were included, with a median follow-up of 34.7 months. Compared to non-rate control, rate control strategy reduced the risk of subsequent MACCEs (adjusted HR, 0.320; 95 % CI 0.220–0.466; $p < 0.001$; $^*p < 0.002$) and all-cause death (adjusted HR, 0.148; 95 % CI 0.093–0.236; $p < 0.001$; $^*p < 0.002$). Similar trends were observed across all predefined subgroups ($p < 0.001$). In the final multivariate model, rhythm control was not associated with a lower subsequent MACCEs but significantly improved all-cause mortality compared to non-rhythm control (adjusted HR, 0.546; 95 % CI 0.313–0.951; $p = 0.033$; $^*p = 0.044$).

Conclusions: In this real-world study, rate control strategy was associated with lower risk of MACCEs and all-cause death in AF and ACS or undergoing PCI. Besides, management with rhythm control strategy may improve all-cause mortality.

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1. Introduction

Acute coronary syndrome (ACS), the acute manifestation of coronary artery disease (CAD), imposes a significant financial burden on the healthcare system [1]. Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, is often comorbid with CAD [2–7]. The incidence of AF in patients with ACS ranges from 10% to 21% in registries and clinical trials [8]. Moreover, a previous study predicted that 10%–15% of AF patients would require percutaneous coronary intervention (PCI) for CAD during their lifetime [9].

In the setting of ACS, AF, an independent predictor of death, is associated with worse prognosis and increased hospitalization charges [8,10]. Currently, the cornerstones of AF therapy are anticoagulation and rate or rhythm control [11]. For patients with AF and ACS or receiving PCI, both rate control and rhythm control are urgent and essential as the rapid or irregular heart rate may exacerbate ischemia [12]. However, the current guidelines and clinical trials for AF and ACS primarily emphasize thromboembolism prevention rather than heart rate or sinus rhythm maintenance [8]. There is a lack of evidence regarding whether rate or rhythm control treatment is associated with long-term prognosis among patients with AF and ACS or undergoing PCI [8].

Therefore, the aim of this study was to demonstrate different baseline characteristics based on rate or rhythm control therapy and to determine the impact of these two therapies on long-term prognosis among patients with AF and ACS or undergoing PCI.

2. Methods

2.1. Study population

This is a post hoc analysis based on data from a single-center, prospective, real-world cohort study focused on the treatment of patients with AF hospitalized for ACS or undergoing PCI. A total of 1945 consecutive patients with AF and ACS or referred for PCI at Fuwai Hospital (National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China) were accessed for eligibility from January 2017 to December 2019. Inclusion criteria were as follows: (1) patients aged $\geq$18 years; (2) patients with AF (new-onset, paroxysmal, persistent, or permanent) verified by clinical records and electrocardiography; (3) patients diagnosed with ACS (unstable angina, non-ST-segment elevation myocardial infarction (MI), or ST-segment elevation MI), or referred for elective or acute PCI. The classification of AF adhered to the 2020 European Society of Cardiology (ESC) guideline [13]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Fuwai Hospital. All participants have signed the informed consent forms.

2.2. Data source

Demographic characteristics (age, sex, body mass index (BMI)), vital signs (systolic blood pressure, diastolic blood pressure, heart rate), AF subtypes, CAD subtypes (chronic coronary syndrome (CCS) and ACS),medical history (previous CAD, MI, heart failure, hypertension, hyperlipidemia, diabetes mellitus, stroke or transient ischemic attack (TIA), valvular heart disease, bleeding, chronic obstructive pulmonary disease, peripheral vascular disease, renal insufficiency, liver disease, tobacco use, alcohol use), laboratory examinations (blood cell count, hemoglobin (Hb), cardiac troponin I (cTNI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP)), echocardiographic parameters (left atrium diameter, left ventricular ejection fraction (LVEF)), in-hospital procedures, and regimens at discharge were systematically collected from the medical records. These records were abstracted by independent research personnel who were unaware of the objectives of the study.

Patients were divided into two main groups: the rate control group and the non-rate control group; alternatively, the rhythm control group and the non-rhythm control group. Rate control strategy was defined by the administration of at least one rate control medication, including β-blockers, calcium channel blockers, and digoxin. Non-rate control was defined as the absence of rate control medication use. Patients in the rate/non-rate control groups were allowed to receive rhythm control medications. Similarly, the rhythm control strategy was defined by receiving at least one of the following rhythm control medication: amiodarone, sotalol, or other antiarrhythmic agents. The non-rhythm control group comprised patients who were not prescribed any rhythm control medications. Patients in the rhythm/non-rhythm control group were also permitted to receive rate control medications.

2.3. Outcomes and follow-up

The primary outcomes of interest were all-cause death and major adverse cardiovascular and cerebrovascular events (MACCEs) defined as a composite of cardiovascular death, MI, ischemic stroke, non-central nervous system embolism, ischemia-driven revascularization, and target vessel revascularization. The secondary outcomes included cardiovascular death, MI, ischemic stroke, and ischemia-driven revascularization, target vessel revascularization and bleeding. All clinical events were adjudicated by an independent clinical event adjudication committee. Clinical follow-up was mandatory at 6 and 12 months after enrollment, and outpatient visits or telephone calls were recommended annually until December 2021.

2.4. Statistical analysis

For each study group, baseline characteristics were compared using Student's *t*-test or Wilcoxon rank-sum test as appropriate for continuous variables, presented as mean ± SD or median [interquartile range (IQR)]. Categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate and presented as percentages (%). Primary and secondary endpoints were described

Table 1
Characteristics and treatments in AF patients with ACS or receiving PCI who treated with rhythm (rate) versus non-rhythm (non-rate) control. AF, atrial fibrillation; ACS, acute coronary syndrome; CCS, chronic coronary syndromes; TIA, transient ischemic attack; OAC, oral anticoagulants; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Variable	Overall n = 1499	Rhythm Control n = 269	Non- Rhythm Control n = 1230	P Value	Rate Control n = 1307	Non- Rate Control n = 192	P Value
Age, y	67.7 ± 9.7	67.7 ± 9.6	67.7 ± 9.7	0.766	67.2 ± 9.4	70.9 ± 10.6	<0.001
Male	1087 (72.5)	193 (71.9)	894 (72.7)	0.756	949 (72.7)	138 (71.9)	0.832
Body mass index, kg/m2	25.7 ± 3.5	25.3 ± 3.6	25.8 ± 3.4	0.091	25.8 ± 3.4	25.1 ± 4.0	0.020
Systolic blood pressure, mmHg	130 ± 20	130 ± 22	129 ± 20	0.602	130 ± 20	122 ± 23	<0.001
Diastolic blood pressure, mmHg	77 ± 12	77 ± 12	77 ± 12	0.435	77 ± 11	73 ± 13	<0.001
Initial Heart Rate, beats/min	77 ± 20	79 ± 22	77 ± 20	0.186	77 ± 19	81 ± 26	0.030
AF subtype				<0.001			0.039
New-onset AF	121 (8.1)	49 (18.2)	72 (5.9)		97 (7.4)	24 (12.5)	
Paroxysmal AF	841 (56.1)	182 (67.7)	659 (53.6)		730 (55.9)	111 (57.8)	
Persistent AF	387 (32.5)	33 (12.3)	454 (36.9)		437 (33.4)	50 (26.0)	
Permanent AF	50 (3.3)	5 (1.9)	45 (3.7)		43 (3.3)	7 (3.6)	
Coronary artery disease subtype				0.006			0.002
CCS	435 (29.0)	59 (21.9)	376 (30.6)		398 (30.5)	37 (19.3)	
ACS	1064 (71.0)	210 (78.1)	854 (69.4)		909 (69.5)	155 (80.7)	
Medical history							
Coronary artery disease	997 (66.5)	169 (62.8)	828 (67.4)	0.157	885 (67.7)	112 (58.3)	0.010
Myocardial infarction	428 (28.6)	82 (30.5)	346 (28.1)	0.439	373 (28.5)	55 (28.6)	0.976
Heart failure	335 (22.3)	57 (21.2)	278 (22.6)	0.615	283 (21.7)	52 (27.1)	0.092
Hypertension	1153 (76.9)	197 (73.2)	956 (77.7)	0.113	1019 (78.0)	134 (69.8)	0.012
Hyperlipidemia	1096 (73.1)	204 (75.8)	892 (72.5)	0.266	968 (74.1)	128 (66.7)	0.031
Diabetes mellitus	638 (42.6)	115 (42.8)	523 (42.5)	0.945	555 (42.5)	83 (43.2)	0.841
Stroke or TIA	382 (25.5)	64 (23.8)	318 (25.9)	0.482	327 (25.0)	55 (28.6)	0.282
Bleeding	120 (8.0)	24 (8.9)	96 (7.8)	0.541	99 (7.6)	21 (10.9)	0.109
Renal insufficiency	244 (16.3)	50 (18.6)	194 (15.8)	0.257	176 (13.5)	68 (35.4)	<0.001
Tobacco use	365 (24.3)	71 (26.4)	294 (23.9)	0.388	316 (24.2)	49 (25.5)	0.686
Alcohol use	352 (23.5)	57 (21.2)	295 (24.0)	0.327	314 (24.0)	38 (19.8)	0.196
Laboratory Examination							
White blood cell count, $*10^9$/l	6.9 (5.7–8.5)	7.4 (6.1–9.2)	6.8 (5.6–8.3)	<0.001	6.8 (5.6–8.2)	7.7 (7.1–11.0)	<0.001
Hemoglobin, g/l	142 ± 20	139 ± 20	142 ± 20	0.037	143 ± 19	135 ± 22	<0.001
Cardiac troponin I	4.0 (0.4–37.6)	6.5 (0.7–87.8)	3.6 (0.3–29.4)	0.001	3.6 (0.3–25.3)	32.9 (1.8–385.5)	<0.001
N-terminal pro-B type natriuretic peptide, pg/ml	1216.3 (342.0–3814.2)	1984.5 (337.5–4908.0)	1151.0 (343.0–3472.0)	0.012	1119.3 (316.6–3182.0)	3829.5 (789.4–16161.3)	<0.001
Echocardiography							
Left atrium diameter, cm	42.0 ± 7.0	41.0 ± 5.9	42.6 ± 7.2	0.002	42.3 ± 6.9	42.3 ± 7.3	0.855
Left ventricular ejection fraction, %	60 ± 11	54 ± 11	56 ± 10	0.002	56 ± 10	51 ± 12	<0.001
Medications at discharge							
Antithrombotic regimens				<0.001			<0.001
None	98 (6.5)	1 (0.4)	97 (7.8)		2 (0.2)	96 (50.0)	
SAPT	23 (1.5)	8 (3.0)	15 (1.2)		20 (1.5)	3 (1.6)	
DAPT	698 (46.6)	140 (52.0)	558 (45.4)		645 (49.3)	53 (27.6)	
OAC + SAPT	249 (16.6)	60 (22.3)	189 (15.4)		237 (18.1)	12 (6.3)	
OAC + DAPT	431 (28.8)	60 (22.3)	371 (30.2)		403 (30.8)	28 (14.6)	
Statins	1378 (91.9)	261 (97.0)	1117 (90.8)	<0.001	1284 (98.2)	94 (49.0)	<0.001
ACEI/ARB	901 (60.1)	173 (64.3)	728 (59.2)	0.120	836 (64.0)	65 (33.9)	<0.001
In hospital procedures, No. (%)							
Conservative treatment	442 (29.5)	95 (35.3)	347 (28.2)	0.021	349 (26.7)	93 (48.4)	<0.001
Reperfusion therapy	1057 (70.5)	174 (64.7)	883 (71.8)	0.021	958 (73.3)	99 (51.6)	<0.001
Treatment strategy, No. (%)							
Rate control	1307 (87.2)	254 (94.4)	1053 (85.6)	<0.001	1307 (100)	0 (0)	
β -blockers	1213 (80.9)	233 (86.6)	980 (79.7)	0.009	1213 (92.8)	0 (0)	
Digoxin	81 (5.4)	12 (4.5)	69 (5.6)	0.450	81 (6.2)	0 (0)	
Calcium channel blockers	496 (33.1)	94 (34.9)	402 (32.7)	0.475	496 (37.9)	0 (0)	
Rhythm control	269 (17.9)	269 (100)	0 (0)		254 (19.4)	15 (7.8)	<0.001
Amiodarone	211 (14.1)	211 (78.4)	0 (0)		197 (15.1)	14 (7.3)	0.004
Sotalol	28 (1.9)	28 (10.4)	0 (0)		27 (2.1)	1 (0.5)	0.376

(*continued on next page*)

Table 1 (*continued*)

Variable	Overall n = 1499	Rhythm Control n = 269	Non- Rhythm Control n = 1230	P Value	Rate Control n = 1307	Non- Rate Control n = 192	P Value
Other Anti-arrhythmic agents	41 (2.7)	41 (15.2)	0 (0)		41 (3.1)	0 (0)	<0.001

Values are means ± SD, median (interquartile range) or n (%).

according to the groups (rhythm control versus non-rhythm control and rate control versus non-rate control). For primary endpoints, incidence was calculated based on Kaplan–Meier estimates, and differences between groups were tested using the log-rank test.

For the primary endpoints and secondary endpoints, Cox proportional hazard modeling was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Covariates chosen for the adjustment model included age, sex, AF subtype (new-onset AF and recurrent AF), CAD subtype (ACS and CCS), history of hypertension, heart failure, diabetes mellitus, stroke or TIA, bleeding, chronic kidney disease, systolic blood pressure at admission, LVEF, in-hospital procedures (conservative treatment, reperfusion therapy) and antithrombotic regimens at discharge. For the primary endpoints, the Benjamini–Hochberg correction was used for multiple comparisons [14].

Differences were considered significant if *p-values were <0.05 after Benjamini–Hochberg correction. We further conducted subgroup analyses to assess rate or rhythm control therapy on MACCEs based on age (<65 versus ≥65), sex (male versus female), AF subtype (new-onset AF versus recurrent AF), heart failure (yes versus no), hypertension (yes versus no), diabetes mellitus (yes versus no), LVEF (≥50% versus <50%), and in-hospital procedures (conservative treatment versus reperfusion therapy). All statistical tests were performed at a significance level of 0.05. All analyses were performed using SPSS version 25.0 (IBM Corporation, New York, NY, USA) and R version 4.1.2 (R Core Team, Vienna, Austria).

3. Results

3.1. Baseline characteristics of the patients

A total of 1499 patients with AF and ACS or undergoing PCI were included (Fig. S1 in Supplemental Materials). The median follow-up period was 34.7 months (IQR 17.7–43.6). Baseline clinical data are summarized in Table 1. The median age was 67.7 ± 9.7 years and 1087 (72.5%) were male. More than half had paroxysmal AF (56.1%), and 8.1 % patients had new-onset AF. A total of 1064 (71.0%) patients were diagnosed with ACS at enrollment; 70.5% underwent reperfusion therapy during hospitalization; 1153 (76.9%) had hypertension and 638 (42.6%) had diabetes mellitus.

3.2. Rate control versus non-rate control

Of 1499 patients, 1307 (87.2%) received rate control therapy and were characterized as rate control group; while192 (12.8%) did not receive rate control medications and were characterized as non-rate control group. Among 1307 patients in the rate control group, 1213 (92.8%) received β-blockers; 81 (6.2%) were taking digoxin; and 496 (37.9%) were taking calcium channel blockers.

As shown in Table 1, patients in the rate control group tended to be younger and have higher blood pressure ($p < 0.001$). They were less likely to have ACS and hypertension but more likely to receive reperfusion therapy during hospitalization (73.3% vs. 51.6%, $p < 0.001$). Besides, they tended to have higher LVEF ($p < 0.001$). Patients in the rate control group were more often medically managed compared with those without rate control therapy [antithrombotic regimens, statins (98.2% vs. 49.0%), ACEI/ARB (64.0% vs. 33.9%)].

3.3. Rhythm control versus non-rhythm control

Of 1499 patients, 269 (17.9%) received the rhythm control and were characterized as rhythm control group; while 1230 (82.1%) did not receive rhythm control and were characterized as non-rhythm control group. Among the 269 patients in the rhythm control group, 211 (78.4%) were treated with amiodarone; 28 (10.4%) were taking sotalol and 41 (15.2%) received other anti-arrhythmic agents.

There were no differences in age, sex, BMI, blood pressure, and initial heart rate between the two groups. Patients who received rhythm control treatment were more likely to have ACS (78.1% vs. 69.4%, $p = 0.006$) but less likely to receive reperfusion therapy during hospitalization (64.7% vs. 71.8%, $p = 0.021$). Patients receiving rhythm control therapy had slightly lower LVEF ($p = 0.002$). The rhythm control group had higher rates of treatment with statins (97.0% vs. 90.8%, $p < 0.001$) and β-blockers (86.6% vs. 79.7%, $p = 0.009$).

3.4. Outcomes

Table 2 provided the incidence of primary endpoints. In the rhythm control group, 48 (17.8%) patients experienced MACCEs; 36 (13.4%) patients experienced all-cause death. In the non-rhythm control group, 285 (23.2%) MACCEs and 195 (15.9%) all-cause deaths occurred during follow up. In the rate control group, there were 230 (17.6%) incidents of MACCEs and 128 (9.8%)

incidents of all-cause deaths during follow up. In the non-rate control group, 103 (53.6%) MACCEs and 103 (53.6%) all-cause deaths occurred during follow up. Fig. 1 demonstrates the Kaplan-Meier curves of cumulative incidence of primary endpoints. The incidence of secondary endpoints for each group is presented in Table S1 (Supplemental Materials).

Fig. 2 shows the HRs for primary endpoints. After multivariable adjustment, prescription for rate control medications was significantly associated with lower risk of MACCEs (adjusted HR, 0.320; 95% CI 0.220–0.466; p <0.001; *p <0.002) and all-cause death (adjusted HR, 0.148; 95% CI 0.093–0.236; p <0.001; *p <0.002) compared to the non-rate control group. After adjustment, no significant association between rhythm control therapy and risk of MACCEs was observed (adjusted HR, 0.664; 95% CI 0.437–1.009; p =0.055; *p =0.055). Patients receiving rhythm control tended to have lower risk of all-cause death compared to the non-rhythm control (adjusted HR, 0.546; 95% CI 0.313–0.951; p =0.033; *p =0.044). Table S2 (Supplemental Materials) shows the HRs of secondary endpoints for rhythm control (reference =non-rhythm control) or rate control (reference =non-rate control) .

With respect to MACCEs, the protective effect of rate control therapy, as compared with non-rate control, was generally consistent across all prespecified subgroups, including those defined according to age, sex, type of episode of AF, presence of HF, hypertension, diabetes mellitus, LVEF, and in-hospital procedures (p <0.001, Fig. 3).

The rhythm control strategy might indicate a reduced risk of MACCEs compared to the non-rhythm control strategy in several specific subgroups. These subgroups included males (p =0.029), patients with new-onset AF (p =0.036), patients with LVEF<50% (p =0.034), and patients who underwent conservative treatment (p =0.002, Fig. 4).

4. Discussion

In the present study of 1499 patients admitted with AF and ACS or undergoing PCI, we found that the rate control group had a significantly lower incidence of MACCEs and all-cause death compared with the non-rate control group. A similar protective trend with the rate control strategy was observed across all predefined subgroups. After adjustment, the difference in MACCEs and all-cause death remained significant. Additionally, in the unadjusted analysis, the risks of MACCEs and all-cause death were not significant different between rhythm control group and non-rhythm control group. Protective effects of rhythm control were observed in several subgroups, including males, patients with new-onset AF, patients with LVEF <50%, and patients who underwent conservative treatment. After adjustment, the use of rhythm control therapy significantly improved all-cause mortality compared with non-rhythm control.

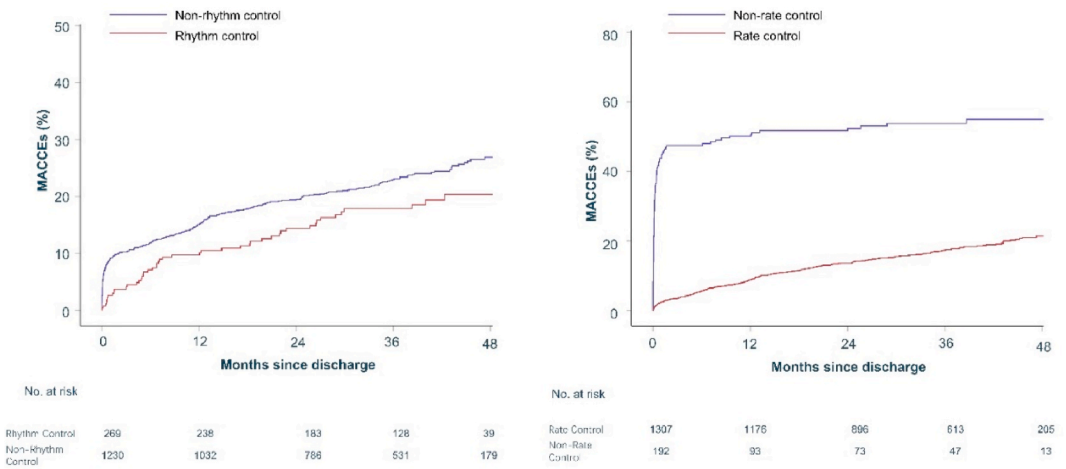
Due to the high prevalence of both AF and CAD, an increasing number of patients with AF are presenting with ACS or undergoing PCI [15]. Patients with AF and ACS have worse outcomes compared to those who remain in normal sinus rhythm [16]. Previous clinical trials have evaluated the impact of heart rate in ACS or AF individually. For instance, Andrade et al. found that high baseline heart rate in sinus rhythm is independently associated with mortality in patients with AF. And the baseline heart rate in AF could predict hospitalizations [17]. Also, Westergaard et al. observed that ventricular rates ≥100 bpm among AF patients in rate control pharmacotherapy were associated with high risk of new-onset heart failure and all-cause mortality [18]. Besides, for patients with ACS, a rest heart rate ≥82 bpm was associated with worse outcome [19]. In the context of ACS, tachycardia and irregular rhythm during AF could lead to greater myocardial oxygen consumption, shorten the duration of diastole, decrease myocardial perfusion, and exacerbate existing subendocardial ischemia [12,20]. AF is a frequent finding in ACS and complicates its course [10]. However, the treatment of AF in patients who have ACS or undergo PCI is currently poorly understood.

In this study, we focused on patients with AF and ACS or undergoing PCI. We found that the incidence of MACCEs and all-cause death was significantly lower in the rate control group compared with the non-rate control group. The beneficial effect of rate control was consistent across subgroups. After adjusting for confounders through multivariable analysis, the risks of MACCEs and all-cause death remained significantly lower with the use of rate control strategy. Our findings are in line with previous studies. RACE II trial found that, among patients with permanent AF, whether implemented through a loose strategy (resting heart rate <110 bpm) or a strict strategy (resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm), rate-control therapy could prevent the composite outcome of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and life threatening arrhythmic [21]. Collectively, our findings suggest that rate control provides protective effects against MACCEs and all-cause death in patients with AF and ACS or undergoing PCI. The optimal heart rate range for these patients requires further study.

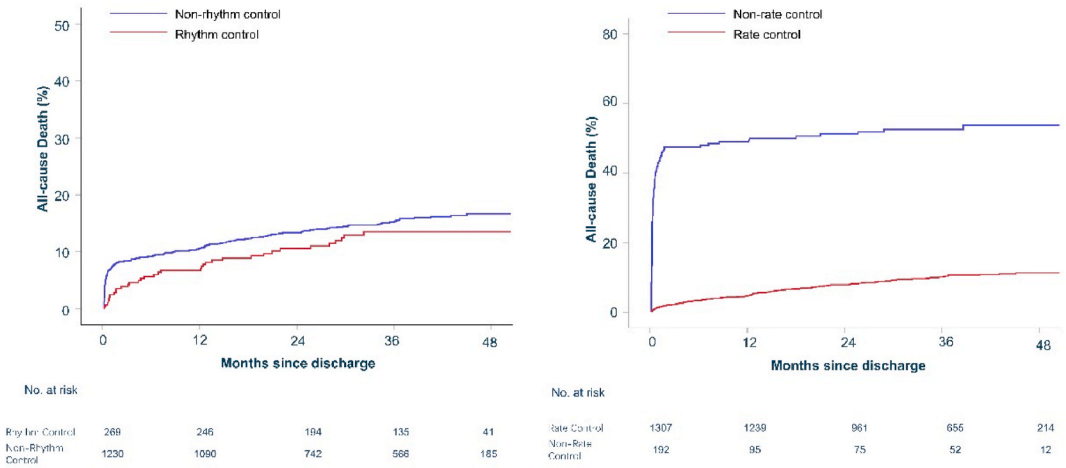
The 2020 ESC guidelines proposed the Atrial fibrillation Better Care (ABC) pathway, consisting of three pillars: 'A' for stroke prevention, 'B' for symptom management, and 'C' for the management of cardiovascular risk factors and other comorbidities [13]. For better symptom management, rate-control and rhythm-control strategies were considered equal in patients with AF. Because landmark studies conducted approximately two decades ago have confirmed that management of AF with the rhythm-control strategy offers no survival advantage over the rate-control strategy [22,23]. Recently, the choice of rhythm therapeutic options has changed with the development of anti-arrhythmic medications and catheter ablation. The EAST-AFNET4 trial showed a clinical benefit of early rhythm-control therapy in patients with recently diagnosed AF (within the past 12 months), which reduced the rate of adverse

Table 2
Primary outcomes for AF patients with ACS or receiving PCI who were treated with rhythm control (ref = non-rhythm control) or rate control (ref = non-rate control). MACCEs, major adverse cardiovascular and cerebrovascular events.

Primary outcomes	Rhythm Control n = 269	Non- Rhythm Control n = 1230	P Value	Rate Control n = 1307	Non-Rate Control n = 197	P Value
MACCEs	48 (17.8)	285 (23.2)	0.068	230 (17.6)	103 (53.6)	<0.001
All-cause death	36 (13.4)	195 (15.9)	0.356	128 (9.8)	103 (53.6)	<0.001



A



B

Fig. 1. A, MACCEs with rhythm (rate) control in patients with AF who develop ACS or undergo PCI (ref = non-rhythm (rate) control); B, All-cause death with rhythm (rate) control in patients with AF who develop ACS or undergo PCI (ref = non-rhythm (rate) control). AF, atrial fibrillation; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; MACCEs, major adverse cardiovascular and cerebrovascular events.

cardiovascular outcomes by ~20 % [24]. Furthermore, in the specific subpopulation of AF patients with heart failure or a high co-morbidity burden, early rhythm control therapy has shown clinical benefits [25,26]. Our study aligns with previous research, emphasizing the importance of rhythm-control therapy for patients with AF and ACS or receiving PCI. We found that administration of antiarrhythmic medications significantly decreased all-cause mortality compared with non-rhythm control strategy. This benefit was significant in male patients, those with new-onset AF, those with LVEF below 50%, and those undergoing conservative treatment. However, attention must be given to the possible disadvantages of the anti-arrhythmic medications. Both the AFFIRM and EAST-AFNET4 trials highlighted the higher risk of adverse drug effects associated with rhythm-control strategy [22,27].

Several limitations should be underscored. First, this study was an observational, prospective, single-center registry with its inherent defects. As a post hoc analysis, the present study should be considered hypothesis-generating rather than providing definitive conclusions. However, our study was built upon real-world clinical practice with strict follow-up. Besides, the relatively large sample size of AF patients with ACS or undergoing PCI supported the reliability of our conclusions. Second, the trial design did not incorporate specific values of heart rate and long-term rhythm monitoring during follow-up. Although the majority of patients in this study demonstrated relatively favorable baseline control, with 92.19% having an admission heart rate of ≤110 beats per minute, the

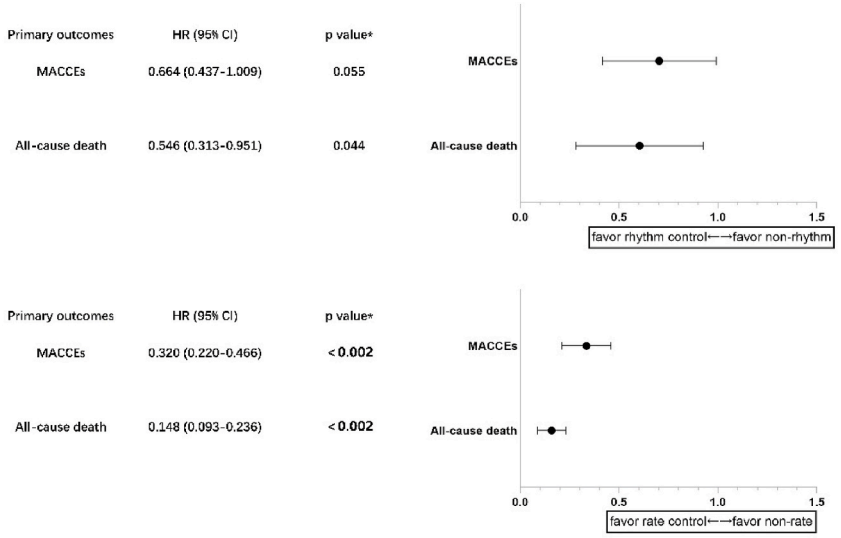


Fig. 2. A. Adjusted HRs of primary outcomes for AF patients with ACS or receiving PCI who treated with rhythm control (ref = non-rhythm control). B. Adjusted HRs of primary outcomes for AF patients with ACS or receiving PCI who treated with rate control (ref = non-rate control). AF, atrial fibrillation; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; HR, hazard ratio; MACCEs, major adverse cardiovascular and cerebrovascular events.

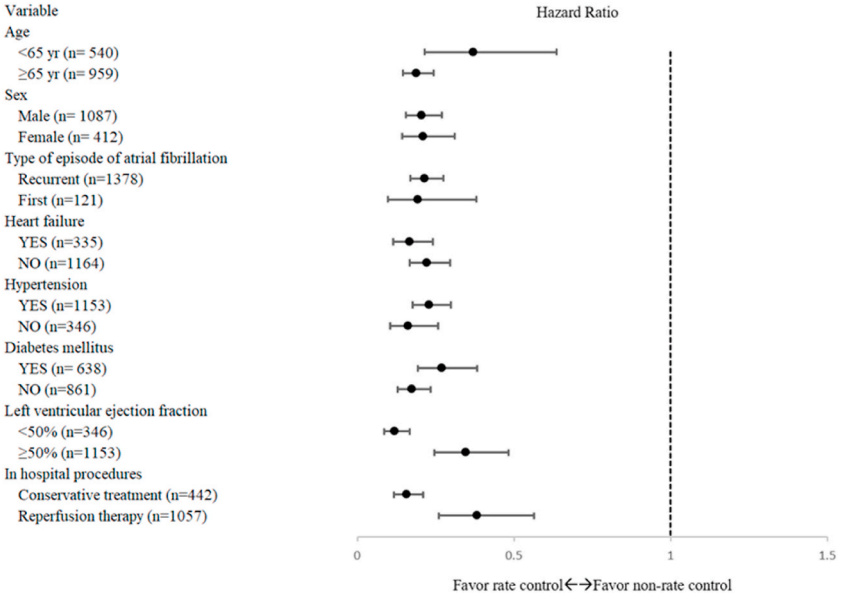


Fig. 3. Forest plot of treatment effects of rate-control compared to non-rate control therapy by predefined subgroups.

effectiveness of rate and rhythm control strategies in future follow-up periods remains uncertain. This potential uncertainty could have an impact on our findings. Third, rhythm control strategy was based on pharmacological therapy, excluding electrical cardioversion and ablation procedures. Patients received symptom-directed rhythm control rather than early rhythm control, which might have further improved outcomes. Fourth, we did not gather data regarding alterations in rate or rhythm therapy throughout the follow-up period. Fifth, the study population was generally older, and therefore the findings of the present study may not be generalizable to younger patients with AF who develop ACS or undergo PCI. Sixth, there were differences in several baseline characteristics between the rate (rhythm) control and non-rate (rhythm) control groups in our study. We had concerns about using propensity score matching (PSM). However, there was a large difference in sample size between these groups. This significant discrepancy might not provide a sufficiently large sample size for successful PSM, potentially leading to a substantial loss of data due to failed matches. Moreover, the relatively large number of baseline characteristics could result in many unmatched individuals, thereby considerably reducing the sample size and increasing susceptibility to bias [28]. Seventh, there existed the potential for bias stemming from unmeasured

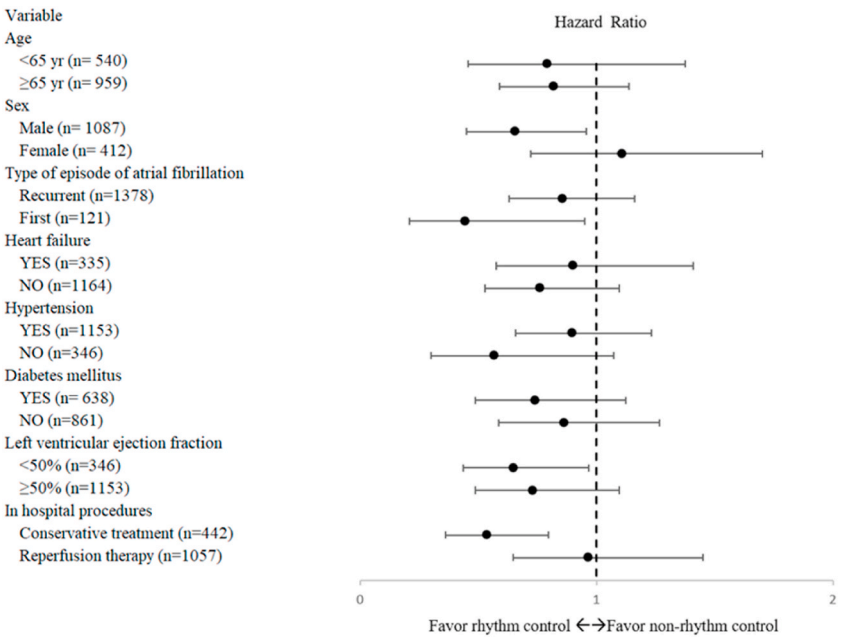


Fig. 4. Forest plot of treatment effects of rhythm-control compared to non-rhythm control therapy by predefined subgroups.

underlying health statuses of the patients in this study. As shown in the Kaplan-Meier curve of MACCEs and death for the rate control group vs. the non-rate control group in Fig. 1, the risk of MACCEs and death was indeed higher in patients who were not rate-controlled. This could be partly due to the rate control therapy being determined by the treating physicians. Their pre-judgment about the patients' unstable hemodynamics, low ejection fraction, or other contraindications might inevitably influence the rate control therapy selection and clinical equipoise. Despite adjustments for clinically relevant risk factors among patients with AF who develop ACS or undergo PCI, it remained impossible to entirely eliminate bias and account for unknown confounders. We attempted to address this by selecting data according to 'The active comparator, new user (ACNU) design', which seeks to emulate the design of a head-to-head randomized controlled trial [29]. However, we found it challenging to obtain the necessary data to meet the criteria of the ACNU design based on the existing dataset, primarily due to missing baseline information and medication usage durations. Finally, due to the high overlap of medication usage in our cohort, our study was unable to compare rhythm control versus rate control strategies. Consequently, we could not further demonstrate the superiority or inferiority of rhythm control versus rate control strategies in patients with AF who develop ACS or undergoing PCI. Well-designed RCT studies are needed to further explore.

5. Conclusion

Among patients with AF and ACS or undergoing PCI, rate control strategy significantly reduced the incidence of MACCEs and all-cause death. Besides, for these patients, rhythm control strategy provided a protective effect against all-cause death.

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Ethics statement

This study was reviewed and approved by the Ethics Board of Fuwai Hospital, with approval number 2017–923, issued on August 22, 2017.

All participants/patients (or their proxies/legal guardians) written informed consent to participate in the study.

Data availability statement

The data used in this study can be made available upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Jing-yan Wang: Writing – original draft, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Ran Mo:** Writing – original draft, Software, Resources, Methodology, Data curation, Conceptualization. **Jun Zhu:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization. **Jiang-Shan Tan:** Writing – review & editing, Validation, Methodology, Conceptualization. **Lu-lu Wang:** Software, Methodology, Investigation. **Wei Xu:** Writing – review & editing. **Juan Wang:** Writing – review & editing, Validation, Methodology, Investigation. **Shuang Wu:** Methodology, Conceptualization. **Si-qi Lyu:** Writing – review & editing. **Han Zhang:** Writing – review & editing, Investigation. **Yan-min Yang:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35218.

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