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Clinical features and outcomes of patients in different age groups with non-valvular atrial fibrillation receiving oral anticoagulants

U Fan O [a,b,1], Tou Kun Chong [b,1], Yulin Wei [a], Bishow Paudel [d], Michael C. Giudici [d], Chi Wa Wong [b], Wai Kit Lei [b], Jian Chen [c], Wei Wu [a,*], Kan Liu [d,*]

[a] Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China
[b] Department of Cardiology, Kiang Wu Hospital, Macau Special Administrative Region, China
[c] Department of Cardiology, Cardiovascular Centre, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China
[d] Division of Cardiology and Heart and Vascular Center, University of Iowa, Iowa City, USA

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ABSTRACT

Background: Patients with non-valvular atrial fibrillation (NVAF) need prophylactically antithrombotic therapies to reduce the risk of stroke. We hypothesized that the prognostic benefits of prophylactic antithrombotic therapies outweighed the bleeding risk among very elderly (≥85 years old) patients.

Methods: We analyzed clinical characteristics and outcomes of patients with NVAF in different age groups who had received different prophylactic antithrombotic therapies. We enrolled 3895 consecutive NVAF patients in the Macau Special Administrative Region (Macau SAR) of China from January 1, 2010, to December 31, 2018. Among 3524 patients [including 1252 (35.53%) very elderly patients] who completed the entire study, 2897 (82.21%) patients had a CHA_2DS_2-VASc score ≥ 2, 2274 (64.53%) had HAS-BLED score < 3, and 1659 (47.08%) had both of the above. The follow-up time was 3.80 (median, interquartile range 1.89–6.56) years. The primary outcome was the first occurrence of ischemic stroke, major bleeding, clinically relevant non-major gastrointestinal bleeding (CRNM-GIB), and all-cause mortality.

Results: A total of 2012 patients (57.09%) received no antithrombotic (NAT), 665 (18.87%) received antiplatelet (AP) agents, 371 (10.53%) received vitamin K antagonist (VKA), and 476 (13.51%) received non-vitamin K antagonist oral anticoagulants (NOACs). Eventually, 610 (17.31%) patients experienced thromboembolic events, with 167 (4.74%) strokes and 483 (13.71%) transient ischemia attack (TIA)/strokes. Bleeding events occurred in 614 (17.42%) patients, with 131 (3.72%) major bleeding, 381 (10.81%) CRNM-GIB and 102 (2.89%) minor bleeding events. All-cause deaths occurred in 483 (13.71%) patients. Compared with patients receiving NAT, patients receiving NOACs and VKA had fewer strokes (hazard ratio [HR]: 0.038; 95 %CI 0.004–0.401; $p = 0.006$ and HR: 0.544; 95 %CI 0.307–0.965; $p = 0.037$, respectively), and lower all-cause mortality (HR: 0.270; 95 %CI 0.170–0.429; $p < 0.001$ and HR: 0.531; 95 %CI 0.373–0.756; $p < 0.001$, respectively). Of note, very elderly patients with NVAF receiving NOACs had fewer strokes (adjust hazard ratio [$_{adj}$HR]: 0.042; 95 %CI 0.002–1.003; $p = 0.050$) and lower all-cause mortality ($_{adj}$HR: 0.308; 95 %CI 0.158–0.601; $p = 0.001$). Meanwhile, despite higher CRNM-GIB events ($_{adj}$HR: 1.736; 95 %CI 1.042–2.892; $p = 0.034$), major bleeding events ($_{adj}$HR: 1.045; 95 %CI 0.366–2.979; $p = 0.935$) did not significantly increase. VKA neither reduced strokes ($_{adj}$HR: 1.015; 95 %CI 0.529–1.948; $p = 0.963$), nor improved all-cause mortality ($_{adj}$HR: 0.995; 95 %CI 0.641–1.542; $p = 0.981$) in very elderly patients with NVAF.

Conclusions: Antithrombotic treatment (VKA and NOACs) reduces stroke and improves prognosis in patients in different age groups with NVAF. The prognostic benefits of NOACs outweigh their bleeding risks in very elderly patients with NVAF.

* Corresponding authors at: Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, 107 West Yanjiang Road, Guangzhou 510120, Guangdong Province, China (W. Wu). Division of Cardiology and Heart and Vascular Center, University of Iowa, Iowa City, IA 52240, USA (K. Liu).
E-mail addresses: wuwei9@mail.sysu.edu.cn (W. Wu), kan-liu@uiowa.edu (K. Liu).
[1] These authors contributed equally to this work.

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1. Introduction

The prevalence of atrial fibrillation (AF) increases with age [1]. Although non-valvular atrial fibrillation (NVAF) is associated with increased mortality and morbidity, essentially from stroke and systemic thromboembolism, very elderly (≥85 years old) patients with NVAF often hesitate to take oral anticoagulants (OACs) due to the overriding concern of OACs associated bleeding risk. While very elderly patients represent an essential portion of the population that needs to be studied for clinical anticoagulation decisions, they have been paradoxically underrepresented in available randomized clinical trials [2–5].

Whether the benefits of prophylactic antithrombotic therapies outweigh the risks among very elderly patients remains inconclusive. The world's older population continues to grow at an unprecedented rate, and it becomes more compelling than ever to examine the "real-world" benefits and risks of very elderly NVAF patients receiving prophylactic antithrombotic therapies. From January 1, 2010, to December 31, 2018, we enrolled and treated a total of 3524 NVAF patients in an anticoagulation cardiology specialty clinic in the Macau Special Administrative Region (Macau SAR) of China, including 1252 (more than 35%) patients older than 85 years, to determine their clinical outcomes from different antithrombotic treatments.

2. Methods

2.1. Definitions of clinical endpoint and risk assessment tools [6–9]

Clinical outcome: Defined as ischemic stroke (ICD-10: I63.0-I63.9), major bleeding, clinically relevant non-major gastrointestinal bleeding, and all-cause deaths (ICD-10: R96, R98, R99, and I46.1).

Major bleeding (MB): Defined as fatal bleeding, symptomatic bleeding in a critical area or organ such as intracranial (intracerebral hemorrhage, ICD-10: I60.x, I61.x), and intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome [ICD-10: I85.0, I98.3, D62.9, K62.5, K92.2, K25-28 (subcodes 0–2 and 4–6)].

Clinically relevant non-major gastrointestinal bleeding (CRNM-GIB): Defined as overt gastrointestinal bleeding not meeting criteria for MB but requiring medical intervention, hospitalization, temporary interruption, or delayed anticoagulation dosing, pain, or impairment of daily activities.

Bleeding risk scoring (HAS-BLED score): Classified into three risk levels according to the HAS-BLED score, the low risk = HAS-BLED score of 0; intermediate risk = HAS-BLED score of 1 or 2, and high risk = HAS-BLED score of 3 or more.

Stroke risk scoring (CHA_2DS_2-VASc score): Classified into three risk levels according to the CHA_2DS_2-VASc score as follows, CHA_2DS_2-VASc

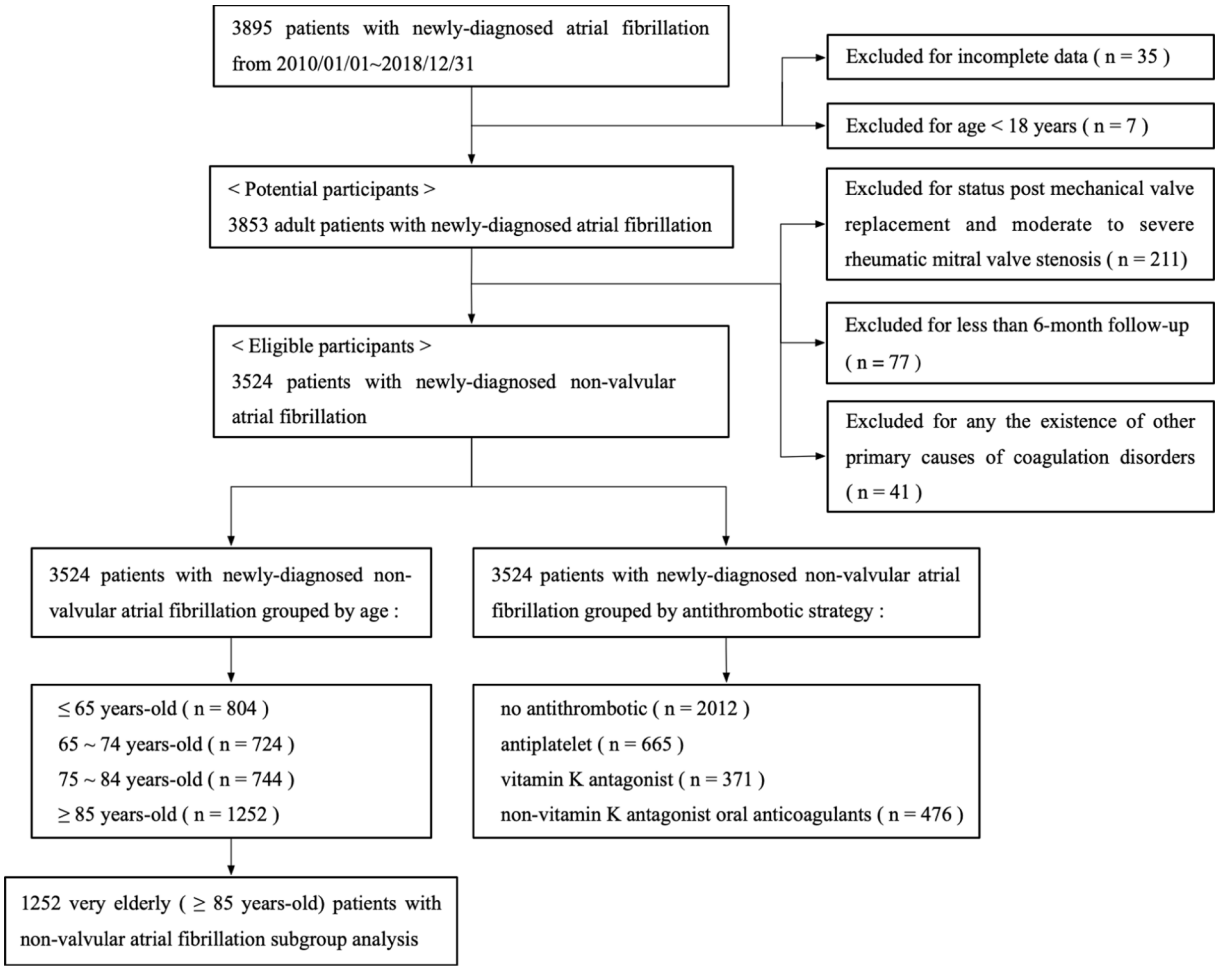


Fig. 1. Flowchart of enrollment of the study.Of 3853 subjects with Atrial fibrillation who survived greater than 6 months after the index date. From these subjects, we identified 3524 with non-valvular atrial fibrillation. Of these 3524 subjects, 804 were ≤ 65 years old, 724 were 65–74 years old, 744 were 75–84 years old, 1252 were ≥ 85 years old. Of these 3524 subjects, 371 were taking vitamin K antagonists, 476 were taking non-vitamin K antagonist oral anticoagulants, 665 were taking antiplatelet, and in 2012 were taking no antithrombotic.

score of 0 for men or 1 for women: recommend no antithrombotic therapy; CHA_2DS_2-VASc score of 1 for men or 2 for women: recommend antithrombotic therapy with oral anticoagulation or antiplatelet treatment but preferably oral anticoagulation, and CHA_2DS_2-VASc score of $\geq$ 2 for men or $\geq$ 3 for women: recommend oral anticoagulation. In clinical practice, both $CHADS_2$ score and CHA_2DS_2-VASc score were used for stroke risk assessment. However, in order to facilitate unified analysis, all patients were analyzed using CHA_2DS_2-VASc score as a stroke risk scoring tool in this study.

2.2. Patients and study design

This was a retrospective observational study conducted at Kiang Wu hospital in Macau SAR. We utilized an electronic healthcare information system to gather all medical information of patients who received medical care in either in-patient or out-patient settings. All eligible patients were $\geq$ 18 years old, of Chinese nationality, diagnosed with NVAF (ICD-10: I48.0–148.9) via either a 12-lead electrocardiogram (ECG) or 24-hour ECG monitor (Holter). Consecutive patients diagnosed with NVAF admitted between January 1, 2010, to December 31, 2018, were followed through December 31, 2019. All enrolled patients survived more than 6 months after AF diagnosis. Patients with the following were excluded: (1) Valvular AF such as post mechanical valve replacement or moderate to severe rheumatic mitral valve stenosis; (2) AF caused by reversible factors including acute myocardial infarction, acute myocarditis, pericarditis, pulmonary embolism, electrocution, or binge drinking; (3) Any primary coagulation disorders.

Of 3895 screened patients, 3524 patients were eventually enrolled in this study. Patients were categorized into four groups based on age and stroke prevention strategy, respectively. Eligible patients were classified into four age groups: $<$ 64 years old, 65–74 years old, 75–84 years old, and $\geq$ 85 years old. Patients aged 75–84 years old were defined as the "elderly" group, and $\geq$ 85 years old were defined as the "very elderly" group. Eligible patients were also classified into four antithrombotic strategy groups: no antithrombotic (NAT), antiplatelet (AP), vitamin K antagonist (VKA) and non-vitamin K antagonist oral anticoagulants (NOACs) (Fig. 1).

2.3. Follow-up and data collection

We collected patients' demographic data and medical history, including hypertension, coronary artery disease, vascular diseases, diabetes mellitus, heart failure, renal function, previous stroke/transient ischemic attack (TIA), peripheral thromboembolism, and bleeding events. We documented all the dosages and duration of anticoagulant medication, comorbidities, laboratory data, ECG, and *X*-ray reports. Each patient in this research was tracked via the electronic healthcare information system and followed-up at an anticoagulation cardiology specialty clinic until the patient developed thromboembolism, bleeding, or death events. In addition, all information related to anticoagulant treatment and clinical outcomes was collected. To ensure sufficient time to collect data, each indexed case was followed up for at least half a year, or a death endpoint event occurred. The study protocol was approved by the Scientific Ethics Committee of Kiang Wu Hospital of Macau, SAR (file no. 2017–001).

2.4. Statistical analysis

Continuous variables are described as mean values and standard deviation (SD). The description of discontinuous variables uses median and interquartile ranges (IQR: 25th, 75th percentile). Statistical analysis for continuous variables was made using the students ***t***-test or analysis of variance (ANOVA). Categorical variables are expressed as percentages. Baseline categorical variables were compared using a Chi-square (χ^2) test when appropriate; otherwise, a Fisher exact test was used. In addition, multiple comparisons between different groups were tested for

Table1
Baseline clinical and demographic characteristics of patients with NVAF by age category.

Characteristics	All group	Age group, years				χ^2/F/H	***p***-value
		$\leq$ 64	65–74	75–84	$\geq$ 85		for trend
No. of patients included; n (%)	3524 (100)	804 (22.81)	724 (20.54)	744 (21.11)	1252 (35.53)	—	—
Female sex; n (%)	1736 (100)	289 (16.65)	259 (14.92)	388 (23.35) † §	800 (46.08) † § △	219.53	< 0.001
Age, years; mean ± SD	76.31 ± 14.59	55.82 ± 8.27	69.59 ± 2.72	80.08 ± 2.81	91.12 ± 4.73	—	—
Age range, years	23–113	23–64	65–74	75–84	85–113	—	—
Comorbidities; n (%)							
HTN	2281 (100)	291 (12.76)	448 (19.64) †	545 (23.89) † §	997 (43.71) † § △	434.80	< 0.001
CHF	833 (100)	104 (12.48)	121 (14.53)	180 (21.61) † §	428 (51.38) † § △	147.55	< 0.001
CHD	610 (100)	55 (9.02)	116 (19.02) †	155 (25.41) † §	284 (46.56) † § △	94.12	< 0.001
T2DM	913 (100)	129 (14.13)	218 (23.88) †	209 (22.89) †	357 (39.10) †	53.69	< 0.001
PVD	128 (100)	10 (7.81)	21 (16.41) †	25 (19.53) †§	72 (56.25) † §△	30.42	< 0.001
CKD	696 (100)	67 (9.63)	104 (14.94) †	151 (21.70) † §	374 (53.74) † §△	160.44	< 0.001
COPD	249 (100)	8 (3.21)	32 (12.85) †	64 (25.70) †§	145 (58.23) †§	94.40	< 0.001
Ischemic stroke/TIA	467 (100)	48 (10.28)	81 (17.34) †	102(21.84) †	236 (50.54) † §△	82.26	< 0.001
History of ICH	50 (100)	6 (12.00)	15 (30.00) †	10 (20.00) †§	19 (38.00) †△	60.80	< 0.001
Hyperthyroidism	139 (100)	73 (52.52)	31 (22.30) †	21 (15.11) †	14 (10.07) † §△	89.30	< 0.001
Chronic anemia	176 (100)	11 (6.25)	23 (13.07)	46 (26.14) †§	96 (54.55) † §	48.39	< 0.001
Previous PCI	320 (100)	35 (10.94)	68 (21.25) †	87 (27.19) †	130 (40.63) †	58.90	< 0.001
Previous CABG	32 (100)	6 (18.75)	12 (37.50) †	8 (25.00) §	6 (18.75) §	79.42	< 0.001
Previous BVR	133 (100)	47 (35.34)	50 (37.59)	27 (20.30) §	9 (6.77) † § △	41.55	< 0.001
Comorbidities burden; n (%)							
Low (0–2)	2298 (100)	683 (29.72)	516 (22.45)	461 (20.06)	638 (27.76)	1.23	0.746
Moderate (3–5)	1150 (100)	119 (10.35)	195 (16.96) †	270 (23.48) † §	566 (49.22) † § △	15.56	0.001
High (≥6)	76 (100)	2 (2.63)	13 (17.11) †	13 (17.11) †	48 (63.15) † § △	37.59	< 0.001
CHA_2DS_2-VASc score※	3.46 ± 1.91	1.30 ± 1.04	2.94 ± 1.42†	4.28 ± 1.38† §	4.66 ± 1.44† § △	1103.95	< 0.001
HAS-BLED score※	2.04 ± 1.19	0.75 ± 0.86	2.11 ± 1.03†	2.37 ± 0.91† §	2.64 ± 0.96†§△	702.69	< 0.001

NVAF, non-valvular atrial fibrillation; HTN, hypertension; CHF, chronic heart failure; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; BVR, biological valve replacement; ICH, intracerebral hemorrhage; T2DM, type 2 diabetes mellitus; PVD, peripheral vascular disease; CKD, chronic kidney disease.

※ mean ± SD.

† compared with $\leq$ 64 age group, ***p***-value $<$ 0.05; § compared with 65–74 age group, ***p***-value $<$ 0.05.

△ compared with 75–84 age group, ***p***-value $<$ 0.05 ; .

statistical significance using Fisher's least significant difference ***t***-test (LSD ***t***-test) or Bonferroni method's ***Z*** test based on distribution. The risk of antithrombotic strategy-associated adverse events for patients with AF was assessed using Cox regression analysis. In very elderly subgroup analysis, the Cox regression model was adjusted for age, CHA_2DS_2-VASc score, HAS-BLED score, weight and renal function. ***p***-value < 0.05 was defined as significant in statistical inference tests. The statistical analyses were performed with Microsoft Excel and IBM SPSS Statistics.

3. Results

3.1. Demographic characteristics and comorbidities

Demographic and clinical characteristics are summarized in Table 1 (based on age group) and Table 2 (based on antithrombotic agents' group). More comorbidities occurred as patients aged. The most prevalent comorbidity was hypertension (2281/3524, 64.73%), followed by diabetes mellitus, heart failure, chronic kidney disease, and coronary artery disease. The median (25th, 75th percentile) of comorbidity burden number was 2 (1, 3) in this study. There was a noticeable high number of NAVF patients with moderate morbidity burden (3–5 comorbidities) in the very elderly group (49.22%, $p = 0.001$). A similar high numbers were observed of NVAF patients with a high morbidity burden (≥6 comorbidities) in the very elderly group (63.16%, $p < 0.001$).

3.2. Stroke/bleeding risk scores and antithrombotic therapy

Overall, 82.21% of the patients with NVAF scored CHA_2DS_2-VASc score of 2 or more, 30.47% scored CHA_2DS_2-VASc score of 5 or more (Fig. 2**A**), and 35.47% scored HAS-BLED score of 3 or more (Fig. 2**B**). Proportionally more patients in the very elderly group scored higher in each category, all at the high stroke risk score and more than half of them at the high bleeding risk score. In terms of a therapy, in this study,

Table 2
Baseline clinical and demographic characteristics of patients with NVAF by antithrombotic strategy category [n (%)].

Characteristics	All group	Antithrombotic strategy				χ^2/F	*p*-value for trend
		NAT	AP	VKA	NOACs		
No. of patients included; n (%)	3524 (100)	2012 (100)	665 (100)	371 (100)	476 (100)	—	—
Female sex; n (%)	1736 (49.26)	966 (48.01)	321 (48.27) †	207 (55.80) †§	242 (50.84) †△	8.33	0.040
Age, years; mean ± SD	76.31 ± 14.59	76.16 ± 15.89	79.53 ± 13.51 †	72.36 ± 12.00†§	75.57 ± 10.70§△	20.69	< 0.001
Age range, years	23–113	25–113	23–106	34–96	33–99	—	—
Risk score; mean ± SD							
CHA_2DS_2-VASc	3.46 ± 1.91	3.09 ± 1.88	4.12 ± 1.96 †	3.65 ± 1.79 †§	3.93 ± 1.72 †△	66.45	< 0.001
HAS-BLED	2.04 ± 1.19	1.88 ± 1.20	2.38 ± 1.17 †	2.00 ± 1.21 §	2.28 ± 1.03 †△	37.48	< 0.001
Comorbidities; n (%)							
HTN	2281 (64.73)	1160 (57.65)	516 (77.57) †	227 (61.19) † §	378 (79.41) †△	139.31	< 0.001
T2DM	913 (25.91)	471 (23.41)	201 (30.23) †	93 (25.07) † §	148 (31.09) †△	19.80	< 0.001
CHF	833 (23.64)	329 (16.35)	209 (31.43) †	157 (42.32) †§	138 (28.99) †△	160.81	< 0.001
CHD	610 (17.31)	200 (9.94)	246 (36.99) †	64 (17.25) †§	100 (21.01) † §	260.88	< 0.001
Previous PCI	320 (9.08)	93 (4.62)	152 (22.86) †	28 (7.55) † §	47 (9.87) † §△	247.30	< 0.001
Previous CABG	32 (0.91)	8 (0.40)	11 (1.65) †	7 (1.89) †	6 (1.26) † § △	668.10	< 0.001
Ischemic stroke/TIA	467 (13.25)	195 (9.69)	137 (20.60) †	43 (11.59) §	92 (19.33) †△	72.35	< 0.001
CKD	696 (19.75)	406 (20.18)	146 (21.95)	93 (25.07) †§	51 (10.71) † § △	33.41	< 0.001
PVD	128 (3.63)	39 (1.94)	47 (7.07) †	17 (4.58) †	25 (5.25) †	43.44	< 0.001
COPD	249 (7.07)	150 (7.46)	51 (7.67)	21 (5.66)	27 (5.67)	3.36	0.340
History of ICH	50 (1.42)	29 (1.44)	7 (1.05)	4 (1.08)	10 (2.10) †§△	68.79	< 0.001
Hyperthyroidism	139 (3.94)	84 (4.17)	23 (3.46) †	12 (3.23) †	20 (4.20) §△	40.47	< 0.001
Chronic anemia	176 (4.99)	86 (4.27)	46 (6.92) †	23 (6.20) †§	21 (4.41) †§	8.86	0.031
Previous BVR	133 (3.77)	26 (1.29)	1 (0.15)	99 (26.68) †§	7 (1.47) △	387.36	< 0.001

NVAF, non-valvular atrial fibrillation; HTN, hypertension; T2DM, type 2 diabetes mellitus; CHF, chronic heart failure; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; CKD, chronic kidney disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; ICH, intracerebral hemorrhage; BVR, biological valve replacement; NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist oral anticoagulants; † compared with NAT, ***p***-value < 0.05; § compared with Antiplatelet, ***p***-value < 0.05; △ compared with VKA, ***p***-value < 0.05.

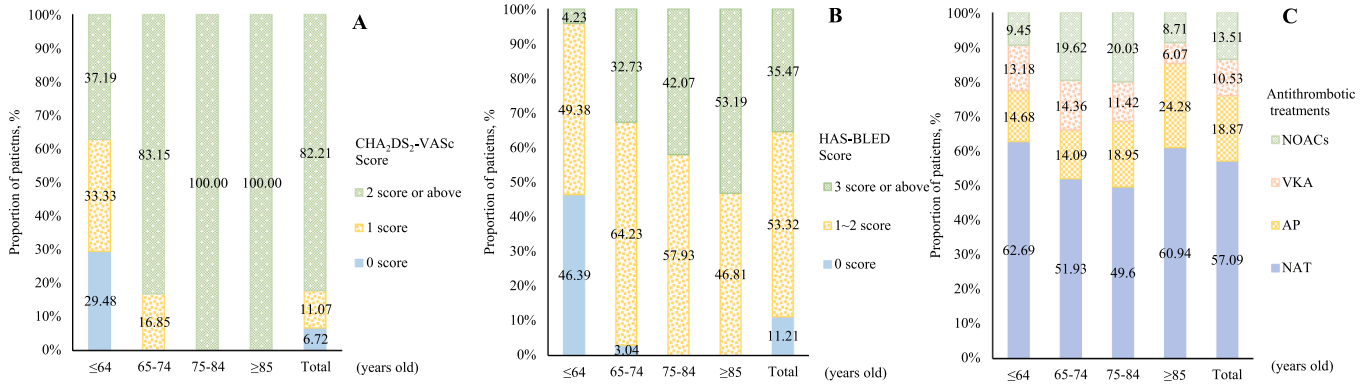


Fig. 2. Distribution of CHA_2DS_2-VASc stroke risk **(A)** / HAS-BLED bleeding risk scores **(B)** in patients with non-valvular atrial fibrillation in different age groups/ Distribution of antithrombotic treatments in patients with non-valvular atrial fibrillation in different age groups **(C)** VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist oral anticoagulants; NAT, no antithrombotic; AP, antiplatelet; NVAF, non-valvular atrial fibrillation.

Table 3
The relationship between stroke/bleeding events in patients with NVAF of different ages and the choice of antithrombotic therapy.

Antithrombotic medications	All groups (n = 3524)	Age group, years	
		< 85 (n = 2272)	≥ 85 (n = 1252)
All stroke/TIA events [n (%)]	483/3524 (13.71)	250/2272 (11.00)	233/1252 (18.61)
Antithrombotic strategy NAT [n/n (%)]	201/483 (41.61)	87/250 (34.80)	114/233 (48.93)
AP [n/n (%)]	145/483 (30.02)	65/250 (26.00)	80/233 (34.33)
VKA [n/n (%)]	39/483 (8.08) †§	27/250 (10.80) †§	12/233 (5.15) †§
NOACs [n/n (%)]	98/483 (20.29) △	71/250 (28.84) △	27/233 (11.59) †§
χ^2	82.63	18.69	21.83
***p*-value**	< 0.001	< 0.001	< 0.001
Stroke events [n (%)]	167/3524 (4.74)	33/2272 (1.45)	134/1252 (10.70)
Antithrombotic strategy NAT [n/n (%)]	119/167 (71.26)	22/33 (66.67)	97/134 (72.39)
AP [n/n (%)]	35/167 (20.96)	8/33 (24.24)	27/134 (20.15)
VKA [n/n (%)]	13/167 (7.78) †§	3/33 (9.09) †§	10/134 (7.46) †§
NOACs [n/n (%)]	0/167 (0) †§	0/33 (0) †§△	0/134 (0) †§△
χ^2	31.50	16.95	17.82
***p*-value**	< 0.001	< 0.001	< 0.001
Major bleeding events [n (%)]	131/3524 (3.72)	76/2272 (3.35)	55/1252 (4.39)
Antithrombotic strategy NAT [n/n (%)]	69/131 (52.67)	35/76 (46.05)	34/55 (61.82)
AP [n/n (%)]	29/131 (22.14) †	14/76 (18.42) †	15/55 (27.27) †
VKA [n/n (%)]	11/131 (8.40) †§	9/76 (11.84) †§	2/55 (3.64) †§
NOACs [n/n (%)]	22/131 (16.79) †§△	18/76 (23.68) †§△	4/55 (7.27) †§△
χ^2	19.89	11.97	41.39
***p*-value**	< 0.001	0.008	< 0.001
CRNM-GIB events [n (%)]	381/3524 (10.81)	184/2272 (8.10)	197/1252 (15.73)
Antithrombotic strategy NAT [n/n (%)]	179/381 (46.98)	75/184 (40.76)	104/197 (52.79)
AP [n/n (%)]	105/381 (27.56)	41/184 (22.28)	64/197 (32.49)
VKA [n/n (%)]	39/381 (10.24) †§	28/184 (15.22)	11/197 (5.58) †§
NOACs [n/n (%)]	58/381 (15.22) †§	40/184 (21.74)	18/197 (9.14) †§
χ^2	25.71	6.54	9.17
***p*-value**	< 0.001	0.088	0.027

NVAF, non-valvular atrial fibrillation; NOACs, non-vitamin K antagonist anticoagulants; VKA, vitamin K antagonist; NAT, no antithrombotic; AP, antiplatelet; CRNM-GIB, gastrointestinal bleeding, the Definition of clinically relevant non-major of GIB.

† compared with NAT, ***p*-value** < 0.05; § compared with Antiplatelet, ***p*-value** < 0.05.

△ compared with VKA, ***p*-value** < 0.05.

Table 4
The relationship between all-cause mortality in patients with NVAF of different ages and the choice of antithrombotic therapy.

Antithrombotic medications	All groups (n = 3524)	Age group, years			
		≤ 64 (n = 804)	65–74 (n = 724)	75–84 (n = 744)	≥ 85 (n = 1252)
All-cause deaths [n (%)]	483 (100)	35 (7.25)	53 (10.97)	72 (14.91)	323 (66.87)
account for [n/n (%)]	483/3524 (13.71)	35/804 (4.35)	53/724 (7.32)	72/744 (9.68)	323/1252 (25.80)
CHA_2DS_2-VASc score※	4.35 ± 1.71	1.51 ± 1.20	2.98 ± 1.56	4.39 ± 1.30	4.87 ± 1.42
HAS-BLED score※	2.77 ± 1.11	1.34 ± 1.08	2.60 ± 1.29	2.81 ± 0.93	2.95 ± 1.00
Antithrombotic strategy					
NAT [n/n (%)]	331/483 (68.53)	27/35 (77.14)	41/53 (77.36)	48/72 (66.67)	215/323 (66.56)
AP [n/n (%)]	99/483 (20.50) †	3/35 (8.57)	5/53 (9.43) †	14/72 (19.44) †	77/323 (23.84) †
VKA [n/n (%)]	34/483 (7.04) †§	2/35 (5.71)	4/53 (7.55) †§	6/72 (8.33) †§	22/323 (6.81) †§
NOACs [n/n (%)]	19/483 (3.93) †§△	3/35 (8.57)	3/53 (9.43) †§△	4/72 (5.56) †§△	9/323 (2.79) †§△
χ^2	58.05	3.73	15.52	13.70	20.21
***p*-value**	< 0.001	0.292	0.001	0.003	< 0.001

NVAF, non-valvular atrial fibrillation; NOACs, non-vitamin K antagonist anticoagulants; VKA, vitamin K antagonist; NAT, no antithrombotic; AP, antiplatelet; GIB, gastrointestinal bleeding, the Definition of clinically relevant non-major of GIB.

※mean ± SD.

† compared with NAT, ***p*-value** < 0.05; § compared with Antiplatelet, ***p*-value** < 0.05.

△ compared with VKA, ***p*-value** < 0.05.

24.04% (847/3524) of all enrolled patients with NVAF were prescribed OACs. Across all age groups, the mean proportion of patients on NAT was 56.29% (49.60–60.94%), and 14.78% (185/1252) of very elderly patients were on anticoagulation (Fig. 2**C**).

In particular, oral anticoagulation prescription rates were lower than average among very elderly NVAF patients compared to other age groups through the years (***p*** < 0.05). Furthermore, the anticoagulation prescription rate increased progressively, from 12.73% to 43.62%, from 2010 to 2018, and each age group showed an upward trend by year. Among all enrolled patients with NVAF, the proportions of OACs use increased from 12.31% to 40.24%, while in patients with CHA_2DS_2-VASc score ≥ 2 (2897/3524, 82.21%), the proportions of OACs use increased from 12.73% to 43.62%.

3.3. Endpoints

3.3.1. Stroke events

A total of 610 (17.31%) patients experienced thromboembolic events. Among them, 483 patients (13.71%) had experienced TIA/stroke events, and 167 (4.74%) patients had an ischemic stroke. The majority of the stroke patients were those over 85 years old (80.24%, 134/167, ***p*** < 0.001), and they also scored significantly high on the risk of stroke scale with a median score of 4.66 ± 1.44 (***p*** < 0.001) (Table 3).

3.3.2. Bleeding events

A total of 614 (17.42%) patients occurred bleeding events. And there were 131 patients (3.72%) who had experienced MB events; 381 patients (10.81%) had had CRNM-GIB, and 102 patients (2.89%) had had minor bleeding events during the follow-up. Most patients with MB [41.98% (55/131)] and CRNM-GIB [51.71% (197/381)] were over 85 years old (Table 3).

3.3.3. All-cause mortality

There were 483 patients had died during the follow-up, for whom the CHA_2DS_2-VASc score was 4.35 ± 1.71, and HAS-BLED score was 2.77 ± 1.11. The rate of death increased by age (***r*** = 0.25, ***p*** < 0.001), by CHA_2DS_2-VASc score (***r*** = 0.13, ***p*** < 0.001), and by HAS-BLED score (***r*** = 0.23, ***p*** < 0.001). Very elderly patients with NVAF accounted for 66.87% (323/1252) of all-cause deaths. Except for the group under 64 years old, the prognosis of patients in other age groups taking OACs was better

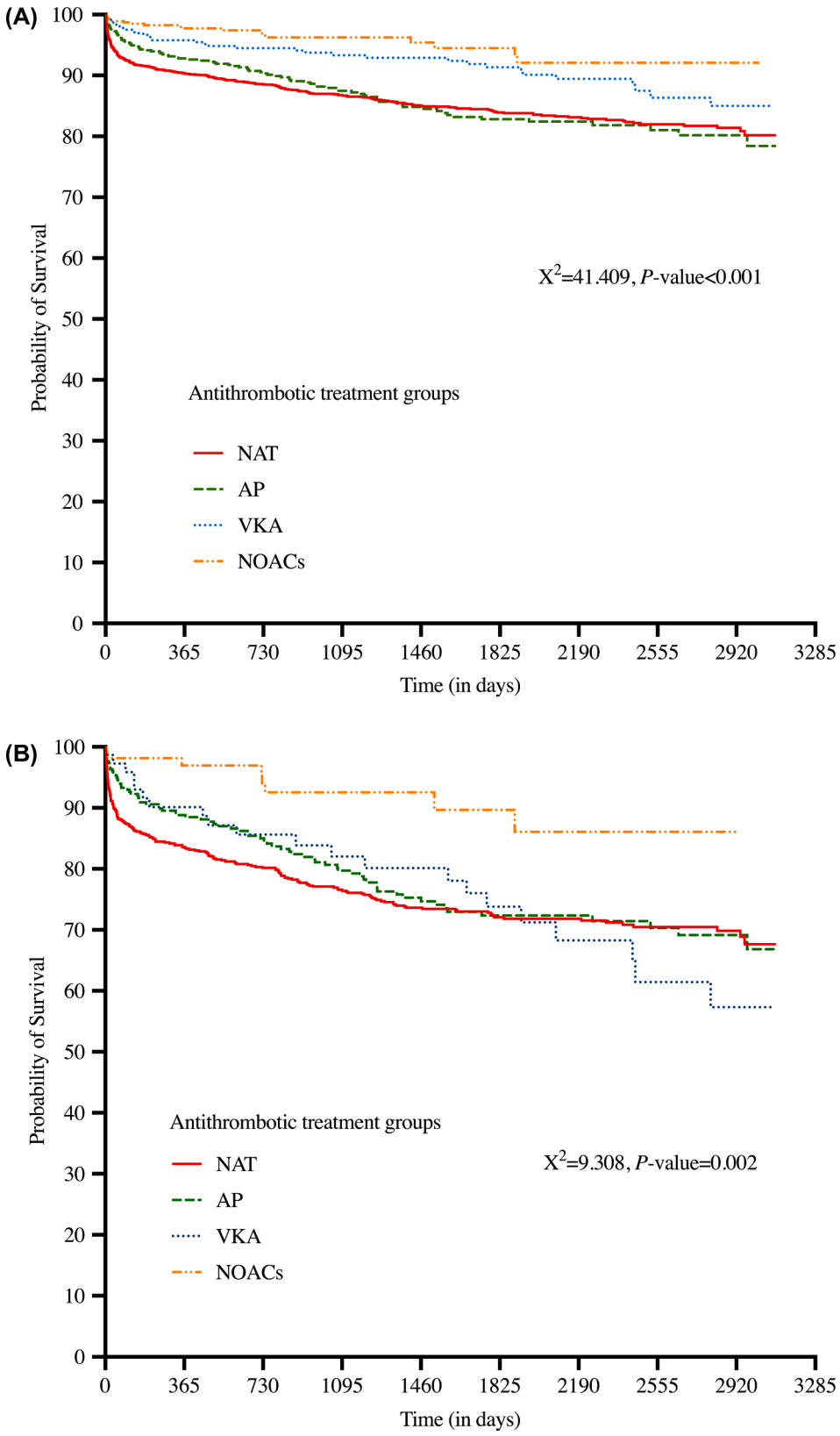


Fig. 3. Kaplan-Meier curves for all-cause mortality according to antithrombotic therapy at baseline discharge in all group patients **(A)** and subgroup patients with 85-year-old or above (**B**). NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist oral anticoagulants; Average follow-up time: 3.80 ± 2.76 years.

Table 5
Compared with different antithrombotic therapy group survival distributions by log-rank test.

Compared with different antithrombotic therapy group (Log-Rank test)	χ^2	*p*-value
All patients		
No antithrombotic (n = 2012) *vs.* Only antiplatelet (n = 665)	0.70	0.405
No antithrombotic (n = 2012) *vs.* VKA (n = 371)	12.80	< 0.001
No antithrombotic (n = 2012) *vs.* NOACs (n = 476)	35.42	< 0.001
Only antiplatelet (n = 665) *vs.* VKA (n = 371)	8.16	0.004
Only antiplatelet (n = 665) *vs.* NOACs (n = 476)	22.94	< 0.001
VKA (n = 371) *vs.* NOACs (n = 476)	3.24	0.072
Very elderly subgroup		
No antithrombotic (n = 763) *vs.* Antiplatelet (n = 304)	0.96	0.327
No antithrombotic (n = 763) *vs.* VKA (n = 76)	0.001	0.981
No antithrombotic (n = 763) *vs.* NOACs (n = 109)	13.42	< 0.001
Antiplatelet (n = 304) *vs.* VKA(n = 76)	0.23	0.630
Antiplatelet (n = 304) *vs.* NOACs (n = 109)	8.58	0.003
VKA (n = 76) *vs.* NOACs (n = 109)	6.22	0.013

than that of NAT or AP ($p < 0.05$) **(**Table 4**)**.

3.4. Outcome and survival analysis

The Kaplan-Meier curves for all-cause mortality according to different antithrombotic therapy in whole study group were shown in Fig. 3**A**. The patients treated with VKA or NOACs have a similar cumulative survival rate ($p = 0.072$) which was higher than those in other groups (AP or NAT) ($\chi^2 = 41.41$, $p < 0.001$). There is no significant difference between NAT and AP in survival analysis ($\chi^2 = 0.70$, $p = 0.405$) (Table 5). In comparison to NAT, VKA and NOACs resulted in significant reduction in all-cause mortality (HR: 0.531; 95 %CI 0.373–0.756; $p < 0.001$ for VKA and HR: 0.270; 95 %CI 0.170–0.429; $p < 0.001$ for NOACs) and stroke (HR: 0.544; 95 %CI 0.307–0.965; $p = 0.037$ for VKA and HR: 0.038; 95 %CI 0.004–0.401; $p = 0.006$ for NOACs). Furthermore, AP, VKA, NOACs did not increase MB compared with NAT, while AP and NOACs increased CRNM-GIB (HR: 1.809; 95 % CI 1.421–2.304; $p < 0.001$ for AP and HR: 2.123; 95 %CI 1.569–2.872; $p < 0.001$ for NOACs) **(**Fig. 4**)**.

The correlations between clinical outcomes and antithrombotic therapy in the whole study group were shown in Table 6. Compared with NAT or AP, NVAF patients treated with VKA or NOAC had a better prognosis, with lower all-cause death ($\chi^2 = 58.05$, $p < 0.001$), lower stroke incidence ($\chi^2 = 31.50$, $p < 0.001$), lower CRNM GIB incidence ($\chi^2 = 25.71$, $p < 0.001$), and no increase in MB events ($\chi^2 = 2.91$, $p = 0.406$).

For very elderly patients with NVAF, lower dosages of NOACs were used or lower INR target of VKA was achieved (e.g., dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, edoxaban 30 mg once daily, apixaban 2.5 mg twice daily, warfarin INR target 1.6–2.6) [10–14]. Decisions to prescribe reduced dose NOACs or low INR target VKA are made based on the specific considerations on age, weight, renal function and use of specific concomitant medications. The Kaplan-Meier curves for all-cause mortality according to different antithrombotic therapy in the very elderly subgroups were shown in Fig. 3**B**. The subgroup of very elderly patients with NVAF treated with NOACs has the highest cumulative survival rate ($\chi^2 = 9.31$, $p = 0.002$). In contrast, patients treated with NAT, AP, or VKA have a similar cumulative survival rate (*p* greater than 0.05) (Table 5). In comparison to NAT, only NOACs resulted in a significant reduction in all-cause mortality ($_{adj}$HR: 0.308; 95 %CI 0.158–0.601; $p < 0.001$). NOACs decreased stroke compared with NAT ($_{adj}$HR: 0.042; 95 %CI 0.002–1.003; $p = 0.050$) without increasing MB. Both AP and NOACs increased CRNM-GIB ($_{adj}$HR: 1.478; 95 %CI 1.081–2.020; $p = 0.014$ for AP and $_{adj}$HR: 1.736; 95 %CI 1.042–2.892; $p = 0.034$ for NOACs) (Fig. 5). The correlation between clinical outcomes and antithrombotic therapy in the very elderly subgroup was shown in Table 6. VKA neither reduced the risk of stroke in very elderly patients with NVAF, nor improve all-cause mortality, which was likely due to low TTR 23.20 ± 22.94 (%), and multiple comorbidities, especially renal insufficiency (most of their renal function were stage 5 and VKA may be the only anticoagulation therapy available to consider).

4. Discussion

The present study showed that the prognostic benefits of NOACs outweighed their bleeding risks in very elderly patients with NVAF. Compared to NAT and AP, NOACs reduced stroke and improved the prognosis of very elderly patients with NVAF.

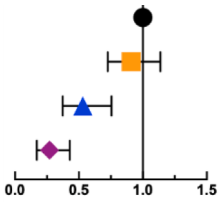
Among all studied NVAF patients the most prevalent comorbidity is hypertension, followed by diabetes mellitus, heart failure, chronic kidney disease, and coronary artery disease. Aging is associated with increased comorbidities, more strokes, and higher incidences of bleeding in NVAF patients (Table 1, Table 3). Although the interest of NVAF patients in anticoagulants has grown in recent years, the use of OACs in elderly and very elderly NVAF patients is still far less than expected [15]. Indeed, despite CHA_2DS_2-VASc ≥ 2, more than 40% of very elderly NVAF patients had not received OACs. Clinical risk stratification (with CHA_2DS_2-VASc and other scoring criteria) itself does not guarantee practical medication utilization or compliance [16]. In clinical practice, we found that other than dementia, poor quality of life, the poor prognosis from other primary diseases, the overriding concern of OACs associated bleeding risk and uncertainty OACs-related clinical benefits were the common reasons for the lack of OACs in very elderly patients or affect the decision-making of anticoagulation treatment after doctor-patient communication. Therefore, those patients at the highest risk of stroke paradoxically tend to be not treated with anticoagulants.

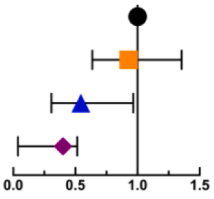
Although many previous randomized trials have demonstrated the efficacy, safety, and benefit of OACs for stroke prevention in NVAF patients, to date very elderly patients have been underrepresented in those studies [17–20]. Also, whether there are different risks and benefits between NOACs and VKA in the very elderly patient population remains largely unclear [21]. As the world's older population grows rapidly, it becomes even more important to determine the optimal anticoagulant choices for these very elderly patients who have increased both stroke and bleeding risk.

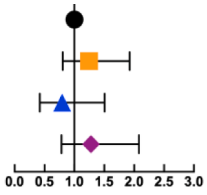
Our study was conducted in a relatively older NVAF patient population, which enrolled more than 35% of very elderly patients with NVAF from Macau SAR, an area well-known for longevity. Meanwhile, very elderly patients in Macau SAR have less economic pressure in choosing anticoagulants since all the medications are fully covered by commercial medical insurance and social security [22]. Therefore, the choice of antithrombotic therapy in patients in our study was mainly based on clinical considerations, which provides an exceptional opportunity to exclude financially confounding factors in previous investigations [20,23]. As a result, this community-based study with a sizable population of very elderly patients with NVAF demonstrates that NOACs effectively prevent stroke without significantly increasing the incidence of MB. Despite higher CRNM-GIB events in patients (compared with NAT), the prognostic benefits of NOACs outweigh their side effects (Fig. 4, Fig. 5), which support the results from some preliminary observations and *meta*-analysis results [24–26].

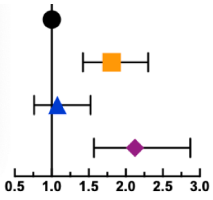
We performed initial AF management consultation and continuous clinic follow-up (once a month) of all patients in an anticoagulation cardiology specialty clinic, including two non-invasive cardiologists (UO and JC), two nurse practitioners, and one outpatient pharmacist. The first visit included a comprehensive consultation on the willingness of the patient or family members, self-management ability, previous bleeding or embolism events, or abnormal liver and renal function. We usually reached a consensus on a long-term anticoagulation plan for very elderly patients with NVAF. To adjust the subsequent antithrombotic strategies, each patient receiving OACs was followed up at least once a month to monitor possibly dynamic changes of hemoglobin,

	Number of patients	Number of events	Incidence (%)	HR (95%CI)	*p*-value
All-cause deaths	3524	483	13.71		
NAT	2012	331	16.45	reference	—
AP	665	99	14.89	0.909 (0.726 - 1.138)	0.405
VKA	371	34	9.16	0.531 (0.373 - 0.756)	<0.001
NOACs	476	19	3.99	0.270 (0.170 - 0.429)	<0.001
Stroke	3524	167	4.74		
NAT	2012	119	5.91	reference	—
AP	665	35	5.26	0.928 (0.636 - 1.354)	0.698
VKA	371	13	3.50	0.544 (0.307 - 0.965)	0.037
NOACs	476	0	0.00	0.038 (0.004 - 0.401)	0.006
Major bleeding	3524	131	3.72		
NAT	2012	69	3.43	reference	—
AP	665	29	4.36	1.246 (0.806 - 1.925)	0.322
VKA	371	11	2.96	0.797 (0.422 - 1.507)	0.485
NOACs	476	22	4.62	1.279 (0.786 - 2.081)	0.322
CRNM-GIB	3524	381	10.81		
NAT	2012	179	8.90	reference	—
AP	665	105	15.79	1.809 (1.421 - 2.304)	<0.001
VKA	371	39	10.51	1.077 (0.761 - 1.523)	0.676
NOACs	476	58	12.18	2.123 (1.569 - 2.872)	<0.001









NVAF, non-valvular atrial fibrillation; NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist anticoagulants; CRNM-GIB, clinically relevant non-major gastrointestinal bleeding; HR, hazard ratio; significant at ***p***-value < 0.05

Fig. 4. Risk of composite adverse events in different treatment groups after propensity matching in patients with NVAF NVAF, non-valvular atrial fibrillation; NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist anticoagulants; CRNM-GIB, clinically relevant non-major gastrointestinal bleeding; HR, hazard ratio; significant at ***p***-value < 0.05.

Table 6
The relationship between clinical outcomes and antithrombotic therapy in patients with NAVF and very elderly NVAF [n (%)].

Clinical outcome	All	NAT	Antiplatelet	VKA	NOACs	χ^2	*p*-value for trend
All patients	n = 3524	n = 2012	n = 665	n = 371	n = 476		
All-cause deaths	483 (100)	331 (68.53)	99 (20.50)	34 (7.04) †§	19 (3.93) †§△	58.05	< 0.001
account for [n/n (%)]	483/3524 (13.71)	331/2012 (16.45)	99/665 (14.89)	34/371 (9.16)	19/476 (3.99)	—	—
Stroke	167 (100)	119 (71.26)	35 (20.96)	13 (7.78) †§	0 (0) †§	31.50	< 0.001
account for [n/n (%)]	167/3425 (4.88)	119/2012 (5.91)	35/665 (5.26)	13/371 (3.50)	0/476 (0)	—	—
Major bleeding	131 (100)	69 (52.67)	29 (22.14)	11 (8.40)	22 (16.79)	2.91	0.406
account for [n/n (%)]	131/3524 (3.72)	67/2012 (3.33)	29/665 (4.36)	11/371 (2.96)	22/476 (4.62)	—	—
CRNM-GIB	381 (100)	179 (46.98)	105 (27.56)	39 (10.24) †§	58 (15.22) †§	25.71	< 0.001
account for [n/n (%)]	381/3524 (10.81)	179/2012 (8.90)	105/665 (115.79)	39/371 (10.51)	58/476 (12.18)	—	—
Very elderly subgroup	n = 1252	n = 763	n = 304	n = 76	n = 109		
All-cause deaths	323 (100)	215 (66.56)	77 (23.84)	22 (6.81)	9 (2.79) †§△	20.21	< 0.001
account for [n/n (%)]	323/1252 (25.80)	215/763 (28.18)	77/304 (25.33)	22/76 (28.95)	9/109 (8.26)	—	—
Stroke	134 (100)	97 (72.39)	27 (20.15)	10 (7.46)	0 (0) †§△	17.82	< 0.001
account for [n/n (%)]	134/1252 (10.70)	97/763 (12.71)	27/304 (8.88)	10/76 (13.16)	0/109 (0)	—	—
Major bleeding	55 (100)	34 (61.82)	15 (27.27)	2 (3.64)	4 (7.27)	0.92	0.821
account for [n/n (%)]	55/1252 (4.39)	34/763 (4.46)	15/304 (4.93)	2/76 (2.63)	4/109 (3.67)	—	—
CRNM-GIB	197 (100)	104 (52.79)	64 (32.49) †	11 (5.58)	18 (9.14) †	9.17	0.027
account for [n/n (%)]	197/1252 (15.73)	104/763 (13.63)	64/304 (21.05)	11/76 (14.47)	18/109 (16.51)	—	—

NVAF, non-valvular atrial fibrillation; NAT, no antithrombotic; CRNM-GIB, clinically relevant non-major gastrointestinal bleeding; † compared with NAT, ***p***-value < 0.05; § compared with Antiplatelet, ***p***-value < 0.05; △ compared with VKA, ***p***-value < 0.05.

liver/kidney function, fecal occult blood to potentially adjust the antithrombotic plan. For particular patients with special needs like mobility inconvenience, we arranged both outreach medical services and video call consultation services. Personalized care appears to play an essential role in maintaining medication compliance: more than 90% of patients in our study had continued to sustain their antithrombotic plan during the entire follow-up duration.

Another personal care strategy in the present study is the dedicated dosage adjustment of NOACs. Some previous studies [27–30] suggest that inappropriate dose reduction has been associated with a higher risk for embolism in patients with NVAF. Therefore, we conditionally adjusted the dosage of NOACs strictly following the recommendations from updated guidelines and consensus (age, glomerular filtration rate [eGFR], weight, history of bleeding or need to be combined with a strong P glycoprotein inhibitor or antiplatelet medicine) in whole study subjects [13,14,31]. The individual lower dosage of NOACs medication plans in our very elderly patients with NVAF included dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, edoxaban 30 mg once daily, apixaban 2.5 mg twice daily. From the results of our study, adjusted dosages of NOACs still effectively reduced stroke events and improved prognosis. Despite more comorbidities and higher clinical complexity, very elderly NVAF patients receiving NOACs experienced few strokes and bleeding events during the entire follow-up.

Over the past decades, novel medications and therapies have been administered to elderly patients with NVAF. The research efforts [32–36] have been increased recently to minimize OACs dosage or consumption frequency. From the ELDERCARE-AF trial [36], very elderly NVAF patients were randomly assigned to receive edoxaban 15 mg or a placebo daily. Their result suggested lower-than-recommended dosage NOACs might be a reasonable choice for the very elderly NVAF patients at high risk of bleeding. Other study results [37,38] also supported that a lower dosage of anticoagulants in very elderly patients with NVAF could become a therapeutic option for stroke prevention, especially for those at high risk of ischemic events. The results from our studies also suggest that an appropriate dosage reduction of NOACs based on individualized risk assessment appears to be a promising approach for those very elderly NVAF patients with both high risks of bleeding and stroke.

In the present study, different from previous publications [39,40], VKA did not show clear benefits in reducing stroke prevention or all-cause mortality in very elderly patients with NVAF (Table 6). One of the most important reasons VKA was originally chosen is the co-existing renal insufficiency (eGFR < 15 ml/min/1.73 m^2) in very elderly patients. Not surprisingly, those patients often had more comorbidities and a long home medication list. Medication noncompliance and a labile INR have been more frequently found during their clinical follow-up. Medication interaction, labile INR, and no-shows on scheduled clinics worsened this condition. Our results suggest that well-controlled clinical trial results may not guarantee practical medication utilization and compliance, to achieve sufficient risk reduction goals in real-world practice. Compared to VKA, NOACs have less adverse medication interaction and no need for INR monitoring, therefore becoming a more attractive medication choice for these very elderly patients with NVAF. Developing novel NOACs that can be readily adjusted per renal dysfunction may become a vital research focus in the future.

5. Study limitations

The main limitations of this study are related to its retrospective nature and possible selection bias. We began to include patients from 2010. $CHADS_2$ score had been used for anticoagulation therapy indication until 2014. From 2014, we started to use updated guidelines with CHA_2DS_2-VASc score. However, all patients in this study were evaluated for stroke risk using CHA_2DS_2-VASc score, which may underestimate the anticoagulation rate in this study. To ensure the integrity of the risk factor assessment and other clinical data, we included only the patients from a southern Chinese population in the Macau Special Administrative Region (Macau SAR) of China, and their genetic backgrounds may be homogeneous. Meanwhile, due to relatively low incidence of stroke events and major bleeding events, the results from our study warrants further validation by multi-center, prospective trials to further define the roles of OACs in a large-scale of very elderly patients with diversity in ethnicity, gender, and age.

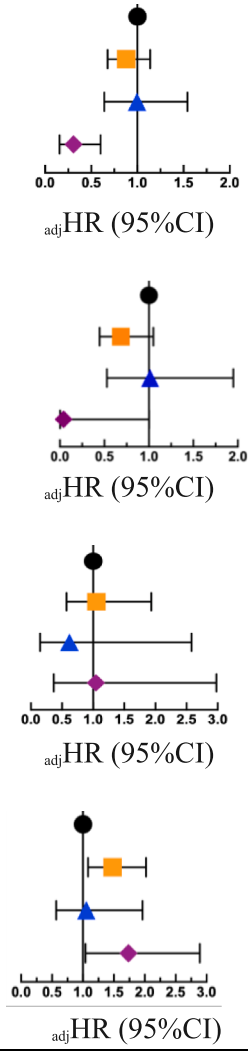
6. Conclusion

Antithrombotic treatment (VKA and NOACs) reduce stroke and improve prognosis in patients in different age groups with NVAF. The prognostic benefits of NOACs outweigh their bleeding risks in very elderly patients with NVAF.

Declaration of Competing Interest

The authors declare that they have no known competing financial

	Number of patients	Number of events	Incidence (%)		$_{adj}$HR (95%CI)	*p*-value
All-cause deaths	1252	323	25.80			
NAT	763	215	28.18		reference	—
AP	304	77	25.33		0.878 (0.677 - 1.139)	0.328
VKA	76	22	28.95		0.995 (0.641 - 1.542)	0.981
NOACs	109	9	8.26		0.308 (0.158 - 0.601)	0.001
Stroke	1252	134	10.70			
NAT	763	97	12.71		reference	—
AP	304	27	8.88		0.686 (0.447 - 1.051)	0.084
VKA	76	10	13.16		1.015 (0.529 - 1.948)	0.963
NOACs	109	0	0		0.042 (0.002 - 1.003)	0.050
Major bleeding	1252	55	4.39			
NAT	763	34	4.46		reference	—
AP	304	15	4.93		1.051 (0.571 - 1.934)	0.873
VKA	76	2	2.63		0.618 (0.148 - 2.581)	0.510
NOACs	109	4	3.67		1.045 (0.366 - 2.979)	0.935
CRNM-GIB	1252	197	15.73			
NAT	763	104	13.63		reference	—
AP	304	64	21.05		1.478 (1.081 - 2.020)	0.014
VKA	76	11	14.47		1.054 (0.566 - 1.963)	0.869
NOACs	109	18	16.51		1.736 (1.042 - 2.892)	0.034



NVAF, non-valvular atrial fibrillation; NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist anticoagulants; CRNM-GIB, clinically relevant non-major gastrointestinal bleeding; $_{adj}$HR, adjusted hazard ratio; CI, confidence interval; significant at ***p***-value < 0.05

Fig. 5. Risk of composite adverse events in different treatment groups after propensity matching in very elderly patients with NVAF NVAF, non-valvular atrial fibrillation; NAT, no antithrombotic; AP, antiplatelet; VKA, vitamin K antagonist; NOACs, non-vitamin K antagonist anticoagulants; CRNM-GIB, clinically relevant non-major gastrointestinal bleeding; $_{adj}$HR, adjusted hazard ratio; CI, confidence interval; significant at ***p***-value < 0.05.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101009.

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