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Atrial Fibrillation, Anticoagulation, and Major Bleeding Episodes in Geriatric Patients at the Risk of Falling

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Abstract

***Background*:** Geriatric patients are at risk of atrial fibrillation (AF) and stroke, and the risk of oral anticoagulation (OAC) related bleeding is also presumed to be higher. Detailed knowledge about the prevalence of AF and bleeding pattern in this population is scarce. This study sought to assess the prevalence of AF, use of OAC, and the rate of major bleeding in geriatric patients who are prone to frequent falls. We expect to find a higher prevalence of AF among geriatric patients compared to elderly people of comparable age.

***Methods*:** This was an observational cohort study conducted at the Fall and Syncope Clinic. Inclusion criteria: age >65 years, availability of both electrocardiogram (ECG) and Holter registration. The use and reasons to withhold OAC and the rate of major bleeding were retrieved from the medical files.

***Results*:** A total of 428 patients with the mean age of 79.8 years were analyzed. The mean number of morbidities was 11 ±5. AF was known in 98 (23%) patients, first diagnosed in 10 (2%). Among them, AF was paroxysmal in 45 (45%) patients, and 50% of them were first

diagnosed cases. Of patients with AF, 84% were using OAC. The rate of major bleeding episodes was 1.1 per 100 treatment years. Major bleeding episodes were not different between the patients using antiplatelet agents (APA), OAC, or no antithrombotic medication.
***Conclusions*:** In this geriatric population, 23% of patients had AF and almost half were paroxysmal. Compared to previous studies, the use of OAC has substantially increased to 84% and no differences were found in the rate of major bleeding episodes between those using APA, OAC, or no antithrombotic medication.

Keywords
Anticoagulation; atrial fibrillation; falling; geriatric; risk of bleeding

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and associated with stroke, heart failure, dementia, and death [1-4]. The prevalence of AF increases with age to around 18% for people at age >85 years [5]. The literature specifically on the incidence and prevalence and types of AF among geriatric patients is scarce. Geriatric patients are the frailest among the old and have multiple chronic conditions such as cognitive impairment, heart failure, diabetes mellitus, and hypertension [6] making them susceptible for the development and complications of AF. In older people, AF occurs often without clear symptoms [2] and it is unknown to which extent AF is paroxysmal [7]. Since AF is often asymptomatic, it is important to know the rate of paroxysmal AF to estimate if opportunistic screening, as suggested by the latest European Society of Cardiology's guideline [1], should be applied on geriatric outpatient services.

A common concern is that falls increase the risk of anticoagulation related bleeding, especially intracranial hemorrhage [8]. Cognitive disorders and dementia increase the risk of falls [9, 10]. However, limited evidence suggests that a high risk of falling does not lead to more anticoagulation related hemorrhages [11-13]. The data from the ORBIT AF registry show that patients with cognitive disorders or frailty are less likely to be treated with OAC, despite their higher stroke risk, but the use of OAC does not lead to more major events of bleeding [14]. Further, a recent review shows that people with dementia even have a 52% lower odd to receive OAC [15].

The use of OAC for AF in geriatric cohorts has increased from around 60% in 2010 [16], as found by Tulner and colleagues, to around 70% in 2016 as found in the FRAIL-AF Study [17]. A recent study applied a hospital-wide protocol and asserted that non-Vitamin K oral anticoagulation (NOAC) should be prescribed instead of a vitamin K antagonist (VKA) [18]. They found that 84% of hospitalized geriatric patients with AF were treated with OAC, of which almost 60% were taking a NOAC, without differences in the rate of complications [18].

This study addresses three questions relevant to the geriatric practice. The first question is to determine the rate of AF in ambulatory patients and the proportion of AF that is paroxysmal. We expect the prevalence of AF among geriatric patients to be higher compared to elderly people of comparable age. The second one is to describe the use of OAC and reasons to discontinue or not prescribe OAC. The third one is to assess the rate of events of major bleeding in patients with and without OAC.

2. Materials and Methods

This study is a part of an ongoing project being carried out at the Fall and Syncope day Clinic (FSC), which was initiated in November 2011. For this study all consecutive patients aged >65 years, without a pacemaker or implantable cardioverter defibrillator (ICD) who visited the FSC from November 2011 until June 2017, were eligible. We included patients who underwent both a 12 lead ECG and 24 h Holter registration. The FSC is a diagnostic program that evaluates elderly patients with unexplained falls with or without transient loss of consciousness. The team is led by a geriatrician and includes a physiotherapist, nurse practitioners, cardiologist, and neurologist. In brief, all patients underwent a comprehensive geriatric assessment (CGA) including a 12 lead ECG. The majority of patients also undergo a 24 h Holter registration. The details and outcomes of this two-day program have been published earlier [6, 19, 20]. The ethical board concluded that the study could be exempted because this study uses archival data of standard geriatric evaluations, and had no implications on therapeutic decisions. Nonetheless, for the ongoing study at the FSC, all patients were asked to give written informed consent for the use of their medical files.

Baseline characteristics were collected including gender, age, medical history, and medication use. The use of OAC in patients known with AF, and the reasons not to prescribe or discontinue OAC were retrieved from the electronic medical files.

The rate of major bleeding episodes was collected retrospectively from the hospital records for all patients, considering the data from the beginning of their digital hospital records until the first of June 2018. Bleeding in a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal or intramuscular with a compartment syndrome), bleeding leading to a decrease in the hemoglobin level to 20 g/L (1.24 mmol/L) or other conditions of fatal bleeding were considered as major bleeding episodes [21]. A bleeding episode was considered fatal if the patient died during a hospital admission, and the discharge letter reported excessive bleeding as the cause of death.

All 12 lead ECGs were reviewed by an independent cardiologist to determine if patients had sinus rhythm (SR) or AF. The judgment of the clinically consulted cardiologists was used to classify the rhythm on the Holter registration. The classification of the rhythm is shown in Figure 1. The patients were classified as having SR if they were not known with AF in their medical history and both their ECG and ambulatory registration showed SR. The long-standing persistent AF, defined as continuous AF >1 year, and permanent AF, defined as AF that is accepted by the patient, were classified as non-paroxysmal AF in this study. Also, if it was assumed that AF lasted for longer than seven days, the rhythm was classified as non-paroxysmal AF. If patients were known with AF and both the ECG and ambulatory registration showed AF, they were classified as having non-paroxysmal AF. Paroxysmal AF was defined as having AF that was assumed to be self-terminating within seven days by direct current cardioversion or with drugs. The patients were classified as having paroxysmal AF if they were known with AF in the medical history but either or both the ECG and ambulatory registration showed SR. In the case of first diagnosed AF, it was considered non-paroxysmal when both the ECG and ambulatory registration showed AF, and it was classified as paroxysmal when either the ECG or ambulatory registration showed SR.

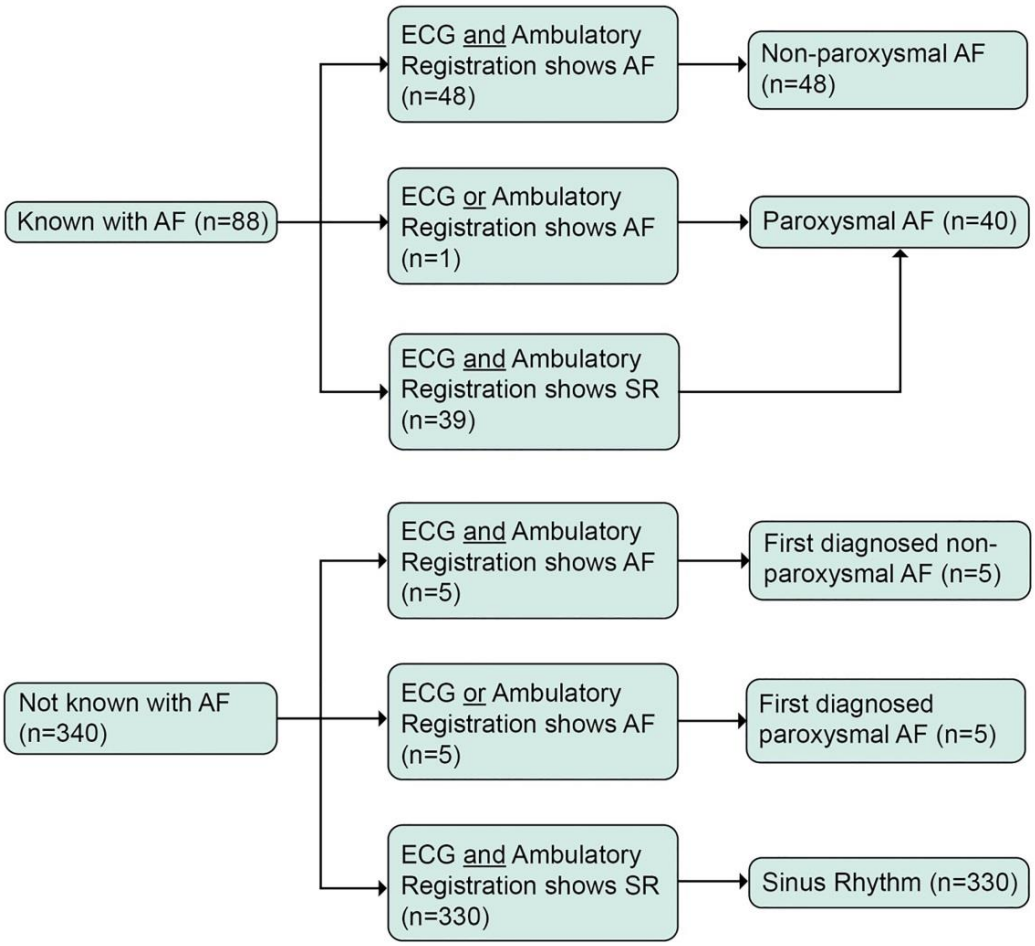

Figure 1 Classification of the rhythm. AF: atrial fibrillation; ECG: electrocardiogram; SR: sinus rhythm.

3. Statistical Analysis

All analyses were performed using SPSS for Windows, version 20 (SPSS, Inc, Chicago, IL). The categorical variables were expressed as counts and percentages, while continuous variables as mean value and standard deviation. Comparisons between participants were made using Pearson's Chi-square test for categorical variables and t-test for continuous variables. *P*-values of <0.05 were considered statistically significant.

4. Results

In total, 518 patients aged >65 years visited the FSC. We considered the data form 428 patients, in which, both a 12 lead ECG and 24 h Holter registration were performed. The baseline characteristics and functional status are shown in Tables 1 and 2. Nearly all patients reported a fall (94%). The mean age was 79.8 ±6.5 years and 65% of them were female. The average number of morbidities was 11 ±5 and the patients used, on average, 7 ±4 different drugs. The five most common morbidities, besides AF, were hypertension (68%), visual impairment (43%), hypercholesterolemia (28%), ischemic heart disease (25%), and cerebrovascular accidents including transient ischemic attacks (23%). The five most commonly used drugs were lipid-lowering drugs (47%), proton pump inhibitors (44%), vitamin supplements (43%), antiplatelet agents (APA) (36%) and diuretics (35%). Medication use is shown in Table 3.

Table 1 Baseline characteristics of the 428 patients.

	Total, n=428	AF, n=98	non AF, n=330	p
n (%)	428	98 (22.9)	330 (77.1)	
Female, n (%)	279 (65.2)	57 (58.1)	222 (67.3)	0.096
Age, years (std.)	79.8 (6.5)	80.6 (6.7)	79.5 (6.5)	0.151
Number of morbidities, mean (std.)	10.6 (5.4)	13.2 (6.0)	9.9 (5.5)	**<0.001**
Number of drugs used, mean (std.)	6.9 (3.7)	8.4 (3.5)	6.4 (3.6)	**<0.001**
Polypharmacy (>5 drugs), n (%)	269 (62.9)	79 (80.6)	140 (57.5)	**<0.001**
Hypertension, n (%)	290 (67.8)	76 (77.6)	214 (64.8)	**0.018**
Hypercholesterolemia, n (%)	118 (27.6)	28 (28.6)	90 (27.30	0.801
Diabetes mellitus, n (%)	90 (21.0)	24 (24.5)	66 (20.0)	0.338
Stroke or TIA, n (%)	97 (22.7)	31 (31.6)	66 (20.0)	**0.016**
Congestive heart failure, n (%)	42 (9.9)	26 (26.5)	16 (4.8)	**<0.001**
Ischemic heart disease, n (%)	107 (25.0)	35 (35.7)	72 (21.8)	**0.005**
CHA_2DS_2VASC, mean (std.)	4.0 (1.55)	4.5 (1.5)	3.8 (1.4)	**<0.001**
HAS-BLED, mean (std.)	2.8 (1.1)	2.9 (1.0)	2.8 (1.1)	0.873
Chronic respiratory disease, n (%)	84 (19.7)	26 (26.5)	58 (17.6)	0.052
Chronic kidney disease, n (%)	53 (12.4)	18 (18.4)	35 (10.6)	**0.041**
Thyroid disease, n (%)	56 (13.1)	16 (16.3)	40 (12.1)	0.278
Valvular disease, n (%)	59 (13.8)	19 (19.4)	40 (12.1)	0.067
History of fractures, n (%)	174 (40.7)	38 (38.8)	136 (41.2)	0.666
Osteoporosis, n (%)	62 (14.5)	16 (16.3)	46 (13.9)	0.555
Mild cognitive impairment, n (%)	56 (13.1)	7 (7.3)	49 (15.7)	0.039
Dementia, all forms, n (%)	21 (4.9)	3 (3.1)	18 (5.5)	0.340
Psychiatric disorders, n (%)	84 (19.6)	18 (18.4)	66 (20.0)	0.721
Parkinsonism, n (%)	48 (11.2)	8 (8.0)	40 (12.2)	0.260

Table 2 Functional state of the 428 patients.

	Valid data	Total, n=428	AF, n=98	non AF, n=330	p
Handgrip strength below Reference, n (%)	302	197 (65.2)	48 (66.7)	149 (64.8)	0.770
Gait disturbance, n (%)	428	61 (14.3)	17 (17.3)	44 (13.3)	0.320
Abnormal Tinetti score, n (%)	396	264 (66.7)	62 (68.9)	202 (66.0)	0.611
Dependent in ADL, n (%)	428	98 (22.9)	27 (27.6)	71 (21.5)	0.080
Dependent in iADL, n (%)	428	159 (37.1)	38 (38.8)	121 (36.6)	0.704
Use of a walking aid, n (%)	428	230 (53.7)	62 (63.2)	168 (50.9)	**0.031**
Visual impairment, n (%)	428	182 (42.5)	41 (41.8)	131 (42.7)	0.876
Institutionalized, n (%)	428	26 (6.0)	7 (7.1)	19 (5.8)	0.724

Abbreviations: ADL - Activities of daily living. iADL - instrumental activities of daily living.

Table 3 Medication used by 428 patients.

	Total, n=428	AF, n=98	non AF, n=330	p
Oral anticoagulation, n (%)	86 (20.3)	75 (75.8)	11 (3.3)	
Vitamin K antagonists, n (%)	84 (19.6)	73 (73.7)	11 (3.3)	
NOAC, n (%)	2 (0.5)	2 (2.0)	0 (0.0)	
Anti-platelet agents, n (%)	52 (35.6)	15 (15.3)	137 (41.5)	
No OAC or APA	190 (44.4)	9 (9.2)	181 (54.8)	
ACE inhibitor or ARB, n (%)	204 (47.7)	59 (60.2)	145 (43.9)	**0.005**
Beta blockers, n (%)	144 (33.6)	42 (42.9)	102 (30.9)	**0.028**
Calcium antagonists, n (%)	78 (18.2)	22 (22.4)	56 (17.0)	0.217
Diuretics, n (%)	150 (35.0)	39 (40.0)	111 (33.6)	0.262
Lipid lowering, n (%)	202 (47.2)	49 (50.0)	153 (46.4)	0.527
Anti diabetics, n (%)	76 (17.8)	20 (20.4)	56 (16.9)	0.434
Proton pump inhibitors, n (%)	188 (43.9)	50 (51.0)	138 (41.8)	0.107
Pain relievers, n (%)	130 (30.4)	34 (34.7)	96 (29.1)	0.290
Vitamin supplements, n (%)	185 (43.2)	46 (46.9)	139 (42.1)	0.398
Pulmonary agents, n (%)	67 (15.7)	17 (17.3)	50 (15.2)	0.599
Antipsychotics, n (%)	10 (2.3)	3 (3.1)	7 (2.1)	0.589
Antidepressants, n (%)	67 (15.7)	15 (15.3)	52 (15.8)	0.914
Benzodiazepine, n (%)	84 (19.6)	23 (23.5)	61 (18.5)	0.275

Abbreviations: NOAC – Non-Vitamin K Oral Anticoagulation. ACE - angiotensin converting enzyme. ARB - angiotensin II receptor blocker.

Gait disturbances were highly prevalent among the patients and the Tinetti score for gait and balance [22] was abnormal in 67%. Of them, 14% had a gait disorder and 54% used a walking aid. Low handgrip strength was present in 65% of patients, 23% need help with activities of daily living (ADL) and 37% were dependent on others for the instrumental ADL. Of the patients, 20% were at risk for malnourishment, 20% had hearing problems, and 43% were known with visual impairment. At baseline, mild cognitive impairment was known in 13% of the patients and 5% were known with dementia. Polypharmacy, defined as using five or more drugs, was present in 63% of patients.

In total 98 patients (23%) had AF, it was non-paroxysmal in 53 patients (54%) and paroxysmal in 45 patients (45%). AF was first diagnosed in ten cases, of these five were paroxysmal (50%). The patients with AF more often had hypertension, diabetes mellitus, previous stroke or TIA, chronic kidney disease, and congestive heart failure, and used more medication. Of the ten patients with first diagnosed AF, in five it was diagnosed on the ECG, but the Holter registration showed AF in all cases of newly found AF.

All patients with AF had a CHA_2DS_2VASC score of 2 points or higher, with a mean score of 4.5 ±1.5. VKA, were prescribed to 72 (82%) of the patients known with AF, two (2%) patients received a NOAC. Among the patients without AF, 11 were using OAC, 5 because of a mechanical heart valve, 5 because of thromboembolic events, and 1 patient for an unknown reason. Further, 14 (16%) patients known with AF did not use OAC at baseline. Eight of these 14 patients used APA and 6 received no antithrombotic medication at all.

Different reasons to withhold or discontinue OAC were described in the medical files. Severe risk of falling was the reason to stop or withhold OAC in five cases. One of these patients started OAC again after the CGA. Three patients discontinued OAC after intracranial or gastrointestinal bleeding, and in one patient, it was discontinued because of anemia. Frailty was not mentioned as

a reason to withhold or discontinue OAC. Seven of the ten patients with first diagnosed AF started OAC after the CGA, VKA were prescribed to five patients and a NOAC in two patients. In the remaining three patients with first diagnosed AF, OAC was not started because of a severe risk of falling (2 patients), and multiple cerebral micro bleeds on MRI imaging (one patient).

OAC was advised to be discontinued in 3 of the 73 patients because of a severe risk of falling. In total, five patients (5%) with AF could not be treated with OAC because the risk of falling was considered too high. None of the patients that started OAC after the CGA reported any major episode of bleeding, after a mean duration of 55 months until the first of June 2018.

The patients were treated with OAC for 8.9 ±4.8 years, in total there were 710 patient-years of treatment with OAC. In the entire cohort, 26 (6%) major bleeding episodes occurred, of which 19 (4%) were intracranial and 14 patients (54%) with a major bleeding episode died. An increasing trend toward major episodes of bleeding in patients with AF was seen (10 bleedings, p 0.056), but the same did not occur for intracranial bleeding (6 bleedings, p 0.372). Table 4 describes the rate of bleeding per type of anticoagulant. There were no statistically significant differences in the rate of major bleeding episodes between the patients who used OAC (9.5%), APA (5.9%) or no antithrombotic medication (4.7%). The rate of intracranial bleeding was comparable between types of anticoagulant. Eight major bleeding episodes occurred in patients using Vitamin K antagonist (major bleeding rate of 1.1 per 100 treatment years).

Table 4 The rate of major and intracranial bleeding episodes per type of antithrombotic medication, until the first of June 2018.

				p	p	p
Type of anticoagulant	No	APA	OAC	APA vs. no	OAC vs. no	APA vs. OAC
n (% of total)	190 (44.4)	152 (35.5)	86 (20.1)			
Major bleeding, n (%)	9 (4.7)	9 (5.9)	8 (9.5)	0.626	0.130	0.305
Intracranial bleeding, n (%)	8 (4.2)	7 (4.6)	4 (4.8)	0.859	0.837	0.956

Abbreviations: APA - Antiplatelet agent, OAC – oral anticoagulants, including both Vitamin K antagonist and Non-vitamin K Anticoagulants.

5. Discussion

In this geriatric cohort, 23% of patients had AF. This rate is much higher than the 12% reported for the same average age patients in the Rotterdam study [5]. Possibly this is due to the high burden of cardiovascular disease. Half of the first diagnosed AF and 45% of known cases of AF were paroxysmal. Therefore, AF can easily remain undiagnosed in geriatric patients, and our findings support the recommendation of the European Society of Cardiology to opportunistically screen for AF in high-risk patients [1].

All patients with AF had an indication for OAC. Traditionally, OAC have been underused in geriatric AF patients at the risk of falls [16, 17]. However, few patients included in the OAC trials also suffered a fall, which makes it difficult to estimate the risk that falls can cause a major or clinically relevant non-major bleeding episode [23, 24]. The study by Banjeree and colleagues showed no significant relationship between prior falls and intracranial bleeding in patients using OAC [11]. In this cohort, 26 cases of major bleeding episodes were reported and, of them, 17 patients used antithrombotic medication (APA or VKA). Nearly all patients in our cohort were known to fall, but no evidence of bleeding as a consequence of a fall could be retrieved from the medical files. Only 8 of the 26 major bleeding episodes occurred in patients that used VKA. The

rate of major bleeding episodes as 1.1 per 100 treatment years is considerably lower than in the NOAC trials, which reported bleeding rates of 3.5–6.0 per 100 treatment years [25]. In the study of Shinohara and colleagues [26], 17% of frail patients had a bleeding episode and a quarter of them (4%) were major or clinically relevant, but the rate of bleeding per 100 treatment years was not reported. Geriatric patients receive more informal or professional care than elderly people that are not or less frail. In this cohort, 37% of patients were dependent on others for instrumental ADL, for example, the timely administration of medication. Thus, it is possible that the patients were supported in the use of medication leading to better compliance than in the general population.

In our population, we found no significant differences in the rates of major bleeding episodes between the types of antithrombotic medication and between the patients with or without antithrombotic medication (APA or VKA). This could suggest that in frail geriatric patients, the risk of major bleeding episodes is mostly determined by other factors than the use of antithrombotic medication. The difference in the rate of bleeding compared to the trial data is large and lower bleeding risk in geriatric patients compared to the general population is counter-intuitive. It is a subject of future research if geriatric patients indeed have a lower risk of bleeding and if so why.

There were 14 patients with AF who did not receive OAC, mainly because of bleeding in the past or a very high risk of falling. In 12 patients, AF was diagnosed before 2012, which was before the recommendation to initiate OAC at a CHA_2DS_2VASC score higher than 2 [2, 27]. It might be possible that the antithrombotic treatment of these patients was not updated after the appearance of the new guidelines. The majority of patients with first diagnosed AF were started with OAC (70%) and 84% of those known with AF were already treated with OAC. This is a considerable increase compared with the geriatric cohorts in 2004 and 2016 [16, 17]. The use of OAC in this study was roughly similar to that reported in the cohort of Djukic but there was a large difference in the use of NOAC [18]. A probable explanation is that in the ambulatory population that we studied, the antithrombotic medication was usually prescribed by the general practitioner. In the Netherlands, the initiation of NOACs was restricted to cardiologists and other hospital-based specialists until 2017.

The main reasons to discontinue OAC were major bleeding episodes or a high risk of falling. After the CGA, a severe risk of falling was considered as a reason to discontinue or withhold OAC only in a minority of patients. This suggests that a CGA can be helpful to identify patients that should receive OAC even though they are at a high risk of falling.

This study had several limitations. The observational design allows a description of the population and associations between the patient characteristics but cannot provide conclusions about causality. The study used the medical history as it was reported by the referring physician, combined with what was retrieved from the hospital files, thus the overall collected information might be imprecise. The outcomes of the evaluation of cognitive functioning were not considered in the analysis and therefore the prevalence of cognitive impairment and dementia could be underestimated.

A large proportion of the patients known with AF showed SR on their ECG and Holter registration. For some patients, we could not retrieve the original ECG to confirm the AF. It remains unknown if these patients only had a period with AF in the past, followed by SR uninterruptedly, or truly paroxysmal AF which we evaluated when they were in SR. Another point of view is that the AF of these patients was secondary to an underlying condition at the time and the absence of AF during our evaluation reflects general treatment effects.

The information about bleeding was retrieved from the medical files and might be incomplete. No reliable account of minor bleeding episode was available, as these bleeding episodes probably did not lead to a hospital visit. The patients who died at home because of major bleeding might have been missed since there would be no documentation on this kind of bleeding in the hospital

files. In this cohort, most major bleeding episodes were intracranial, contrary to the prospective trials [25]. It is likely that non-intracranial bleeding events were missed due to the retrospective nature of this study and that the overall rate of major bleeding in this cohort is underestimated.

6. Conclusions

In this geriatric population, 23% of patients had AF and almost half of the cases were paroxysmal. By evaluating the patients with both ECG and Holter registration, a total of 10 (2.3%) new cases of AF were found. Our findings are supportive of screening opportunistically for AF in high-risk populations.

The majority of AF patients were treated with OAC (84%). The reasons to withhold or discontinue OAC were a severe risk of falling or major bleeding episode. Even though 94% patients in the cohort faced frequent falls, it was considered a contraindication for OAC only in a minority of patients (5%). The rate of major bleeding episodes was low and we found no differences in major bleeding episodes between the patients using APA, OAC, or no antithrombotic medication at all. This finding should be confirmed in future prospective and randomized trials, which possibly could lead to a better understanding of the mechanism on which the risk of the major bleeding episode in geriatric patients depends.

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Author Contributions

L.A.R. Zwart: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft and editing.

T. Germans: Conceptualization; Validation; Writing – review & editing.

S. Simsek: Conceptualization; Validation; Writing – review & editing.

J.H. Ruiter: Conceptualization; Validation; Writing – review & editing.

R.W.M.M. Jansen: Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Resources; Roles/Writing – original draft; Writing – review & editing.

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Competing Interests

The authors have declared that no competing interests exist.

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