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General population screening for atrial fibrillation with an automated rhythm-detection blood pressure device☆

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ABSTRACT

Background: Screening strategies to diagnose previously undetected atrial fibrillation (AF), especially silent AF (SAF), in at-risk populations may help reduce the number of strokes. We prospectively assessed the incidence rate of AF, including SAF, using an automated AF-detection capable sphygmomanometer in the General Practitioner (GP) setting.
Methods: This was a population-based prospective study of unselected general population of ≥65 years without prior AF. Participating GPs were requested, in the period February 2018–April 2019, to record all AF diagnoses including those derived from the AF-detection capable sphygmomanometer and confirmed by 12-lead ECG or ECG Holter in asymptomatic patients.
Results: Overall, 14,987 patients assisted by 76 GPs accumulated 16,838 patient-years of follow up. The incidence rate of AF was 2.25% patient-years (95%CI 2.03–2.48). AF was more frequently detected in male, older, overweight, and patients with prior stroke, congestive heart failure, and chronic kidney disease. One in four patients had device-detected SAF (0.56% patient-years, 95%CI 0.46–0.69). Age, overweight, and the number of annual visits, were independent predictors of both SAF and AF. In addition, congestive heart failure, mitral valve disease were independent predictors of AF. Due to the interaction between blood pressure and age the risk of AF increased exponentially after 75 years of age in patients with higher systolic blood pressure values.
Conclusion: We found a higher than previously reported incidence rate of AF possibly by capturing SAF. Our simple protocol might be feasible in large-scale screening for AF and SAF in routine GP care.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 1–2% in the general population [1], and is associated with a five-fold increase in stroke risk [2]. AF may be symptomatic or asymptomatic and both carry an increased risk of stroke [3]. The presence of symptoms may lead to diagnosis of AF, however, in almost 10–40% of cases AF is clinically silent (SAF) [4]. In the latter case, it goes potentially undiagnosed until the occurrence of a sudden complication, such as ischemic stroke [5]. The societal burden of the largely preventable strokes could be substantially reduced by early detection of AF [6], but the cost-effectiveness of systematic population-level screening with ECG has been doubted [7]. Opportunistic screening has improved AF detection compared to routine care [7], thus, pulse palpation, followed by electrocardiogram (ECG) when pulse is irregular, is already recommended in patients ≥65 years when symptoms suggestive of AF are present [6]. Pulse palpation is seldom used in general practice [8] and, when used, has a low accuracy in detecting AF [9]. Technological instruments outperform pulse palpation and may aid in a timely diagnosis of AF in asymptomatic patients [9]. Blood pressure (BP) monitoring devices with pulse analysis capabilities offer an opportunity for screening of SAF, however they have not been used in large-scale setting.

We implemented a protocol for population-level screening of SAF with the aid of automated rhythm detection BP monitor during general practitioner (GP) visits. We expected that a validated device [10,11] would be more appropriate [9] and more frequently used, than pulse palpation [8], without impacting routine care. In the present analysis we aimed to prospectively assess the incidence rate of AF and SAF, in a large-scale population organized screening program of patients ≥65 years in the GP setting. In addition, we describe the characteristics of subjects with newly diagnosed AF and the predictors of AF and SAF.

☆ All above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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2. Materials and methods

2.1. Study setting and procedures

This was a population-based prospective study of unselected general population referred for routine visits in GP practices in the period February 2018 – April 2019. The study was conducted in the Veneto region (Italy), in the period February 2018 until April 2019. The GPs were geographically representative of the whole area. All identified GPs accepting to participate in the study were part of the Italian network of GPs that use the same office software (Millewin, Millenium srl, Florence, Italy) that uses International Classification of Diseases (ICD9) codes. The study protocol required each GP to (i) provide a minimum 1-month period of patient recruitment; (ii) report a sufficient and plausible number of AF during the study period: this number was established by a 'post hoc' statistical analysis (supplementary material 1.1.); (iii) confirm through a final check the goodness of the reported data.

The protocol required that for each patient presenting in the GP office blood pressure was measured with a WatchBP Office AFIB sphygmomanometer (Microlife, Microlife AG, Switzerland) [10]. Before the study started, GPs underwent training on the use of the device. The WatchBP-AFIB monitor measures blood pressure in triplicate and flashes an "AFIB" symbol in the display of the device if it detects rhythm irregularities compatible with AF [12]. The device can detect AF with a specificity and sensitivity value that is high enough to be used for AF screening in clinical practice [11]. The systolic and diastolic BP, pulse rates, and the eventual AF diagnosis (AF, yes/no), were recorded by flagging a specifically created entry (WatchBP-AF diagnosis) in the electronic record. All participating GPs were requested to record all AF diagnoses derived from the device and confirmed by 12-lead ECG or ECG Holter in asymptomatic patients, or confirmed by ECG in symptomatic patients. Thus, patients with suspected AF diagnosis were sent to an emergency department to perform a 12-lead ECG, interpreted by a Cardiologist, or schedule an ECG Holter.

2.2. Population

Initially, a database search was performed to identify all the patients ≥65 years of age. Of these, the final dataset included all records flagged for newly diagnosed AF or WatchBP-AFIB detected AF, i.e. SAF. Demographic data and the presence comorbidities were retrieved from the electronic medical records. In this non-interventional study, analyses were carried out on collected health records submitted to an anonymization process allowing linkage of archives without any possibility of identification of patients. The study complies with the Declaration of Helsinki and was approved by Ethics Committee of the Padua University Hospital.

2.3. Sample size calculation

Sample size (supplementary material 1.4.) was determined to achieve a relative accuracy of ±25% (Fig. A.1.4.1). We determined that for an estimated annual rate of incident AF of 1.6% [7] a sample size of 3944 patients should have been screened to yield an absolute <1% margin of error at the 95% confidence level (2-sided significance level of 0.05).

To ensure the maximum precision of the WatchBP-AFIB in intercepting AF, we decided to recruit a sufficient number of GPs to generate a big enough sample size that would be suitable even in case of an unlikely condition in which all new AF cases were represented by silent AF. At a pre-test probability of $p = 0.016$ and a sensitivity and specificity of 0.98 and 0.92, respectively, the probability of false positive results with WatchBP-AFIB would be 83.0% (supplementary material 1.3). A catchment area of 158,014 patients of every sex and age (Table A.1.4.1) was determined considering: (i) a prevalence of ≥65-year-old patients of 24.5%, a prevalence of 88.2% of the population not affected by AF derived from a preliminary epidemiological research of the electronic records of the involved GPs (Table A.1.2.1); (ii) a probability of a self-referral to the GP's office of 93.9%; (iii) a patient compliance with second-level assessments of 80% (intentionally set higher than Hobbs et al. [7], as we expected larger patient involvement given the differences in the methodology in capturing AF); (iv) a median of 1573 patients for every general practitioner.

2.4. Statistical analysis

Descriptive statistics are reported as appropriate; categorical data are expressed as frequencies (percentage) and compared using the Fisher exact test or the Chi-square test when appropriate. Continuous data are reported as mean and standard deviation (SD) and compared using the non-parametric Mann-Whitney test. The rate of events for the assessed endpoints is expressed as number per 100 patient-years. The cumulative incidence of AF was calculated using Kaplan-Meier estimate. We compared the incidence of subsamples of recruited patients using incidence estimates and their confidence intervals, while possible predictors of variance (such as age, sex, number of visits, number of comorbidities) were sought using multivariate Cox regression. We assessed proportional risk assumptions of this model through the Schoenfeld's residuals distribution analysis, and evaluated the congruity of the covariate-pattern with the Pregibon test and the goodness of fit with the Harrell's C-statistic. Missing data were treated through Multivariate Imputation using Chained Equations (detailed in the supplementary material 2.2 and 2.3). All calculations were performed using the Stata14® and PASS®2008.

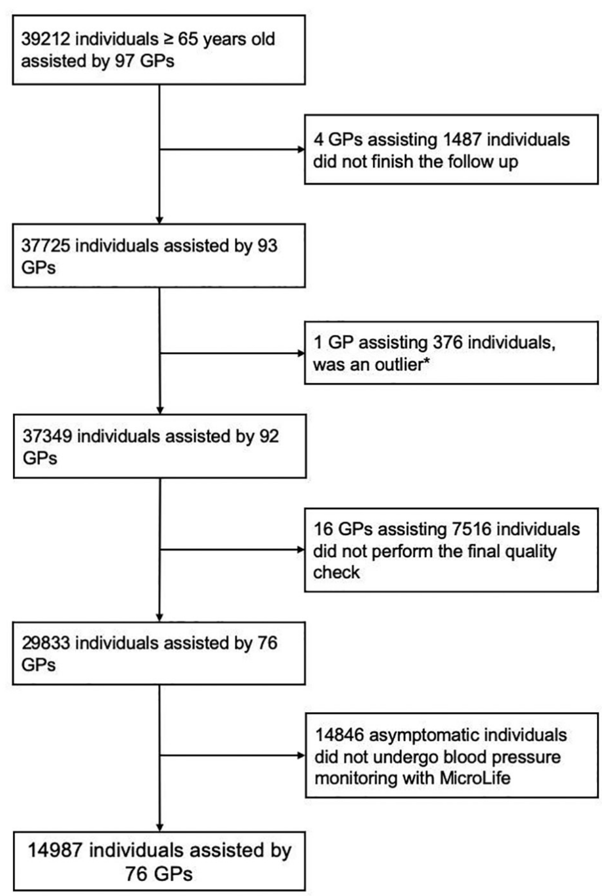

Fig. 1. Study flow and participants (*details in supplementary material 1.1).

Table 1
Demographic and clinical characteristics of the study population and of the patients with and without incident AF.[a]

	All patients (N = 14,987)	Patients without incident AF (N = 14,608)	Patients with incident AF (N = 379)	Patients with SAF (N = 95)	P value incident AF vs no-AF
Male gender, No. (%)	6339 (42.3)	6155 (42.1)	184 (48.6)	43 (45.3)	$P = 0.013$
Age years, mean (±SD)	75.5 (7.0)	75.4 (7.0)	79.1 (7.3)	79.7 (± 6.7)	$P < 0.0001$
Age groups, No. (%)					
65–69	4002 (26.7)	3953 (27.1)	49 (12.9)	8 (8.4)	$P < 0.001$
70–74	3791(25.3)	3725 (25.5)	66 (17.4)	17 (17.9)	
75–79	3305 (22.1)	3211 (22.0)	94 (24.8)	21 (22.1)	
≥ 80	3889 (25.9)	3719 (25.5)	170 (44.9)	49 (51.6)	
BMI kg/m^2, mean (±SD)[b]	27.1 (4.7)	27.0 (4.7)	28.2 (4.8)	28.4 (± 4.6)	P < 0.0001
Current Smoking, No. (%)[b]	1377 (11.4)	1352 (11.5)	25 (9.3)	7 (9.0)	$P = 0.288$
sBP mmHg, mean (±SD)[b]	136.9 (16.1)	136.9 (16.1)	138.9 (15.7)	141 (± 16.4)	$P = 0.0318$
dBP mmHg, mean (±SD)[b]	78.4 (8.8)	78.4 (8.8)	78.4 (9.0)	80 (± 9)	$P = 0.9274$
Heart rate bpm, mean (±SD)[b]	72.8 (10.9)	72.8 (10.8)	72.9 (13.1)	73 (±11)	$P = 0.8392$
Congestive heart failure, No. (%)	463 (3.1)	433 (3.0)	30 (7.9)	2 (2.1)	P < 0.0001
Coronary artery disease, No. (%)	640 (4.3)	618 (4.2)	22 (5.8)	1 (1.1)	$P = 0.155$
Mitral valve disease, No. (%)	151 (1.0)	137 (0.9)	14 (3.7)	24 (25.3)	P < 0.0001
Prior stroke/TIA, No. (%)	2844 (19.0)	2751 (18.8)	93 (24.5)	0 (0)	$P = 0.006$
Peripheral artery disease, No. (%)	445 (3.0)	429 (2.9)	16 (4.2)	1 (1.1)	$P = 0.164$
Chronic kidney disease, No. (%)	806 (5.4)	768 (5.3)	38 (10.0)	9 (9.5)	P < 0.0001
Hypertension, No. (%)	10,426 (69.6)	10,166 (69.6)	260 (68.6)	72 (75.8)	$P = 0.692$
Diabetes, No. (%)	3589 (24.0)	3503 (24.0)	86 (22.7)	25 (26.3)	$P = 0.584$
VTE, No. (%)	613 (4.0)	590 (4.0)	23 (6.1)	4 (4.2)	$P = 0.064$
Thyroid Disease, No. (%)	85 (0.6)	84 (0.6)	1 (0.3)	1 (1.1)	$P = 0.727$
COPD, No. (%)	416 (2.8)	407 (2.8)	9 (2.4)	1 (1.1)	$P = 0.752$
Gastric disease, No. (%)	1290 (8.6)	1257 (8.6)	33 (8.7)	12 (12.6)	$P = 0.926$
Neoplastic disease No. (%)	3038 (20.3)	2955 (20.3)	83 (21.9)	16 (16.8)	$P = 0.437$
Hepatic disease No. (%)	359 (2.4)	350 (2.4)	9 (2.4)		$P = 1.000$
CHA2DSVASC2 score					
$CHA_2DS_2VASc < 3$, No. (%)[b]	2972 (21.9)	2930 (22.0)	42 (14.1)	7 (8.2)	P < 0.001
$CHA_2DS_2VASc \geq 3$, No. (%)[b]	10,622 (78.1)	10,366 (77.9)	256 (85.9)	78 (91.8)	
Number of visits per year (%)					
0–9	8815 (58.8)	8684 (59.5)	131 (34.6)	35 (36.8)	P < 0.0001
10–19	4690 (31.3)	4555 (31.2)	135 (35.6)	32 (33.6)	
≥20	1482 (9.9)	1369 (9.4)	113 (29.8)	28 (29.4)	

BMI – body mass index; sBP – systolic blood pressure; dBP – diastolic blood pressure; COPD – Chronic Obstructive Pulmonary Disease; VTE – Venous Thromboembolism; TIA – transient ischaemic attack.

[a] Some variables had missing values: supplementary material Table A.2.1.1 shows the number of patients with available data for those variables.

[b] Calculated on the available data.

3. Results

Of the 97 initially recruited GPs, 76 complied with the study protocol (Fig. 1). From an initial population of 39,212 patients ≥65 years, 24,225 were excluded for the reasons shown in Fig. 1. The data base validation was optimal for the 76 GPs as their total index score (ITOT), an index of the overall quality of data recording [13], was very high (median 0.778, interquartile range 0.729–0.809; reliability cut-off ≥0.65). The final population comprised of 14,987 patients of ≥65 years. The follow up extended to 16,838 patient-years. Most patients were female (57.7%) and the mean age of the population was 75 years, with patients well distributed among age strata. The Kolmogorov-Smirnov test results showed that the studied and the Italian population were similar with regard to age distribution (supplementary material Fig. A.2.1.1). The characteristics of the overall population and sub-groups with and without AF are summarized in Table 1.

Incidence rate of AF was 2.25 (95% CI 2.03–2.48) per 100 patient-years (Fig. 2). AF incidence was higher in males with an incidence rate of 2.58% patient-years (95% CI 2.24–2.99) vs 2.0% patient-years (95% CI 1.74–2.30) with a M/F Ratio of 1.29 (Fig. A.2.4.2.). Overall, patients with an incident AF were more likely to be older (mean age 79.1 vs 75.4 years old), with 44.9% belonging to the ≥80-year-old group and overweight (BMI: 28.2 kg/m2 vs 27.0 kg/m2). Clinically, AF patients had higher systolic BP measurements, more frequently, a diagnosis of congestive heart failure, mitral valve disease, a history of stroke/TIA and chronic kidney disease. Patients with a higher number of annual visits, during the study period, had higher chances of being diagnosed AF. The crude incidence of AF in the overall population and in different subgroups is detailed in supplementary material 2.4.

In the multivariate model, age (per each year increment), overweight (BMI ≥ 28.4 kg/m^2), mitral valve disease, congestive heart failure, and the number annual of visits, were independent predictors of incident AF (Table 2). The finding of basal systolic pressure values higher than 137 mmHg was found to be an important effect modifier on age (supplementary material Fig. A.2.2.1). In fact, in patients ≥75 years of age, the risk of atrial fibrillation increases exponentially with age when the systolic blood pressure exceeds the 137-mmHg cut off.

Silent AF was found in 95 patients (25% of the total incident AF) yielding an incidence rate of 0.56 (95% CI 0.46–0.69) per 100 patient-

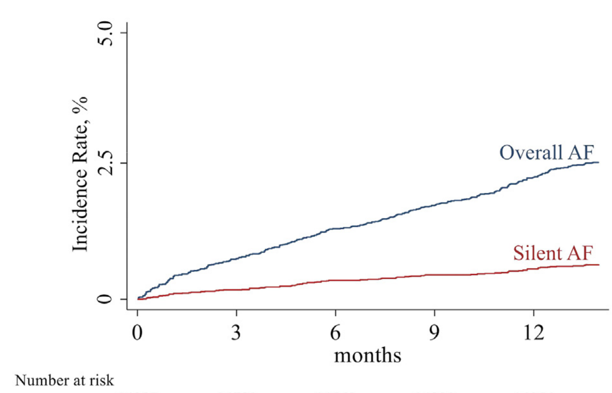

Fig. 2. Cumulative incidence of AF and silent AF.

Table 2
Predictors of overall incident atrial fibrillation and silent atrial fibrillation.

	Overall Atrial Fibrillation				Silent Atrial Fibrillation			
	Univariate analysis		Multivariate analysis*		Univariate analysis		Multivariate analysis*	
	HR	95%CI	HR	95% CI	HR	95%CI	HR	95% CI
Male gender	1.29	1.05–1.57	–	–	1.13	0.75–1.69	–	–
Age (per year increment)	1.07	1.05–1.08	1.04	1.02–1.06	1.08	1.05–1.11	1.08	1.05–1.11
sBP at the time of visit								
80–137 mmHg	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00
138–230 mmHg	1.27	1.01–1.59	0.67	0.41–1.08	1.61	1.02–2.54	1.48	0.93–2.36
sBP – Age interaction	–	–	1.04	1.00–1.07	–	–	–	–
BMI								
13.30–28.39 kg/m^2	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00
28.40–30.23 kg/m^2	1.71	1.34–2.17	1.52	1.19–1.94	1.85	1.17–2.94	1.92	1.22–3.02
Mitral valve disease	3.88	2.28–6.63	2.97	1.74–5.09	–	–	–	–
Prior stroke/TIA	1.38	1.09–1.75	1.02	0.80–1.29	–	–	–	–
Congestive heart failure	2.79	1.92–4.06	1.58	1.07–2.32	–	–	–	–
Venous thromboembolism	1.51	0.99–2.31	–	–	–	–	–	–
Chronic kidney disease	1.98	1.42–2.78	–	–	1.86	0.93–3.71	–	–
Number of visits per year								
0–9	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00	1.00	1.00–1.00
10–19	1.91	1.50–2.43	1.91	1.50–2.43	1.69	1.05–2.74	1.71	1.05–2.76
≥20	5.21	4.05–6.7	4.57	3.54–5.89	4.84	2.94–7.95	4.22	2.56–6.95

sBP – systolic blood pressure; BMI – body mass index; TIA – transient ischaemic attack.
* Multiple Imputation Cox Regression model; see supplementary material 2.2, 2.3 and supplementary tables A.2.2.2 and A.2.2.3 for more details.

years (Fig. 2). The characteristics of patients with SAF are shown in Table 1. Most patients were female (54.7%). The mean age was 79.7 years, with most patients belonging to the ≥80 age-group. The crude incidence of silent AF in the overall population and in different subgroups is detailed in supplementary material 2.5.

In comparison with patients without AF, patients with SAF were older, had higher basal systolic blood pressure and were more overweight. The chances of detecting SAF were higher with an increasing number of visits per year. In the multivariate model (Table 2), each year increment in age, and overweight were found to be independent predictors of SAF. Indeed, for each year increment in age the risk of SAF increases by 8%, while for a BMI ≥28.4 kg/m^2 the risk increases by 92%. The model also showed that the chances of diagnosing SAF increased with the increasing number of visits per year (more than 4 times with ≥20 visits). Although statistically not significant, basal systolic blood pressure of >130 mmHg was correlated to an increased SAF risk (HR 1.48, 95%CI 0.93–2.36).

4. Discussion

The incident rate of AF in this study was 2.25 per 100 patient-years. The rate of reported incident AF largely depends on the population screened and the method used [14–17]. A systematic review of AF screening reported an incidence of previously undiagnosed AF of 1.4%, in adults aged ≥65 years, with single time-point pulse palpation or ECG [14]. At least three aspects might account for the difference with our finding. First, our higher incidence might be due to the actual increase of AF incidence [18] given the temporal differences in the studies. Second, as opposed to pulse palpation [15], we used an automated method with a higher probability [9] of capturing silent AF. Third, opportunistic detection of AF using single time-point pulse palpation or ECGs will underestimate the incidence of AF [17], while we assessed patients on multiple intermittent time-points. We found the number of visits per year to be an independent predictor of both AF and SAF. It is likely that unaccounted for comorbidities might have increased the frequency of GP visits thus increasing the chances of capturing AF. However, this further underlines the fact that increasing screening timepoints for any reason will increase the chances of detecting AF.

Demographic and clinical characteristics differentiate patients with incident AF from the remaining population. As expected [18,19], patients with AF were older and more frequently male. Furthermore, clinical conditions associated to AF [6] such as elevated systolic blood pressure, congestive heart failure, mitral valve disease, stroke/TIA, and chronic kidney disease were more frequent in patients with incident AF. Despite the well-established link between AF and stroke, almost 25% of strokes cannot be directly attributed to AF. The etiology of stroke in such cases is suspected to be silent or subclinical AF, but continuous long-term monitoring for such arrhythmia is impractical [20] and remains an unresolved issue. In this respect, detection of SAF may be significantly improved with our approach were high rates of coverage over time can be practically achieved with minimal change to routine care.

We found some characteristics to be independent predictors of AF. We confirm that the incidence of AF increases with age [15,21,22], and is predominantly higher in octogenarians. Moreover, AF is commonly associated with overweight and obesity [23] with an estimated 3.5–5.3% excess risk of AF for every unit of BMI increase [24]. We also found that about one in three of overweight AF patients did not present any symptoms, but overweight was an independent predictor of AF and SAF. Other independent predictors of AF in our study were the presence of congestive heart failure and mitral valve disease. Interestingly, we found that elevated systolic blood pressure is an important effect modifier for age; in fact, the risk of AF increases exponentially in patients over 75 years old.

Patients diagnosed with SAF had different characteristics. Octogenarians accounted for more than half of cases in the SAF group, while gender was similarly distributed. Furthermore, age and overweight (BMI ≥28.4 kg/m2) were found to be independent predictors of SAF. Physicians should be aware of the characteristics predisposing to AF and increase the efforts in actively screening such patients even in the absence of symptoms.

Gaps in evidence exist and there is an ongoing debate on whether to perform screening and which might be the best approach [25]. Our results show that an organized screening program of an at-risk population diagnoses a consistent number of AF particularly SAF (≥65 years that would likely benefit from anticoagulation). The frequency of assessments independently predicted AF diagnoses, and our approach, using an automated rhythm detection BP monitor contributed in making possible an elevated number of repeated assessments per patient per year.

Several studies have found AF screening likely to be cost effective especially when using existing infrastructure, healthcare pathways, and the more readily available handheld devices [26–29]. In order to reduce costs and reach a high population coverage we based our protocol on usual GP care, and blood pressure measuring is part of the routine GP visits. Eventual indirect costs are likely to be related to the 12-lead ECG confirmation, however, it is still likely to be cost effective [30]. Although we cannot directly draw cost-effectiveness conclusions, we think this protocol is affordable, as it does not impact the routine care.

4.1. Limitations and strengths of the study

Although efforts were made to evenly represent the complete geographical area, some areas in our region might have been more represented than others. However, the larger number of screened patients in comparison to that calculated to achieve a relative accuracy, reassure on the quality of results that can be made general for the region and the entire country. Differences between physicians pertaining to the input of data in electronic records could lead to misclassifications of the outcome or its predictive factors. We tried to limit this by asking the participating GPs to provide a final data check in the electronic records. On the other hand, the calculated quality of recruited physician in terms of quality of data recording was optimal. Our population was representative of the general age- sex-matched general population. The sample size is much larger than that predicted to prove the efficacy of this approach. Unlike others [31,32] we had a high number of very high-risk population (≥80 years), with about 80% of the patients with a $CHA_2DS_2VASc \geq 3$. We cannot draw conclusions on how early diagnosis of AF in this screening program impacted on anticoagulation initiation and this deserves further investigation.

5. Conclusions

In conclusion, we found a higher than previously reported incidence rate of AF, even by possibly increasing the chance of capturing SAF. Age and overweight are independent predictors of AF and SAF while the odds of diagnosing AF increase with the number of visits. Our simple screening protocol is feasible and easily implemented on the routine GP care were high rates of coverage can be achieved.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.08.097.

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