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Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-010745
Article Type:	Research
Date Submitted by the Author:	02-Dec-2015
Complete List of Authors:	Omboni, Stefano; Italian Institute of Telemedicine, Clinical Research Unit Verberk, Willem; University of Maastricht, Cardiovascular Research Institute Maastricht (CARIM); Microlife AG
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Diagnostics
Keywords:	Atrial fibrillation, Blood pressure measurement, Italy

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**ASYMPTOMATIC ATRIAL FIBRILLATION: THE CASE FOR OPPORTUNISTIC
SCREENING BY AUTOMATIC BLOOD PRESSURE MEASUREMENT IN THE
COMMUNITY**

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Short title: atrial fibrillation in an Italian community

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Manuscript word count (excluding references and abstract): 2,982

Abstract word count: 277

Number of references: 40

Number of Tables: 2.

Abstract

Objective: Timely detection of atrial fibrillation (AF) may effectively prevent cardiovascular consequences. However, traditional diagnostic tools are either poorly reliable (pulse palpation) or not readily accessible (electrocardiogram, ECG) in the general practice. We tested whether an automatic oscillometric blood pressure (BP) monitor embedding an algorithm for AF detection might be effective for opportunistic screening of asymptomatic AF in the community.

Setting: Community-based screening campaign in an unselected population to verify the feasibility of AF screening with a Microlife WatchBP Office BP monitor with patented AFIB algorithm.

When, a possible AF was detected (≥ 2 out of 3 BP measurements reporting AF) a doctor immediately performed a single-lead ECG in order to confirm or exclude the presence of the arrhythmia. Main demographic and clinical data were collected prior to any BP measurement

Participants: 220 consecutive subjects from an unselected sample of individuals of a small Italian community

Primary and secondary outcome measures: number of patients detected with AF and diagnosed risk factors for AF.

Results: In 12 of 220 subjects the device detected a possible AF during the BP measurement: in 4 of them (1.8%) the arrhythmia was confirmed by the ECG. In univariate analyses, subjects with AF were more likely to be older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, $p=0.010$), obese (50.0 vs. 14.4%, $p=0.048$) and to suffer from a cardiovascular disease (50.0 vs. 10.6%, $p=0.014$) than non-AF subjects. In a multivariate analysis, aged subjects had a 21% significantly larger risk of AF [odds ratio (95% confidence interval): 1.21 (1.02, 1.44), $p=0.031$].

Conclusions: Opportunistic screening of AF by BP measurement, confirmed by ECG monitoring, is feasible to detect this arrhythmia in unaware subjects dwelled in the community.

Keywords: atrial fibrillation; blood pressure measurement; Italy

Strengths and limitations of this study

- A blood pressure monitor with atrial fibrillation (AF) detecting algorithm was tested in an unselected population resident in the community
- Each case of AF finding was immediately verified with an ECG device by an experienced cardiologist
- Additional demographic and clinical data were collected to verify risk factors for AF
- The screening tool allowed to unmask 4 unaware cases of AF in the community, a prevalence which is expected in such a setting
- Main risk factor for AF was advanced age, followed by a positive medical history for cardiovascular disease or obesity

INTRODUCTION

Atrial fibrillation (AF) is the most common form of sustained arrhythmia in clinical practice¹. Its prevalence in developed countries approximates 1.5-2% in the general population and varies with age and sex: it is present in <0.5% of subjects younger than 50 years, 3-4% of those aged 60-70 years and 5-15% of those aged 80 years or older^{2,3}. However, recent insights indicate that this most likely is an underestimation as improved screening with innovative tools leads to significant increase in detection of patients with AF^{4,5}. This arrhythmia is associated with a 5-fold increased risk of stroke and 3-fold increased incidence of congestive heart failure, and high mortality^{2,6,7}. Usually, AF progresses from short, rare episodes (paroxysmal) to longer and more stable forms (persistent, long-standing persistent and permanent): in 25 to 40% of patients it remains silent for long before diagnosis^{8,9}. As AF is often asymptomatic, stroke is the initial dramatic presentation that leads to its detection in up to 25% of subjects¹⁰⁻¹².

Early detection and treatment of patients with asymptomatic AF before the first complications occur is a recognised priority for the prevention of strokes by all major guidelines^{11,13-17}. In particular the European Society of Cardiology recommends pulse-taking in all subjects aged ≥ 65 years, followed by an electrocardiogram (ECG) in case of irregular beats, to allow timely detection of AF¹⁵. However, pulse palpation has a low specificity and is much less reliable than ECG¹⁸. Moreover, despite the fact that most guidelines recommend it, pulse palpation is often not performed by doctors or nurses in clinical practice¹⁹.

Because hypertension is the most common risk factor associated with AF²⁰, using an automatic blood pressure monitor to detect AF would benefit the large number of hypertensive patients who monitor their blood pressure at home, in the doctor's office or in community pharmacies²⁰.

Recently, an automatic blood pressure device with an algorithm that can detect AF has been proposed for opportunistic screening of AF when blood pressure is measured. Such a device showed a very high sensitivity and specificity when compared to ECG monitoring [on average

(95% confidence interval), 0.98 (0.95, 1.00) and 0.92 (0.88, 0.96), respectively] and was expected to detect twice as many patients with AF as pulse palpation²¹⁻²⁷. Following results from studies including approximately 2,300 subjects, the NICE has now recommended the use of such technology to screen AF in primary care clinics²⁸.

The objective of the present investigation was to evaluate the ability of such a validated, electronic, oscillometric, blood pressure monitor embedding an algorithm for AF detection, to identify new cases of AF in an unselected population of a small community located in northern Italy, during a hypertension screening campaign.

METHODS

Study design and participants

A community-based screening campaign focusing on blood pressure measurement and collection of basic information on main cardiovascular risk factors was performed. It was carried out in an unselected population of subjects aged ≥18 years, living in two small villages (Besnate and Solbiate Arno) in the Northern area of Italy, close to the city of Varese, in the Lombardy region. Visits took place in mobile units located in villages’ main squares. A questionnaire was administered to all subjects in order to record their age, gender, height and body weight, family history for cardiovascular diseases, smoking and drinking habits, personal clinical history for cardiovascular diseases, presence and treatment of arterial hypertension, diabetes mellitus and dyslipidemia. Following the interview, blood pressure was measured in triplicate at 1 minute interval with the patient in the sitting position since at least 5 minutes, according to current recommendations, by a validated, automatic, electronic, upper-arm sphygmomanometer (Microlife WatchBP Office AFIB, Microlife AG, Switzerland). The oscillometric blood pressure monitor embeds an algorithm that can identify pulse irregularities compatible with AF during the automatic blood pressure measurement: if at least 2 out of 3 measurements detected AF the “AFIB” symbol flashed on the display of the

device indicating a possible case of AF. In such a case, the doctor immediately performed a single-lead ECG recording with a hand-held ECG recorder (Cardio-A Palm ECG, Shenzhen Creative Industry Co Ltd., China), in order to check the patient's rhythm. The ECG was performed by the patient with the assistance of the doctor: he or she was asked to grab the device with the right hand (palm and fingers) and to press the left side of the device with the centre of the left hand palm. The ECG detected by such palm measurement is equivalent to a lead I ECG signal. A 30 sec recording was performed and, if considered of poor quality by the assisting physician (a cardiologist adequately trained and experienced in ECG interpretation), it was repeated. ECG tracings were immediately visually inspected and checked by the doctor for confirming or excluding the presence of AF. This arrhythmia was defined as the absence of distinct 'p' waves, an absolutely irregular RR interval and an atrial cycle length <200 msec (300 bpm) on the recorded 30-sec ECG.

Prior to the examination, participants were asked to give written informed consent for collection and analysis of their clinical data, according to current Italian law. All visits took place between June 2013 and June 2015. The study design did not foresee any patients' follow-up.

All data collected at the time of the examination were reported on a paper sheet. Individual data were then entered in an electronic database to allow pooled analysis. Patients were considered having AF when detection by the blood pressure monitor was confirmed by the single-lead ECG.

Statistical analysis

Data analysis was performed by grouping the patients according to the presence or absence of AF. Given the observational nature of the study no sample size estimation was done. All subjects provide valid data and thus no methodology for replacing missing data was implemented. Main demographic and clinical data of the two subgroups were summarized by calculating the mean ($\pm$ SD) in case of continuous variables and the absolute (n) and relative (%) frequency in case of categorical variables. Differences across groups were evaluated by analysis of variance or Chi-square test, depending on the type of variable. A logistic regression analysis was used by entering in

the analysis AF (condition present vs. condition absent) as dependent variable, and all the demographic and clinical variables collected in the study as covariates. The logistic regression analysis was first run by forcing all covariates in the model and then by applying a stepwise binary approach (forward selection), in order to exclude variables irrelevant to the model. The variables entered in the multivariate model were: age, gender (male vs. female), body mass index, systolic and diastolic blood pressure, heart rate, smoking (yes vs. no), alcohol drinking (yes vs. no), known arterial hypertension (yes vs. no), previous cardiovascular diseases (yes vs. no), known diabetes mellitus (yes vs. no) and dyslipidemia (yes vs. no). Results were presented as odds ratio and 95% confidence interval. A p value of <0.05 was considered significant. Data analysis was performed using IBM SPSS Statistics ver. 20 for Windows.

RESULTS

A total of 220 subjects were enrolled: all of them provided relevant information and were included in the analysis. In 12 subjects the device detected a possible AF during the blood pressure measurement: in 4 of them (1.8% of the whole population) this arrhythmia was confirmed by the one-lead ECG, whereas for the remaining 8 subjects sinus arrhythmia (n=1) or supraventricular ectopic beats (n=7) were diagnosed. All subjects diagnosed for AF apparently were unaware of this arrhythmia.

Demographic, anthropometric and clinical data of the participants, grouped by absence or presence of AF, are summarised in **Table 1**. Mean subjects' age was 57.7 ± 15.2 years, and males were slightly more prevalent than females (51.4 vs. 48.6%). A personal history for cardiovascular disease was recorded in 11.4% of subjects. Hypertension was previously diagnosed in 36.4%, whereas an additional 17.2% of subjects had elevated blood pressure values (≥140/90 mmHg) during the automatic measurement. Diabetes and dyslipidemia were reported by 7.7% and 27.3% of subjects, respectively. Obesity was documented in 15.0% of the sample.

Subjects with AF were older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, $p=0.010$), were more often obese (50.0 vs. 14.4% , $p=0.048$) and were more likely to display a positive history for cardiovascular disease (50.0 vs. 10.6% , $p=0.014$) than those without this arrhythmia. None of the patients diagnosed with AF had a previous stroke, whereas two had a positive history for myocardial infarction, one for heart failure and one for peripheral artery disease. AF patients also had higher levels of systolic blood pressure than those free from AF being nearly statically significant (151.5 ± 6.1 vs. 133.9 ± 18.5 years, $p=0.059$).

In order to evaluate possible patient's determinant of AF, all the variables listed in **Table 1** were forced in the logistic regression analysis. Although none of them resulted significantly associated with the risk of AF, the largest odds ratios were found for male gender and advanced age. When a stepwise logistic regression was run, only age was kept in the equation, whereas all the others were removed because not significantly related with the occurrence of AF. Being older was associated with a 21% significantly larger risk of AF [odds ratio (95% confidence interval): 1.21 (1.02, 1.44), $p=0.031$].

DISCUSSION

Our community survey documented a 1.8% prevalence of AF in an unselected sample of the population. Although based on a limited number of subjects, our results confirm those of larger surveys. The estimated prevalence of AF in epidemiological studies carried out in Europe in the general population in the last decade ranged between 1.9% and 2.9%²⁹. In a recent nationwide, retrospective, observational Italian study involving 233 general practitioners and screening almost 300,000 patients representative of the population, the prevalence of AF was 2.0%.

In our study, consistent with previous evidence, age was the main independent risk factor of AF³⁰.

In the multivariate model, after correcting for other demographic and clinical confounders, advanced age was associated with a 21% significantly increased risk of developing AF. Many

studies have also shown that individuals with an antecedent cardiac disease, high blood pressure or obesity have a higher risk of occurrence of AF compared with healthy, normotensive or slim subjects³¹⁻³⁵. The relationship between other established cardiovascular risk markers, such as smoking, diabetes or dyslipidemia and the development of new-onset AF is less clear and poorly understood¹. In the univariate comparison of our study, patients with AF were more likely to report a previous cardiovascular disease and were more often obese. A trend was observed for a larger prevalence of hypertension, whereas diabetes and dyslipidemia were not reported in our patients with AF. The weight of such risk factors was overtaken by age in the multivariate model. Despite this and the fact that our sample was limited in size, our results seem to confirm the strong association between major markers of cardiovascular disease and the risk of AF. The fact that we did not find any positive relationship between alcohol consumption and risk of AF, as previously reported^{31 32 35}, may be explained by the fact the majority of subjects (56.8%) were not drinking alcoholics and 40.9% were only moderate alcohol drinkers (no more than 2-3 glasses of wine per day). Only 2.3% of interviewed subjects were drinking more than 3 glasses of wine per day or spirits (a figure which is in line with the 2.4% rate reported by the National Institute of Statistics for the Italian population)³⁶, and it is recognized that only repeated acute ingestion of excessive amounts of alcohol may increase the risk of AF¹. Screening for AF in people over the age of 65 years leads to improved detection of AF as compared to routine clinical practice. However, in a large randomized trial, the effect on overall AF diagnosis rate for systematic and for opportunistic screening was comparable [odds ratio and 95% confidence interval: 1.57 (1.08, 2.26) and 1.58 (1.10, 2.29), respectively]. The number of subjects needed to be screened in order to detect one additional case compared to routine practice was 172 subjects (95% confidence interval: 94 to 927) for systematic screening and 167 (92 to 806) for opportunistic screening^{37 38}.

The present study reported that one out of four subjects who were positively diagnosed for AF with the blood pressure monitor actually had the disease as was confirmed with ECG. This result is worse than a previous study performed among 1,000 primary care patients aged 75 years and older

which found a positive predictive value of 44% with the Microlife WatchBP Home A device²⁵. However, it seems to be an improvement in comparison to pulse palpation as demonstrated in the SAFE trial where one in 5.7 ECG referrals led to a positive AF detection³⁸. In addition, as pulse palpation generally has a lower sensitivity value (87%)³⁸ for detecting AF than the blood pressure monitor (98%)²⁷ it is not unlikely that the latter has led to the detection of more patients with AF. A disadvantage of opportunistic screening is that it is generally performed in primary care practice. As a matter of fact, ECG interpretation by a primary care doctor often leads to misinterpretation³⁹. For this reason some ECG devices provide auto-analysis as a supportive tool but a direct comparison study showed that the blood pressure monitor with AF detector outperforms an ECG with auto-analysis software²⁵. This means that the ECG performance may have no added value in primary care or in community pharmacies, unless the ECG reading is directly transferred to a cardiologist for interpretation by means of telemonitoring⁴⁰.

Study limitations and strength

Our study suffers from some limitations. First of all, the diagnosis of AF was confirmed by a cardiologist using a one-lead ECG device whereas the gold standard is a 12-lead ECG. Although the ECG device employed in the study is of high quality, previous studies with one-lead ECG devices showed sensitivity values varying between 88 and 98% and specificity values ranging from 75 to 98% for detecting AF among different cardiologists²⁵. However, we are of the opinion that readings from the hand-held ECG recorder have sufficient quality to make an appropriate diagnosis, particularly because in our case 30-sec tracings were repeated several times in case of doubt and correct interpretation was immediately warranted by an experienced cardiologist. Second, given the opportunistic nature of the screening campaign we could not systematically check the possible presence of AF in all subjects, including those apparently negative during the blood pressure measurement. However, since several studies have shown a good specificity (89-92%) and a high sensitivity (97-100%) of the methodology of ≥ 2 out of 3 measurements²⁷ we may assume that the

chance that subjects with true AF could be diagnosed is reasonably high and much higher than that of missing a false negative. Third, AF usually occurs more frequently in males than in females^{2 29}, gender representing one of the most powerful risk factors for AF together with age and cardiovascular comorbidities. However, this was not the case for our survey, where the proportion of men and women reporting AF was exactly the same. We cannot exclude that the observational nature of our study and the relatively unselected sample of the population might have prevented an accurate estimation of the relative importance of various factors contributing to the genesis of the arrhythmia. Moreover, we must acknowledge that the prevalence of AF in our population, though very close to that observed in a large nationwide Italian survey, might not be representative of the phenomenon in the whole country, also because undetermined selection related to the willingness of being screened cannot be excluded. In addition, we cannot rule out possible regional differences in the prevalence of AF, and consequent representation bias, particularly because data have been collected in a population resident in a highly developed area of the country.

The strength of the presented approach for the screening of AF is that screening is automatically performed during consecutive automatic blood pressure measurements without extra efforts. This means that the current finding of AF cases comes on top of the detection of hypertension which was present in 53.6% of the screened population, with 36.4% of the overall population aware and 17.2% (approximately one-third) unaware of their condition.

Conclusions

In conclusion, our small-scale observational study indicates that opportunistic screening of AF by blood pressure measurement confirmed by ECG monitoring, is feasible to detect this arrhythmia in unaware subjects dwelled in the community. Whether such an approach might have a positive impact on clinical, social and economic outcomes needs to be demonstrated in large well-designed prospective studies.

Acknowledgements

We are grateful for the logistic support provided by the following volunteers who helped collecting the data during the screening campaign: Lara Brianese, Armando De Falco, Edoardo Ghirardi, Daniela Ghiringhelli, Andrea Niglia, Federica Pagliarin, Massimo Protasoni, Alberto Riganti, Andrea Zerbi.

Funding statement

This work was supported by Biotechmed Ltd. which sponsored the campaign by providing for free the blood pressure monitors used in the study. No specific grants were received for conducting the study. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Transparency Declaration

The lead author SO affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. STROBE guidelines for cohort studies have been followed, where appropriate, for manuscript preparation.

Author Contributions

SO wrote the first draft of the manuscript. WJV contributed to the writing and finalisation of the manuscript. Both author met ICMJE criteria for authorship.

Disclosure

SO received lecture fees from Colpharma, the Italian distributor of Microlife AG, and is scientific consultant of Biotechmed Ltd. provider of telemedicine services. WJV is an employee of Microlife AG.

Data Sharing Statement

There are no additional unpublished data for this work. All the available data are reported in the manuscript.

Table 1. Demographic and clinical characteristics of the subjects enrolled in the study. P-values refer to the statistical significance of the difference between subjects with and those without atrial fibrillation (AF).

	Subjects without AF (n=216)	Subjects with AF (n=4)	p- value	All subjects (n=220)
Age (years)	57.2 ± 15.2 (20 – 84)	77.0 ± 1.2 (76 – 78)	0.010	57.5 ± 15.3 (20 – 84)
Male / Female (%)	111 / 105 (51.4) / (48.6)	2 / 2 (50.0) / (50.0)	0.956	113 / 107 (51.4) / (48.6)
Height (cm)	166.7 ± 9.3	170.3 ± 8.2	0.447	166.8 ± 9.3
Weight (kg)	71.6 ± 15.0	80.8 ± 17.5	0.226	71.7 ± 15.0
BMI (kg/m ²)	25.6 ± 4.3	27.7 ± 4.5	0.337	25.7 ± 4.3
Obesity (BMI ≥30 kg/m ²)	31 (14.4)	2 (50.0)	0.048	3.3 (15.0)
Current smokers (%)	37 (17.1)	1 (25.0)	0.680	38 (17.3)
Alcohol drinkers (%)	94 (43.5)	1 (25.0)	0.459	95 (43.2)
Cardiovascular diseases (%)	23 (10.6)	2 (50.0)	0.014	25 (11.4)
Hypertension (%)	78 (36.1)	2 (50.0)	0.567	80 (36.4)
Diabetes (%)	17 (7.9)	0 (0.0)	0.559	17 (7.7)
Dyslipidemia (%)	60 (27.8)	0 (0.0)	0.216	60 (27.3)
SBP (mmHg)	133.9 ± 18.5	151.5 ± 6.1	0.059	134.2 ± 18.5
DBP (mmHg)	81.0 ± 12.0	88.3 ± 12.0	0.233	81.1 ±12.1
HR (bpm)	72.9 ± 11.3	72.3 ± 3.6	0.905	72.9 ± 11.2

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate.

Table 2. Odds ratio and 95% confidence interval of atrial fibrillation in the 220 subjects of the study, for the different demographic and clinical variables entered as covariate in the logistic regression analysis. Odds ratio for dyslipidemia and diabetes mellitus could not be calculated because no such condition was reported in patients with atrial fibrillation. P values refer to the statistical significance of the odds ratio.

	Odds ratio (95% confidence interval)	p-value
Sex (male vs. female)	1.31 (0.02, 83.1)	0.898
Age (years)	1.25 (0.91, 1.72)	0.161
Alcohol drinking (yes vs. no)	1.06 (0.04, 27.0)	0.972
DBP (mmHg)	1.06 (0.97, 1.16)	0.209
SBP (mmHg)	1.03 (0.92, 1.16)	0.566
HR (bpm)	0.96 (0.75, 1.24)	0.772
Hypertension (yes vs. no)	0.94 (0.01, 114.1)	0.979
BMI (kg/m ²)	0.92 (0.54, 1.54)	0.742
Cardiovascular diseases (yes vs. no)	0.11 (0.00, 5.75)	0.271
Smoking (yes vs. no)	0.07 (0.00, 19.5)	0.353
Obesity (yes vs. no)	0.06 (0.00, 76.8)	0.440

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	Table 1

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	7,8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8,Table 2
		(b) Report category boundaries when continuous variables were categorized	7,8,Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

OPPORTUNISTIC SCREENING OF ATRIAL FIBRILLATION BY AUTOMATIC BLOOD PRESSURE MEASUREMENT IN THE COMMUNITY

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-010745.R1
Article Type:	Research
Date Submitted by the Author:	01-Feb-2016
Complete List of Authors:	Omboni, Stefano; Italian Institute of Telemedicine, Clinical Research Unit Verberk, Willem; University of Maastricht, Cardiovascular Research Institute Maastricht (CARIM); Microlife AG
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Diagnostics
Keywords:	Atrial fibrillation, Blood pressure measurement, Italy

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**OPPORTUNISTIC SCREENING OF ATRIAL FIBRILLATION BY AUTOMATIC BLOOD
PRESSURE MEASUREMENT IN THE COMMUNITY**

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Short title: atrial fibrillation in an Italian community

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Manuscript word count (excluding references and abstract): 2,942

Abstract word count: 298

Number of references: 41

Number of Tables: 1

Abstract

Objective: Timely detection of atrial fibrillation (AF) may effectively prevent cardiovascular consequences. However, traditional diagnostic tools are either poorly reliable (pulse palpation) or not readily accessible (electrocardiogram, ECG) in the general practice. We tested whether an automatic oscillometric blood pressure (BP) monitor embedding an algorithm for AF detection might be effective for opportunistic screening of asymptomatic AF in the community.

Setting: Community-based screening campaign in an unselected population to verify the feasibility of AF screening with a Microlife WatchBP Office BP monitor with patented AFIB algorithm.

When, a possible AF was detected (≥ 2 out of 3 BP measurements reporting AF) a doctor immediately performed a single-lead ECG in order to confirm or exclude the presence of the arrhythmia. Main demographic and clinical data were collected prior to any BP measurement

Participants: 220 consecutive subjects from an unselected sample of individuals of a small Italian community

Primary and secondary outcome measures: number of patients detected with AF and diagnosed risk factors for AF.

Results: In 12 of 220 subjects the device detected a possible AF during the BP measurement: in 4 of them (1.8%) the arrhythmia was confirmed by the ECG. Subjects with AF were more likely to be older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, $p=0.010$), obese (50.0 vs. 14.4%, $p=0.048$) and to suffer from a cardiovascular disease (50.0 vs. 10.6%, $p=0.014$) than non-AF subjects. False positive AF subjects ($n=8$) did not differ for their general characteristics from true negative AF subjects and were younger than AF subjects (mean age 56.4 ± 14.8 , $p=0.027$; 5 of 8 subjects aged <65 years).

Conclusions: Opportunistic screening of AF by BP measurement is feasible to diagnose this arrhythmia in unaware subjects dwelled in the community, particularly in those older than 65 years, who are the target recommended by current AF screening guidelines.

Keywords: atrial fibrillation; blood pressure measurement; Italy

Strengths and limitations of this study

- A blood pressure monitor with atrial fibrillation (AF) detecting algorithm was tested in an unselected population resident in the community
- Each case of AF finding was immediately verified with an ECG device by an experienced cardiologist
- Additional demographic and clinical data were collected to verify risk factors for AF
- The screening tool allowed to unmask 4 unaware cases of AF in the community, corresponding to 1.8% of the screened population
- Main risk factor for AF was advanced age, followed by a positive medical history for cardiovascular disease or obesity
- Sixty three percent (63%) of AF false positive subjects (n=5) were younger than 65 years of age. All of the true positive AF subjects were older than 65 years of age, indicating that the screening would have been more efficient if only those older than 65 years would have been considered
- Screening of AF by BP measurement, confirmed by ECG monitoring, in subjects older than 65 years in whom a possible AF is detected, is useful for diagnosing AF in unaware subjects dwelled in the community

INTRODUCTION

Atrial fibrillation (AF) is the most common form of sustained arrhythmia in clinical practice¹. Its prevalence in developed countries approximates 1.5-2% in the general population and varies with age and sex: it is present in <0.5% of subjects younger than 50 years, 3-4% of those aged 60-70 years and 5-15% of those aged 80 years or older^{2,3}. However, recent insights indicate that this most likely is an underestimation as improved screening with innovative tools leads to significant increase in detection of patients with AF^{4,5}. This arrhythmia is associated with a 5-fold increased risk of stroke and 3-fold increased incidence of congestive heart failure, and high mortality^{2,6,7}. Usually, AF progresses from short, rare episodes (paroxysmal) to longer and more stable forms (persistent, long-standing persistent and permanent): in 25 to 40% of patients it remains silent for long before diagnosis^{8,9}. As AF is often asymptomatic, stroke is the initial dramatic presentation that leads to its detection in up to 25% of subjects¹⁰⁻¹².

Early detection and treatment of patients with asymptomatic AF before the first complications occur is a recognised priority for the prevention of strokes by all major guidelines^{11,13-17}. In particular the European Society of Cardiology recommends pulse-taking in all subjects aged ≥ 65 years, followed by an electrocardiogram (ECG) in case of irregular beats, to allow timely detection of AF¹⁵. However, pulse palpation has a low specificity and is much less reliable than ECG¹⁸. Moreover, despite the fact that most guidelines recommend it, pulse palpation is often not performed by doctors or nurses in clinical practice¹⁹.

Because hypertension is the most common risk factor associated with AF²⁰, using an automatic blood pressure monitor to detect AF would benefit the large number of hypertensive patients who monitor their blood pressure at home, in the doctor's office or in community pharmacies²⁰.

Recently, an automatic blood pressure device with an algorithm that can detect AF has been proposed for opportunistic screening of AF when blood pressure is measured. Such a device showed a very high sensitivity and specificity when compared to ECG monitoring [on average

(95% confidence interval), 0.98 (0.95, 1.00) and 0.92 (0.88, 0.96), respectively] and was expected to detect twice as many patients with AF as pulse palpation²¹⁻²⁷. Following results from studies including approximately 2,300 subjects, the NICE has now recommended the use of such technology to screen AF in primary care clinics²⁸.

The objective of the present investigation was to evaluate the ability of such a validated, electronic, oscillometric, blood pressure monitor embedding an algorithm for AF detection, to identify new cases of AF in an unselected population of a small community located in northern Italy, during a hypertension screening campaign.

METHODS

Study design and participants

A community-based screening campaign focusing on blood pressure measurement and collection of basic information on main cardiovascular risk factors was performed. It was carried out in an unselected population of subjects aged ≥18 years, living in two small villages (Besnate and Solbiate Arno) in the Northern area of Italy, close to the city of Varese, in the Lombardy region. Visits took place in mobile units located in villages' main squares. A questionnaire was administered to all subjects and blood pressure was measured by non-healthcare operators, previously trained by a physician who coordinated and supervised all the on-field activities. Information about subject's age, gender, height and body weight, family history for cardiovascular diseases, smoking and drinking habits, personal clinical history for cardiovascular diseases, presence and treatment of arterial hypertension, diabetes mellitus and dyslipidaemia, were collected and recorded on paper. Following the interview, blood pressure was measured in triplicate at 1 minute interval with the patient in the sitting position since at least 5 minutes, according to current recommendations, by a validated, automatic, electronic, upper-arm sphygmomanometer (Microlife WatchBP Office AFIB, Microlife AG, Switzerland). The oscillometric blood pressure monitor embeds an algorithm that can

identify pulse irregularities compatible with AF during the automatic blood pressure measurement: if at least 2 out of 3 measurements detected AF the “AFIB” symbol flashed on the display of the device indicating a possible case of AF. In such a case, the doctor immediately performed a single-lead ECG recording with a hand-held ECG recorder (Cardio-A Palm ECG, Shenzhen Creative Industry Co Ltd., China), in order to check the patient’s rhythm. The ECG was performed by the patient with the assistance of the doctor: he or she was asked to grab the device with the right hand (palm and fingers) and to press the left side of the device with the centre of the left hand palm. The ECG detected by such palm measurement is equivalent to a lead I ECG signal. A 30 sec recording was performed and, if considered of poor quality by the assisting physician (a cardiologist adequately trained and experienced in ECG interpretation), it was repeated. ECG tracings were immediately visually inspected and checked by the doctor for confirming or excluding the presence of AF. This arrhythmia was defined as the absence of distinct ‘p’ waves, an absolutely irregular RR interval and an atrial cycle length <200 msec (300 bpm) on the recorded 30-sec ECG.

Prior to the examination, participants were asked to give written informed consent for collection and analysis of their clinical data, according to current Italian law. All visits took place between June 2013 and June 2015. The study design did not foresee any patients’ follow-up.

All data collected at the time of the examination were reported on a paper sheet. Individual data were then entered in an electronic database to allow pooled analysis. Patients were considered having AF when detection by the blood pressure monitor was confirmed by the single-lead ECG.

Statistical analysis

Data analysis was performed by grouping the patients according to the presence or absence of AF. Given the observational nature of the study no sample size estimation was done. All subjects provided valid data and thus no methodology for replacing missing data was implemented. Main demographic and clinical data of the two subgroups were summarized by calculating the mean ($\pm$ SD) in case of continuous variables and the absolute (n) and relative (%) frequency in case of

categorical variables. Differences across groups were evaluated by analysis of variance or Chi-square test, depending on the type of variable. A p value of <0.05 was considered significant. Data analysis was performed using IBM SPSS Statistics ver. 20 for Windows.

RESULTS

A total of 220 subjects were enrolled: all of them provided relevant information and were included in the analysis. In 12 subjects the device detected a possible AF during the blood pressure measurement: in 4 of them (1.8% of the whole population) this arrhythmia was confirmed by the one-lead ECG, whereas for the remaining 8 subjects sinus arrhythmia (n=1) or supraventricular ectopic beats (n=7) were diagnosed. All subjects diagnosed for AF apparently were unaware of this arrhythmia.

Demographic, anthropometric and clinical data of the participants, grouped by absence or presence of AF or other arrhythmias, are summarised in **Table 1**. In the whole sample, mean subjects' age was 57.5 ± 15.3 years, and males were slightly more prevalent than females (51.4 vs. 48.6%). A personal history for cardiovascular disease was recorded in 11.4% of subjects. Hypertension was previously diagnosed in 36.4%, whereas an additional 17.2% of subjects had elevated blood pressure values (≥140/90 mmHg) during the automatic measurement. Diabetes and dyslipidaemia were reported by 7.7% and 27.3% of subjects, respectively. Obesity was documented in 15.0% of the sample.

Subjects with AF were older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, p=0.010), were more often obese (50.0 vs. 14.4%, p=0.048) and were more likely to display a positive history for cardiovascular disease (50.0 vs. 10.6%, p=0.014) than those without this arrhythmia. None of the patients diagnosed with AF had a previous stroke, whereas two had a positive history for myocardial infarction, one for heart failure and one for peripheral artery disease. AF patients also had higher

levels of systolic blood pressure than those free from AF being nearly statically significant (151.5 ± 6.1 vs. 133.9 ± 18.5 years, $p=0.059$).

When subjects with other types of arrhythmias were removed from the pool of subjects with no AF, a statistically significant difference vs. AF subjects was still observed for age ($p=0.010$) and concomitant cardiovascular diseases (0.017) (**Table 1**). The demographic and clinical features of these subjects were superimposable to those of subjects without any arrhythmia, suggesting that “false positive” subjects for AF have a lower risk than AF subjects. As a matter of fact, they were younger ($p=0.027$), with 63% of subjects (5 out of 8) aged less than 65 years, less frequently obese ($p=0.028$), less likely to have a cardiovascular disease ($p=0.028$) or high blood pressure ($p=0.028$).

DISCUSSION

Our community survey documented a 1.8% prevalence of AF in an unselected sample of the population. Although based on a limited number of subjects, our results add a new piece of information to existing evidence from larger surveys. The estimated prevalence of AF in epidemiological studies carried out in Europe in the general population in the last decade ranged between 1.9% and 2.9%²⁹. In a recent nationwide, retrospective, observational Italian study involving 233 general practitioners and screening almost 300,000 patients representative of the population, the prevalence of AF was 2.0%. Population based studies report the prevalence of mostly known AF, whereas in our study all subjects in whom AF was detected were unaware of their condition. This may be possibly related to a sampling bias in that people with known AF may have decided not to be screened because they were already aware of their condition and regularly followed by their physician. Thus, our approach may be useful to detect unaware cases of AF, and our results suggest that the true prevalence of AF in the community may be higher than that reported in population studies.

In our study, consistent with previous evidence, age, obesity, previous cardiovascular diseases and hypertension were important independent risk factors for AF³⁰⁻³⁵. We did not find any significant relationship between other established cardiovascular risk markers, such as smoking, diabetes or dyslipidaemia and the development of new-onset AF, but this may be related to the small sample of subjects with AF included in our survey.

Interestingly, our study showed that subjects who were falsely diagnosed as having AF during blood pressure measurement had demographic and clinical characteristics similar to those of subjects without any arrhythmia. Notably, they were younger than 65 years, this confirming the consistency of the common indication to screen AF in subjects older than 65 years¹⁵. Our results seem also to suggest that, when a community screening approach based on blood pressure measurement with the AFIB technique is followed, it would be more practical, economical and logistically affordable, to seek for AF confirmation by ECG only in older subjects, for whom the chance of true positivity is much larger.

Screening for AF in people over the age of 65 years leads to improved detection of AF as compared to routine clinical practice. However, in a large randomized trial, the effect on overall AF diagnosis rate for systematic and for opportunistic screening was comparable [odds ratio and 95% confidence interval: 1.57 (1.08, 2.26) and 1.58 (1.10, 2.29), respectively]. The number of subjects needed to be screened in order to detect one additional case compared to routine practice was 172 subjects (95% confidence interval: 94 to 927) for systematic screening and 167 (92 to 806) for opportunistic screening^{36,37}.

The present study reported that one out of four subjects who were positively diagnosed for AF with the blood pressure monitor actually had the disease as was confirmed with ECG. This result is worse than a previous study performed among 1,000 primary care patients which found a positive predictive value of 44% with the Microlife WatchBP Home A device²⁵. However, this study was performed among subjects 75 years and older. If, for our study, only patients older than 65 years would have been considered this would have led to a positive predictive value of 57% obtained with

the blood pressure monitor. In any case, the result of the present study seems to be an improvement in comparison to pulse palpation as demonstrated in the SAFE trial where one in 5.7 ECG referrals led to a positive AF detection³⁷. In addition, as pulse palpation generally has a lower sensitivity value (87%)³⁷ for detecting AF than the blood pressure monitor (98%)²⁷ it is not unlikely that the latter has led to the detection of more patients with AF.

Although single-lead ECG approaches with either automatic interpretation or cardiologist over-reading have been successfully used for screening AF in primary care practices or community pharmacies³⁸⁻⁴⁰, they may not always be accurate when interpreted by a primary care doctor⁴¹. The use of a blood pressure monitor with AF detector may, therefore, be a possible efficacious alternative to single-lead ECG, as recently documented in a direct comparison study²⁵.

Study limitations and strength

Our study suffers from some limitations. First of all, the diagnosis of AF was confirmed by a cardiologist using a one-lead ECG device whereas the gold standard is a 12-lead ECG. However, as mentioned before, recent studies have shown high accuracy and feasibility, as well as cost-effectiveness, of AF screening with one-lead ECG devices either with automatic or physician's interpretation^{24,38-40}. We are of the opinion that readings from a hand-held one-lead ECG recorder may have sufficient quality to make an appropriate diagnosis, particularly because in our case 30-sec tracings were repeated several times in case of doubt and correct interpretation was immediately warranted by an experienced cardiologist. Second, given the opportunistic nature of the screening campaign we could not systematically check the possible presence of AF in all subjects, including those apparently negative during the blood pressure measurement. However, since several studies have shown a good specificity (89-92%) and a high sensitivity (97-100%) of the methodology of ≥ 2 out of 3 measurements²⁷ we may assume that the chance that subjects with true AF could be diagnosed is reasonably high and much higher than that of missing a false negative. Third, AF usually occurs more frequently in males than in females^{2,29}, gender representing one of the most

powerful risk factors for AF together with age and cardiovascular comorbidities. However, this was not the case for our survey, where the proportion of men and women reporting AF was exactly the same. We cannot exclude that the observational nature of our study, the relatively unselected sample of the population and the small number of AF subjects, might have prevented an accurate estimation of the relative importance of various factors contributing to the genesis of the arrhythmia. Moreover, we must acknowledge that the prevalence of AF in our population, though very close to that observed in a large nationwide Italian survey, might not be representative of the phenomenon in the whole country, also because undetermined selection related to the willingness of being screened cannot be excluded. In addition, we cannot rule out possible regional differences in the prevalence of AF, and consequent representation bias, particularly because data have been collected in a population resident in a highly developed area of the country.

The strength of the presented approach for the screening of AF is that screening is automatically performed during consecutive automatic blood pressure measurements without extra efforts. This means that the current finding of AF cases comes on top of the detection of hypertension which was present in 53.6% of the screened population, with 36.4% of the overall population aware and 17.2% (approximately one-third) unaware of their condition.

Conclusions

In conclusion, our small-scale observational study indicates that opportunistic screening of AF by blood pressure measurement, with confirmation by one lead ECG monitoring if AF is detected, is feasible to diagnose this arrhythmia in unaware subjects dwelled in the community. Since the majority of the false AF positive subjects were younger than 65 years of age and all of the AF positive subjects was older than 65 years, this study confirms validity of recommending opportunistic screening of AF by BP measurements in patients older than 65 years [27].

Whether such an approach might have a positive impact on clinical, social and economic outcomes needs to be demonstrated in large well-designed prospective studies.

For peer review only

Acknowledgements

We are grateful for the logistic support provided by the following volunteers who helped collecting the data during the screening campaign: Lara Brianese, Armando De Falco, Edoardo Ghirardi, Daniela Ghiringhelli, Antonio Miranda, Andrea Niglia, Federica Pagliarin, Massimo Protasoni, Alberto Riganti, Andrea Zerbi.

Funding statement

This work was supported by Biotechmed Ltd. which sponsored the campaign by providing for free the blood pressure monitors used in the study. No specific grants were received for conducting the study. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Transparency Declaration

The lead author SO affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. STROBE guidelines for cohort studies have been followed, where appropriate, for manuscript preparation.

Author Contributions

SO wrote the first draft of the manuscript. WJV contributed to the writing and finalisation of the manuscript. Both author met ICMJE criteria for authorship.

Disclosure

SO received lecture fees from Colpharma, the Italian distributor of Microlife AG, and is scientific consultant of Biotechmed Ltd. provider of telemedicine services. WJV is an employee of Microlife AG.

Data sharing

No additional data available.

Table 1. Demographic and clinical characteristics of the subjects enrolled in the study. P-values refer to the statistical significance of the difference across the different study subgroups.

	Subjects with no AF (n=216)	Subjects without AF or any other arrhythmia (n=208)	Subjects with other arrhythmias (n=8)	<i>p-value subjects without AF or any other arrhythmia vs. subjects with other arrhythmias</i>	Subjects with AF (n=4)	<i>p-value subjects with AF vs. subjects with no AF</i>	<i>p-value subjects with AF vs. subjects without AF or any other arrhythmia</i>	<i>p-value subjects with AF vs. subjects with other arrhythmias</i>	All subjects (n=220)
Age (years)	57.2 ± 15.2 (20 – 84)	57.2 ± 15.3 (20-84)	56.4 ± 14.8 (32-74)	0.880	77.0 ± 1.2 (76 – 78)	0.010	0.010	0.027	57.5 ± 15.3 (20 – 84)
Male / Female (%)	111 / 105 (51.4) / (48.6)	106 / 102 (51.0) / (49.0)	5 / 3 (62.5) / (37.5)	0.522	2 / 2 (50.0) / (50.0)	0.956	0.970	0.679	113 / 107 (51.4) / (48.6)
Height (cm)	166.7 ± 9.3	166.6 ± 9.3	169.5 ± 8.2	0.383	170.3 ± 8.2	0.447	0.434	0.895	166.8 ± 9.3
Weight (kg)	71.6 ± 15.0	71.7 ± 15.1	67.1 ± 11.0	0.397	80.8 ± 17.5	0.226	0.235	0.140	71.7 ± 15.0
BMI (kg/m ²)	25.6 ± 4.3	25.7 ± 4.3	23.3 ± 3.1	0.122	27.7 ± 4.5	0.337	0.357	0.096	25.7 ± 4.3
Obesity (BMI ≥30 kg/m ²)	31 (14.4)	31 (14.9)	0 (0.0)	0.238	2 (50.0)	0.048	0.055	0.028	3.3 (15.0)
Current smokers (%)	37 (17.1)	34 (16.3)	3 (37.5)	0.119	1 (25.0)	0.680	0.644	0.665	38 (17.3)
Alcohol drinkers (%)	94 (43.5)	91 (43.8)	3 (37.5)	0.726	1 (25.0)	0.459	0.454	0.665	95 (43.2)
Cardiovascular diseases (%)	23 (10.6)	23 (11.1)	0 (0.0)	0.320	2 (50.0)	0.014	0.017	0.028	25 (11.4)
Hypertension (%)	78 (36.1)	78 (37.5)	0 (0.0)	0.053	2 (50.0)	0.567	0.609	0.028	80 (36.4)
Diabetes (%)	17 (7.9)	17 (8.2)	0 (0.0)	0.400	0 (0.0)	0.559	0.551	-	17 (7.7)
Dyslipidaemia (%)	60 (27.8)	60 (28.8)	0 (0.0)	0.074	0 (0.0)	0.216	0.205	-	60 (27.3)
SBP (mmHg)	133.9 ± 18.5	133.8 ± 18.4	136.4 ± 22.2	0.697	151.5 ± 6.1	0.059	0.058	0.182	134.2 ± 18.5
DBP (mmHg)	81.0 ± 12.0	80.4 ± 10.0	82.8 ± 10.5	0.524	88.3 ± 12.0	0.233	0.125	0.372	81.1 ± 12.1
HR (bpm)	72.9 ± 11.3	73.2 ± 11.4	67.0 ± 5.9	0.129	72.3 ± 3.6	0.905	0.873	0.445	72.9 ± 11.2

AF: Atrial Fibrillation; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	Table 1

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	7,8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8, Table 2
		(b) Report category boundaries when continuous variables were categorized	7,8, Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

OPPORTUNISTIC SCREENING OF ATRIAL FIBRILLATION BY AUTOMATIC BLOOD PRESSURE MEASUREMENT IN THE COMMUNITY

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-010745.R2
Article Type:	Research
Date Submitted by the Author:	17-Feb-2016
Complete List of Authors:	Omboni, Stefano; Italian Institute of Telemedicine, Clinical Research Unit Verberk, Willem; University of Maastricht, Cardiovascular Research Institute Maastricht (CARIM); Microlife AG
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Diagnostics
Keywords:	Atrial fibrillation, Blood pressure measurement, Italy

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**OPPORTUNISTIC SCREENING OF ATRIAL FIBRILLATION BY AUTOMATIC BLOOD
PRESSURE MEASUREMENT IN THE COMMUNITY**

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Short title: atrial fibrillation in an Italian community

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Manuscript word count (excluding references and abstract): 2,860

Abstract word count: 299

Number of references: 41

Number of Tables: 1

Abstract

Objective: Timely detection of atrial fibrillation (AF) may effectively prevent cardiovascular consequences. However, traditional diagnostic tools are either poorly reliable (pulse palpation) or not readily accessible (electrocardiogram, ECG) in the general practice. We tested whether an automatic oscillometric blood pressure (BP) monitor embedded with an algorithm for AF detection might be effective for opportunistic screening of asymptomatic AF in the community.

Setting: Community-based screening campaign in an unselected population to verify the feasibility of AF screening with a Microlife WatchBP Office BP monitor with patented AFIB algorithm. When possible AF was detected (≥ 2 of 3 BP measurements reporting AF) a doctor immediately performed a single-lead ECG in order to confirm or exclude the presence of the arrhythmia. Main demographic and clinical data was also collected.

Participants: 220 consecutive subjects from an unselected sample of individuals of a small Italian community.

Primary and secondary outcome measures: number of patients detected with AF and diagnosed risk factors for AF.

Results: In 12 of 220 subjects the device detected possible AF during the BP measurement: in 4 of them (1.8%) the arrhythmia was confirmed by the ECG. Subjects with AF were more likely to be older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, $p=0.010$), obese (50.0 vs. 14.4%, $p=0.048$) and to suffer from a cardiovascular disease (50.0 vs. 10.6%, $p=0.014$) than non-AF subjects. Subjects with positive BP AF reading and non-AF arrhythmias ($n=8$) did not differ in their general characteristics from subjects with negative BP AF reading and were younger than AF subjects (mean age 56.4 ± 14.8 , $p=0.027$; 5 of 8 subjects aged <65 years).

Conclusions: Opportunistic screening of AF by BP measurement is feasible to diagnose this arrhythmia in unaware subjects, particularly in those older than 65 years, who are the target patient group recommended by current AF screening guidelines.

Keywords: atrial fibrillation; blood pressure measurement; Italy

Strengths and limitations of this study

- A blood pressure (BP) monitor with atrial fibrillation (AF) detecting algorithm was tested in an unselected population resident in the community
- Each case of AF found was immediately verified with an ECG device by an experienced cardiologist
- Additional demographic and clinical data was collected to verify risk factors for AF
- The screening tool unmasked 4 unaware cases of AF in the community, corresponding to 1.8% of the screened population
- Main risk factor for AF was advanced age, followed by a positive medical history for cardiovascular disease or obesity
- Five out of the 8 subjects with positive BP AF readings with non-AF arrhythmia were younger than 65 years of age. All of the true positive AF subjects were older than 65 years of age, indicating that the screening would have been more efficient if only those older than 65 years would have been considered
- Screening of AF by BP measurement, confirmed by ECG monitoring, in subjects older than 65 years where possible AF is detected, is useful for diagnosing AF in unaware subjects.

INTRODUCTION

Atrial fibrillation (AF) is the most common form of sustained arrhythmia in clinical practice.[1] Its prevalence in developed countries approximates 1.5-2% in the general population and varies with age and sex: it is present in <0.5% of subjects younger than 50 years, 3-4% of those aged 60-70 years and 5-15% of those aged 80 years or older.[2,3] However, recent insights indicate that this most likely is an underestimation as improved screening with innovative tools leads to significant increase in detection of patients with AF.[4,5] This arrhythmia is associated with a 5-fold increased risk of stroke and 3-fold increased incidence of congestive heart failure, and high mortality.[2,6,7] Usually, AF progresses from short, rare episodes (paroxysmal) to longer and more stable forms (persistent, long-standing persistent and permanent): in 25 to 40% of patients it remains silent for long before diagnosis.[8,9] As AF is often asymptomatic, stroke is the initial dramatic presentation that leads to its detection in up to 25% of subjects.[10-12]

Early detection and treatment of patients with asymptomatic AF before the first complications occur is a recognised priority for the prevention of strokes by all major guidelines.[11,13-17] In particular the European Society of Cardiology recommends pulse-taking in all subjects aged ≥ 65 years, followed by an electrocardiogram (ECG) in case of irregular beats, to allow timely detection of AF.[15] However, pulse palpation has a low specificity and is much less reliable than ECG.[18] Moreover, despite the fact that most guidelines recommend it, pulse palpation is often not performed by doctors or nurses in clinical practice.[19]

Because hypertension is the most common risk factor associated with AF,[20] using an automatic blood pressure (BP) monitor to detect AF would benefit the large number of hypertensive patients who monitor their BP at home, in the doctor's office or in community pharmacies.[20] Recently, an automatic BP device with an algorithm that can detect AF has been proposed for opportunistic screening of AF when BP is measured. Such a device showed a very high sensitivity and specificity when compared to ECG monitoring [on average (95% confidence interval), 0.98 (0.95, 1.00) and

0.92 (0.88, 0.96), respectively] and was expected to detect twice as many patients with AF as pulse palpation.[21-27] Following results from studies including approximately 2,300 subjects, the NICE has now recommended the use of such technology to screen AF in primary care clinics.[28] The objective of the present investigation was to evaluate the ability of such a validated, electronic, oscillometric, BP monitor embedded with an algorithm for AF detection, to identify new cases of AF in an unselected population of a small community located in northern Italy, during a hypertension screening campaign.

METHODS

Study design and participants

A community-based screening campaign focusing on BP measurement and the collection of basic information on main cardiovascular risk factors was performed. It was carried out in an unselected population of subjects aged ≥18 years, living in two small villages (Besnate and Solbiate Arno) in the Northern area of Italy, close to the city of Varese, in the Lombardy region. Visits took place in mobile units located in the villages' main squares. A questionnaire was administered to all subjects and BP was measured by non-healthcare operators, previously trained by a physician who coordinated and supervised all the on-field activities. Information about the subject's age, gender, height, body weight and family history for cardiovascular diseases were collected. Also recorded were their habits in relation to smoking drinking and personal clinical history for cardiovascular diseases, presence and treatment of arterial hypertension, diabetes mellitus and dyslipidaemia. Following the interview, BP was measured in triplicate at 1 minute interval time with the patient in the sitting position having rested for at least 5 minutes, according to current recommendations, by a validated, automatic, electronic, upper-arm sphygmomanometer (Microlife WatchBP Office AFIB, Microlife AG, Switzerland). The oscillometric BP monitor is embedded with an algorithm that can identify pulse irregularities compatible with AF during the automatic BP measurement: if at least 2

out of 3 measurements detected AF the “AFIB” symbol flashed on the display of the device indicating a possible case of AF. In such a case, the doctor immediately performed a single-lead ECG recording with a hand-held ECG recorder (Cardio-A Palm ECG, Shenzhen Creative Industry Co Ltd., China), in order to check the patient’s heart rhythm. The ECG was performed by the patient with the assistance of the doctor: he or she was asked to grab the device with the right hand (palm and fingers) and to press the left side of the device with the centre of the left hand palm. The ECG detected by such palm measurement is equivalent to a single lead ECG signal. A 30 sec recording was performed and, if considered of poor quality by the assisting physician (a cardiologist adequately trained and experienced in ECG interpretation), it was repeated. ECG tracings were immediately visually inspected and checked by the doctor who either confirmed or excluded the presence of AF. This arrhythmia was defined by the absence of distinct ‘p’ waves, an absolutely irregular RR interval and an atrial cycle length <200 msec (300 bpm) on the recorded 30-sec ECG. Since this was a health awareness campaign no approval by any Ethics Committee was required, according to the Italian regulations. However, prior to the examination, all participants were asked to give written informed consent for the collection and analysis of their clinical data, according to the Italian Personal Data Protection Code. All visits took place between June 2013 and June 2015. The design of the study did not envisage any patients’ follow-up. All data collected at the time of the examination was recorded on a paper sheet. The individuals’ data was then entered in an electronic database to allow pooled analysis. Patients were considered having AF when detection by the BP monitor was confirmed by the single-lead ECG.

Statistical analysis

Data analysis was performed by grouping the patients according to the presence or absence of AF. Given the observational nature of the study no sample size estimation was done. All subjects provided valid data and thus no methodology for replacing missing data was implemented. Main demographic and clinical data of the two subgroups were summarized by calculating the mean

($\pm$ SD) in case of continuous variables and the absolute (n) and relative (%) frequency in case of categorical variables. Differences across groups were evaluated by analysis of variance or Chi-square test, depending on the type of variable. A p value of <0.05 was considered significant. Data analysis was performed using IBM SPSS Statistics ver. 20 for Windows.

RESULTS

A total of 220 subjects were enrolled: all of them provided the relevant information and were included in the analysis. In 12 subjects the device detected possible AF during the BP measurement: in 4 of them (1.8% of the whole population) this arrhythmia was confirmed by the one-lead ECG, whereas for the remaining 8 subjects sinus arrhythmia ($n=1$) or supraventricular ectopic beats ($n=7$) were diagnosed. All subjects diagnosed for AF apparently were unaware of this arrhythmia. Demographic, anthropometric and clinical data of the participants, grouped by absence or presence of AF or other arrhythmias, are summarised in **Table 1**. In the whole sample, mean subjects' age was 57.5 ± 15.3 years, and males were slightly more prevalent than females (51.4 vs. 48.6%). A personal history for cardiovascular disease was recorded in 11.4% of subjects. Hypertension was previously diagnosed in 36.4%, whereas an additional 17.2% of subjects had elevated BP values ($\geq 140/90$ mmHg) during the automatic measurement. Diabetes and dyslipidaemia were reported by 7.7% and 27.3% of subjects, respectively. Obesity was documented in 15.0% of the sample. Subjects with AF were older (77.0 ± 1.2 vs. 57.2 ± 15.2 years, $p=0.010$), were more often obese (50.0 vs. 14.4%, $p=0.048$) and were more likely to display a positive history for cardiovascular disease (50.0 vs. 10.6%, $p=0.014$) than those without this arrhythmia. None of the patients diagnosed with AF had a previous stroke, whereas two had a positive history for myocardial infarction, one for heart failure and one for peripheral artery disease. AF patients also had higher levels of systolic BP than those free from AF, but the difference was not statically significant (151.5 ± 6.1 vs. 133.9 ± 18.5 years, $p=0.059$).

When subjects with positive BP AF reading with non-AF arrhythmias were removed from the pool of subjects with no AF, a statistically significant difference vs. AF subjects was still observed for age ($p=0.010$) and concomitant cardiovascular diseases (0.017) (**Table 1**). The demographic and clinical features of these subjects were superimposable to those of subjects without any arrhythmia detected during BP measurement, suggesting that subjects with positive BP AF reading with non-AF arrhythmias have a lower risk than those with positive BP AF reading with AF. As a matter of fact, they were younger ($p=0.027$), with 5 out of 8 subjects aged less than 65 years, less frequently obese ($p=0.028$), less likely to have a cardiovascular disease ($p=0.028$) or high BP ($p=0.028$).

DISCUSSION

Our community survey documented a 1.8% prevalence of AF in an unselected sample of the population. Although based on a limited number of subjects, our results add a new piece of information to existing evidence from larger surveys. The estimated prevalence of AF in epidemiological studies carried out in Europe in the general population in the last decade ranged between 1.9% and 2.9%. [29] In a recent nationwide, retrospective, observational Italian study involving 233 general practitioners and screening almost 300,000 patients representative of the population, the prevalence of AF was 2.0%. [30] Population based studies report the prevalence of mostly known AF, whereas in our study all subjects in whom AF was detected were unaware of their condition. This may be possibly related to a sampling bias in that people with known AF may have decided not to be screened because they were already aware of their condition and regularly followed by their physician. Thus, our approach may be useful to detect unaware cases of AF, and our results suggest that the true prevalence of AF in the community may be higher than that reported in population studies.

In our study, consistent with previous evidence, age, obesity, previous cardiovascular diseases and hypertension were important independent risk factors for AF. [31-36] We did not find any

significant relationship between other established cardiovascular risk markers, such as smoking, diabetes or dyslipidaemia and the development of new-onset AF, but this may be related to the small sample of subjects with AF included in our survey.

Interestingly, our study showed that subjects who were falsely diagnosed as having AF during BP measurement had demographic and clinical characteristics similar to those of subjects with negative BP AF reading. Notably, they were younger than 65 years, which implies lower need for treatment than those who are older. Therefore, our results, seem to suggest that, when a community screening approach based on BP measurement with the AFIB technique is followed, it would be more practical, economical and logistically affordable, to seek for AF confirmation by ECG only subjects older than 65 years of age. This is related to both the higher AF incidence, which increases the chance of true positivity, and the higher need for treatment among those older than 65 years of age as compared to those who are younger.

Screening for AF in people over the age of 65 years leads to improved detection of AF as compared to routine clinical practice. However, in a large randomized trial, the effect on overall AF diagnosis rate for systematic and for opportunistic screening was comparable [odds ratio and 95% confidence interval: 1.57 (1.08, 2.26) and 1.58 (1.10, 2.29), respectively]. The number of subjects needed to be screened in order to detect one additional case compared to routine practice was 172 subjects (95% confidence interval: 94 to 927) for systematic screening and 167 (92 to 806) for opportunistic screening.[37,38]

The present study reported that one out of four subjects who were positively diagnosed for AF with the BP monitor actually had the disease as was confirmed with ECG. This result is worse than a previous study performed among 1,000 primary care patients which found a positive predictive value of 44% with the Microlife WatchBP Home A device.[25] However, this study was performed among subjects 75 years and older. If, for our study, only patients older than 65 years would have been considered this would have led to a positive predictive value of 57% obtained with the BP monitor. In any case, the result of the present study seems to be an improvement in comparison to

pulse palpation as demonstrated in the SAFE trial where one in 5.7 ECG referrals led to a positive AF detection.[38] In addition, as pulse palpation generally has a lower sensitivity value (87%) [38] for detecting AF than the BP monitor (98%) [27] it is not unlikely that the latter has led to the detection of more patients with AF.

Although in our study the use of a BP monitor with AF detector showed to be useful, it needed confirmation by a single-lead ECG. The latter approach, coupled with cardiologist interpretation has been successfully tested for screening AF in primary care practices or community pharmacies and it is presently considered the first-choice method for screening programmes for detection of undiagnosed AF. [39-41]

Study limitations and strength

Our study suffers from some limitations. First of all, the diagnosis of AF was confirmed by a cardiologist using a one-lead ECG device whereas the gold standard is a 12-lead ECG. However, as mentioned before, recent studies have shown high accuracy and feasibility, as well as cost-effectiveness, of AF screening with one-lead ECG devices with physician's interpretation. [24,39-41] We are of the opinion that readings from a hand-held one-lead ECG recorder may have sufficient quality to make an appropriate diagnosis, particularly because in our case 30-sec tracings were repeated several times in case of doubt and correct interpretation was immediately warranted by an experienced cardiologist. Second, at the present research setting an experienced cardiologist verified the presence of AF when detected during the BP measurement and transmitted the results to the person's practitioner in order to initiate the therapy. Although this may seem to limit the application of this approach for community screening, as a matter of fact, the presence of a cardiologist is not required for general community screening. Similar to other public health screening events (e.g. BP measurement) creating awareness and refer people to their general practitioners (perhaps with an ECG print-out) after an AF positive BP measurement can also have a positive healthcare effect.

Third, given the opportunistic nature of the screening campaign we could not systematically check the possible presence of AF in all subjects, including those apparently negative during the BP measurement. However, since several studies have shown a good specificity (89-92%) and a high sensitivity (97-100%) of the methodology of ≥ 2 out of 3 measurements [27] we may assume that the chance that subjects with true AF could be diagnosed is reasonably high and much higher than that of missing a false negative. Fourth, AF usually occurs more frequently in males than in females, [2,29] gender representing one of the most powerful risk factors for AF together with age and cardiovascular comorbidities. However, this was not the case for our survey, where the proportion of men and women reporting AF was exactly the same. We cannot exclude that the observational nature of our study, the relatively unselected sample of the population and the small number of AF subjects, might have prevented an accurate estimation of the relative importance of various factors contributing to the genesis of the arrhythmia. Moreover, we must acknowledge that the prevalence of AF in our population, though very close to that observed in a large nationwide Italian survey, [30] might not be representative of the phenomenon in the whole country; also because undetermined selection bias related to the willingness of being screened cannot be excluded. In addition, we cannot rule out possible regional differences in the prevalence of AF, and consequent representation bias, particularly because data has been collected in a population resident in a highly developed area of the country.

The strength of the presented approach for the screening of AF is that screening is automatically performed during consecutive automatic BP measurements without extra effort. This means that the current finding of AF cases comes on top of the detection of hypertension which was present in 53.6% of the screened population, with 36.4% of the overall population aware and 17.2% (approximately one-third) unaware of their condition.

Conclusions

In conclusion, our small-scale observational study indicates that opportunistic screening of AF by BP measurement, with confirmation by one lead ECG monitoring if AF is detected, is feasible to diagnose this arrhythmia in unaware subjects. Since the majority of the subjects with positive BP AF reading and non-AF arrhythmias were younger than 65 years of age and all of the AF positive subjects were older than 65 years, this study confirms validity of recommending opportunistic screening of AF by BP measurements in patients older than 65 years²⁷.

Whether such an approach might have a positive impact on clinical, social and economic outcomes needs to be demonstrated in large well-designed prospective studies.

Acknowledgements

We are grateful for the logistic support provided by the following volunteers who helped collecting the data during the screening campaign: Lara Brianese, Armando De Falco, Edoardo Ghirardi, Daniela Ghiringhelli, Antonio Miranda, Andrea Niglia, Federica Pagliarin, Massimo Protasoni, Alberto Riganti, Andrea Zerbi.

Funding statement

This work was supported by Biotechmed Ltd. which sponsored the campaign by providing for free the blood pressure monitors used in the study. No specific grants were received for conducting the study. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Transparency Declaration

The lead author SO affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. STROBE guidelines for cohort studies have been followed, where appropriate, for manuscript preparation.

Author Contributions

SO wrote the first draft of the manuscript. WJV contributed to the writing and finalisation of the manuscript. Both authors met the ICMJE criteria for authorship.

Disclosure

SO received lecture fees from Colpharma Ltd., the Italian distributor of Microlife AG, and is scientific consultant of Biotechmed Ltd. provider of telemedicine services. WJV is an employee of Microlife AG.

Table 1. Demographic and clinical characteristics of the subjects enrolled in the study. P-values refer to the statistical significance of the difference across the different study subgroups.

	Subjects with no AF (n=216)	Subjects without AF or any other arrhythmia (n=208)	Subjects with positive BP AF readings with non-AF arrhythmias (n=8)	<i>p-value subjects without AF or any other arrhythmia vs. subjects with positive BP AF readings with non-AF arrhythmias</i>	Subjects with AF (n=4)	<i>p-value subjects with AF vs. subjects with no AF</i>	<i>p-value subjects with AF vs. subjects without AF or any other arrhythmia</i>	<i>p-value subjects with AF vs. subjects with positive BP AF readings with non-AF arrhythmias</i>	All subjects (n=220)
Age (years)	57.2 ± 15.2 (20 – 84)	57.2 ± 15.3 (20-84)	56.4 ± 14.8 (32-74)	0.880	77.0 ± 1.2 (76 – 78)	0.010	0.010	0.027	57.5 ± 15.3 (20 – 84)
Male / Female (%)	111 / 105 (51.4) / (48.6)	106 / 102 (51.0) / (49.0)	5 / 3 (62.5) / (37.5)	0.522	2 / 2 (50.0) / (50.0)	0.956	0.970	0.679	113 / 107 (51.4) / (48.6)
Height (cm)	166.7 ± 9.3	166.6 ± 9.3	169.5 ± 8.2	0.383	170.3 ± 8.2	0.447	0.434	0.895	166.8 ± 9.3
Weight (kg)	71.6 ± 15.0	71.7 ± 15.1	67.1 ± 11.0	0.397	80.8 ± 17.5	0.226	0.235	0.140	71.7 ± 15.0
BMI (kg/m ²)	25.6 ± 4.3	25.7 ± 4.3	23.3 ± 3.1	0.122	27.7 ± 4.5	0.337	0.357	0.096	25.7 ± 4.3
Obesity (BMI ≥30 kg/m ²)	31 (14.4)	31 (14.9)	0 (0.0)	0.238	2 (50.0)	0.048	0.055	0.028	3.3 (15.0)
Current smokers (%)	37 (17.1)	34 (16.3)	3 (37.5)	0.119	1 (25.0)	0.680	0.644	0.665	38 (17.3)
Alcohol drinkers (%)	94 (43.5)	91 (43.8)	3 (37.5)	0.726	1 (25.0)	0.459	0.454	0.665	95 (43.2)
Cardiovascular diseases (%)	23 (10.6)	23 (11.1)	0 (0.0)	0.320	2 (50.0)	0.014	0.017	0.028	25 (11.4)
Hypertension (%)	78 (36.1)	78 (37.5)	0 (0.0)	0.053	2 (50.0)	0.567	0.609	0.028	80 (36.4)
Diabetes (%)	17 (7.9)	17 (8.2)	0 (0.0)	0.400	0 (0.0)	0.559	0.551	-	17 (7.7)
Dyslipidaemia (%)	60 (27.8)	60 (28.8)	0 (0.0)	0.074	0 (0.0)	0.216	0.205	-	60 (27.3)
SBP (mmHg)	133.9 ± 18.5	133.8 ± 18.4	136.4 ± 22.2	0.697	151.5 ± 6.1	0.059	0.058	0.182	134.2 ± 18.5
DBP (mmHg)	81.0 ± 12.0	80.4 ± 10.0	82.8 ± 10.5	0.524	88.3 ± 12.0	0.233	0.125	0.372	81.1 ± 12.1
HR (bpm)	72.9 ± 11.3	73.2 ± 11.4	67.0 ± 5.9	0.129	72.3 ± 3.6	0.905	0.873	0.445	72.9 ± 11.2

AF: Atrial Fibrillation; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	N.A.
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	Table 1

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	7,8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8,Table 1
		(b) Report category boundaries when continuous variables were categorized	7,8,Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.