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Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multi-country patient-level meta-analysis of 141,220 screened individuals

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Abstract:	ABSTRACT BACKGROUND: The precise age distribution and calculated stroke risk of screen-detected atrial fibrillation (AF) is not known. Therefore, it is not possible to determine the number needed to screen to identify one treatable new AF case (NNS-Rx) (i.e. Class-1 oral anticoagulation (OAC) treatment recommendation) in each age stratum. If the NNS-Rx is known for each age stratum, precise cost-effectiveness and sensitivity simulations can be performed, based on the age distribution of the population/region to be screened. Such calculations are required by national authorities, and organisations responsible for health-system budgets, to determine the best age cut-offs for screening programs and decide whether programs of screening should be funded. Therefore, we aimed to determine the exact yield and calculated stroke-risk profile of screen-detected AF, and NNS-Rx in 5-year age strata. METHODS AND FINDINGS: A systematic review of Medline, Pubmed, and Embase was performed (January 2007 to February 2018), and AF-SCREEN international collaboration members were contacted to identify additional studies. 24 eligible studies were identified, which performed a single timepoint screen for AF in a general ambulant population, including people 65 years. Authors from eligible studies were invited to collaborate and share patient-level data. Statistical analysis was performed using random effects logistic regression for AF detection rate, and Poisson regression modelling for CHA2DS2-VASc scores. 19 studies (14 countries from a mix of low to middle-, and high-income countries) collaborated, with 141,220 participants screened and 1,539 new AF cases. Pooled yield of screening was greater in males across all age strata. The age/sex adjusted detection rate for screen-detected AF in ≥65-year-olds was 1.44% (95% CI, 1.13 to 1.82%); and 0.41% (95% CI, 0.31 to 0.53%) for <65-year-olds. New AF detection rate increased progressively with age from 0.34% (<60 years) to 2.73% (≥85 years). Neither the choice of screening methodology or device, the geographical region, nor the screening setting influenced the detection rate of AF. Mean CHA2DS2-VASc scores (n=1,369) increased with age from 1.1 (<60 years) to 3.9 (≥85 years); 72% ≥65 years had ≥1 additional stroke risk factor other than age/sex. All new AF ≥75 years and 66% between 65-74 years had a Class-1 OAC recommendation. The NNS-Rx is 83 for ≥65 years; 926 for 60-64 years; and 1089 for <60 years. The main limitation of this study is there are insufficient data on socio-

	demographic variables of the populations and possible ascertainment biases to explain the variance in the samples. CONCLUSIONS: People with screen-detected AF are at elevated calculated stroke risk: above age 65, the majority have a Class-1 OAC recommendation for stroke prevention, and >70% have ≥1 additional stroke risk factor other than age/sex. Our data based on the largest number of screen-detected AF collected to date show the precise relationship between yield and estimated stroke risk profile with age, and strong dependence for NNS-RX on the age distribution of the population to be screened; essential information for precise cost-effectiveness calculations.
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Competing Interests Use the instructions below to enter a competing interest statement for this submission. On behalf of all authors, disclose any competing interests that could be perceived to bias this work—acknowledging all financial support and any other relevant financial or non-financial competing interests.	I have read the journal's policy and the authors of this manuscript have the following competing interests: GYHL reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo outside the submitted work. No fees received personally. YC reports grants from Bayer, during the conduct of the study. DDM reports grants from National Institutes of Health, grants and other research support from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, grants, personal fees and other from Bristol Myers Squibb and Pfizer, other research support from Apple, Samsung Electronics, grants from National Science Foundation, during the conduct of the study; other from Mobile Sense Technologies, LLC, grants from Philips, outside the submitted work. MP reports consultancy activity for Boehringer Ingelheim. JJO reports grants from Pfizer, non-financial support from Alivecor, outside the submitted work. JW reports grants from

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Data Availability Authors are required to make all data underlying the findings described fully available, without restriction, and from the time of publication. PLOS allows rare exceptions to address legal and ethical concerns. See the PLOS Data Policy and FAQ for detailed information. A Data Availability Statement describing where the data can be found is required at submission. Your answers to this question constitute the Data Availability Statement and **will be published in the article**, if accepted. **Important:** Stating 'data available on request from the author' is not sufficient. If your data are only available upon request, select 'No' for the first question and explain your exceptional situation in the text box.	No - some restrictions will apply

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20 August 2019
Prof Clare Stone, Acting Chief Editor
PLOS Medicine

Dear Prof Stone,

Once again, we would like to thank the editorial team for their time and effort in reviewing our manuscript. We have carefully considered each of the remaining comments and have outlined a response to each in the table provided in the attached document.

We thank you for your further consideration of our manuscript.

Yours Sincerely,

Nicole Lowres and Ben Freedman, for and on behalf of all authors

Response to comments from third editorial review (PMEDICINE-D-19-00916R1)

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Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multi-country patient-level meta-analysis of 141,220 screened individuals

Short title: Estimated stroke risk, yield, and number needed to screen for atrial fibrillation

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Tables/Figures:	8

ABSTRACT

BACKGROUND: The precise age distribution and calculated stroke risk of screen-detected atrial fibrillation (AF) is not known. Therefore, it is not possible to determine the number needed to screen to identify one treatable new AF case (NNS-Rx) (i.e. Class-1 oral anticoagulation (OAC) treatment recommendation) in each age stratum. If the NNS-Rx is known for each age stratum, precise cost-effectiveness and sensitivity simulations can be performed, based on the age distribution of the population/region to be screened. Such calculations are required by national authorities, and organisations responsible for health-system budgets, to determine the best age cut-offs for screening programs and decide whether programs of screening should be funded. Therefore, we aimed to determine the exact yield and calculated stroke-risk profile of screen-detected AF, and NNS-Rx in 5-year age strata.

METHODS AND FINDINGS: A systematic review of Medline, Pubmed, and Embase was performed (January 2007 to February 2018), and AF-SCREEN international collaboration members were contacted to identify additional studies. 24 eligible studies were identified, which performed a single timepoint screen for AF in a general ambulant population, including people ≥65 years. Authors from eligible studies were invited to collaborate and share patient-level data. Statistical analysis was performed using random effects logistic regression for AF detection rate, and Poisson regression modelling for CHA_2DS_2-VASc scores. 19 studies (14 countries from a mix of low to middle-, and high-income countries) collaborated, with 141,220 participants screened and 1,539 new AF cases. Pooled yield of screening was greater in males across all age strata. The age/sex adjusted detection rate for screen-detected AF in ≥65-year-olds was 1.44% (95% CI, 1.13 to 1.82%); and 0.41% (95% CI, 0.31 to 0.53%) for <65-year-olds. New AF detection rate increased progressively with age from 0.34% (<60 years) to 2.73% (≥85 years). Neither the choice of screening methodology or device, the geographical region, nor the screening setting influenced the detection rate of AF. Mean CHA_2DS_2-VASc scores (n=1,369) increased with age from 1.1 (<60 years) to 3.9 (≥85 years); 72% ≥65 years had ≥1 additional stroke risk factor other than age/sex. All new

AF ≥75 years and 66% between 65-74 years had a Class-1 OAC recommendation. The NNS-Rx is 83 for ≥65 years; 926 for 60-64 years; and 1089 for <60 years. The main limitation of this study is there are insufficient data on socio-demographic variables of the populations and possible ascertainment biases to explain the variance in the samples.

CONCLUSIONS: People with screen-detected AF are at elevated calculated stroke risk: above age 65, the majority have a Class-1 OAC recommendation for stroke prevention, and >70% have ≥1 additional stroke risk factor other than age/sex. Our data based on the largest number of screen-detected AF collected to date show the precise relationship between yield and estimated stroke risk profile with age, and strong dependence for NNS-RX on the age distribution of the population to be screened; essential information for precise cost-effectiveness calculations.

AUTHOR SUMMARY

Why was this study done?

- Atrial fibrillation is a common heart rhythm problem that often has no symptoms, so people are unaware they have this condition
- People with atrial fibrillation can have a very high stroke risk if they are not appropriately treated with anticoagulant medications, and this risk increases with age
- Screening for atrial fibrillation is recommended in many guidelines, although the precise age distribution and calculated stroke risk of atrial fibrillation detected by screening is not known
- Accurate age-specific data are required for cost-effectiveness analysis, to inform the most appropriate age cut-off for screening based on the age distribution of the population to be screened

What did the researchers do and find?

- Investigators from 19 atrial fibrillation screening studies across the world agreed to collaborate and share patient level data, providing a combined database of 141,220 people screened and 1,539 screen-detected cases of atrial fibrillation
- Our study was able to quantify the yield and stroke risk for atrial fibrillation in 5-year age brackets, showing the exact relationship of how the yield of screening and stroke risk of screen-detected atrial fibrillation increases with age
- The yield of screening was not influenced by the screening method used or the recruitment setting, indicating that screening programs can be established based on available resources
- To our knowledge, this is the first study to demonstrate the precise relationship of the number that you need to screen to identify one new atrial fibrillation case, or one new atrial fibrillation case in whom anticoagulant treatment is guideline recommended, in 5-year age brackets

What do these findings mean?

- This study demonstrates the high calculated stroke risk of screen-detected AF and the high proportion with at least one additional stroke risk factor other than age or sex
- These data allow for accurate simulations of cost-effectiveness of screening including sensitivity analyses, based on the age distribution of the population to be screened
- Ultimately these data may be used to assist development of health policy around the development of atrial fibrillation screening programs, tailored to the specific health system and resources available.

INTRODUCTION

The role of opportunistic or systematic atrial fibrillation (AF) screening for people aged ≥65 years remains contested, with variation in recommendations between international AF clinical guidelines. However, 10% of all ischaemic strokes are in individuals with undiagnosed AF [1], and early identification of AF and appropriate guideline-based treatment with oral-anticoagulants (OAC) can prevent strokes and thus reduce health costs related to AF [2]. Organisations supporting the recommendation to screen include the European Society of Cardiology (ESC) [3], the European Heart Rhythm Association [4], the Royal College of Physicians of Edinburgh [5], AF-SCREEN International Collaboration [6], and recently the Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand [7].

The evidence to support screening has mainly been extrapolated from studies of people with clinically or incidentally diagnosed AF, and from prevalence studies that show both AF prevalence and stroke risk increase substantially from age 65. No large outcome trial of screen-detected AF using hard events, including stroke and death, has been reported to date. Few studies have reported the baseline estimated stroke risk of screen-detected AF patients. In the SAFE trial the calculated stroke risk was the same in screen-detected and symptomatically identified AF patients [8], but it was not possible to accurately determine the stroke risk in discrete age strata, or the number needed to screen to identify one treatable new AF case (NNS-Rx) in each age stratum. This information is important for precise cost-effectiveness and sensitivity simulations based on the age distribution of the population to be screened. Such calculations are required by payers to determine the best age cut-offs for screening programs and decide whether programs of screening should be funded.

We therefore performed a systematic review and meta-analysis to investigate the yield of new AF identified in contemporary AF screening studies (single time-point), and to explore the stroke risk profile, and OAC eligibility of those identified, in order to determine the precise

age distribution and calculated stroke risk of atrial fibrillation in 5-year age strata to enable accurate cost-effectiveness modelling.

METHODS

This systematic review and patient level meta-analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis (S1 PRISMA checklist) and the meta-analyses of observational studies in epidemiology guidelines [9,10]. All collaborating studies had ethical approval for their study, the details of which are reported in the individual study manuscripts [11-29]. Ethical approval was not required for this collaborative secondary analysis of data.

Search strategy and selection criteria

Relevant studies were identified by two independent reviewers (NL and BF) through electronic database searching of MEDLINE, Pubmed, Embase and Google. The keyword search terms used were: atrial fibrillation AND [screening OR incidence OR prevalence OR detection OR identification] up to February 2018. To ensure a relevant contemporary sample was obtained, limits were applied to years 2007 onwards, and human research. Studies published in any language were permitted. Additional studies were identified through directly contacting members of the AF-SCREEN International Collaboration [6]. Study authors from all eligible studies were contacted via email, with an explanation of the proposed study and an invitation to collaborate.

The inclusion criteria for screening studies were (i) evaluated a general ambulant population; (ii) included people ≥65 years within their screened population; (iii) used a valid method to identify AF, as accepted by the ESC 2016 AF guidelines (i.e. pulse palpation, 12-lead electrocardiogram (ECG), or ECG rhythm strip, with a validated device) [3]; (iv) assessed the rate of newly identified AF using a single time-point screen; (v) distinguished between newly

identified AF and previously diagnosed AF; (vi) screened a sample size of at least 1,000 people; (vii) collected participant age and gender for all new AF; and (viii) collected participant age for all participants screened. Studies were excluded if they performed repeated, intermittent, or continuous recordings over a period to identify unknown AF; or if screening was targeted at a specific sub-group (e.g. limited age range, hypertension, diabetes, post stroke).

Assessment of Quality of Reporting was not performed, as some participating studies had not published their results. However, to ensure only studies of appropriate quality were included, our study inclusion criteria were intentionally developed based on the modified Newcastle-Ottawa scale criteria, specifically: (i) source population is representative, (ii) ascertainment of past history of AF, (iii) validated measurement tool used, (iv) adequate sample size, (v) appropriate methodology for outcomes, and (vi) variables clearly defined.

Study Outcomes

The primary study outcome was the detection rate for cases of new AF identified through screening of people aged ≥65 years with one screen at a single time-point (reported as [number of positive cases/100 persons screened] and 95% confidence intervals [CI]). Secondary outcomes of interest were: (i) detection rate for cases of new AF identified through screening with one screen at a single time-point; stratified according to each age group (<60; 60-64; 65-69; 70-74; 75-79; 80-84; ≥85 years) (reported as [number of positive cases/100 persons screened] and 95% CI), (ii) CHA_2DS_2-VASc stroke risk score; stratified according to age group (reported as means and 95% CI); (iii) eligibility for OAC according to ESC 2016 guidelines; stratified according to age group (reported as number and percentage); (iv) proportion of new AF cases with stroke risk factors other than age and sex (i.e. chronic heart failure, hypertension, diabetes, prior stroke or transient ischaemic attack, or vascular disease); stratified according to age group (reported as number and percentage); (v) number needed to screen (NNS) to identify 1 new AF case for age ≥65 years; and

158 stratified according to age group; and (vi) NNS to identify 1 treatable new AF case (NNS-Rx)
159 (i.e. new AF with a Class-1 recommendation to prescribe OAC) for age ≥65 years; and
160 stratified according to age group.
161
162 **Statistical analysis**
163 Data from each study were exported into Microsoft Excel (version 1802) and checked for
164 errors. Data fields collected from each study are summarised in S1 Text. Descriptive
165 analyses were carried out to describe characteristics of participating studies, total numbers
166 screened, and total numbers of AF identified through screening, stratified according to age
167 group and sex.
168
169 *Detection rate of new AF*
170 The number of new AF cases among those screened was assumed to follow a binomial
171 distribution, as only a binary outcome was possible from screening each participant (AF
172 positive or AF negative). In accordance with our statistical analysis plan, the detection rate of
173 new AF cases was estimated by random effects logistic regression. As binary data are
174 unlikely to have a 'normal distribution', random effects logistic regression is preferred over
175 conventional meta-analysis approaches which assume study-level effect sizes are normally
176 distributed.[30] The consequence of choosing this approach is that the standard meta-
177 analytic methods for detecting heterogeneity and publication bias cannot be applied.
178 Heterogeneity was therefore assessed using the study-level random effect and standard
179 error.
180
181 Individual level data were available for the screening outcome (AF positive or AF negative),
182 sex, and age group. Study-level information was available for country; geographical region;
183 urban/rural population; screening method/device; screening setting/design; era screened;
184 and screening age eligibility. Due to the combination of both individual and study-level data,

the individual level data was modelled first, and then the study-level variables were added. Study was included as a random effect in all models.

For the individual level data, three models were considered: the intercept only (overall mean), then the addition of age groups, and then gender. The appropriateness of including each variable was based on comparison of Akaike's information criterion for each model. The study-level covariates were then added to the model one at a time, and Akaike's information criterion was used to determine if they should be included or not, based on comparison to Akaike's information criterion of the final individual level model.

Individual logistic regression models were used for study-level estimates and summary estimates were computed from a random effects logistic regression model using SAS GLIMMIX (v9.4) while adjusted for covariates. Age group estimates were computed using least square means from the final random effects logistic regression model. The results of the analysis from SAS GLIMMIX were imported into R and the metafor package (R 3.4.3 "Kite-Eating Tree") was used to create a forest plot. The results were reported for age ≥65 years; and also stratified according to each age group (<60; 60-64; 65-69; 70-74; 75-79; 80-84; ≥85 years).

Stroke risk profile of new AF cases

Stroke risk of new AF cases was determined using the CHA_2DS_2-VASc score (range 0-9 points), which is the sum of risk factors: Congestive heart failure/left ventricular dysfunction (1 point); High blood pressure (1 point); Age >75 years (2 points); Diabetes (1 point); Stroke/transient ischemic attack/thromboembolism (2 points); Vascular disease [coronary artery disease, myocardial infarction, peripheral artery disease, aortic plaque] (1 point); Age 65–74 years (1 point); Sex category female (1 point). The CHA_2DS_2-VASc score was chosen to measure stroke risk as it is recommended by most international guidelines [3,7,31], and it

has demonstrated accuracy identifying AF patients who are at low risk of stroke and therefore do not require OAC [32,33].

Random-effects Poisson regression modelling was performed for CHA_2DS_2-VASc score. As the maximum data value of the CHA_2DS_2-VASc score is 9, we modelled the Poisson mean for the data (1.04) and calculated the probability that the value could be larger than 9 (1.58×10^{-7}) to ensure truncation of data relative to the Poisson distribution was not an issue.

For Poisson regression with study as a random effect, age groups were included to stratify the CHA_2DS_2-VASc mean estimates according to age brackets. The study-level covariates (i.e. geographical region, country, rural/urban population) were then added to the model one at a time, and Akaike's information criterion was used to determine if they should be included or not, based on comparison to Akaike's information criterion of the individual level model. The mean CHA_2DS_2-VASc scores were similar for each country with one exception. The mean score for this country was 1.7 (CI 1.2-2.4) while the next lowest was 2.4 (CI 1.6-3.5). The inclusion of this country could unduly influence the overall summary estimates. To assess the impact of this data in a sensitivity analysis, the model was refit without data from this country and the summary estimates were compared. The final model included data from all countries.

Guideline recommendations for OAC were calculated for each new AF case with CHA_2DS_2-VASc score and sex data. The ESC 2016 guidelines were used to classify OAC recommendations into (i) Class-1 OAC recommendation [CHA_2DS_2-VASc score: men≥2; women≥3], (ii) Consider OAC [CHA_2DS_2-VASc score: men=1; women=2], or (iii) OAC not recommended [CHA_2DS_2-VASc score: men=0; women=1] [3]. Data are reported as pooled number and percentages for each category; stratified according to age group (<60; 60-64; 65-69; 70-74; 75-79; 80-84; ≥85 years).

The number of additional stroke risk factors other than age and sex were calculated for each person with new AF using the formula (CHA_2DS_2-VASc score - female sex point - age points); and reported as a pooled percentage of all new AF; stratified according to age group.

Number needed to screen

The NNS to identify one new AF case was calculated using the inverse of the detection rate derived from the meta-regression; stratified according to age group. The NNS-Rx was calculated using the inverse of the determined yield of newly-identified AF with a 2016 ESC Class-1 recommendation for OAC; stratified according to age group.

RESULTS

The search strategy identified 41 screening studies, of which 17 did not meet the eligibility criteria (Fig 1). Study authors from the 24 eligible studies were contacted via email, and 19 studies [11-29] from 14 countries agreed to the collaboration and contributed screening data.

Fig 1: Study selection

A combined total of 141,220 participants were screened (~44% men; sample size range 1,000 – 59,505) (table 1). Rates of detection of AF ranged from 0.35% in studies recruiting ≥40 years, to 2.34% in studies recruiting ≥65 years. Studies recruited from community or population screening (n=7), general practice (n=6), outpatient clinics (n=3), and pharmacies (n=3). The screening methods used were single-lead ECG (n=12), 12-lead ECG (n=4), pulse palpation (n=2), and modified blood pressure machine (n=1).

Table 1: Characteristics of studies

Author; Year	Country; Study name	Setting	Screening method	Year screened	Age eligibility (years)	Number screened
Proietti et al; 2016[16]	Belgium; Belgian Heart Rhythm Week	Community/ Population	Single-lead ECG (Omron HCG-801)	2010-2014	≥20	59505
Schnabel et al; 2012[11]	Germany; Gutenberg Health Study	Community/ Population	12-lead ECG	2007-2017	35-74	14937
Yan et al; 2017[12]	Hong Kong	Outpatient clinic	Single-lead ECG (AliveCor)	2015-2017	≥40	12928
Gomez-Doblas et al; 2014[13]	Spain; OFRECE	Community/ Population	12-lead ECG	2010-2012	≥40	8396
Deif et al; 2013[14]	Australia	Outpatient clinic	12-lead ECG	2011	≥40	3430
Soni et al; 2017[15]	India	Community/ Population	Single-lead ECG (AliveCor)	2016-2017	≥50	1947
Li et al; 2015[17]	China	Community/ Population	12-lead ECG	2006-2011	≥60	3922
Smyth et al; 2016[18]	Ireland	General practice	Pulse palpation (confirmed with 12-lead ECG)	2014	≥60	7262
Chao et al; 2017[19]	Taiwan; SAFE-Taiwan	Pharmacy	Modified blood pressure device (Microlife WatchBP Office AFIB)	2015-2016	≥60	2672
Kvist et al; 2017[20]	Denmark; DANCAVAS	Community/ Population	Single-lead ECG (Lead-II during Cardiac-CT scan)	2015-2016	65-74	1318

Kaasenbrood et al; 2016[21]	Netherlands	General practice	Single-lead ECG (MyDiagnostick)	2013	≥65	2557
Lowres et al; 2014[22]	Australia: SEARCH-AF	Pharmacy	Single-lead ECG (AliveCor)	2012-2013	≥65	1000
Sandhu et al; 2016[23]	Canada: PIAAF-Pharmacy	Pharmacy	Single-lead ECG (HeartCheck, CardioComm)	2014-2015	≥65	1145
Quinn et al; 2018[24]	Canada: PIAAF- Family Practice	General practice	Single-lead ECG (HeartCheck, CardioComm); modified blood pressure device (Microlife WatchBP Home A); and pulse palpation (confirmed with 12-lead ECG ± holter)	2016-2017	≥65	2054
González Blanco et al; 2017[25]	Spain; DOFA	General practice	Pulse palpation (confirmed with 12-lead ECG)	2015-2016	≥65	7063
Fitzmaurice et al; 2007[26]	England; SAFE (systematic screening arm)	General practice	12-lead ECG	2001-2003	≥65	2357
Orchard et al; 2018[27]	Australia; AF-SMART	General practice	Single-lead ECG (AliveCor)	2016-2017	≥65	1574
Keen et al; 2017[28]	USA	Outpatient Clinic	Single-lead ECG (AliveCor)	2016-2017	≥65	2732
Wang et al; 2017[29]	China	Community/ Population	Single-lead ECG (AliveCor)	2017-2018	≥65	4421

New atrial fibrillation cases

From the pooled data (n=19 studies), 1,539 new cases of AF were identified from 141,220 participants screened. Limiting the results to people ≥65 years: 1,162 new cases of AF were identified from 74,104 participants screened. Absolute numbers of new AF identified were greatest within the range of 70-74 years (Fig 2). The pooled yield of screening was greater in males across all age strata and increased in both men and women with increasing age (Fig 3).

Fig 2: Total numbers of new atrial fibrillation by sex

AF: Atrial fibrillation

Fig 3: Atrial fibrillation pooled yield by sex

AF: Atrial fibrillation

Atrial fibrillation detection rate

The inclusion of sex, age group, and cohort improved the fit of the random effects logistic regression model. The variables of setting, method, region, country, urban/rural, era screened, and screen age eligibility did not appear to influence the results. The final model was adjusted for age group and sex, and incorporated 18/19 studies (n=138,663) for which data on total numbers screened were stratified by both age and sex [11-20,22-29]. The study-level random effect estimate was 0.2320 (se=0.0889) indicating a heterogeneous sample.

The detection rate for cases of new AF identified through screening increased progressively with increasing age, as presented in the summary estimates (Fig 4). Below age 60 years yield was 0.34%, increasing to 2.73% for ages 85 years and over. For screening people ≥65 years (as per guideline recommendations) the detection rate of new AF was 1.44% (95% CI,

1.13 to 1.82%); compared to only 0.41% (95% CI, 0.31 to 0.53%) for people aged <65 years (rate ratio=3.57, 95% CI, 3.10 to 4.10) (Fig 5).

Fig 4: Atrial fibrillation detection rate (adjusted for age and sex)

*Summary estimates are calculated from the 18/19 studies which provided both gender and age for total numbers screened

Fig 5: Atrial fibrillation detection rate for <65 years and 65+ years

*Summary estimates are calculated from the 18/19 studies which provided both gender and age for total numbers screened

Stroke risk profile

CHA_2DS_2-VASc scores were available for 1,369 new AF cases, collected at the time of screening, from 18/19 studies [11-24,26-29]. As expected, mean CHA_2DS_2-VASc scores increased progressively with age, with step increases at age 65 and 75 years (table 2). CHA_2DS_2-VASc results appeared to be influenced by a country/cohort effect with the highest CHA_2DS_2-VASc means (>3.0) observed in Germany, Hong Kong and America, and the lowest (<2.0) in India. The results did not appear to be influenced by setting, method, urban/rural, era screened, or screen age eligibility.

Table 2: Stroke risk profile of new atrial fibrillation cases (n=1369)

Age group *years*	Number *n*	CHA_2DS_2-VASc *mean* (95% CI)*	≥1 non-age/sex stroke risk-factor *% of age group*	Guideline Recommendation†		
				No OAC *%*	Consider OAC *%*	Prescribe OAC (Class-1) *%*
<60	251	1.1 (0.7 to 1.5)	46	54	19	27
60-64	125	1.4 (1.2 to 1.6)	54	45.5	32	22.5

65-69	223	2.5 (2.2 to 2.8)	65	0	35	65
70-74	240	2.7 (2.4 to 2.9)	69	0	32.5	67.5
75-79	228	3.8 (3.4 to 4.1)	76	0	0	100
80-84	151	3.8 (3.4 to 4.2)	75	0	0	100
85+	151	3.9 (3.6 to 4.4)	77	0	0	100

CHA_2DS_2-VASc score = (Congestive heart failure/left ventricular dysfunction, High blood pressure, Age >75 years, Diabetes, Stroke/transient ischemic attack/thromboembolism, Vascular disease [coronary artery disease, myocardial infarction, peripheral artery disease, aortic plaque], Age 65–74 years, Sex category female); OAC = oral-anticoagulation; * = least square means; † = Recommendation according to the 2016 ESC atrial fibrillation guidelines

When considering only 'non-age and non-sex' factors of the CHA_2DS_2-VASc score, 72% (712/993) of new AF ≥65 years had at least 1 additional stroke risk factor (co-morbidity) other than age or sex (table 2). The number with co-morbidities was lower in age groups 65-69 and 70-74 years (65% and 69% respectively), however it was >75% in all three age strata over 75 years.

Above age 65 years, the clear majority (84%) of screen-detected new AF was eligible for OAC with a Class-1 recommendation according to the 2016 ESC guidelines (table 2) [3]. For people aged ≥75 years, 100% had a Class-1 recommendation because of age alone. In the age range 65-74 years, 66% received a Class-1 recommendation, and the remaining 34% had a recommendation to consider OAC (table 2). In contrast, for those <65 years only 26% received a Class-1 recommendation, 23% were consider OAC, and half (51%) had a recommendation to not prescribe OAC (table 2).

Number needed to screen

When screening people ≥65 years the NNS to identify one new AF is 69, rising to 83 to identify one treatable new AF (i.e. those with a Class-1 OAC recommendation). A progressive increase was observed in both NNS to identify one new AF, and NNS-Rx as the

age group decreased (table 3). Specifically, there was a large jump noted between age 65-69 to 60-64 years where the NNS-Rx rose steeply from 211 to 926, and a further increase to 1,089 for people aged <60 years (table 3).

Table 3: Number needed to screen (NNS)

Age group (years)	NNS to identify 1 new AF (n)	NNS to identify 1 treatable new AF (n) ‡
<60	294	1089
60-64	208	926
65-69	137	211
70-74	92	136
75-79	67	67
80-84	53	53
85+	37	37

‡ = newly identified atrial fibrillation with a class-1 recommendation to prescribe oral-anticoagulation

DISCUSSION

To our knowledge, this is the first study to show the actual yield of screen-detected AF, and estimated stroke risk by age group, in very large numbers. Our data show that both yield and stroke risk are very sensitive to age, and the estimated stroke risk profile of new cases is high. When screening ≥65 years, the detection rate of new AF cases is 1.44% (95% CI, 1.13 to 1.82%), and 84% of new AF cases have a Class-1 recommendation for OAC prophylaxis. Of note, under the 2016 Canadian AF Guidelines all people aged ≥65 years receive an OAC recommendation based on age alone [34]. The high stroke risk profile is not solely due to age and sex, as 72% of new cases aged ≥65 years have at least one additional CHA_2DS_2-VASc stroke risk factor (co-morbidity) other than age or sex. As expected, with increasing age there is a corresponding continuous increase in detection rate of new AF, mean

CHA_2DS_2-VASc scores, and additional CHA_2DS_2-VASc stroke risk factors. The yield of screening was higher in men across all age groups, even though larger numbers of women were screened.

The detection rate of 1.44% for screening people ≥65 years is comparable to the result of 1.4% determined from a systematic review of AF screening in 2013 [35]. Both these results are based on single time-point screening, and as such may be an underestimate of undetected AF, as some cases of paroxysmal AF may be missed. Intermittent or continuous screening over 2-weeks or longer will identify additional cases of paroxysmal AF, leading to a larger yield [36-38]. Indeed, only one sixth of new AF cases were detected at baseline ECG testing in the STROKESTOP trial, with the remainder detected during the subsequent 2-weeks of intermittent screening [36]. The REHEARSE-AF study detected 3.8% with new AF by 1-2 ECGs per week over 1-year, although in that study, 1.8% of patients screened for eligibility by a single ECG had new AF detected [39]. With 2-weeks of ambulatory ECG monitoring using an adhesive patch in the mSToPS study, 5.1% were detected with new AF [38]. Although additional new AF cases are identified and the cost-effectiveness of intermittent screening has been demonstrated in a targeted population of 75 year-olds; intensive screening is more expensive, and stroke risk is lower for the most intensive screening programs (e.g. implanted cardiac monitors) [40], therefore intensive screening is not currently recommended for a generalised population [41]. For this reason, this review focused solely on single time-point screening, as it corresponds with clinical practice and is well suited for opportunistic screening according to guideline recommendations.

For implementation of opportunistic screening, our review indicates that the choice of screening setting and the methodology/device chosen to screen (i.e. pulse palpation, single-lead ECG, 12-lead ECG, or modified blood pressure machine) do not influence the detection rate. Therefore, decisions on how to implement screening can be tailored to available local or national resources, practice preference, the requirements of the health system, and the

379 population to be screened. Decisions around developing a screening program also critically
380 require consideration of the pathway to treatment, as 84% of new AF identified (aged ≥65
381 years) will require a consultation for consideration of OAC prescription.
382
383 Our data do not support screening a general population younger than 65 years, as the yield
384 is low, and only 26% of new AF cases would receive a Class-1 recommendation to treat with
385 OAC. Even to consider screening people aged 60-64, the NNS-Rx increases markedly to
386 926, compared to 211 for age 65-69 years. For the population below 60 years, to identify
387 one treatable person requires screening 1,089 people. Screening people younger than 65
388 may be appropriate in targeted populations (e.g. post-stroke or in those with additional
389 stroke risk factors) as both yield and stroke risk profile is likely to be higher, in which case
390 the NNS-Rx would reduce significantly [42,43].
391
392 The NNS data will be very important to determine precise estimates of cost-effectiveness. To
393 date, health-economic analyses from many countries, based on a similar yield of new AF,
394 have all demonstrated the likely cost-effectiveness of AF screening based on quality-
395 adjusted life years gained and strokes avoided [8,22,41,44-46]. Cost-effectiveness is
396 sensitive to OAC prescription rates, and improves as OAC prescription rates increase [22].
397 Given the recent trend of increased guideline-based prescription rates from 48% to 78.6%
398 noted in the United Kingdom since the introduction of non-vitamin K antagonist OACs [47],
399 guideline based screening of people ≥65 years, assuming a yield of 1.44%, is likely to be
400 more cost-effective than some previously published estimates. However, cost effectiveness
401 calculations will also need to consider the possible influence of increased bleeding risk, and
402 the associated costs including hospitalisations, related to treatment with OAC for those with
403 screen-detected AF [48].
404
405 Furthermore, it is widely acknowledged there are no published outcome data (stroke and
406 death) for screen-detected AF [6,49]. In response to this, large screening studies with these

endpoints are currently underway (e.g. ClinicalTrials.gov Identifier: NCT02743416 (STROKESTOP II); and NCT01593553). Once these and similar studies in the planning stages report, the outcome data can be combined with data from this review to calculate Number Needed to Treat to more precisely inform cost-effectiveness analyses and policy decisions on screening, based on the age-distribution of the specific population to be screened. It appears that screening for AF in a general population is likely to be cost-effective if screening is commenced at age 65, in line with current international guidelines. However, actual cost-effectiveness will depend on the age distribution of the population to be screened as well as stroke rates in each stratum of the new AF cases discovered. Our estimates of likely yield of both atrial fibrillation cases and proportion of cases with an elevated calculated stroke risk, enable organisations responsible for health-care delivery to determine the best age cut-offs to suit their own budgets. For example, some organisations may decide on setting an age threshold of 70 or even 75 years, accepting a trade-off in missed opportunities to prevent strokes.

Limitations

The heterogeneity between the included studies was high. We do not have sufficient data on the socio-demographic variables of the populations screened, or possible ascertainment biases, to explain the variance in the samples. As a logistic regression approach was chosen, we were unable to assess funnel plot asymmetry, however the rigorous methods for identification of relevant studies will likely reduce the chance of publication bias. The detection rate of unknown AF could also be inflated in a minority of studies as self-knowledge/recall of past AF history may be inaccurate, and studies performed in areas with reduced access to medical services may have lesser rates of previous AF diagnoses. Furthermore, the data reported in this review cannot take into account what proportion of new AF would have been detected, albeit with some delay, without screening. Few of the included studies included a control population, but in the large SAFE trial, the detection rate of new AF in practices screening people ≥65 years was 1.63% per annum, 1.04% per

annum in control practices, and 1.0% in 1 year in the control group of REHEARSE-AF [26,39].

CONCLUSIONS

People detected with new AF through screening are at elevated calculated stroke risk: above age 65, the majority are eligible for, and would benefit from OAC to prevent stroke, and >70% have at least one additional stroke risk factor other than age or sex. Screening for AF in people aged ≥65 years identifies new AF in 1.44% of those screened. The detection rate was not influenced by the screening method, recruitment setting, country, or year screened. Detection rate of new AF by screening rises progressively with age, with a male predominance in all age strata. One treatable new AF will be identified for every 83 people screened in people aged ≥65 years. Our data show that the yield and stroke risk profile of new AF are sensitive to age, so the NNS-Rx is dependent on the age distribution of the population to be screened; this information is essential for precise calculations of cost-effectiveness of different age cut-offs for screening. Screening for AF in a general population is likely to be cost-effective if screening is commenced at age 65, in line with current international guidelines. However, actual cost-effectiveness will depend on the age distribution of the population to be screened as well as stroke rates in each age-stratum of the new AF cases discovered.

SUPPORTING INFORMATION LEGEND

S1 PRISMA Checklist

S1 Text: Study data collected

S2 Text: Statistical analysis plan

ACKNOWLEDGEMENTS - NIL

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Figure 1

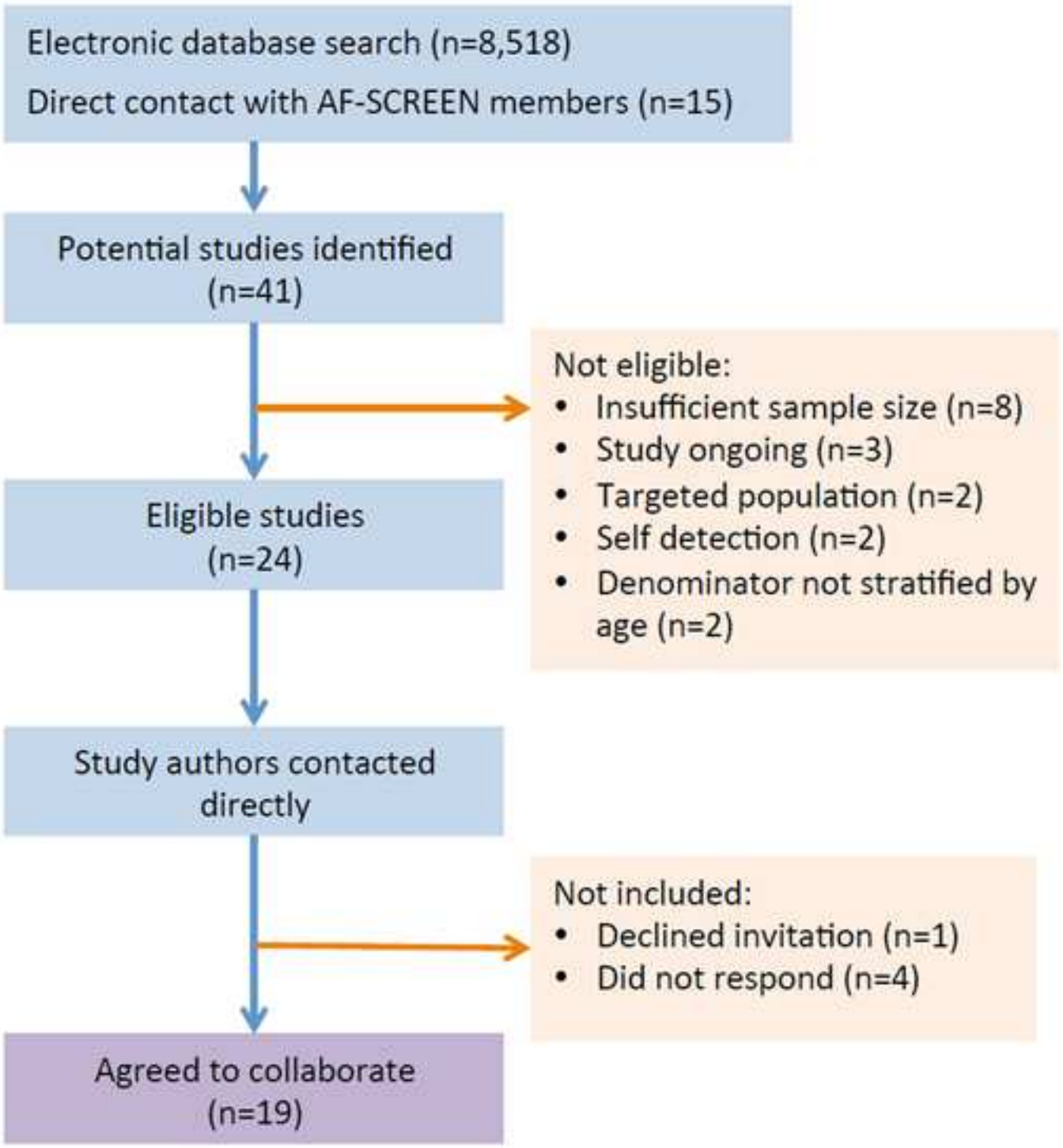
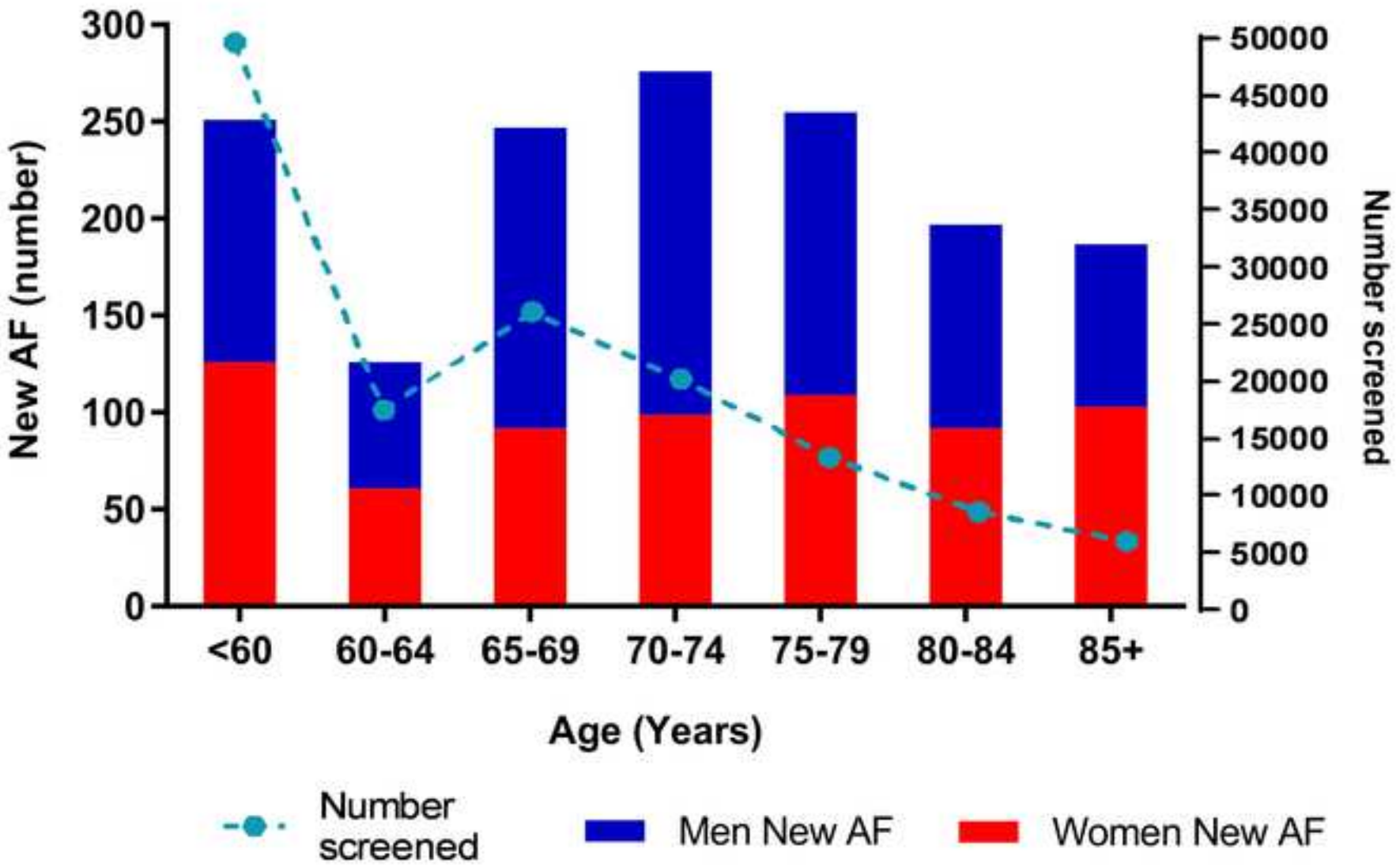


Figure 2



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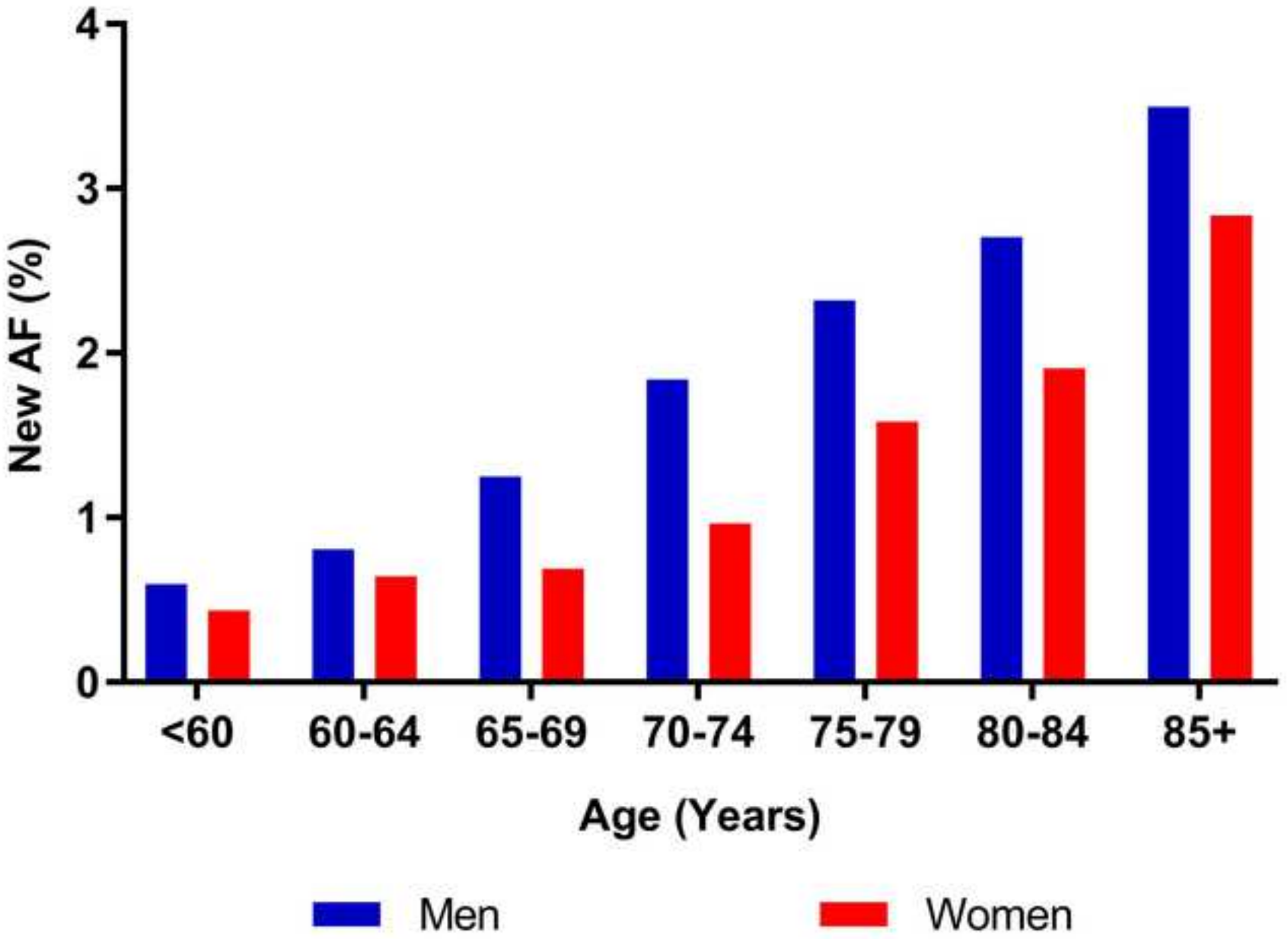

Figure 4

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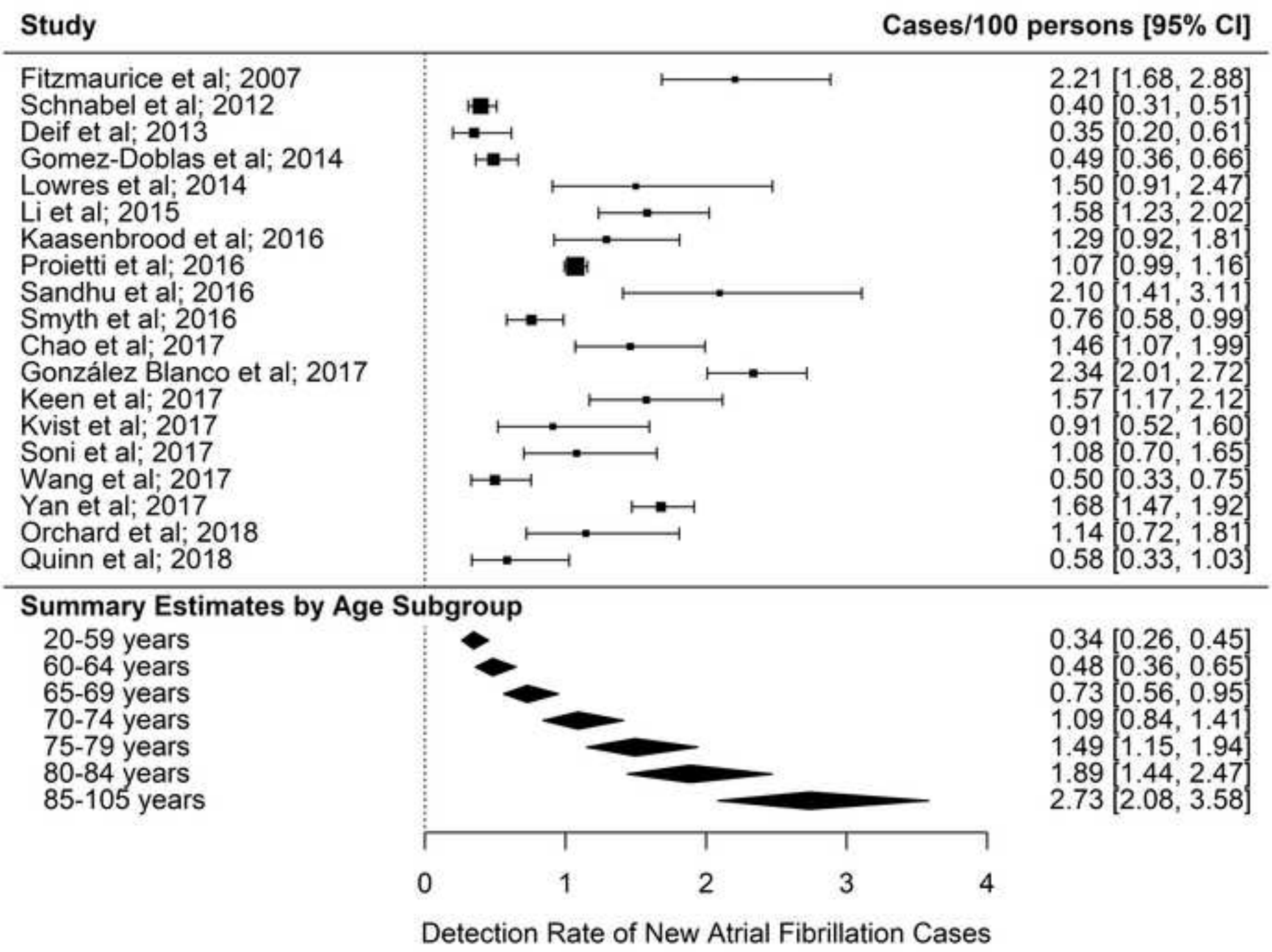

Figure 5

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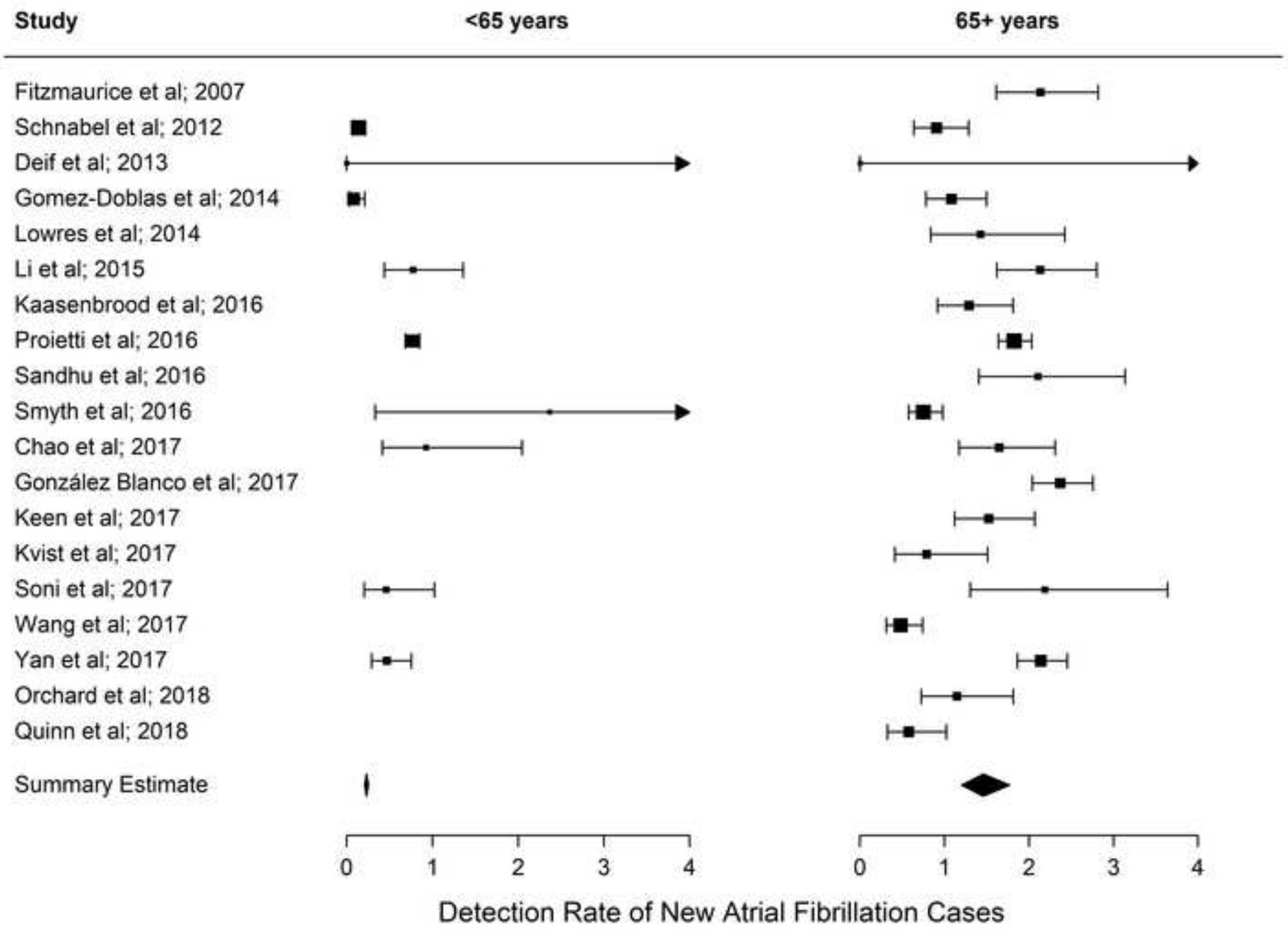

S1 Text Study Data collected