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Cost-effectiveness of screening for atrial fibrillation in a single primary care center at a 3-year follow-up

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ABSTRACT

Objectives. The aim of this study was to estimate the cost-effectiveness of intermittent electrocardiogram (ECG) screening for atrial fibrillation (AF) among 70–74-year old individuals in primary care. We also aimed to assess adherence to anticoagulants, severe bleeding, stroke and mortality among screening-detected AF cases at three-year follow-up.

Methods. A post hoc analysis based on a cross-sectional screening study for AF among 70–74-year old patients, who were registered at a single primary care center, was followed for three years for mortality. Data about adherence to anticoagulants, incidence of stroke and severe bleeding among screening-detected AF cases, were collected from patient's records. Markov model and Monte Carlo simulation were used to assess the cost-effectiveness of the screening program.

Results. The mortality rate among screening-detected AF cases ($n = 16$) did not differ compared to the 274 individuals with no AF (hazard ratio 0.86, CI 0.12–6.44). Adherence to anticoagulants was 92%. There was no stroke or severe bleeding. The incremental cost-effectiveness ratio of screening versus no screening was EUR 2389/quality-adjusted life year (QALY) gained. The screening showed a 99% probability of being cost-effective compared to no screening at a willingness-to-pay threshold of EUR 20,000 per QALY.

Conclusion. Screening for AF among 70–74-year olds in primary care using intermittent ECG appears to be cost-effective at 3-year follow-up with high anticoagulants adherence and no increased mortality.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia [1] and AF increases with increasing age [2]. Without treatment, atrial fibrillation carries an increased risk of ischemic stroke [3]. Stroke associated with AF is more fatal [4] than non-AF stroke and linked to reduced quality of life [5] and high cost [6].

Oral anticoagulant (OAC) is an effective treatment for preventing stroke associated with AF [7]. Unfortunately, AF is often asymptomatic [8] and ischemic stroke may be the first presentation of AF [9]. Thus, it has been suggested that high-risk populations should be screened for AF.

Numerous studies have been conducted on screening for atrial fibrillation but only a few of these studies have evaluated the cost-effectiveness [10–13]. Hence, there is still not concluded how and where such screening should be performed. Moreover, there is a controversy surrounding the efficacy and safety of using anticoagulant treatment for screening-detected atrial fibrillation [14].

The aim of this study was to evaluate the cost-effectiveness of AF screening based on data from a previous study [15] using intermittent electrocardiogram (ECG) among 70–74-year old patients in primary care. A secondary aim was to evaluate mortality, incidental stroke and severe bleeding as well as OAC adherence during a 3-year follow-up.

Methods

Design and study population

This is a retrospective cohort study as a post hoc analysis the results of a previously published cross-sectional AF-screening study [15] in which the target group comprised 415 patients aged 70–74 years registered at a single primary care center in 2015. Details of the demographic and essential background of the original study population are described in Supplemental Table 1. This population comprised a total of 34 (8.2%) cases with known AF and screening using intermittent ECG detected 16 (5.5%) new AF cases, whereas 274 individuals had no detected AF. Participants in this study received written and oral information about the study and provided informed consent to participate. All participants in this screening study were followed for up to three years for mortality as an outcome. In addition, screening-detected AF cases were followed for

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OAC adherence, incidence of stroke, and life-threatening bleeding.

Data collection on participants during the follow-up

Data on date of death (Supplemental Table 2), cause of death, adherence to OAC, incidence of stroke, and life-threatening bleeding were collected from the patients' records. There were no missing data or loss to follow-up. OAC adherence was defined as a proportion of days covered by claims during observations period. The adherence was calculated by percentage of covered days with OAC treatment of all observations days. The adherence was assessed by the amount of prescribed OAC taken under the observation period.

Cost-effectiveness analysis

A previously published [10] Markov model was used to assess the cost-effectiveness of screening for AF in primary care. A life-long decision-analytic model was deemed necessary as events such as AF, stroke, and major bleeding will affect individuals for the rest of their lives and such events can rarely be captured in clinical trials. Before this study was conducted, there was limited access to data on the long-term effects of screening in a primary care population. Thus, in order to provide a reliable cost-effectiveness estimate, we used the results obtained at the three-year follow-up. Figure 1 describes the core model structure. This study is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Supplemental Table 3). The protocol is described on protocols.io (https://www.protocols.io/view/safety-and-cost-effectiveness-of-screening-for-atr-mtrc6m6).

### Other assumptions and input for the economic model

The economic model used for this analysis, which had a health care payer perspective, has been described in detail elsewhere [10]. Briefly, we analyzed 1000 hypothetical individuals who matched the primary care population included in the cohort study in terms of baseline characteristics and adherence. Simulation of the natural disease progression and the effect of screening require additional data, including prevalence, incidence, risk of events, morbidity and mortality. These data were obtained primarily from the published literature [4,7,16] and a Swedish nationwide cohort study [17]:

- Mortality rates and risk of cardiovascular events (such as ischemic and bleeding strokes) in the population were obtained from ARISTOTELE [16], a Swedish nationwide cohort study [17] and the published literature [4,7].
- Cost data were mainly obtained from the healthcare regions of Sweden. The mean cost of a stroke was obtained from a calculation of stroke costs in Sweden [6]. Monthly medication costs were obtained from Pharmaceutical Specialties in Sweden (https://www.fass.se). Other unit costs were obtained from the published literature [18]. These are all listed in Table 1. A discount rate of 3% was used for both costs and effects in the base-case scenario. All unit costs were adjusted to 2019 and converted into euros using the exchange rate as of 18 February, 2019 (EUR 1.00 = SEK 10.5).
- The quality-adjusted life year (QALY) weights used in the model were derived from the participants' age based on the utility in the overall population of Sweden [19]. Ischemic and hemorrhagic stroke were expected to reduce the quality of life of the individuals [20]. Important parameters used in the model are presented in Table 1.

Statistical methods

The mortality rate as outcome was treated as a time-dependent variable and calculated as the incidence rates for the three cohorts. Follow-up time was defined as years from inclusion in the AF screening to the date of death or censored at the end of our observation (28 February 2019). The cumulative incidence of the three cohorts was plotted using the Kaplan–Meier method and a log-rank test was used to compare the differences between cohorts with no AF as the reference group and the other two groups. Cox proportional hazards regression models were used to assess the mortality risk and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. These analyses were performed using STATA statistical software version 10 and the two-sided significance level was set at $p < 0.05$.
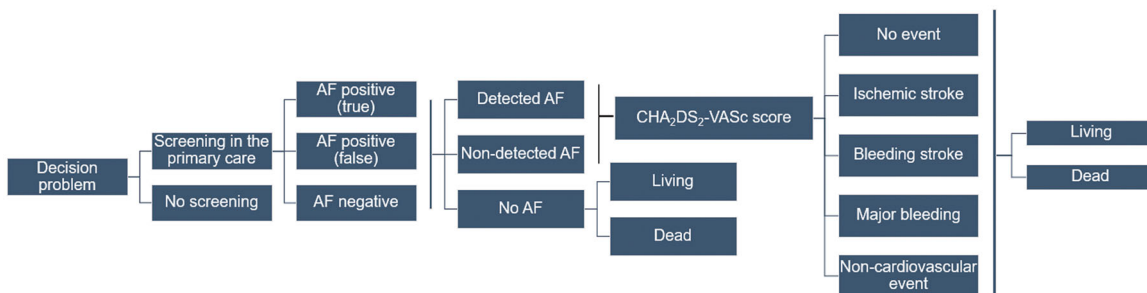
Figure 1. Depicts the core model. AF: atrial fibrillation; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, female sex.

Table 1. Important parameters in the AF screening model.

Parameter	Mean	Reference	Distribution
Baseline characteristics			
Age	72	[15]	Not varied
Female gender	52%	[15]	Not varied
CHA2DS2-VASc score	3.45	[15]	Normal
Prevalence unknown AF	5.8%	[15]	Beta
Probabilities			
Mortality stroke (CHADS2 = 2)	0.269	[4]	Beta
AF detected after stroke	88.2%	[9]	Beta
Intracranial bleeding	0.6	[17]	Beta
Major bleeding warfarin	5.2	[17]	Beta
Major bleeding no OAC	2.3	[17]	Beta
Yearly stroke risk in AF patients with apixaban			
CHA2DS2-VASc = 2	0.008	[7,16,17]	Beta
CHA2DS2-VASc = 3	0.012	[7,16,17]	Beta
CHA2DS2-VASc = 4	0.018	[7,16,17]	Beta
CHA2DS2-VASc = 5	0.027	[7,16,17]	Beta
CHA2DS2-VASc = 6	0.037	[7,16,17]	Beta
Yearly stroke risk in AF patients without anticoagulants			
CHA2DS2-VASc = 2	0.024	[17]	Beta
CHA2DS2-VASc = 3	0.036	[17]	Beta
CHA2DS2-VASc = 4	0.054	[17]	Beta
CHA2DS2-VASc = 5	0.083	[17]	Beta
CHA2DS2-VASc = 6	0.113	[17]	Beta
Proportion treated with (AF-patients)			
Warfarin	12.5%	[15]	Beta
Apixaban	81.3%	[15]	Beta
Aspirin	0%	[15]	Beta
Costs (EUR)			
Total cost per screened patient	119		Not varied
Rental of hand-held ECG	47.61[a]	[15]	Not varied
One-hour physician time	156.3[a] 0.33	[a]	Not varied
Holter for confirmation	121.9[a] 0.15	[a]	Not varied
Administration of results	1	Assumption	Not varied
Apixaban (yearly)	724	[21]	Not varied
Stroke ≤1 year	19,390	[22]	Gamma
Stroke > 1 year	4627	[22]	Gamma
Severe bleeding	3123	[23]	Gamma
Minor bleeding	43	Assumption	Not varied
Quality of life			
Age 50–59 years	0.839	[19]	Normal
Age 60–69 years	0.808	[19]	Normal
Age 70–79 years	0.794	[19]	Normal
Age 80–88 years	0.733	[19]	Normal
QALY-loss ischemic stroke (yearly)	0.15	[20]	Normal
QALY-loss bleeding stroke (yearly)	0.30	[20]	Normal
Yearly spontaneous detection of asymptomatic AF	5%	Assumption	Beta
OAC therapy at 3 years	92%	Cohort results	Beta
Discontinuation rate >3 years after initiation	8%	[24]	Beta

[a]Cost at Department of Cardiology, Linkoping University Hospital.

Table 2. Base-case cost-effectiveness results of screening for AF in primary care (per 1000 screened individuals).

Treatment arms	Total costs (EUR)	Total life years	Total QALYs	Incremental costs (EUR)	Incremental life years	Incremental QALYs	ICER incremental (EUR/ QALY)
No screening	2,346,586	11,229	7744				
Screening	2,380,911	11,244	7759	59,254	15.0	14	2389

Ethics approval

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Stockholm (DNR 2014/2061-31 and 2017/129- 32).

Results

Cost-effectiveness results

Table 2 presents total costs, life-year gained, QALYs and incremental costs per QALY for screening in primary care compared to no screening. The introduction of one-off screening in primary care generated 14 incremental QALYs and 15 incremental life years gained per 1,000 screened individuals. The incremental cost-effectiveness ratio (ICER) was EUR 2389 per QALY gained.

A second-order Monte Carlo simulation was run for 1000 iterations. Figure 2 presents the cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve shows that screening in primary care has a 99% probability of being cost-effective compared with no screening at a willingness-to-pay threshold of EUR 20,000 per QALY.
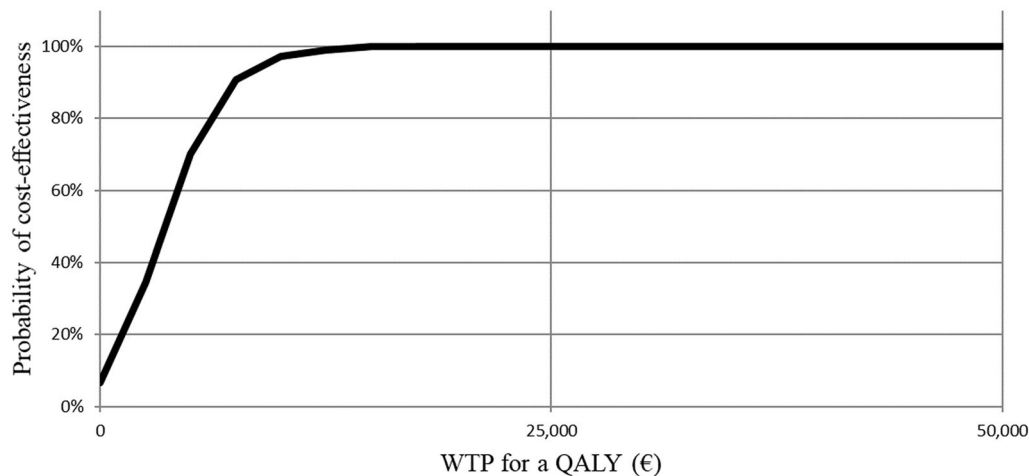
Figure 2. The cost-effectiveness acceptability curve of screening for AF in primary care. WTP: willingness-to-pay; QALY: quality-adjusted life year.

Table 3. Deterministic sensitivity analysis.

Parameter	Base-case value	Analysis	Values for analysis	Incremental cost EUR per QALY
Base-case analysis				2389
Per patient cost of screening	119	Lower	59.5	Cost-saving
		Higher	178.5	5482
Risk of asymptomatic AF compared to symptomatic	100%	Lower	50%	30,971
		Higher	150%	Cost-saving
Discount rate	3%	Lower	0%	Cost-saving
		Higher	5%	5478
Spontaneous detection	5%	Lower	2.5%	318
		Higher	7.5%	3976
Stroke costs	Stroke ≤1 year: 19,390,	Lower	20% lower	6618
	Stroke >1 year: 4627	Higher	20% higher	Cost-saving

Table 3 summarizes the deterministic sensitivity analyses. It is evident from the table that, across the scenarios tested, the ICER for screening does not change significantly. The largest impact on the ICER is driven by changes in the underlying risk of cardiovascular events, particularly ischemic stroke.

External validation of the model

Compared with the results from the cohort, the model provided similar output as both the model and the cohort study showed that approximately 94% of patients were alive after 36 months.

Mortality rates and cause of death

While the mortality rate of patients with known AF was higher than those patients with no AF (hazard ratio 3.6, CI 1.5–8.7), there was no difference in mortality rate between cases of new AF compared to cases of no AF (hazard ratio 0.86, CI 0.12–6.44) (Table 4 and Supplemental Figure 1). The cause of death is shown in Supplemental Table 4.

OAC adherence and stroke-bleeding outcomes

Regarding AF detection in the previous screening study [25], 14 out of 16 new AF cases received OAC. Of the two cases that did not receive OAC, one had a contraindication for OAC due to concomitantly diagnosed bowel cancer,

which was operated on 6 months later and following the operation he has been taking OAC regularly. The other patient refused OAC treatment. At the 3-year follow-up, one patient died, one had taken OAC 50% of the time, and 13 patients had taken OAC regularly. Among all new AF cases, overall OAC treatment has been taken in 92% of follow-up period. Two patients were treated with vitamin K antagonists and the other patients were treated with non-vitamin K antagonists. No stroke or severe bleeding was detected.

Discussion

This is one of the few cost-effectiveness studies for AF screening and the first study of intermittent screening in a primary prevention population in which follow-up data are included. Thus, the cost-effectiveness results for this age group in primary care were interesting as it is debated at what age and where the screening for AF should be performed. Moreover, followed up the cohort showed that adherence to anticoagulant treatment was high.

Cost-effectiveness of AF screening

With the available resources, the goal of most publicly funded healthcare systems is to provide as much health care as possible. Thus, any screening program should be cost-effective even if other parameters such as ethical perspectives must be considered. AF screening has been shown to

Table 4. Mortality rates and hazard ratios for AF-groups.

	Total persons	Total observation period (persons. year)	No. of deaths	Mortality rate (death/100 persons. year)	Hazard ratio (CI)	*p-value
No AF	274	923	20	2.17	Reference	
New AF	16	53	1	1.89	0.86 (0.12–6.44)	.887
Known AF	34	89	7	7.84	3.6 (1.5–8.7)	.004

*Cox-regression.

be cost-effective in a number of settings and when using different types of screening technologies [10–13].

However, the cost and outcome of AF screening varies according to the screening method and the target population. Screening using single time-point ECG measurement or pulse palpation is easy and inexpensive. However, it is difficult to detect paroxysmal AF using such a screening method. While continuous ECG monitoring [26] or intermittent ECG recording [27] over a long duration are sensitive methods for detecting all types of AF, such screening methods are more costly and time consuming. One study showed that it is more cost-effective to screen using intermittent ECG than with single time-point ECG screening [28]. Another screening study [12] indicate that pulse palpation is the most cost-effective approach depending on the screening setting.

Our study is, therefore, an important addition in this debate as it demonstrated that screening in primary care with a handheld-ECG is a possible solution that should be considered when implementing AF screening programs. Further studies, with larger randomized study populations, in other settings and with other screening technologies are necessary before fully informed decisions can be made. Several such initiatives have recently been initiated but before the results from those studies are published, decisions should be made based on the available evidence.

In order to identify an optimal screening program design from a cost-effectiveness perspective, it is important to consider a number of parameters, for instance, whom to be screened and where to identify them. Screening individuals at a high risk of AF detected a relatively high proportion of AF cases [29]. A systematic review [30] of systematic single time-point screening studies showed that the total AF prevalence was 14% among patients 75 years and older versus 5.1% among 65–74-year olds, in which around one third of AF cases were undiagnosed. Thus, screening of elderly persons over 75 years of age yields more AF cases than screening a younger age group such as 65–74-year olds [31]. However, detecting AF cases in a younger age group may be more beneficial in preventing a high number of strokes in a relatively young age group compared to screening elderly persons over 75 years of age. Our study showed that screening target population aged 70–74 year is highly cost-effective.

Patients with high morbidity generally visit primary healthcare centers frequently and have a good relationship to their doctors in these centers. This close relationship could result in a high participation rate in AF screening programs when driven in these centers. Increased participation in AF screening could result in higher participation rates also by patients with higher morbidity and higher AF risk. Moreover, good patient–doctor relationship, may also result in high initiation rate of anticoagulant therapy among detected AF cases and improved adherence to this therapy. In our study, the participation rate and AF detection rate was high. Initiation rate and adherence of anticoagulant therapy was also high. This supporting that AF screening in the primary care could be a cost-effective intervention.

OAC adherence, mortality, and stroke-bleeding outcomes

The adherence to OAC was high (92%) and this is comparable with the results of a previous screening study [32] in which the 5-year follow-up after AF screening showed 85% adherence to OAC. This pilot screening study was not designed to evaluate stroke prevention. However, the 3-year follow-up showed no stroke or severe bleeding. The higher mortality rate among patients with known AF is probably related to the higher cardiovascular morbidity in this group. In contrast, there was no difference in the mortality rate between new AF cases and those cases with no AF. This may be related to relatively similar cardiovascular morbidity among these groups.

Limitations

The sample size of this study was small. The screening for this study was conducted at a single primary care center. It is likely that this will affect the generalization of the results to the Swedish general population. As with all simulation model analyses, our results are indicative and need to be validated with empirical, clinical, and cost evidence. Currently missing data comprise the spontaneous detection rate of AF when no screening has been conducted. However, our assumptions were tested in scenario analyses and have previously been used in cost-effectiveness studies. There is considerable uncertainty surrounding the prevalence of undiagnosed AF. There is also uncertainty surrounding the risk of cerebrovascular events in patients with asymptomatic AF compared to those with symptomatic AF.

Conclusions

This study demonstrates that screening for AF among 70–74-year olds in primary care using intermittent ECG is cost-effective (EUR 2389/QALY) at the 3-year follow-up with high OAC adherence (92%) and no increased mortality among screening-detected AF cases. These results should be validated by a randomized control study.

Author contributions

Disclosure statement

Funding

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