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A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke

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Aims The purpose of this study was to estimate the cost-effectiveness of two screening methods for detection of silent AF, intermittent electrocardiogram (ECG) recordings using a handheld recording device, at regular time intervals for 30 days, and short-term 24 h continuous Holter ECG, in comparison with a no-screening alternative in 75-year-old patients with a recent ischaemic stroke.

Methods and results The long-term (20-year) costs and effects of all alternatives were estimated with a decision analytic model combining the result of a clinical study and epidemiological data from Sweden. The structure of a cost-effectiveness analysis was used in this study. The short-term decision tree model analysed the screening procedure until the onset of anticoagulant treatment. The second part of the decision model followed a Markov design, simulating the patients' health states for 20 years. Continuous 24 h ECG recording was inferior to intermittent ECG in terms of cost-effectiveness, due to both lower sensitivity and higher costs. The base-case analysis compared intermittent ECG screening with no screening of patients with recent stroke. The implementation of the screening programme on 1000 patients resulted over a 20-year period in 11 avoided strokes and the gain of 29 life-years, or 23 quality-adjusted life years, and cost savings of €55 400.

Conclusion Screening of silent AF by intermittent ECG recordings in patients with a recent ischaemic stroke is a cost-effective use of health care resources saving costs and lives and improving the quality of life.

Keywords Atrial fibrillation • Screening • Ischaemic stroke • Cost-effectiveness • QALY • Secondary prevention

Introduction

Atrial fibrillation (AF) is a major risk factor for ischaemic stroke.[1,2] A previous stroke in a patient with AF indicates a high risk for a new stroke. In patients with ischaemic stroke without known cardio embolic source, routine investigations for AF often reveal normal findings. In the presence of AF in combination with previous ischaemic stroke, oral anticoagulation treatment is indicated.[3]

As the presence of AF in patients with an ischaemic stroke is of pivotal role for further secondary prophylactic treatment and hence stroke risk, several studies have been conducted aimed at determining the amount of asymptomatic paroxysmal AF in patients with cryptogenic stroke.[4] It has been observed that prolonged monitoring times of the heart rhythm results in a higher yield of newly detected AF.[5–7] In a previously published study, intermittent arrhythmia screening with handheld electrocardiogram (ECG) has shown significant increase of detection for silent paroxysmal AF in patients with a recent ischaemic stroke/transient ischaemic attack (TIA),[8] and thus facilitate the detection of patients who should receive oral anticoagulant treatment (OAC).

Generally, screening is best applied in conditions who are relatively common and have an important impact on quality of life, and for which acceptable tests and treatments are available. Even if 9 out of 10 of the World Health Organization's screening criteria are fulfilled when screening for silent AF in stroke patients,[9] one important requirement remains to be analysed in health care systems with limited resources: is silent AF screening a cost-effective use of scarce resources?

The purpose of this study was to estimate the cost-effectiveness of two screening methods for detection of silent AF, brief intermittent long-term ECG recordings with handheld ECG at regular time intervals (handheld ECG), and short-term continuous Holter-ECG and to

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What's new?

- This is the first study estimating the cost-effectiveness of AF screening programmes in 75-year-old stroke patients.
- We investigated the value of screening recent stroke patients for silent AF by handheld ECG recordings, using a decision analytic model. Our results show that screening in this case is highly cost-effective. After 7 years it is even cost saving.
- The explanation for this is a relatively low-cost screening technology in combination with a high-risk target population and effective and cost-effective treatments.

compare them with a no-screening alternative in 75-year-old patients with a recent ischaemic stroke.

Materials and methods

The structure of a cost-effectiveness analysis was used in this study,[10] and the recommendations made by the Swedish Dental and Pharmaceutical Benefits Agency (TLV) were followed.[11] A societal perspective was chosen, but productivity losses were not estimated, due to the age of patients (75 years). The long-term (20-year) costs and effects of no screening and screening using brief intermittent long-term handheld ECG recordings at regular time intervals and short-term continuous Holter ECG were estimated with a decision analytic model combining the result of a clinical study and epidemiological data.

The observational prospective controlled study that was our point of departure has been reported elsewhere.[8] Briefly, 249 patients (57% male) with a recent ischaemic stroke/TIA, mean National Institute of Health stroke scale (NIHSS) score was 0.9, and previously undiagnosed AF were recruited from three Swedish hospitals.

The inclusion criteria were a diagnosis of ischaemic stroke/TIA in the stroke unit, based on clinical signs and/or a computed tomography with findings consistent with a recent ischaemic stroke/TIA, and no previously known AF. Study inclusion was within 14 days from the index event. Exclusion criteria were haemorrhagic stroke; inability to perform recordings, due to, for example, dementia; grave neurological deficit; presence of a continuous pacemaker rhythm; age $<$70 years according to a study amendment halfway through the inclusion period; and an index event surpassing 14 days. Patients who were diagnosed with AF during hospitalization before enrolment using, for example, continuous ECG recording due to recurrent TIAs were excluded and were considered to have previously known AF.[8]

Patients performed an ambulatory continuous 24 h Holter-ECG recording (Braemar DL700 analysed by Aspect 3.81R3a; GE Healthcare, Chalfont St. Giles) before or within the first few days after hospital discharge. Concomitantly, patients were equipped with a handheld ECG recorder (Zenicor-EKG; Zenicor Medical Systems AB) and instructed to perform 10 s rhythm recordings once in the morning and once in the evening for 30 days. In addition, patients were instructed to perform recordings in case of any arrhythmia symptoms. The handheld ECG recorder has been used and validated previously.[12,13]

The device is equipped with two handheld sensors providing a bipolar extremity ECG lead I. The patient's' thumbs are applied onto the sensors for 10 s for rhythm registration. The ECG recording is transferred sonically via a mobile phone to a centralized, secure socket layer encrypted digital ECG database on the Internet and is then available for evaluation at the investigators' discretion at a web address.

A total of 17 patients were diagnosed with AF by both methods. Intermittent handheld ECG recordings detected AF in 15 patients and 2 by 24 h continuous ECG. In three patients AF was diagnosed by both methods. Patients transmitted a mean of 59 (range 10–123) intermittent ECG recordings during 30 days. Out of those diagnosed with AF during follow-up, 2 (13%) patients had AF detected only on extra symptom activated registrations, and 13 (87%) of the patients had AF detected by scheduled recordings. A median of five (range 1–23) recordings during AF were transmitted per patient (mean 7.8) out of which 73% of the patients transmitted three or more AF recordings. All patients with more than one AF registration had at least on one occasion AF on sequential transmissions. For the final per protocol analysis, most included patients had suffered a TIA or minor stroke as reflected by the rather low NIHSS scores. Grave neurological deficit with resulting inability to handle the handheld ECG device was however not a major reason for exclusion from the study.

A significant difference in favour of the handheld ECG compared with the Holter ECG was shown ($P = 0.013$). The total prevalence of AF was 6.8% and increased to 11.8% in patients' $\geq$75 years. No AF was found in patients $<$65 years. These figures are used in our analyses.

Decision analytic model

Having AF means having a lifelong increased risk of stroke and other thromboembolic events, and so the costs and effects of AF and when detected, anticoagulation treatment, occur throughout the patient's lifetime. Therefore, a decision analytic model was used in this article to study the economic impact over a time horizon of 20 years.[14] Annual mortality risks and risks of thromboembolic events and complications due to anticoagulation treatments were applied in the model. The events and complications that can occur in the model are ischaemic, and haemorrhagic strokes, and major and minor bleeding. Ischaemic and haemorrhagic strokes cause lifelong costs and deterioration of quality of life. Other complications in the model are assumed to affect costs and quality of life only in the year in which they occur.

The short-term decision tree model is illustrated in the left part of *Figure 1*, analysing the screening procedure until the onset of anticoagulant treatment. Not all patients are eligible for anticoagulant treatment, the probability of getting treatment is denoted as pAnticoagulant. The second part of the decision model followed a Markov design. The model structure is illustrated in the right part of *Figure 1*. In such a model, the patient is always in one of the several specified states. The patients can move between the specified states annually with certain probabilities.

The states are defined according to whether the patient has detected AF or not. The ellipses illustrate health state, where the patients remain for at least one cycle, while the squares are events. Finally, patients may end up in the 'dead' state. Furthermore, all

events can occur annually. The model therefore represents the average of a large population.

Risks of events

Absolute risks of complications for patients with warfarin used in these calculations were taken from the RE-LY trial.[15] A sub-study from the RE-LY trial has presented risks of total stroke or systemic embolism, intracranial bleeding, and major bleeding divided by the background risk of stroke according to $CHADS_2$.[16] The corresponding risks for the patients not receiving warfarin were taken from a recent Swedish registry study.[17] *Table 1* presents the estimated absolute annual risks of complications arising from warfarin or no anticoagulant treatment that were used in the model.

As many patients have been shown to discontinue their warfarin treatment, we assumed that the discontinuation rate is 20% in the first year based on registers in Sweden, and we furthermore assumed that the discontinuation rate decreases by 30% annually, that is, another 14% of the patients discontinue during the second year and another 10% the third year, and so on.

Some of the silent AF would be detected within the following years and this was included in the modelling. The share of detected silent AF without screening was assumed to be 5% annually. Main parameters in the model are presented in *Table 2*.

Costs

All unit costs were adjusted to the price levels of 2013 and converted to Euros using the exchange rate of 31 December 2013 (1€ = 8.83 SEK).

Screening costs were based on actual costs in the clinical study that this analysis is based on minus costs that were related to initiating the study.[7] Inviting a patient to screening was estimated to cost €2.2, and the screening investigation was estimated to cost €108 including cardiological assessment. The Holter-ECG-based screening cost €471 per patient.

Ghatnekar *et al.*[20] estimated the cost of stroke in Sweden in 2009 using an incidence cost approach; the direct costs amounted to €58 066. This estimate included admission costs, re-stroke admission costs, outpatient costs, and costs for social services. These values, divided into annual costs, were used for the calculations of both ischaemic and haemorrhagic stroke in this study. Studies have found that the costs of stroke are higher for patients with a history of AF compared with patients without an AF history,[24,25] which makes our estimate of the stroke cost conservative.

Existing data on the cost of bleeding are poor, partly due to the difficulty of defining major and minor bleeding. On the basis of registry data, the average cost of major bleeding has been estimated to be €2711. A Canadian study estimated the cost of GI bleeding to be

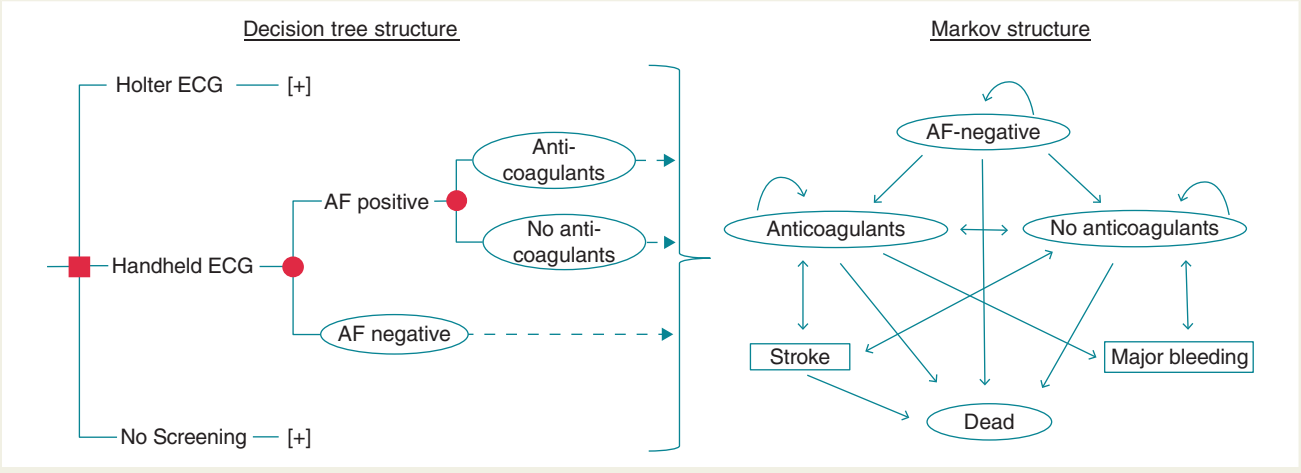

Figure 1 The structure of the decision analytic model: the first part follows a decision tree that represents the screening outcome. The second part consists of a Markov structure where patients' costs and effects are simulated for the analyzed horizon. Ellipses represent health states and squares represent events.

Table 1 Absolute annual risks for complications with warfarin or no anticoagulants for patients with AF in $CHADS_2$ 3–6

	Warfarin		No anticoagulants	
	Rate per patient year	Reference	Rate per patient year	Reference
Stroke or systemic embolism	2.73%	Oldgren *et al.*[16]	9.00%	Friberg *et al.*[17]
Intracranial bleeding	1.07%	Friberg *et al.*[17]	0.60%	Friberg *et al.*[17]
Major bleeding	4.60%	Oldgren *et al.*[16]	2.70% (all risk groups)	Friberg *et al.*[17]
Minor bleeding	16.37%	Connolly *et al.*[18]	7.10%	Assumption

Table 2 Main parameters in the model

Parameter	Estimate	Reference
Probabilities		
Prevalence of AF at 75 years of age after stroke/TIA	0.068	8
Screening handheld ECG		
Sensitivity	0.88	8
Specificity	1	Assumption
pAnticoagulants	0.85	Assumption
Screening 24 h Holter ECG		
Sensitivity	0.29	8
Specificity	1	Assumption
pAnticoagulants	0.85	Assumption
No screening		
pAF-positive	0	8
pAnticoagulants	0.85	Assumption
Annual incidence of AF		
75–79 years	0.015	19
80–84 years	0.021	19
85–years	0.018	19
Costs (€)		
Inviting a patient to screening	2.2	a
Screening investigation handheld ECG	108	a
Screening investigation Holter ECG	271	b
Warfarin treatment per year	757	1
Cost per monitoring visit (warfarin)	22	1
Stroke, admission costs	11 502	20
Stroke, outpatient costs, first year	3894	20
Stroke, outpatient costs, second year onwards	549	20
Stroke, social services costs, first year	3148	20
Stroke, social service costs, second year onwards	3875	20
Major bleeding	2704	21
QALY weights		
75–79 years with AF	0.76	22
80–84 years with AF	0.71	22
QALY weight decrement: ischaemic stroke	0.15	23
QALY weight decrement: hemorrhagic stroke	0.30	23

[a]Mats Palerius Zenicor Medical Systems AB (personal communication 10 October 2012).
[b]Purchasing costs for the Department of Cardiology, Linköping University Hospital, Sweden.

€3221, based on the cost of hospitalization and outpatient care. These estimates of bleeding costs were applied in this study.

Quality-adjusted life year weights and mortality rates

A study from Sweden used the EQ-5D instrument to estimate quality-adjusted life-year (QALY) weights for various ages in Sweden.[26] These QALY weights were used as a basis for the patients in the model. Reductions in the QALY weights were made for stroke.[23] The model uses age-based standard mortality for Sweden in 2010 according to data from Statistics Sweden.[27] Increased mortality due to stroke is modelled using the results of a study by Henriksson *et al.*,[28] which presented the stroke-associated mortality rates in Sweden based on data from the national stroke register; stroke patients with $CHADS_2$ scores of 3–6 had a mortality rate of 39.2%, which was used for the first year after the stroke, and standard mortality rates were used thereafter.[27] This is a conservative assumption, as long-term survival for patients who have had a stroke likely is lower than for patients with no history of stroke.

Analyses

The analyses were undertaken for a cohort of 75-year-old patients with a recent stroke, followed for 20 years, and being screened for silent AF or not. A vast majority of the patients are assumed to have died during this time. The effects were measured in a number of prevented strokes, number of life-years gained, and number of QALYs gained. Both costs and effects (life-years and QALYs) were discounted by 3% annually.[11] One screening intervention was considered dominant when it costs less and was more effective than its comparator. To analyse how different assumptions and simplifications in the base-case analysis affect the results, nine one-way sensitivity analyses were performed where key assumptions were varied.

Results

The analysis showed that continuous 24 h Holter ECG recording was dominated by handheld ECG, due to its lower sensitivity and higher costs (€4 255 000/1000 screened patients). Continuous 24 h ECG screening was therefore excluded in the analyses, due to simple dominance.

The base-case cost-effectiveness analysis therefore includes handheld ECG screening compared with no screening. The implementation of the handheld ECG screening programme on 1000 patients resulted in 11 avoided strokes and the gain of 29 life-years or 23 QALYs.

The total costs were lower for the handheld ECG-screened patients (€ −53 600), which also makes the screening programme dominant compared with the no screening alternative. The results are summarized in *Table 3*. The costs over time were higher for the first year in the screening group due to the screening procedure's upfront cost. *Figure 2A* illustrates the cumulative AF-related total cost of 1000 patients with recent stroke undergoing AF screening with handheld ECG or 24 h Holter ECG compared with no screening. After 7 years, the screening program with handheld ECG would become cost saving. The 24 h Holter-ECG screening programme would never become cost saving.

The screening would identify silent AF in stroke patients during the first month. However, during the years after the screening new patients would develop AF, and some of them would be detected clinically, in both the screening and the non-screening groups. *Figure 2B* illustrates the modelled number of identified AF patients in the screening and non-screening groups during their remaining lives, and how the difference in detected AF would decline over time after the screening event. As only living patients are included, all figures decrease during the last years of the modelling.

Table 3 **Cost-effectiveness of screening compared with no screening, costs, and effects calculated for 1000 screened patients**

	Costs €	Number of strokes	Life years	QALY	Cost per life year gained	Cost per QALY gained
No screening	4 020 000	143	9528	6435	–	–
Holter ECG	4 255 000	140	9537	6442	–	–
Handheld ECG	3 976 000	133	9557	6458	Dominant	Dominant

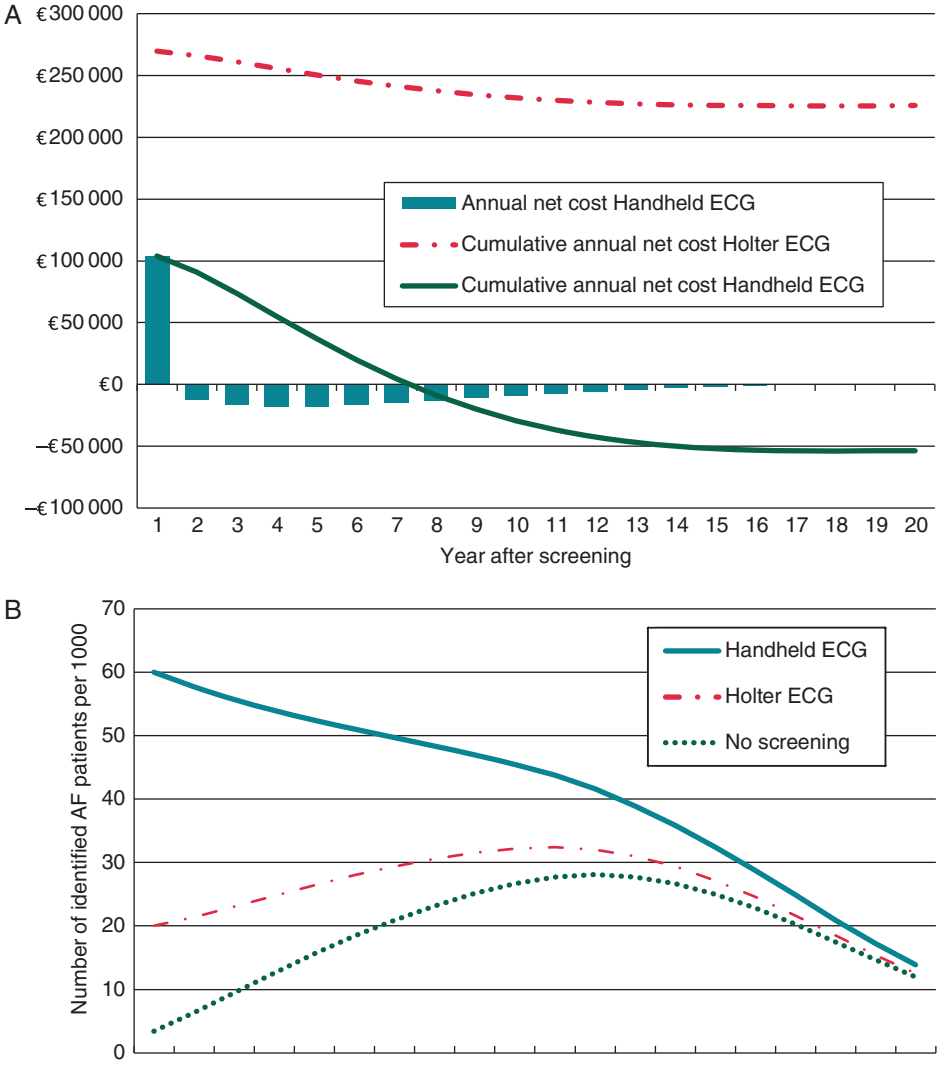

Figure 2 (*A*) Cumulative AF-related net cost in Euros of 1000 patients with recent stroke undergoing AF screening with handheld ECG or Holter ECG compared with no screening. The bars represent annual net cost of handheld ECG compared with no screening. After 7 years, the handheld-ECG strategy becomes cost saving. (*B*) The number of identified AF patients per 1000 patient in the screening and the non-screening groups during 20 years after screening.

Sensitivity analyses

Table 4 presents one-way sensitivity analyses of alternative scenarios. One of the assumptions in the base-case analysis was that 85% of the detected patients received anticoagulant treatment. Changing the assumption to 50% the screening was not cost saving, anymore, but still cost-effective. If the warfarin treatment discontinuation rate was 10% instead of 20%, the cost savings were higher. The cost of the screening procedure was estimated to be €108, when this cost

Table 4 One-way sensitivity analyses of cost-effectiveness for screening with handheld ECG compared with no screening (€)

	Cost per QALY gained €
Base case	Dominant
Rate of detected AF receiving warfarin 100%	Dominant
Rate of detected AF receiving warfarin 50%	1600
Warfarin treatment discontinuation rate 10%	Dominant
Cost of screening: €50	Dominant
Cost of screening: €220	2600
Time horizon 5 years	4900
Time horizon 10 years	Dominant
Discounting rate 0%	Dominant
Discounting rate 5%	Dominant

was raised to €220, the screening was not cost saving, anymore, and the cost per QALY was estimated to be €2600, which still is considered as a low cost per QALY. If the time horizon of the analysis was reduced to 5 years, the cost per QALY was estimated to be €6400.

Discussion

A general problem with the cost-effectiveness of screening programmes is that they seldom are shown to be good value for money. In fact, cost savings that result from screening programmes have been hard to determine.[29] There are several reasons for this, such as, high upfront costs for the screening intervention, low sensitivity or/and specificity of the screening technology, low incidence of the disease, or lack of an effective treatment. In a health care system with scarce resources and an unappeasable demand for health care, screening programmes are often regarded with sound skepticism.

This study investigated the value of screening recent stroke patients for silent AF by handheld ECG recordings, using a decision analytic model to estimate the cost-effectiveness. Our results show that screening in this case is highly cost-effective. After 7 years, it is even cost saving. The explanation for this is a relatively low-cost screening technology in combination with a high-risk target population and effective and cost-effective treatments.

We did not find any other economic evaluation of screening for silent AF in stroke patients. Our results can be compared with other studies estimating the cost-effectiveness of AF screening programmes. Hobbs *et al.* calculated in 2005 the cost-effectiveness of systematic or opportunistic screening (targeted and total population screening) using 12-lead, pulse-taking lead II rhythm strip from standard ECG limb, or leads alone and single-lead thoracic placement ECG, vs. routine practice for the detection of AF in people aged ≥65, that is, for people not suffering from stroke. The cost per detected AF was estimated to be £337 with opportunistic screening, which dominated systematic screening.[30]

Compared with other screening programmes of cardiovascular diseases, our study is the only one that shows cost savings, for example, computed tomography screening for coronary artery calcium in asymptomatic individuals was estimated to be $33 000/QALY,[31] neonatal ECG screening for the long QT syndrome to be €5400/life year gained,[32] and blood pressure in adolescents to be $18 000/QALY for boys and $47 000/QALY for girls.[33]

Screening for AF can be conducted both for secondary prevention, as this study is based on, and for primary stroke prevention.[34] For primary prevention, the most common form is one point opportunistic screening yielding a mean prevalence of 1% of previously undiagnosed AF in unselected age cohorts and 1.4% in cohorts over the age of 65.[35] The primary reason for one-point opportunistic screening is the difficulty of recruiting the general public who, in the majority of cases, are asymptomatic, and therefore difficult to motivate to participate in more elaborate screening programmes. As Hobbs *et al.* also concluded, systematic screening did not yield more new AF diagnoses compared with opportunistic screening in an GP setting.[30] A recent study performed by Lowres *et al.* used a similar technology,[36] where patients visiting pharmacies were asked to perform rhythm recordings, using an iPhone application yielding a similar prevalence of newly detected AF as other studies. This study exemplifies how novel, user friendly, technology can be applied to AF screening. In secondary prevention screening for AF, patients who have suffered an ischaemic stroke are more likely to be motivated for screening. This is also a group of patients with higher likelihood of AF motivating a more elaborate screening approach. A recent meta-analysis of studies aimed at the detection of previously unknown AF in stroke patients[37] using extended ECG monitoring by Holter recordings and cardiac event recorders up to 1 week have yielded numbers of up to 12.5% newly detected AF in unselected stroke patient cohorts compared with 6.2% newly detected AF episodes using 24–48 h Holter recordings proving the benefit of extended monitoring.[6] In the study that this economic analysis is based on, it was shown that intermittent ECG recordings over an extended time period is superior compared with short continuous cardiac rhythm monitoring in detecting AF, a finding consistent with findings of the other similar studies. It is however of interest that the numbers of newly detected AF were similar to the NIHSS scores were quite low in this study. As the method is user friendly, it is suitable for primary screening as observed by Lowres *et al.* Whether the approach of intermittent ECG monitoring over an extended time period can be applied for primary screening has to be established. In an ongoing Swedish study, patients aged 75 to 76 without known AF are screened using the handheld ECG recorder for 30 s in mornings and evenings during 2 weeks to evaluate the yield of newly detected AF and if this may reduce the number of strokes in the cohort and be cost-effective.[38] Invasive cardiac devices such as the Iimplantable loop recorder is likely to be the most reliable method of screening for arrhythmias but implies high up-front costs and therefore not suitable for screening in general. Novel non-invasive technologies such as the handheld recording device are therefore of interest for screening purposes, as they allow for prolonged screening of patients with minimal inconvenience for the patient. Another such modality is the patch that is applied to the patients' skin with the ability to monitor the heart rhythm for 2 weeks.[39]

The calculations in our study have limitations. They are based on one single study of a Swedish cohort. Current AF consensus statements and guidelines deem AF episodes of ≥30 s to be clinically relevant.[40] It was not possible to achieve recordings of this duration in the underlying study, due to technical limitations pertaining to the intermittent ECG device, which makes an assessment of the actual AF duration not possible and may further raise suspicion of AF oversensing. In contrast, the median number of registered AF episodes per patient was five, and often seen on subsequent registrations, which adds strength to the diagnosis by the number of registrations. Our per protocol analysis approach caused some excessive exclusion of patients, which may raise questions of generalizability of the method. However, this was deemed necessary to enable a comparison between the two investigated methods. Exemplifying this failed Holter recording was as much a reason for exclusion as was inability to use the handheld device. It is therefore plausible that in a real-life scenario, the handheld device would be an alternative in a far larger scale than in this study. We have estimated the cost-effectiveness of silent AF screening on 75-year-old stroke patients. In reality, stroke events hit patients at different ages, where younger patients have lower probability of having AF, but more remaining years to live, while older patients have higher likelihood of AF, but shorter life expectancy. We believe our estimation is valid as a proxy for a wide range of ages (such as 65–85 years), as the fact that the patients had already a stroke overrules other risk factors. We have made model parameter assumptions that we have tested in sensitivity analyses. If the time horizon of the study had been limited to 5 years, the screening programme would no longer be cost saving. Do health care systems have the patience for a 7-year time perspective? Otherwise, the 5-year cost-effectiveness ratio of €7900/QALY is also advantageous. It is, however, important to note that the first year will incur higher costs, due to the implementation of the screening program. No probabilistic sensitivity analysis was performed in this study, as we did not have complete data about the uncertainty intervals for several important parameters such as test specificity and relative risk between warfarin and no treatment. A probabilistic analysis may provide a false picture of the result. In this case, it is more valuable for a decision maker to use one-way sensitivity analyses, where important assumptions are varied.

There are still unanswered questions concerning the cost-effectiveness of silent AF screening using the handheld ECG. We have seen that the number of cases of detected AF declines over time, therefore, one should analyse whether the screening should be repeated. Another important remaining issue is the cost-effectiveness of using the handheld ECG for broader, population-based screening of persons not suffering from stroke. The risks will in that case be lower, and the costs higher.

Conclusions

This study suggests that silent AF screening by intermittent ECG recordings in 75-year-old patients with a recent ischaemic stroke is a cost-effective use of health care resources, saving costs extending lives, and improving the quality of life.

Conflict of interest: L-A.L. reports economic support for lecturing, advisory boards, and research from AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer, St Jude Medicals. Dr Sobocinski Doliwa and Mr Husberg: none declared. V.F. reports lecture fees from AstraZeneca, consultant fees from Boehringer Ingelheim, and conducted research studies in collaboration with AstraZeneca, Sanofi Aventis, Guidant, Medtronic, and St Jude Medical. L.F. reports economic support for research, lecturing, and advisory boards from Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Pfizer, and Sanofi-Aventis. M.R. reports economic support for lecturing, advisory board, and research from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Pfizer, Sanofi, Medtronic, Zenicor, Nycomed, and St Jude Medical. T.D. reports lecture fees from Boehringer Ingelheim.

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