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CLINICAL RESEARCH

Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands

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Aims Atrial fibrillation (AF) is the most common arrhythmia and prevalence increases with age. Patients with AF have a high risk of stroke, and screening for AF is recommended in all people aged 65 years or older to identify patients eligible for stroke prevention. A handheld, single-lead electrocardiogram (ECG) device can be used for systematic screening in the population at risk. The objective of this study is to estimate the cost-effectiveness of screening for AF in primary care with the MyDiagnostick® during seasonal influenza vaccination in the Netherlands.

Methods and results Lifetime costs and effects of a single screening session for AF detection were assessed from a societal perspective with a decision analytic model consisting of a straightforward decision tree and a joining Markov model. The decision model simulated all patients aged 65 years and over attending the seasonal influenza vaccination in the Netherlands. Event probabilities were derived from clinical trials. Sensitivity analyses were performed to assess the impact of important model assumptions as well as determining the relative effect of individual parameters. Screening for AF with the MyDiagnostick® in all patients older than 65 years that attend seasonal influenza vaccination in the Netherlands would decrease the overall costs by €764 and increase the quality-adjusted life-years (QALYs) by 0.27 years per patient. Early detection of AF would prevent strokes and leads to beneficial health effects with subsequent cost savings. This screening method would have an estimated probability of 99.8% for being cost-effective at a conservative willingness-to-pay of €20 000/QALY.

Conclusion Screening for AF in primary care with a handheld, single-lead ECG during seasonal influenza vaccination is very likely to be cost saving for identifying new cases of AF in the Dutch population aged 65 years and over. Active screening for AF with a single-lead, handheld ECG device during seasonal influenza vaccination could be implemented in primary care.

Keywords Atrial fibrillation • Screening • Primary care • Single-lead ECG • Stroke prevention • Cost-effectiveness • Health economic modelling

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence of 1.5–2.0% in the general population, increasing with age up to 5.9% above 65 and 8.8% in those aged 80 years or older.[1,2] Patients with AF have a five-fold higher risk for stroke.[3] A prevailing arrhythmia is unknown in almost 30–50% of the patients who are admitted with an ischaemic stroke (IS).[4,5] Screening for AF, as recommended by the European Society of Cardiology (ESC), in combination with the CHA_2DS_2-VASc score can help to identify patients

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What's new?

- A straightforward decision analytic model can be used to assess the cost-effectiveness of population-based screening for atrial fibrillation (AF) with a handheld, single-lead electrocardiogram (ECG) device.
- Screening for AF in primary care with a handheld, single-lead ECG during seasonal influenza vaccination is very likely to be cost saving for identifying new cases.
- Active screening for AF with a single-lead, handheld ECG device during seasonal influenza vaccination could be implemented in primary care.

who are eligible for stroke prevention irrespective of the occurrence of symptoms.[6–8] Anticoagulation prevents IS by at least 60% and mortality by at least 25%, with non-vitamin K antagonist oral anticoagulants (NOACs) having non-inferior efficacy compared with vitamin K antagonists (VKAs).[9,10]

The seasonal influenza vaccination session in primary care provides an ideal setting for systematic screening, since participants are at an increased risk for AF because risk factors for AF overlap with indications for seasonal influenza vaccination, e.g. the age group (≥65 years) and co-morbidity such as diabetes, ischaemic heart disease, and heart failure.[11] A recent pilot study demonstrated the feasibility of AF screening with an innovative handheld, single-lead electrocardiogram (ECG) device called the MyDiagnostick® during seasonal flu vaccination.[12] The MyDiagnostick® is a validated, easy-to-apply device that registers and automatically analyses a single-lead I ECG rhythm strip after holding the device with both hands for 1 min. It signals a red light in case of rhythm irregularity suspicious for AF and a green light in case of absence of AF. The ECG rhythm strip can be visualized and analysed by linking the device to a computer.[13] In this pilot study, silent AF was detected in 1.3% of the screened population aged ≥65 years and anticoagulation was indicated for all of these patients.[12] Screening for AF based on the yield of screening seemed feasible; however, the question remained whether the costs of screening could outweigh the resulting beneficial effects. Cost-effectiveness studies on AF screening so far assumed newly detected cases ranging from 1% (SAFE study) up to 3% (STROKESTOP study). Incremental cost-effectiveness ratios (ICERs) for AF screening in these studies ranged from £337 per additional case detected up to €4313 per quality-adjusted life-year (QALY) gained.[14–16]

The objective of this study is to estimate the cost-effectiveness of screening for AF in those aged at least 65 years in primary care with the MyDiagnostick® during seasonal influenza vaccination in the Netherlands using a decision analytic model.

Methods

Design and setting

A static, decision analytic model was used to study the economic impact of a single screening session over a lifetime horizon. The patient population in the model was based on the newly detected AF cases of the previous conducted pilot study where patients were screened for AF with the MyDiagnostick® during seasonal influenza vaccination.[12] A short decision tree (*Figure 1*) described the screening procedure and served as the input for the Markov model (see Supplementary material online, *Figure S1*). The decision tree started with a hypothetical cohort of all people aged ≥65 years in the Netherlands, a total population of 2 919 000 persons in 2014. Subsequently, people attending the seasonal influenza vaccination programme were included in the analyses. The vaccination coverage in the population aged ≥65 years with or without a medical indication was 66.9%. Atrial fibrillation was newly detected in 1.3% of the hypothetical screened population that attended the seasonal influenza vaccination.[12] In the base-case scenario, we assumed that 3% of the undetected AF patients would be detected in routine practice per year. The average age of individuals aged 65 years and older with newly detected AF was 77.4 years with a mean CHA_2DS_2-VASc score of 3.7.

Patients with newly diagnosed AF were followed in 3-month cycles lifelong or until death using a Markov model approach. In the base case, anticoagulation therapy with an NOAC (apixaban, dabigatran, or rivaroxaban equally distributed) or dose-adjusted VKA with a target international normalized ratio (INR) of 2.0–3.0 was compared with no treatment. The NOAC/VKA ratio was 50%/50% in the base case. Patient preference for an anticoagulant was 85% in the base case. A patient preference of 85% was based on unpublished data from the pilot study and anticoagulant persistence after 1 year found in literature. We assumed that the treatment discontinuation rate was 20% in the first year with a 30% decrease annually. The efficacy and adherence were assumed to remain constant over time. The following health states were included in the base case: stable AF, IS (minor, major, or fatal), intracranial haemorrhage (ICH; minor, major, or fatal), myocardial infarction (MI), systemic embolism (SE), gastrointestinal (GI) haemorrhage, and death-by-age. All major extracranial haemorrhages were assumed to be a GI haemorrhage. All patients who experienced an event moved to a matching post-event phase after one cycle of 3 months. Costs and effects were reflected in a societal perspective but productivity losses were not taken into account owing to the high age of the patients. The model was developed in Microsoft Excel 2010 software (Microsoft® Inc.). Health gains were discounted by 1.5%; all unit costs were converted to costs for 2014 by correcting for inflation (factor 1.035) and discounted by 4%. All event probabilities, utilities, costs, and remainder model input including their references are listed in the Supplementary material online, *Table S1*.

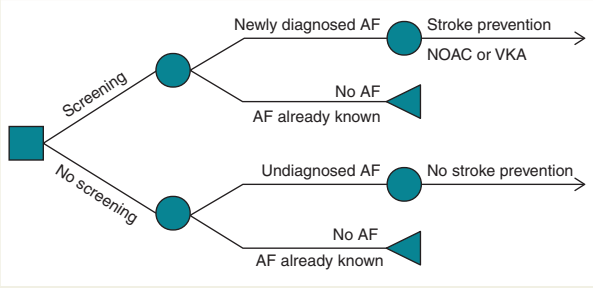

Figure 1 Short decision tree representing AF screening outcome. A total of 1 952 811 patients enter the decision tree, which is 66.9% of the total population of 65 years or older in the Netherlands. In all screened patients, 6.5% has a positive ECG and 1.3% has newly detected AF. The decision tree output was used as input for the Markov model. A schematic representation of the Markov structure can be found in the Supplementary material online, *Figure S1*.

Event probabilities

The risks of clinical events for NOACs and VKA (warfarin) were based on combined clinical trial data from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), and ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). The combined event rates for VKA and NOACs were calculated as weighted means from the trials. The event rate for SE was based on the event rate percentage/year and relative risk in ARISTOTLE since the other trials did not report this specific event. Minor IS were all events classified minor or non-disabling (40.6 vs. 50.6% base case), IS major were all events classified major or disabling (37.1 vs. 39.2% base case), and IS fatal were all events leading to death (22.3 vs. 10.2% base case). For ICH, 17.0% of the events were considered minor, 41% major, and 42% fatal. The severity of ICH was assumed to be equal in the base case. The clinical events for patients with AF without stroke prevention were based on relative risks compared with warfarin. The mortality rate for the simulated population was adjusted for age by increasing the age-specific mortality rate during a patient's lifetime, starting at 75 years. The mortality rate was 3.7 times higher after an ischaemic event or ICH; after a MI, the age-related mortality was 1.051 times higher.

Utilities

The majority of baseline patient utilities and disutilities were calculated on the basis of EQ-5D scores matching the International Classification of Diseases (ICD) codes of the specific clinical events. Anticoagulant therapy disutility was applied for NOACs and VKAs, assuming that the disutility was comparable for both treatments. The utilities for IS and ICH were based on a non-randomized controlled cluster trial, which explored the medical costs concerning stroke services. Quality of life for IS and ICH was measured at hospital discharge and 6 months after the event occurred, subdivided based on modified Rankin Scales (mRS) of 0–1, 2–3, 4, and 5. The utilities from the trial were recalculated for a pharmaco-economic evaluation of rivaroxaban. For IS, the utilities were based on two categories: mRS 1–2 (minor) and 3–5 (major). For ICH, a weighted average was calculated between the mRS scores based on frequency. A higher disutility was allocated to the first cycle of IS and ICH; after the first cycle all patients moved to the post-event phase with matching utility. The utility of major GI haemorrhage was based on the assumption that a temporary utility of 0.8 applied during 1 week. Minor haemorrhage had no disutility.

Costs

Screening costs for AF consisted of costs for the MyDiagnostick®, primary care costs, and costs for the evaluation of the ECGs of positive MyDiagnostick® results, including false-positive results and newly diagnosed AF patients. The costs for the ECG device were based on one device for every general practitioner (GP) practice in the Netherlands and amortized over a 3-year period. The costs were also calculated if every GP would get their own ECG device. Personnel costs were an estimation based on the hour tariff and the number of hours needed for the total screening programme. In the primary care costs, we assumed that nurses would perform the screening. Costs of a cardiologist were included, meaning cardiologist costs for evaluating all positive MyDiagnostick® readings suspicious for AF (6.5% with red signal).

Drug costs for NOACs and VKAs were based on total costs as presented by the Dutch Care Institute (see Supplementary material online, *Table S1*). The ratio of the NOACs (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) was assumed to be equally distributed. International normalized ratio monitoring costs were based on average costs per patient per year with no differentiation for the frequency of INR monitoring. For the NOAC users, we included the costs of an annual GP visit with the measurement of renal function.

The costs for IS and ICH are described in Supplementary material online, *Table S1*. The same underlying calculation based on the severity of the event applied for the costs as mentioned for the utilities of the IS and ICH states. Higher costs were applied to the acute IS and ICH; after the first cycle, all patients moved to the post-event phase with matching costs. Costs for fatal IS and fatal ICH were applied separately; costs of fatal IS were derived from a study evaluating cost-effectiveness of treatment with statins in the prevention of coronary heart disease. The costs for SE are based on the assumption that 50% of the patients do not need intensive treatment; the costs are an average of the lowest and highest costs as defined by the Dutch Health Authority (NZA). The costs for acute MI are the mean treatment costs, non-differentiating for type of MI and type of intervention applied. Costs for minor ECH were based on one emergency room (ER) visit; costs for major ECH were based on treatment costs for a GI haemorrhage. For both minor and major ECH, it was assumed that full recovery occurred within 3 months.

Sensitivity analysis

A series of univariate sensitivity analysis were performed to assess the impact of important model assumptions as well as determining the relative effect of individual parameters. The effect of costs was assessed by taking 50% of the mean value as the lower value and 200% of the mean value as the upper value. The total costs for screening were explored with plausible variations in key assumptions. The event probabilities of IS (minor, major, or fatal) and ICH (non-fatal or fatal) were varied in the base and case at the same time, with the calculation of the lower and upper being the same as for the costs. The model was designed to estimate the uncertainty surrounding the cost-effectiveness results by using probabilistic sensitivity analysis (PSA). All model parameters, except for total screening costs, were varied over plausible ranges mainly based on their statistical distribution [95% confidence interval (95% CI)]. Event probabilities and utilities were assumed to have β distributions; costs were assumed to have γ distributions. The sensitivity analyses were also used to consider the broader issue of the generalizability of the results.

Results

Base case

Compared with no screening, screened patients who were newly diagnosed with AF and treated with an NOAC or VKA over lifetime horizon experienced fewer IS (minor, major, or fatal), MI, and SE but more ICH (non-fatal or fatal), GI haemorrhage, and minor haemorrhage. Total events that occurred are summarized in *Table 1*. Compared with no screening, screening provided an additional 0.27 QALYs with cost savings of €764 per patient. Undiscounted, screening provided an additional 0.32 QALYs with cost savings of €216 per patient (*Table 2*). Total costs of screening for AF were €8 152 835, with 5068 participating GP offices receiving one MyDiagnostick® per office. Screening of the 1 952 811 patients will yield 25 387 new cases with screen-detected AF. Total screening costs per newly detected AF patients were €321 and €4.17 per patient screened independent of AF detection.

Sensitivity analysis

Total costs of screening for AF would be €8 812 458 if every independent GP received a device. Variation in total screening costs was based on variance in costs per single-lead ECG, GP costs, and number

Table 1 Total number of events in the base-case scenario over lifetime horizon in 25 387 patients

	Total events	
	No screening	Screening
Ischaemic stroke minor	1775	1172
Ischaemic stroke major	1605	954
Fatal ischaemic stroke	952	478
Myocardial infarction	3413	1945
Systemic embolism	194	149
Intracranial haemorrhage	194	292
Fatal intracranial haemorrhage	141	211
Gastrointestinal haemorrhage (major)	737	947
Minor haemorrhage	9751	12 880

Table 2 Model results: total costs per patient, QALYs per patient with AF, and ICER over lifetime horizon in 25 387 patients

	Base case		
	Total costs	QALYs	ICER
No screening	€12 554.08	7.75	Dominant
Screening	€11 790.33	8.02	

of ECGs to be evaluated. General practitioner costs had the largest share in total costs. The screening costs had a lower value of €5 696 955 and a higher value of €20 204 427 with resulting total costs saving of €860 and €289 per patient, respectively, for the base-case scenario.

Univariate sensitivity analyses were conducted for yield of screening, patient preference on anticoagulation, AF detection in general practice, percentage of NOAC vs. VKA users, costs for IS/ICH/GI haemorrhage, event probabilities of IS/ICH, and costs for NOACs and VKAs to determine the impact on the results of the model (*Figure 2*). Costs of IS were of particular influence with the upper limit, leading to a more dominant ICER with a reduction in costs of €3764 per patient over a lifetime horizon compared with mean IS costs. With half of the mean costs for all IS events, the screening was not cost saving anymore, but still cost-effective at a willingness-to-pay (WTP) threshold of €20 000 per QALY gained. Variation in the event probabilities of IS did not influence the probability of AF screening being cost-effective. Higher costs for NOACs and a higher ratio of NOAC users also had a negative influence on the ICER. When costs for NOACs would be €471 instead of €235 per 3 months, this lead to a cost increase of €2257 per patient over lifetime horizon, making total cost €1493 per patient compared with no treatment. Assuming all patients would be using NOACs, the costs and effects were dominant. A patient preference of 70% for initiating anticoagulant treatment after AF detection leads to a cost increase of €187 and QALY loss of 0.05 per patient compared with 85% patient preference over lifetime horizon. Atrial fibrillation screening was cost saving with this lower patient preference. The yield of screening was of marginal influence.

Figure 3 presents the results of the PSA comparing the joint distribution of costs and QALYs after 10 000 simulations. The PSA showed that ICERs for screening for AF are below a WTP threshold of €20 000 per QALY gained in 99.8% of the simulations (*Figure 3*). Screening for AF was cost saving in 61.9% of the simulations. Mean cost savings in the Monte Carlo simulation with 10 000 simulations were €381 (95% CI −€4142 to €2834) per newly detected AF patient, and mean QALYs were 0.27 (95% CI 0.22–0.71) per newly detected AF patient when comparing screening vs. no screening.

Discussion

This study evaluated the cost-effectiveness of screening for AF in patients aged 65 years and older during seasonal influenza vaccination, using a handheld, single-lead ECG device. Screening for AF would decrease the overall costs by €764 and increase the QALYs by 0.27 years per patient over lifetime horizon. These results were sensitive to variability in a number of parameters, predominantly the costs associated with IS, the costs for NOACs, and the ratio of patients using an NOAC for stroke prevention. Cost-effectiveness of screening programmes is scarcely shown to be worth the investment relative to the benefits. One of the reasons is the high upfront costs that are associated with systematic, population-based screening. Early detection of AF can help identify patients who are eligible for anticoagulation irrespective of the occurrence of symptoms and thus reduce high future costs associated with stroke. Screening for AF with MyDiagnostick® in all patients of at least 65 years who attend seasonal influenza vaccination in the Netherlands would have a probability of being cost saving in 61.9% of the time (less costly and more efficacious) with a probability of being cost-effective of 99.8% at a conservative WTP of €20 000/QALY.[17] By linking AF screening to the seasonal influenza vaccination and assuming all patients attending the vaccination will be screened for AF, we indirectly assume an uptake rate of 66.9% for AF screening in the 'intention to treat' population. The univariate sensitivity analyses demonstrated the robustness of the outcome and did not identify any parameters with a negative influence on the probability of being cost-effective.

The yield of screening was assumed to be 1.3% based on the previously conducted pilot study.[12] The sensitivity analysis showed that the variation in detection of new AF cases was of minor influence on the cost-effectiveness. Asymptomatic AF detection during routine practice (i.e. without screening) was based on the randomized controlled trial of Fitzmaurice and calculated into a 3-month probability relative to the yield of screening of 1.3% in the pilot study.[14] Detection in general practice was assumed 3% of the asymptomatic AF patients; in the sensitivity analysis, we explored the effect of 1 and 5% detection based on the assumption made in cost-effectiveness analyses of the STROKESTOP study and the SAFE study.[15,16] A higher or lower detection rate of asymptomatic AF in general practice had only minor influence on the costs and benefits and did not influence the probability of cost-effectiveness with AF screening.

To our knowledge, this health-economic analysis is the first to evaluate preventive AF screening with a single-lead ECG device using a straightforward Markov model approach that includes stroke

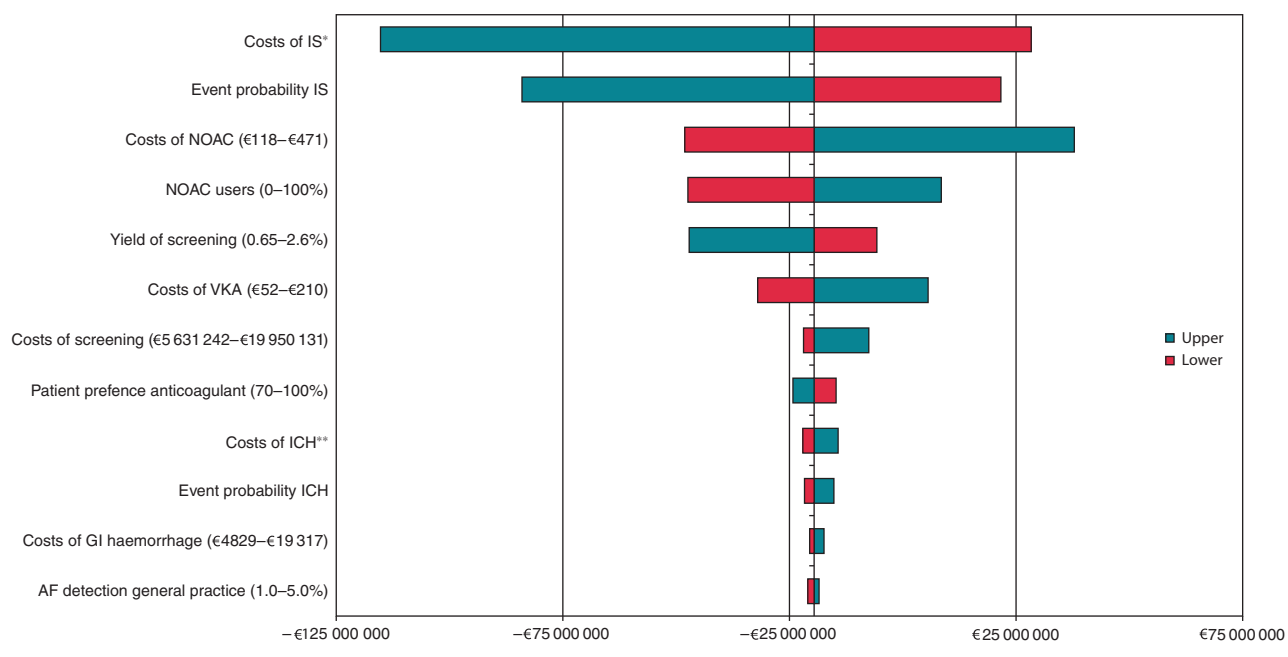

Figure 2 Tornado diagram representing the incremental costs expected from a lower and upper value for each variable in the univariate sensitivity analyses. The incremental effects (QALYs) were >0 within the explored ranges in all scenarios. For IS and ICH, base and case probabilities for minor, major, and fatal events were varied at the same time. The vertical line represent the mean incremental costs of −€19 388 935. *Acute minor (€9537–€38 293); post minor (€742–€2968); acute major (€22 069–€88 275); post major (€1979–€7915); fatal (€5589–€22356). **Acute (€12 146–€48 585); post (€846–€3382); fatal (€3019–€12 074). Lower values of event probabilities were half the mean value; upper values were twice the mean value. The event probabilities used in the sensitivity analysis can be found in the Supplementary material online, *Table S1*.

Figure 3 Incremental cost-effectiveness plane showing 10 000 Monte Carlo estimates of incremental costs per patient and benefits per patient of AF screening compared with no screening. Points falling above the dotted line have an ICER >€20000 per QALY gained. Atrial fibrillation screening was found to be cost-effective strategy (less costly, more effective) in 99.8% of the simulations. Screening for AF was cost saving in 61.9% of the simulations.

prevention. Hobbs *et al*. conducted a discrete event simulation (DES) approach to explore the cost-effectiveness of screening strategies and subsequent treatment decision. They found systematic population screening to result in 27 cases detected at a cost of £48 260; £1787 per additional case detected were compared with no screening using a 12-lead ECG.[16] Our study found the costs of systematic AF screening to be lower, with €321 per newly detected AF case. One cause of the difference in costs per newly detected AF case presumably lies in the ECG method used; our single-lead ECG device with automated rhythm irregularity detection is less costly than a full 12-lead ECG. Desteghe *et al*. reported that the costs of screening for AF with the MyDiagnostick® were €134 and €293 per newly detected AF patient at the geriatric ward and cardiology ward, respectively, when using the algorithm. When a physician also reviewed all ECG results regardless of AF detection, the costs were €200 and €681, respectively, per newly detected AF patient.[18] In our scenario, because of a sensitivity of 100%, only the positive MyDiagnostick® readings suspicious for AF were reviewed to confirm the diagnosis. On the basis of a 65-year-old male cohort, Hobbs *et al*. calculated that opportunistic screening with a single lead had mean costs of £6719 and 10.4250 QALYs compared with £6756 and 10.4153 QALYs in the 'no screening' scenario with approximately 12 ISs averted and 2.5 haemorrhagic strokes caused (500 000 patients).[16] This would mean costs savings of €37 per patient with 0.0097 QALYs gained per patient. Non-vitamin K antagonist oral anticoagulants for stroke prevention were not incorporated into the model of Hobbs *et al*.; incorporation would have additional beneficial effect but also higher costs. Our results found AF screening to be more cost-effective, with more IS events averted but more ICH events caused. Levin *et al*. estimated the cost-effectiveness of screening for silent AF after IS using a handheld ECG. This study assessed that the implementation of a AF screening programme on 1000 patients with recent stroke over a 20-year period resulted in 23 QALYs gained and cost savings of €55 400 compared with no screening.[19]

Limitations of study

The event probabilities for stroke prevention were derived from three studies (ARISTOTLE, RE-LY, and ROCKET AF) with a relatively short follow-up period. One limitation is that we extrapolated these results to a lifetime horizon, assuming the effect would remain constant over time. It is nevertheless possible that adverse events would be higher with a longer follow-up. The disadvantage of using clinical trial data is that they do not always reflect real-life efficacy and safety, e.g. by superior adherence and a more complete follow-up. A second limitation is the external validity of the patient characteristics of the clinical trials compared with the characteristics of the population to be screened. The clinical trials had an average age somewhat lower than the screen-detected AF population in the pilot study (70–73 years compared with 77.4 years old), and the stroke risk was comparable in the pilot study with an average CHA_2DS_2-VASc of 3.7. We used a straightforward, static Markov model that did not correct for any changes in the $CHADS_2$ score during a patient's lifetime. A limitation of our model is an expected underestimation of the total events occurred, mainly IS, and is thus an underestimation of the event-associated costs. The event probabilities derived from the clinical studies are somewhat conservative for the population being evaluated. In our univariate sensitivity analysis, we explored the effect of the event probability of IS, which indirectly represents the effect of lower and higher $CHADS_2$ scores in the population. A lower or higher stroke risk did not influence the cost-effectiveness. We indirectly explored the effect of higher event probabilities in the PSA and did not find any major influence on the cost-effectiveness. Also, the higher occurrence of events would affect the base as well as the case group and would probably not affect the overall probability of AF screening being cost-effective. We discourse that our conservative approach represents the minimal cost savings with associated benefits and that it is an accurate approximation of the costs and benefits resulting from AF screening.

Stroke risk and eligibility for stroke prevention in screen-detected AF patients were based on CHA_2DS_2-VASc score according to guidelines nowadays.[6] It is debatable whether it is reasonable to apply this risk assessment on screen-detected AF patients because this method is mainly based on research performed in AF detected in usual care. Two studies showed that asymptomatic AF patients did not significantly differ from symptomatic patients on mortality rate and major events (death, disabling stroke, major haemorrhage) and even have increased risk for IS (hazard ratio 1.8, 95% CI 1.0–3.8).[7,8] The absence of symptoms does not necessarily imply a more favourable prognosis. The thromboembolic risk appears not to be affected by the asymptomatic status of an AF patient, and the clinical status should therefore not determine the stroke prevention approach.[20]

Conclusions

In conclusion, with the use of a decision analytic model, we demonstrated that screening for AF in primary care with a handheld, single-lead ECG device during seasonal influenza vaccination is very likely to be cost saving for identifying new cases of AF with subsequent introduction of stroke prevention in the Dutch population aged 65 years and over. Active screening for AF with a single-lead, handheld ECG device during seasonal influenza vaccination could be implemented in primary care.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: R.G.T. reports grants and personal fees from Boehringer Ingelheim, personal fees from Bayer and Pfizer/Bristol Meyer Squibb, all outside the submitted work. M.J.P. received grants and honoraria from various pharmaceutical companies, inclusive those developing, producing, and marketing new oral anticoagulants (NOACs). None of these grants or honoraria were directly related to this study. M.v.H. reports grants from Bayer and personal fees from Boehringer Ingelheim during the conduct of the study. R.G.T. is co-inventor of the MyDiagnostick and receives royalties from Applied Biomedical Systems (ABS).

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