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ORIGINAL ARTICLE

Health economic evaluation of nation-wide screening programmes for atrial fibrillation in the Netherlands

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Aims Screening for atrial fibrillation (AF) is recommended by the European Society of Cardiology guidelines to prevent strokes. Cost-effectiveness analyses of different screening programmes for AF are difficult to compare because of varying settings and models used. We compared the impact and cost-effectiveness of various AF screening programmes in the Netherlands.

Methods and results The base case economic analysis was conducted from the societal perspective. Health effects and costs were analysed using a Markov model. The main model inputs were derived from the ARISTOTLE, RE-LY, and ROCKET AF trials combined with Dutch observational data. Univariate, probabilistic sensitivity, and various scenario analyses were performed. The maximum number of newly detected AF patients in the Netherlands ranged from 4554 to 39 270, depending on the screening strategy used. Adequate treatment with anticoagulation would result in a maximum of >3000 strokes prevented using single-time point AF screening. Compared with no screening, screening 100 000 people provided a gain in QALYs ranging from 984 to 8727 and a mean cost difference ranging from –6650 000€ to 898 000€, depending on the screening strategy used. The probabilistic sensitivity analysis (PSA) demonstrated a 100% likelihood that screening all patients ≥75 years visiting the geriatric outpatient clinic was cost-saving. Four out of six strategies were cost-saving in ≥74% of the PSA simulations. Out of these, opportunistic screening of all patients ≥65 years visiting the GPs office had the highest impact on strokes prevented.

Conclusion Most single-time point AF screening strategies are cost-saving and have an important impact on stroke prevention.

Keywords Cost-effectiveness • Atrial fibrillation • Screening

What's new?

- A single decision analytic model can be used to assess the cost-effectiveness of single-time point screening for atrial fibrillation (AF) for several nationwide screening strategies, thus enhancing comparability.
- Both opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic as well as opportunistic screening of

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Table 1 Screening strategies for atrial fibrillation in the Netherlands

Screening strategy	Number screened	Detection rate	Specificity(%)	Costs of screening per person screened(€)	Confirmation[a](€)
A: Opportunistic screening of all patients 65 years and older visiting a GP	3374 697	Age-dependent from Lowres *et al.*	90	19.40	27.60
B: Opportunistic screening of patients 65 years and older visiting a GP with blood pressure measurement (e.g. hypertension clinic, coronary heart disease clinic)	1449 316	Age-dependent from Lowres *et al.*	90	19.20	82.00
C: Systematic screening at the GP of people 75 years and older	1437 430	Age-dependent from Lowres *et al.*	90	39.40	27.60
D: Opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic	75 732	Age-dependent from Lowres *et al.*	90	53.75	27.60
E: Opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP	2150 240	Age-dependent from Lowres *et al.*	90	20.40	27.60
F: Self-screening using a smartphone app and confirmation by a GP in people 65 years and older	3374 697	Age-dependent from Lowres *et al.*	90	4.00	82.00

For a detailed breakdown and description of the costs of screening and confirmation, please refer to Supplementary material online, *Table S2*. 'Costs of atrial fibrillation (AF) screening in the Netherlands'.
GP, general practitioner.
[a]Cost of confirmation per positive screening result.

all people 65 years and older during seasonal influenza vaccination at the GP are very likely to be cost saving in the Netherlands.
- Opportunistic screening of all patients 65 years and older visiting the GPs office had the highest impact on strokes prevented in the Netherlands.

Introduction

The ESC guideline on atrial fibrillation (AF) treatment advises opportunistic screening for AF to prevent ischemic stroke (IS) in patients ≥65 years of age (class 1, level of evidence B), and systematic screening in ≥75 years of age or with a high thrombo-embolic risk (class 2A, level of evidence B).[1] Opportunistic screening can be done in various ways, e.g. in all patients ≥65 years of age visiting the GPs office, only in ≥65-year-old during blood pressure measurement, or during vaccination programmes such as influenza vaccination.[2] Systematic screening for AF in patients ≥75 years of age has a class two recommendation, based on the STROKESTOP study.[3] Furthermore, screening can be performed in high-risk populations, e.g. in geriatric patients visiting a specialized outpatient clinic.[4] Screening programmes utilizing mHealth solutions offer the potential of screening at home, possibly increasing the number of people screened.[5,6] Many AF screening programmes have been analysed for cost-effectiveness, all with their own inputs in modelling and calculations, in different countries, and with different perspectives (societal or health insurance).[6–9] This makes it difficult to compare the cost-effectiveness of the different strategies. Apart from the different cost-effectiveness of the various programmes, the diagnostic yield, i.e. the potential total number of patients detected or strokes prevented by screening may also differ. In the present study, we compared the cost-effectiveness of different AF screening scenarios using the same inputs in a Markov-model and calculated the total potential number of strokes prevented by the different screening scenarios when implemented in the Netherlands.

Methods

Design and setting

A static decision analytic model was developed to study the economic impact of AF screening over a life-time horizon. The patient population explored in the model was a population of newly detected AF cases that would be diagnosed with screening for AF. Various screening strategies were evaluated, please see *Table 1*. A decision tree incorporated all relevant variables in the screening procedure, and this decision tree served as the input for the Markov model, see *Figure 1*.

The decision tree started with hypothetical cohorts for the following AF screening strategies:

1. Opportunistic screening of all patients >65 years and older visiting a GP.
2. Opportunistic screening of patients 65 years of age and older visiting a GP with blood pressure measurement (e.g. hypertension clinic, coronary heart disease clinic).
3. Systematic screening at the GP of people 75 years and older.
4. Opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic.

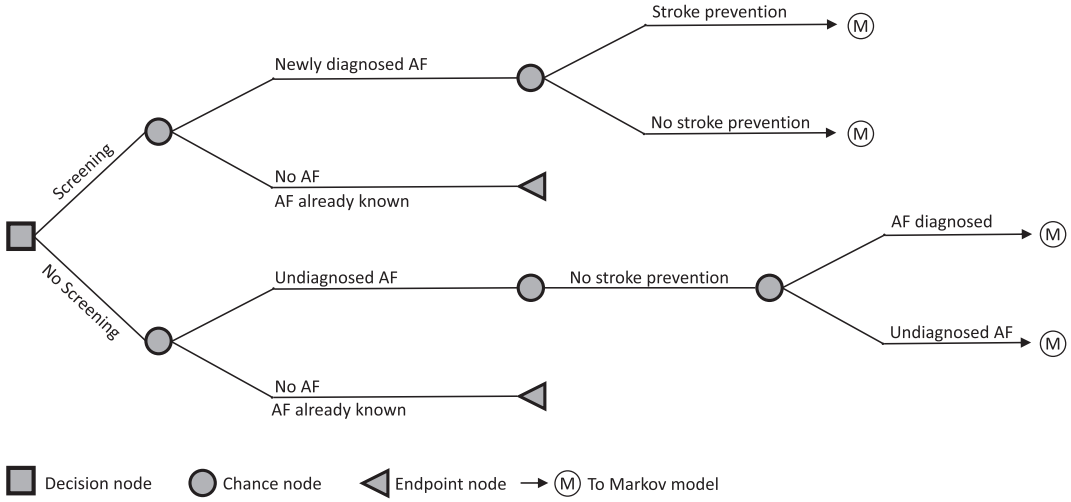

Figure 1 Short decision tree representing the AF screening outcome. The decision tree output was used as an input for the Markov model. A schematic representation of the Markov structure can be found in the Supplementary material online, *Figure S1*.

5. Opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP.
6. Self-screening using a smartphone app and confirmation by a GP in people 65 years and older.

The screening strategies are described in detail in *Table 1*. For the evaluation of the costs and gain in quality adjusted life-years (QALYs), these cohorts were transformed into cohorts of 100 000 people screened per strategy. Newly detected AF patients were based on the age-dependent detection rates described by Lowres *et al.*,[10] see Table A1. In the base-case scenario, we assumed that 3% of the undetected AF patients would be detected per year in routine medical practice.[8]

Model

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 a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban equally distributed) was used as stroke prevention. Patient preference for treatment initiation of an anticoagulant was 85% in the base case, except for self-screening. A patient preference of 85% was based on unpublished data and anticoagulant persistence after 1 year found in the literature.[8] After self-screening, a smaller share of patients (50%) initiated anticoagulation.[5, 11] We assumed that the treatment continuation rate was 98% per 3-month cycle.[12] 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 (ECHs) were assumed to be GI haemorrhages. 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 exclusion of productivity losses may underestimate the cost-effectiveness of AF screening because indirect costs such as informal care by children after an event and the patients' inability to babysit are not included in the evaluation. The model was developed in STATA (version 16.0 MP; StataCorp LLC). Health gains were discounted by 1.5%; all unit costs were converted to costs for 2019 by correcting for inflation and discounted by 4%. All event probabilities, utilities, costs, and other parameters, including their references, are listed in the Supplementary material online, please refer to Supplementary material online, *Table S1*: Markov model inputs: event probabilities, utilities, and costs.

Events

The risks of clinical events for NOACs were based on combined clinical trial data from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),[13] RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy),[14,15] 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).[16] The event rates for 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 published data of relative risks of patients without stroke prevention compared with warfarin.[17,18] 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 to NOACs. 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, and subdivided based on modified Rankin Scales (mRSs) of 0–1, 2–3, 4, and 5. 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

Table 2 **Total number of events, mean costs, and mean utilities compared with no screening in the base-case over a lifetime horizon**

Screening strategy	AF cases detected	Ischemic stroke minor	Ischemic stroke major	Ischemic stroke fatal	MI	SE	ICH	Fatal ICH	GIH	MH	Total cost of screening (mln €)
A: Opportunistic screening of all patients 65 years and older visiting a GP	39 270	–1022	–1157	–883	–2501	–72	105	75	662	8827	75.9
B: Opportunistic screening of patients 65 years and older visiting a GP with blood pressure measurement	16 550	–434	–490	–377	–1063	–29	42	34	282	3774	41.1
C: Systematic screening at the GP of people 75 years and older	27 629	–762	–856	–648	–1681	–48	67	50	431	5757	61.4
D: Opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic	4554	–129	–145	–109	–291	–8	12	8	75	1028	4.3
E: Opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP	27 110	–713	–806	–614	–1708	–50	73	52	453	5999	50.6
F: Self-screening using a smartphone app and confirmation by a GP in people 65 years and older	39 270	–602	–683	–519	–1471	–42	63	42	391	5194	44.4

GP, general practitioner; GIH, gastrointestinal haemorrhage; ICH, intracranial haemorrhage; MH, minor haemorrhage; MI, myocardial infarction; SE, systemic embolism; QALY, quality adjusted life-year.

Table 3 Base-case results from the health economic evaluation of screening for AF in the Netherlands

Screening strategy	Mean costs per 100 000[a] (1000€)	Mean utilities per 100 000[a] (QALYs)	ICER (additional € per QALY gained)	Relative CER (€ per QALY gained)	Probability cost-saving (%)
D: Opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic	–6650	8727	Dominant	–762	100.0
E: Opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP	–146	1756	Dominated	–83	73.8
A: Opportunistic screening of all patients 65 years and older visiting a GP	–140	1673	Dominated	–84	73.9
F: Self-screening using a smartphone app and confirmation by a GP in people 65 years and older	–89	984	Dominated	–91	75.2
NS: No screening	0	0	Dominated	N.A.	N.A.
B: Opportunistic screening of patients 65 years and older visiting a GP with blood pressure measurement	424	1686	Dominated	251	2.3
C: Systematic screening at the GP of people 75 years and older	898	2392	Dominated	375	0.9

Screening strategies are in ascending order from lowest to highest mean costs per 100 000 screened people.
Incremental costs and utilities are not shown because all strategies are dominated by screening strategy D. GP, general practitioner; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; N.A., not applicable; QALY, quality adjusted life-year.
[a]Hypothetical cohort of 100 000 people screened.

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 for one week. Minor haemorrhage had no disutility.

Costs

Screening costs for AF consisted of costs of screening, primary care costs, and costs for the evaluation of the confirmatory ECGs of positive screening results, including false-positive results and newly diagnosed AF patients, see *Table 1*.

The costs of screening were based on material costs (i.e. MyDiagnostick or Microlife Office). Personnel costs were an estimation based on the hour tariff and the number of hours needed for the screening scenario. The costs of a cardiologist for confirmation were included, meaning cardiologist costs for evaluating all ECGs of people suspicious for AF. Please refer to Supplementary material online, *Table S2*, 'Costs of AF screening in the Netherlands'.

Drug costs for NOACs 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, edoxaban 60 mg, and rivaroxaban 20 mg) was assumed to be equally distributed. For the NOAC users, we included the cost 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 is applied to 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 for fatal IS were derived from a study evaluating the 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 analyses 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 of screening were explored with plausible variations in key assumptions. 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 Beta distributions; costs were assumed to have Gamma distributions. The sensitivity analyses were also used to consider the broader issue of the generalizability of the results.

Results

Base case

The maximum number of newly detected AF patients in the Netherlands ranged from 4554 to 39 270, depending on the screening strategy used. Compared with no screening, screened people who were

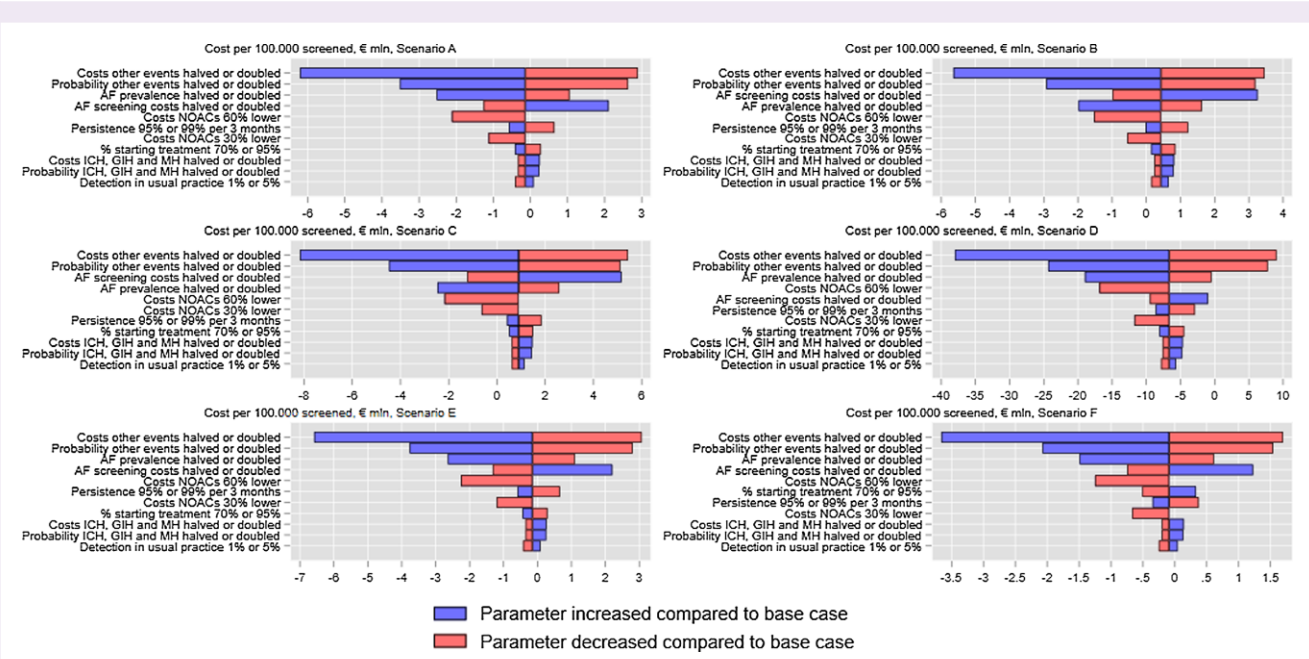

Figure 2 Tornado diagram representing the incremental costs expected from a lower and upper value for each variable in the univariate sensitivity analyses. The values for each value used in the sensitivity analysis can be found in the Supplementary material online, *Table S1*. (*A*) opportunistic screening of all patients >65 years and older visiting a GP; (*B*) opportunistic screening patients 65 years of age and older visiting a GP with blood pressure measurement; (*C*) systematic screening at the GP of people 75 years and older; (*D*) opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic; (*E*) opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP; (*F*) self-screening using a smartphone app and confirmation by a GP in people 65 years and older. GIH, gastrointestinal haemorrhage; GP, general practitioner; ICH, intracranial haemorrhage; MH, major haemorrhage; NOAC, Non-Vitamin K anticoagulant. Other events include events other than ICH, GIH, and MH (such as systemic embolism and myocardial infarction).

newly diagnosed with AF and treated with an NOAC over a 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 cost of screening ranged from €4.3 to 75.9 million. Newly detected AF patients and total number of events that occurred in combination with total screening costs are summarized in *Table 2*.

Compared with no screening, screening 100 000 people provided a gain in QALYs ranging from 984 to 8727. The mean cost difference between screening and no screening ranged from €–6650 000 to 898 000 per 100 000 screened people. Relative to no screening, strategies A, D, E, and F were cost saving. Screening strategy D was the dominant strategy; all other strategies were dominated (*Table 3*). As AF screening in strategy D is directed only towards a small specific population, introducing either nationwide screening strategy A, E, or F is cost-saving compared with no screening.

Undiscounted for costs and effects, screening provided an additional gain in QALYs ranging from 1948—10 036 and a mean cost difference ranging from €–9136 000–299 000 (Supplementary material online, *Table S3*). Strategy D remained the dominant strategy. Also, for nationwide screening, screening strategies A, E, and F remained cost-saving (mutually exclusive) options without discounting.

Sensitivity analysis

Univariate sensitivity analyses were conducted for the prevalence of AF, AF detection in usual practice, costs for IS/ICH/all events, probability of all events, costs of NOACs, persistence of NOACs use, screening costs, and utilities to determine the impact on the net cost compared with no screening of the model (*Figure*)*2*

The costs of IS, MI, and SE (defined as 'other costs' in *Figure 2*) were of particular influence with the upper limit, leading to more cost-savings for all screening strategies compared with the costs used in the base case. With half of the base case costs for IS, MI and SE, screening for AF was not cost saving anymore for any of the evaluated screening strategies. Variation in the event probabilities of IS, MI and SE (defined as 'Probabilities other events' in *Figure 2*) yielded a similar although less sensitive pattern. Doubling the event probabilities would give more cost savings of AF screening; halving the event probabilities would render the AF screening strategies with net costs compared with no screening. Only halving the costs of or event probabilities of IS, MI, and SE would lead to a net cost of screening strategy D compared with no screening. Strategy D and E were sensitive to the prevalence of AF. Net cost of screening strategy C compared with no screening was sensitive to the screening costs. Decreasing the cost of stroke prevention with NOACs would give more cost savings for AF screening. In general, the impact of persistence, costs, and event probabilities of bleeding and detection in usual practice is modest to minor.

The PSA with 1000 Monte Carlo simulations showed that the probability of cost-saving ranged from 0.9 to 100% for screening strategies relative to no screening (*Figure 3* and *Table 3*). At a willingness to pay above €10 000 per QALY gained, screening strategies A, D, E, and F reached a probability of >90% to be cost-effective, increasing to >95% at a willingness to pay of €20 000 per QALY gained (results not shown). As the probability of cost-saving was 100% for strategy D,

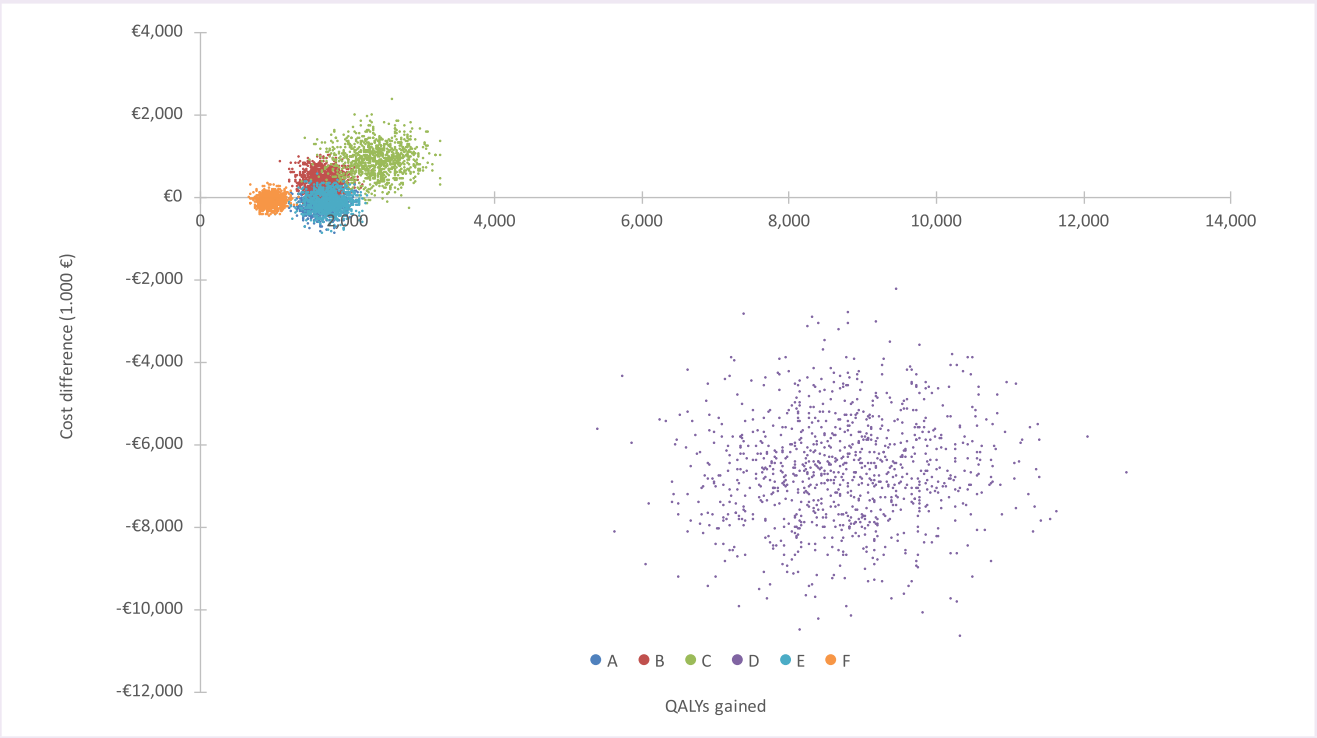

Figure 3 Results of 1000 Monte-Carlo model simulations of AF screening strategies in the Netherlands. The cost difference (€) and QALYs gained are compared with no screening for 100 000 screened people. (*A*) opportunistic screening of all patients >65 years and older visiting a GP; (*B*) opportunistic screening of patients 65 years of age and older visiting a GP with blood pressure measurement; (*C*) systematic screening at the GP of people 75 years and older; (*D*) opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic; (*E*) opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP; (*F*) self-screening using a smartphone app and confirmation by a GP in people 65 years and older. GP, general practitioner; QALY, quality adjusted life-year.

a cost-effectiveness acceptability curve (CEAC) was drawn without strategy D (*Figure 4*). Excluding strategy D, the probability that either strategy A or E was cost-saving, i.e. a willingness to pay of €0 per QALY gained, reached 72.4%. In this case, the probability that strategy F was cost-saving reached 27.6%. The probability of strategies B and C being cost-saving was 0%. At increasing willingness to pay, also the probability of either A or E being cost-effective increased. At a willingness to pay of €20 000 per QALY gained, the probability of either strategy A or E being cost-effective was 99.4%. Overall, strategy E showed the highest probability of cost-effectiveness in the CEAC.

Discussion

This study evaluated the cost-effectiveness of nationwide screening programmes for AF in the Netherlands. AF screening programmes gave net health/utility gains, with QALYs gained ranging from 984 to 8727 per 100 000 screened people. Relative to no screening, screening programmes A (opportunistic screening of all patients of 65 years and older visiting a GP), D (opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic), E (opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP), and F (self-screening using a smartphone app and confirmation by a GP in people 65 years and older) was cost-saving, reducing costs €140 000, €6650 000, €148 000, and €89 000 per 100 000 screened people, respectively. The cost-effectiveness ratios of screening programmes B [opportunistic screening patients 65 years of age and older visiting a GP with blood pressure measurement (e.g. hypertension clinic, coronary heart disease clinic)] and C (systematic screening at the GP of people 75 years and older) relative to no screening were €251 and €375 per QALY gained, respectively. Such cost-effectiveness ratios are very acceptable when compared with an informal cost-effectiveness threshold of willingness to pay of €20 000 per QALY gained in the Netherlands. Formally, the cost-effectiveness of mutually exclusive health care programmes is evaluated in an incremental cost-effectiveness analysis. In this incremental cost-effectiveness analysis, strategy D (opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic) was dominant. All other evaluated screening strategies for AF were dominated by strategy D. Moreover, the probability that strategy D is cost-saving is 100%. Therefore, when only cost-effectiveness is taken into account, our study shows a preference for implementing AF screening strategy D. However, apart from the cost-effectiveness of the different screening strategies, the total number of strokes prevented also determines the impact of the screening programmes. For instance, screening strategy D is directed towards a specific population limited in size, with a moderate impact on the total number of strokes prevented. Focussing the evaluation on nation-wide screening of larger populations (strategies A, B, C, E, and F; so excluding D), showed that either strategy A or E are cost-effective screening strategies with the highest probability of cost-saving and cost-effectiveness. Overall, in the evaluation excluding strategy D, Strategy E displayed the most favourable cost-effectiveness ratio and probability of cost-saving and cost-effectiveness, probably due to the fact that—in line with screening patients visiting a geriatric outpatient clinic—this concerns a patient population with an increased risk of (asymptomatic) AF.

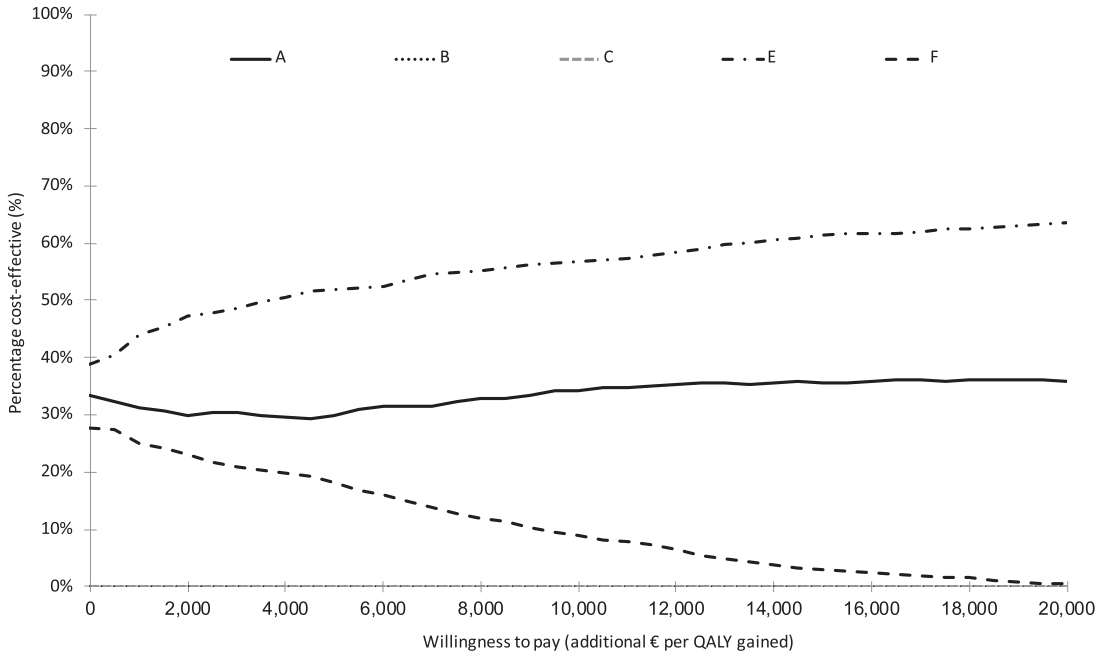

Figure 4 Cost-effectiveness acceptability curve for screening for AF in the Netherlands. Strategy D—opportunistic screening of all patients 75 years and older visiting a geriatric outpatient clinic was excluded from the evaluation. Screening scenarios are compared with no screening. (*A*) opportunistic screening of all patients >65 years and older visiting a GP; (*B*) opportunistic screening of patients 65 years of age and older visiting a GP with blood pressure measurement; (*C*) systematic screening at the GP of people 75 years and older; (*E*) opportunistic screening of all people 65 years and older during seasonal influenza vaccination at the GP; (*F*) self-screening using a smartphone app and confirmation by a GP in people 65 years and older. GP, general practitioner; QALY, quality adjusted life-year. The percentage cost-effectiveness of strategies (*B*) and (*C*) is 0%.

Next to cost-effectiveness, being so close in our evaluation, one could also aim at the screening strategy with the highest impact on stroke reduction. In this case, strategy A (screening all 65 years and older patients visiting the GPs office) is the preferred option. This approach can prevent >3000 fatal and non-fatal strokes in the Netherlands, resulting in a significant reduction in costs over a life-time horizon.

One could presume that opportunistic screening of all patients ≥75 years who visit the GPs office would probably be a good mix between strategy A (most impact) and D (most cost-effective), but this was not evaluated in the present study. Strategy C (systematic screening of patients ≥75 years of age) was the least cost-effective strategy because of high screening costs.

Although strategy F (self-screening using a smartphone app and confirmation by a GP in people 65 years and older) aims at more or less the same population as strategy E, it is less preferred due to fewer health gains. In strategy F, we expected 50% of participants would self-refer to a GP after a positive signal for AF. Hence, lower use of OAC in patients with self-detected AF and relatively high costs of confirmation by a 12-lead ECG at the GPs office are to be expected.[5,11] In the Apple Heart Study, only 21% of participants with an irregular pulse returned the ECG patch.[5] So, our self-referral rate of 50% can actually be considered in favour of strategy F. To make this self-screening approach work, low-cost confirmation and high uptake of anticoagulation in positive individuals could make it more cost-effective. Therefore, this screening strategy might work better in combination with one of the strategies where the GP has access to a single-lead ECG AF detection device and is aware of the importance of OAC in screen-detected AF.

Regarding the attendance or willingness to participate in (systematic) screening programmes, the STROKESTOP study showed that non-participants had more comorbidities, and more often polypharmacy, a lower grade of education, were more likely to live alone, had a lower income, and developed more events during follow-up compared with the participants and controls.[19] This means that special attention and more efforts need to be made to target these groups within screening programmes in order to improve public health. In particular, due to the socio-economic and demographic status and associated risk factors for stroke, such as hypertension, smoking, obesity and alcohol intake, the impact of screening and subsequent stroke prevention with anticoagulation and focus on the reduction of modifiable, lifestyle, risk factors for stroke is expected to give more health-gains and reduction of health care usage in non-participants compared with the screened population. From a societal perspective, it would be worthwhile to explore this research question in a future study.

The present study evaluated strategies all using a single-time point screening to detect persistent/permanent AF or paroxysmal AF with a high burden. Controversies exist about screening for shorter episodes of paroxysmal AF, since the thrombotic risk of these episodes may be lower and prophylactic anticoagulation may not result in fewer strokes, while the costs of screening and verification may increase substantially.[20] Despite health economic evaluations of AF screening have been published for various screening strategies, countries, and target populations, it is difficult to compare our evaluation with other studies due to the underlying heterogeneity.[6–9] A recent health economic evaluation of a photoplethysmographic procedure for screening for AF (Preventicus Heartbeats) in six European countries showed that

for the Netherlands, screening for AF was close to cost-neutral.[21] In this multi-country analysis, the authors also showed that in countries with high healthcare costs, screening for AF is favourable from a health economic point of view.

The cost-effectiveness of screening for AF is particularly sensitive to the costs and transition probabilities of IS, MI, and SE. Therefore, if decision makers require a reduction in the uncertainty of the cost-effectiveness of AF screening, despite being cost-saving in most strategies, investments in future studies which reduce the uncertainty in the costs and transition probabilities of IS, MI, and SE should be considered. The cost-effectiveness of AF screening is not sensitive to the detection of AF in usual, routine medical care. Simplified, the cost-effectiveness of AF screening is based on the number of detected AF patients due to screening programme in addition to the number of AF patients detected in usual care *minus* the number of AF patients detected in usual care. So, in an incremental cost-effectiveness evaluation comparing an AF screening programme to usual care, the impact of detection AF in usual care is mostly cancelled out. As with most cost-effectiveness analyses, the impact of AF screening on deaths and strokes prevented is modelled. Real-world data on the impact of AF screening on strokes and deaths prevented is rife. Therefore, we suggest to evaluate AF screening programmes when implemented with population studies and registries such as the DUTCH-AF registry.[22] As NOACs coming available as generic drugs in the next few years, it may be expected that due to the decreasing cost of stroke prevention, AF screening becomes even more cost-effective than presented in our current evaluation.

Conclusion

In conclusion, the majority of single-time point AF screening strategies are cost-saving. Screening all patients visiting the geriatric outpatient clinic was shown to be the most cost-effective. Opportunistically screening of all patients ≥65 years visiting the GPs office had the highest impact on strokes prevented.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

A request for data and/or the underlying model will be discussed in the writing committee.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. Erratum in: *Eur Heart J* 2021;**42**:507. Erratum in: *Eur Heart J* 2021;**42**:546–547. Erratum in: *Eur Heart J* 2021;**42**:4194. PMID: 32860505.
2. Kaasenbrood F, Hollander M, Rutten FH, Gerhards LJ, Hoes AW, Tieleman RG. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. *Europace* 2016;**18**:1514–1520.
3. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. *Circulation* 2015;**131**:2176–2184.
4. Zwart LA, Jansen RW, Ruiter JH, Germans T, Simsek S, Hemels ME. Opportunistic screening for atrial fibrillation with a single lead device in geriatric patients. *J Geriatr Cardiol* 2020;**17**:149–154.
5. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T *et al.* Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;**381**:1909–1917.
6. Birkemeyer R, Müller A, Wahler S, von der Schulenburg JM. A cost-effectiveness analysis model of Preventicus atrial fibrillation screening from the point of view of statutory health insurance in Germany. *Health Econ Rev* 2020;**10**:16.
7. Sciera LK, Frost L, Dybro L, Poulsen PB. The cost-effectiveness of one-time opportunistic screening for atrial fibrillation in different age cohorts of inhabitants in Denmark Aged 65 years and above. A Markov modelled analysis. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:177–186.
8. Jacobs MS, Kaasenbrood F, Postma MJ, van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. *Europace* 2018;**20**:12–18.
9. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP *et al.* Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2017;**21**:1–236.
10. Lowres N, Olivier J, Chao TF, Chen SA, Chen Y, Diederichsen A *et al.* Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. *PLoS Med* 2019;**16**:e1002903.
11. Tieleman RG, Hemels ME. Obey the first recommendation: start screening programmes for atrial fibrillation. *Europace* 2016;**18**:1753–1755.
12. Anonymous. Zorgkosten, kenmerken en persistentie van patiënten met antistollingszorg. In: *Evaluatie van de ervaringen en kosten van antistollingszorg*. Diemen: National Health Care Institute [in Dutch: Zorginstituut]; 2020.
13. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
14. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151..
15. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Newly identified events in the RE-LY trial. *N Engl J Med* 2010;**363**:1875–1876.
16. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
17. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
18. Sorenson SV, Kansal AR, Connoly S, Peng S, Linnehan J, Bradley-Kennedy C *et al.* Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost* 2011;**105**:908–919.
19. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021;**398**:1498–1506.
20. Svendsen JH, Diederichsen SZ, Højberg S, Krieger DW, Graff C, Kronborg C *et al.* Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet* 2021;**398**:1507–1516.
21. Wahler S, Birkemeyer R, Alexopoulos D, Siudak Z, Müller A, von der Schulenburg JM. Cost-effectiveness of a photopethysmographic procedure for screening for atrial fibrillation in 6 European countries. *Health Econ Rev* 2022;**12**:17.
22. Chu G, Seelig J, Trinks-Roerdink EM, van Alem AP, Alings M, van den Bemt B *et al.* Design and rationale of DUTCH-AF: a prospective nationwide registry programme and observational study on long-term oral antithrombotic treatment in patients with atrial fibrillation. *BMJ Open* 2020;**10**:e036220.