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Project Acronym: AFFECT-EU

DIGITAL, RISK-BASED SCREENING FOR ATRIAL FIBRILLATION IN THE EUROPEAN COMMUNITY

Deliverable D4.1

Systematic review of economic evaluations literature of AF screening (Month 9)

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Project

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Abbreviation

Abbreviation	Name
AF	Atrial Fibrillation
BP	Blood Pressure
DES	Discrete Event Simulation
DOAC	Direct Oral Anticoagulation
ECG	Electrocardiogram
GI	Gastrointestinal Haemorrhage
GP	General Practitioner
ICER	Incremental Cost-Effectiveness Ratio
ICH	Intracranial Haemorrhage
IS	Ischemic Stroke
NBM	Net Monetary Benefit
NHS	National Health Services
OAC	Oral Anticoagulation
QALYs	Quality Adjusted Life Years
SE	Systemic Embolism
SL	Single Lead
SLR	Systematic Literature Review
TE	Thromboembolic
TTO	Time Trade-Off

Table Legends

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Table of Content

Revised Executive Summary

This report describes the results of a systematic review of economic evaluations literature in AF screening

Eligible types of economic evaluations included cost-effectiveness analyses, cost–benefit analyses, cost–utility analyses, cost consequences analyses and cost-minimization analyses. Each study was required to include both costs and consequences and compared one intervention to at least one other intervention or control. Outcome measures included measures of cost-effectiveness, e.g. an incremental cost-effectiveness ratio (ICER) or a measure of net monetary benefit (NMB).

The electronic databases Web of Science, PubMed, and Scopus were searched for articles on economic evaluation of screening for atrial fibrillation (AF). Searches were made without limitation back in time and until May 15, 2020.

In the Web of Science database 111 references on economic evaluation of AF screening were found., in PubMed 24 references, and in Scopus 42 references. Excluding duplicates and irrelevant references, 100 references on economic evaluation of AF screening was identified altogether.

Out of the 100 references, ten studies fulfilled the inclusion criteria applied in the review. The 10 included studies were published between 2004 and 2018.

The review showed that all earlier economic evaluation proved AF screening to be cost-effective regardless of strategy and method. Opportunistic screening led to lowest costs, but has also a potential limitation in coverage, population screening programs find more AF and save more QALYs at a higher cost per QALY. The cost-effectiveness results are driven by the efficacy of the program in terms of discovering new AF patients, and compliance to anticoagulation treatment.

All economic evaluations were based on simulation models with similar approaches, consisting of two parts – A decision-tree describing the initial screening procedure and its' results, followed by a model (Markov or Discrete Event Simulation) to trace long-term costs and benefits (QALYs).

In older models the cycle length was 12 months. In more recently developed models, shorter cycle length of 3 months has been used in the analysis. Similar set of health states reoccur in all model studies. In the decision tree: screening or no screening (uptake), thereafter detected/undetected AF or No AF (dependent on sensitivity and specificity – i.e. True/False AF-positive and AF-negative).
In the long-term model the most important health states/events are stroke and bleeding events.

The most common target group in the reviewed models is 65 years or older, and due to gain in survival a lifetime perspective is used. Productivity loss is not included in the models due to the target populations high age.

In the reviewed studies the cost-effectiveness results were reported sensitive to a few parameters. The most important parameter is the stroke risk in patients with asymptomatic AF which is partly based on assumptions. Other parameters affecting the results significantly are the magnitude of short- and long-term costs related to stroke, the anticoagulant treatment adherence, the time horizon of the analysis.

This systematic review found ten economic evaluations, all showing that AF-screening is cost-effective use of health care resources. However, all evaluations were based on similar model approaches with an inherent uncertainty due to parameter assumptions. This implies a potential for important improvement concerning parameter estimations in future analyses.

Introduction

The objective of this work is to perform an SLR of economic evidence relevant to the development of an economic model that will evaluate AF screening programs and technologies.

Specific objectives of the SLR is:

- Identify cost-effectiveness and cost-utility analyses of AF screening programs and technologies
- Critically appraise the studies using validated appraisal tools

Methods

The electronic databases Web of Science, PubMed, and Scopus were searched for articles on economic evaluations of screening for atrial fibrillation (AF). Searches were made without limitation back in time and until May 15, 2020. The searches were conducted as exemplified in the description of the literature search in the Web of Science database, presented in Table 1.

Table 1. Description of literature search in the Web of Science database.

Search no.	References found	Search terms
# 36	111	#35 AND #34 AND #4
# 35	4,461	#33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21
# 34	10,464,861	TS=((cost OR "cost benefit analysis" OR "health economics" OR pharmacoeconomics OR "cost analysis" OR cost-analysis OR "cost effectiveness analysis" OR "cost effective" OR cost-effective OR "cost utility analysis" OR "cost utility" OR cost-utility OR modeling OR modelling OR "economic model" OR "cost minimization analysis" OR costminimization OR costminimisation OR cost-minimisation OR cost-minimization OR "cost minimization" OR (model AND (cost OR economy OR economics OR pharmacoeconomic)) OR "economic model" OR "statistical model" OR "budget impact analysis" OR "budget impact" OR econometrics OR econometric OR markov OR "decision analysis" OR "discrete event simulation" OR "economic evaluation" OR "cost control" OR cost AND (effective OR utility OR benefit OR minimization OR minimisation)))
# 33	679	#20 AND #5
# 32	1,944	#19 AND #5
# 31	187	#18 AND #5
# 30	33	#17 AND #5
# 29	14	#16 AND #5
# 28	11	#15 AND #5
# 27	186	#14 AND #5
# 26	84	#13 AND #5

Search no.	References found	Search terms
# 25	82	#12 AND #5
# 24	515	#11 AND #5
# 23	205	#10 AND #5
# 22	956	#9 AND #5
# 21	22	#8 AND #5
# 20	11,307	TS=(((mobile OR i-phone) AND app))
# 19	93,507	TS=(((reveal OR implantable) AND device))
# 18	4,698	TS=(photoplethysmograph*)
# 17	211	TS=(((modified OR “atrial fibrillation” OR PAF OR AF) AND (“BP monitor” OR “blood pressure monitor” OR sphygmomanometer)))
# 16	307	TS=((Sphygmomanometers OR “Blood pressure monitoring”, ambulatory/) AND (modified OR “atrial fibrillation” OR PAF OR AF))
# 15	44	TS=(Watchbp)
# 14	2,22	TS=(finger probe)
# 13	568	TS=((pulse AND (finger-tip or palpation)))
# 12	499	TS=(pulse AND palpation)
# 11	14,08	TS=(((holter OR “cardiac event” OR R-test OR 7-day) AND monitor))
# 10	3,975	TS=(((ECG OR iECG OR electrocardiography OR EKG) AND (ELR OR holter OR “event monitor” OR “event record” OR “loop record”)))
# 9	13,708	TS=(((ECG OR iECG OR electrocardiography OR EKG) AND (“single lead” OR serial OR intermittent OR bipolar OR bi-polar OR thumb OR short-term OR 12-lead OR ambulatory OR portable)))
# 8	340	#7 AND #6
# 7	19,151	TS=(holter OR “single lead” OR 12-lead OR “event monitor” OR “event record” OR “loop record” OR ELR)
# 6	1,116	TS=(Electrocardiography, Ambulatory)
# 5	937,259	TS=(Screening)
# 4	102,587	#3 OR #2 OR #1
# 3	5,01	TS=(supraventricular arrhythmia)
# 2	191	TS=(auricular fibrillation)
# 1	99,422	TS=(Atrial fibrillation)

So, in the Web of Science database 111 references on economic evaluation of AF screening were found. Corresponding result, using the same search terms, from PubMed was 24 references and for Scopus 42 references. After exclusion of duplicates and obviously irrelevant references, 100 references on economic evaluation of AF screening remained.

Inclusion criteria and methodology

Economic evaluations of screening for AF were searched for. Eligible types of economic evaluations included cost-effectiveness analyses, cost–benefit analyses, cost–utility analyses, cost consequences analyses and cost-minimization analyses. Each study was required to have reported both costs and consequences and compared one intervention to at least one other intervention or control.

Outcome measures included measures of cost-effectiveness, e.g. an incremental cost-effectiveness ratio (ICER) or a measure of net monetary benefit (NMB). All identified titles and abstracts were screened independently by two authors (LÅL and LB) and, where relevant, full-text articles were obtained and assessed against the study inclusion criteria. Disagreements at each stage (title and abstract stage, full report stage) were resolved by discussion for final assessment.

Results

Ten studies fulfilled the inclusion criteria applied in this review. The 10 included studies were published between 2004 and 2018.

Summaries of included studies

Table 2 shows results-oriented summaries, and table 3 shows methods-oriented summaries of the included studies

Table 2. Results-oriented summaries of included studies.

Study	Setting	Analytic perspective	Screening methods	Screening tests	Model structure	Costs	Outcomes	Results
Maeda, 2004 [1]	Japan, general population	Health service perspective, 20-year time horizon	Systematic population screening of 65-year-olds (annually until age 85)	12-lead ECG compared with pulse palpation followed by a 12-lead ECG	Decision tree for screening outcomes, Markov model for long-term consequences	USD 2001, discounted by 3%, increased costs by $120-150	Quality-Adjusted Lifedays (QALDs), disc. By 3%, 5-6 QALDs gained	USD 8000/ QALY (men) USD 10,000/ QALY (women)
Hobbs, 2005 [2]	UK, general population (50 general practices)	NHS- and societal perspective, time horizon?	Systematic opportunistic screening (consult with GP). Systematic pop. screening of ≥65 years	Compared 12-lead ECG, limb-lead rhythm strip ECG, single-lead ECG, and different interpreters and screening intervals	Discrete event simulation model	GBP 2003, disc by 3.5%. Data from the trial and from official records. Base case: warfarin treatment	AF detection rate (within-trial). QALYs for longer-term analysis, disc by 3.5%	£337 per detected AF case. Very small differences in QALYs and costs. Opportunistic screening most likely to be cost-effective
Lord, 2013 [3]	England and Wales, primary care	NHS perspective, lifetime horizon. A model is built that covers the complete process from	Patients ≥65 years with suspected AF in primary care	Referred to specialist for ECG if suspected AF	Discrete event simulation model		QALYs	No results reported

Study	Setting	Analytic perspective	Screening methods	Screening tests	Model structure	Costs	Outcomes	Results
		screening to available treatments of AF						
Lowres, 2014 [4]	Australia, pharmacy customers Control: cohort data from registers (5555 UK patients with asymptomatic AF 'detected incidentally')	Australian health funder perspective, 10-year time horizon	Systematic opportunistic screening of people 65-84 years, compared with no screening	Pulse palpation and hand-held iPhone-based single-lead ECG, interpreted by nurse and cardiologist	Not reported explicitly. Monte Carlo-simulation to create confidence intervals	$AUD	QALYs, prevented strokes	$AUD5,988/QALYs $AUD30,481 per prevented stroke
Aronsson, 2015 [5]	Sweden, general population (2 regions)	Societal perspective, lifetime horizon	Systematic population screening of 75- and 76-year-olds, compared with no screening	Intermittent hand-held ECG twice daily (or when palpitations) for two weeks	Initial decision tree, and Markov model for long-term consequences	Euro 2014, disc by 3%. Extra costs of €50,012 per 1,000 screened individuals	QALYs (EQ-5D), disc by 3% Avoided strokes 12 more QALYs and 8 avoided strokes per 1,000 screened individuals	€4,313 per QALY, €6,583 per avoided stroke

Study	Setting	Analytic perspective	Screening methods	Screening tests	Model structure	Costs	Outcomes	Results
Moran, 2015 [6]	Ireland, primary care	Societal perspective, 25-year time horizon	Systematic opportunistic screening (at GP visits). Various age-thresholds, base-case ≥65 years	National AF screening program - annual opportunistic pulse palpation (at GP visit) and ECG if irregular pulse compared with no screening	Decision tree for the screening stage, Markov model for long-term costs and benefits	Euro 2014, 5% disc. Incremental costs: €84	QALYs, disc by 5% Incremental QALYs: 0,0036	Euro23,004/QALY
Levin, 2015 [7]	Sweden	Societal perspective, 20-year time horizon	Screening directed towards 75-year old patients with a recent stroke	2 methods for detection of silent AF (ECG using a handheld recording device (for 30 days) AND 24 h Holter ECG compared with a no screening strategy	Decision tree for the screening stage, Markov model for long-term consequences	Euro 2013, 3% disc. Cost savings: €55 400 (per 1,000 screened individuals)	QALYs (EQ-5D), 3% disc. Avoided strokes 23 QALYs gained and 11 strokes avoided, per 1,000 screened individuals	Intermittent ECG superior to continuous Holter ECG, Intermittent ECG dominant compared with no screening

Study	Setting	Analytic perspective	Screening methods	Screening tests	Model structure	Costs	Outcomes	Results
Welton, 2017 [8]	UK	NHS perspective, lifetime horizon	Hypothetical cohort from the general population (55, 60, 65, 70, 75, 80 years). Sensitivity analyses with repeated screening every 5 years	12-lead ECG, single-lead ECG, >1 but <12-lead ECG, pulse palpation, modified blood pressure monitor, photoplethysmography,	Decision tree for the screening stage, Markov model (3-month cycles) for long-term consequences	GBP 2017, 3,5% disc, costs retrieved from the literature and official records (e.g. prices for different personnel categories)	QALYs, 3.5% disc QALY-weights from systematic literature review	Several ICERs for different comparisons. The conclusion made is that screening for AF seems to be generally cost-effective
Jacobs, 2018 [9]	The Netherlands, primary care	Societal perspective, lifetime horizon	Opportunistic screening for AF in people ≥65 years attending a primary care center for seasonal influenza vaccination	Handheld single-lead ECG (single screening session) compared with no screening	Decision tree for the screening stage, Markov model (3-month cycles) for long-term costs and benefits	Euro 2014, 4% disc. Costs decreased by €764 per patient screened	QALYs, 1,5% disc, 0,27 QALYs gained per patient screened	Screening dominant compared with no screening. (99,8% probability of an ICER<€20 000)

Study	Setting	Analytic perspective	Screening methods	Screening tests	Model structure	Costs	Outcomes	Results
Tarride, 2018 [10]	Canada, family practices	Public payer perspective, lifetime horizon	A cohort of people ≥65 years (n=2,054) were screened for AF	Three different screening strategies (pulse check, BP-AF, SL-ECG) were compared to no screening	Decision tree for the screening stage, Markov model for long-term consequences	CAD$ (Price year?) 1,5% disc. No screen $214,21 PC $202,48 BP-AF $211,03 SL-ECG $222,18	QALYs, 1,5% disc. No screen: Ref. PC: 0,00166 BP-AF: 0,00106 SL-ECG: 0,00166	Pulse check and BP-AF dominant compared with no screening, SL-ECG vs no screening: CAD$4788/QALY

Table 3. Methods-oriented summaries of included studies.

Study and trial (if applicable)	Model and states	Cost items and sources	Outcomes, methods/sources	Stroke risk	Sensitive parameters	Comments
Maeda, 2004 [1]	Markov, states: AF, no AF, IS (with/without disability), ICH (with/without disability), Dead Probabilities from previous studies[11, 12].	Screening, palpation, anticoagulants, IS, ICH, GI haemorrhage, disability state per year Costs from official Japanese records [13].	QALY-weights from previous study [14] (TTO) and own assumptions	Incidence of IS from Framingham 2.45% per year (base case, 65-84 years) Fatal 25% Disabled 44% Not disabled 31%	Incidence of ischemic stroke, anticoagulant prescription rate	AF prevalence from Framingham Uncertain data on AF incidence in Japan.
Hobbs, 2005 (SAFE) [2]	Discrete event simulation (DES) model, 12-month cycles	Data from the SAFE trial, the literature [15, 16], and own estimates. Items: Screening-related, anti-coagulants, Ischemic events, haemorrhagic events	AF-cases detected, cost per detected case QALY-weights from previous studies [14, 17-19].	Risks (%) by age (men/women): 65-74: 0.7/0.5 75-84: 1.3/1.1 ≥85: 1.5/1.6	Robust results	Data on sensitivity and specificity from the SAFE trial Uncertain data on prevalence and incidence of AF
Lord, 2013 [3]	Builds a DES model covering all treatment paths in AF. Covers everything from screening to different treatments. AF progression, risks for TE, bleed, other events, and non-AF-related mortality	Data on costs from official records and previous studies. Items: Screening, initial GP consultation, initial specialist consultation, 12-lead ECG, anticoagulants, and monitoring	QALY-weights from previous studies[20-22].	According to CHA_2DS_2- VASc Rates of TE from Swedish AF cohort study [23]	Stroke risks	Not an economic evaluation of AF screening

Study and trial (if applicable)	Model and states	Cost items and sources	Outcomes, methods/sources	Stroke risk	Sensitive parameters	Comments
Lowres, 2014 (SEARCH-AF) [4]	No model, but Monte Carlo-simulation to achieve confidence intervals	Costs from administrative systems and the literature [24]. Items: Screening, stroke, warfarin	QALYs, strokes avoided. QALYs gained from preventing a stroke from previous study [24].	Estimated stroke risk calculated using CHA_2DS_2-VASc score (Camm et al. 2012)	Treatment adherence	
Aronsson, 2015 (STROKESTOP) [5]	Markov model for cohort analysis. States: Alive, Dead, Detected AF, Non-detected AF, No AF, Events (No event, Ischemic stroke, Bleeding stroke, Severe bleeding, Minor bleeding, MI, Non-cardiac events)	Production loss not included. Direct costs primarily from regional administrative systems. Costs for e.g. stroke from the literature, Drug costs from Swedish official sources (FASS). Cost items: Screening (hand-held ECG), Invitation to screening, 24-h ECG, Apixaban, Stroke ≤ 1 year, Stroke > 1-year, Severe bleeding, Minor bleeding	Population based QALY-weights [25] and decrements if stroke [26].	CHA_2DS_2- VASc score to predict the risk of stroke	Time horizon, the prevalence of undetected AF, the stroke risk in asymptomatic AF	

Study and trial (if applicable)	Model and states	Cost items and sources	Outcomes, methods/sources	Stroke risk	Sensitive parameters	Comments
Moran, 2015 [6]	Markov model. Probabilities from literature. States: No AF, Undiagnosed AF, Diagnosed AF, IS (mild/moderate/severe), Hemorrhagic stroke, dead	Cost data from the literature and Irish official data. Indirect costs according to the human capital approach. Items: Palpation, ECG, warfarin, NOAC, acute and annual costs for IS, and hemorrhagic stroke, Systemic embolism, major bleedings, production loss	QALYs through EQ-5D (UK population study and published literature for certain events/states)	Data on incidence of first ever stroke (no AF) from the Irish hospital inpatient enquiry system Population data to calculate stroke incidence rates from the Central Statistics Office. Relative risk of stroke with AF from the Framingham Study	Results were robust (with respect to rate of undiagnosed AF by age, repeat screening, treatment rates for detected patients, stroke risk profiles, uptake of opportunistic screening)	
Levin, 2015 [7]	Markov model. Based on a clinical study + Swedish epidemiological data. States: AF-negative, Anticoagulants, No anticoagulants, Dead. Events: Stroke, Major bleeding	Production loss not included. Direct costs from clinical study and the literature [27-29].	QALYs through EQ-5D, from the literature [26, 30].	Stroke or SE per year, with warfarin: 2.73% No anti-coagulation: 9% (Patients with AF in $CHADS_2$ 3–6) (RE-LY + Swedish study)	Some sensitivity to: Rate of anticoagulant therapy to AF-patients. Screening costs. Time horizon.	Calculations based on a single Swedish cohort study. Should screening be repeated?

Study and trial (if applicable)	Model and states	Cost items and sources	Outcomes, methods/sources	Stroke risk	Sensitive parameters	Comments
Welton, 2017 [8]	Markov model (3-month cycles). Data from systematic review (prevalence, disease progression, HRs for stroke and death, quality of life, etc.) (True positive, false positive, true negative, false negative, did not attend screening, Detected AF (+risk assessment with CHA_2DS_2- VASc), No AF after confirmatory test, No AF, Undetected AF) Long-term: Events (MI, Major bleeding, Intracranial haemorrhage, Stroke, Dead)	Costs from the systematic review, the SAFE study, and to some extent official records. Cost items: Screening (invitation, material, time for nurse/GP/cardiologist). Events (MI, Major bleeding, Intracranial haemorrhage, Stroke)	QALYs	Based on risk factors (CHA_2DS_2-VASc score, previous MI, previous stroke) Sensitivity analysis: HRs for stroke and mortality risk by AF type and whether asymptomatic or not	Uptake of systematic opportunistic screening.	Screening seems cost-effective irrespective of method and assumptions.

Study and trial (if applicable)	Model and states	Cost items and sources	Outcomes, methods/sources	Stroke risk	Sensitive parameters	Comments
Jacobs, 2018 [9]	Markov model (3-month cycles). States: Stable AF, IS (minor, major or fatal), ICH (minor, major or fatal), MI, SE, GI haemorrhage, death. Event probabilities from clinical trials (ARISTOTLE, RE-LY, ROCKET AF).	Production loss not included. Cost data from the literature and official records. Cost items: Screening, IS (acute and annual), ICH (acute and annual), anticoagulants.	QALYs through EQ-5D (scores matching the ICD codes of events. Disutilities for anticoagulant therapy.	Stroke risk according to CHA_2DS_2- VASc. The average CHA_2DS_2- VASc score of individuals ≥ 65 years with newly detected AF was 3.7.	Results most sensitive to costs of IS.	Event probabilities were based on clinical studies with relatively short follow-up (extrapolation to a lifetime horizon is associated with uncertainty).
Tarride, 2018 (PIAAF-FP) [10]	Initial trial data (PIAAF-FP) followed by a Markov model (3-month cycles) for simulation over a lifetime horizon. States/events: ischemic stroke, intracranial haemorrhage (ICH), non-ICH major bleeding, and death	Data from 'the PIAAF-FP clinical study' and the literature [31-36].	QALYs, data from the literature [37-39].	Stroke risk: (CHA_2DS_2- VASc = 3.1) = 3.9%/year (Friberg) RR warfarin vs no OAC: 0.33 RR DOAC vs warfarin: 0.92	Robust results according to sensitivity analyses	Data from 'the PIAAF-FP clinical study' and published literature. Small differences in costs and benefits.

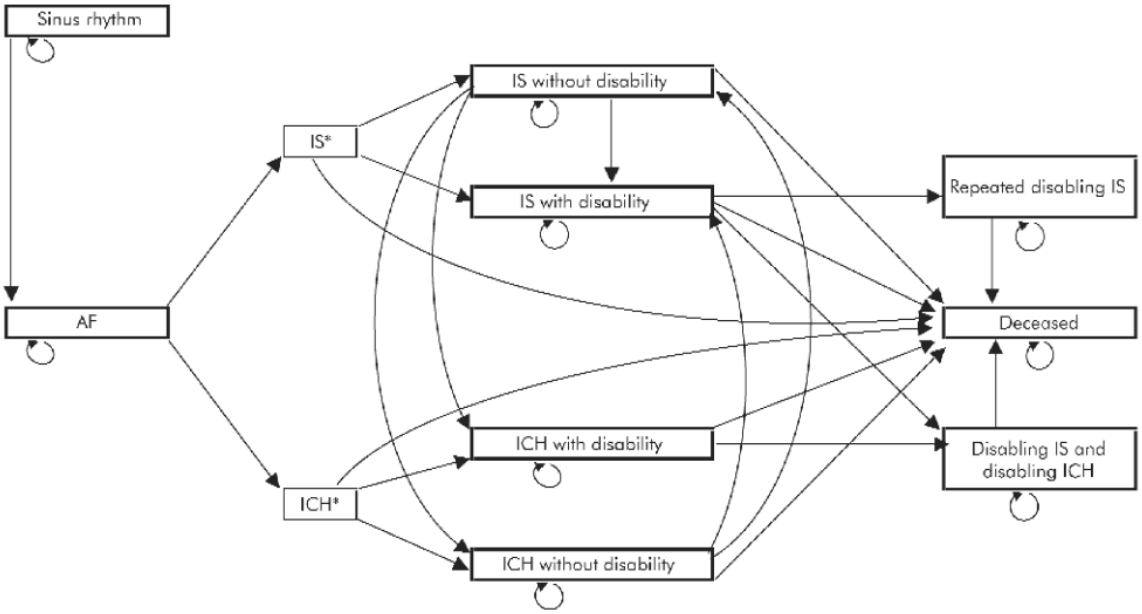
Descriptions of included studies

Maeda et al

The study by Maeda et al. [1] compared three community-based screening strategies in Japan for people aged 65 years. The three screening strategies were:

- Annual screening with an ECG
- Annual screening with pulse palpation, with referral of patients with arrhythmias to an ECG
- No screening

To calculate costs and outcomes (QALYs) over a 20-year period, until patients reached the age of 85, a Markov model was used. The structure of the Markov model, and the states included is described in Figure 1.



*As transient health status IS or ICH were only presented at first episodes. ICH, intracranial haemorrhage. IS, ischaemic stroke.

Figure 1. Markov decision model from Maeda et al.

Patients who had repeated disabling ischaemic stroke or ICH were assumed to die if they developed another episode of ischaemic stroke. The two different screening strategies gave similar results. The ICERs when compared to the no-screening strategy were approximately US$8,000 in men and US$10,000 in women. The results were sensitive to the incidence of ischemic stroke assumed, and the proportion of AF patients prescribed anticoagulants. Increasing the incidence of ischemic stroke made screening more cost-effective, and so did an increase in the proportion of patients prescribed anticoagulants. An increase of the interval between repeat screenings to five years decreased costs while QALYs gained were hardly affected at all. These findings suggest that screening tests repeated every five years would be the optimal strategy.

Hobbs et al

The study by Hobbs et al. [2] is based on the SAFE study, and results were presented from both a within-trial cost-effectiveness analysis (reporting cost per additional true-positive AF case detected), and a long-term economic model capturing costs and benefits beyond the follow-up period of the trial (reporting cost per QALY). The screening method analysed was a 12-lead ECG interpreted by a cardiologist. The screening strategies analysed were directed to 65-year old's in the UK. Screening strategies compared were:

- Systematic opportunistic screening
- Systematic population screening
- Screening targeted at high-risk individuals according to stroke risk
- No screening

The model used for the analysis is described in Figure 2.

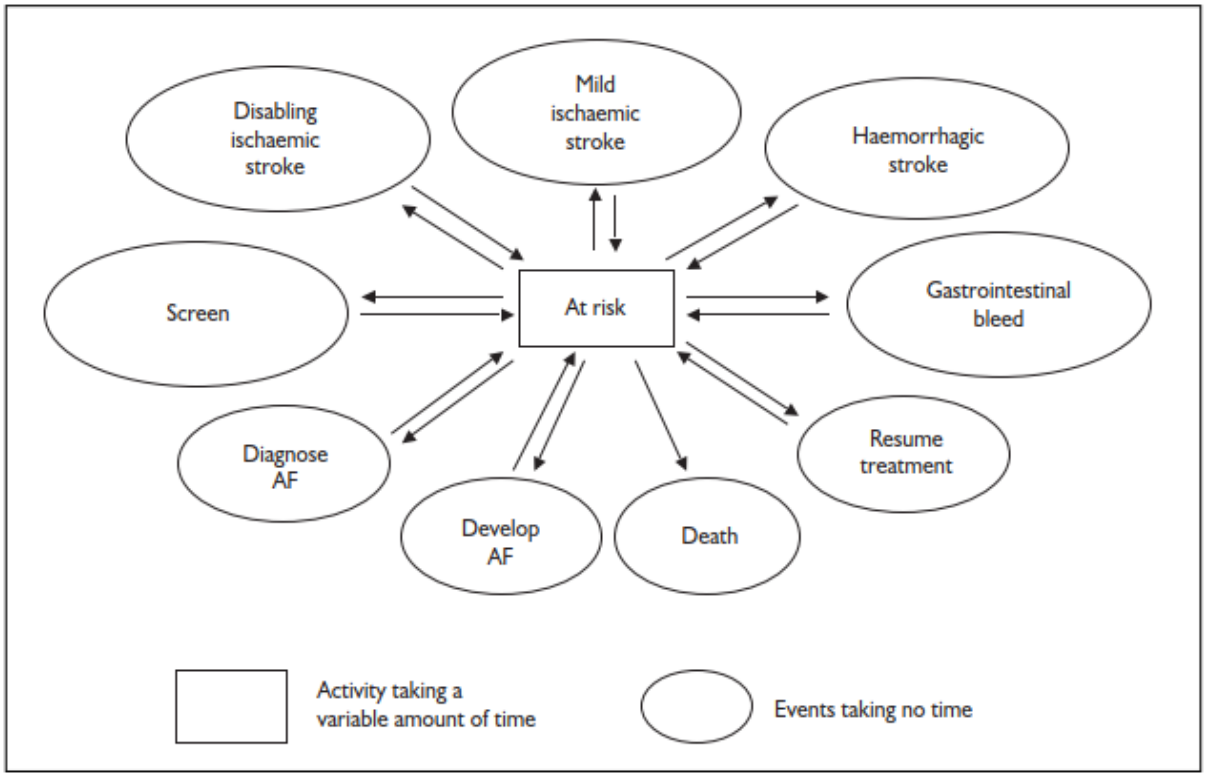


Figure 2. Individual sampling mode, from Hobbs et al.

The within-trial analysis showed that the systematic population screening and the target screening strategies were dominated (identified fewer new cases at a higher cost to the NHS) by the systematic opportunistic screening strategy. Systematic opportunistic screening compared to no screening resulted in a cost per detected case of GBP 337 (2003 prices).

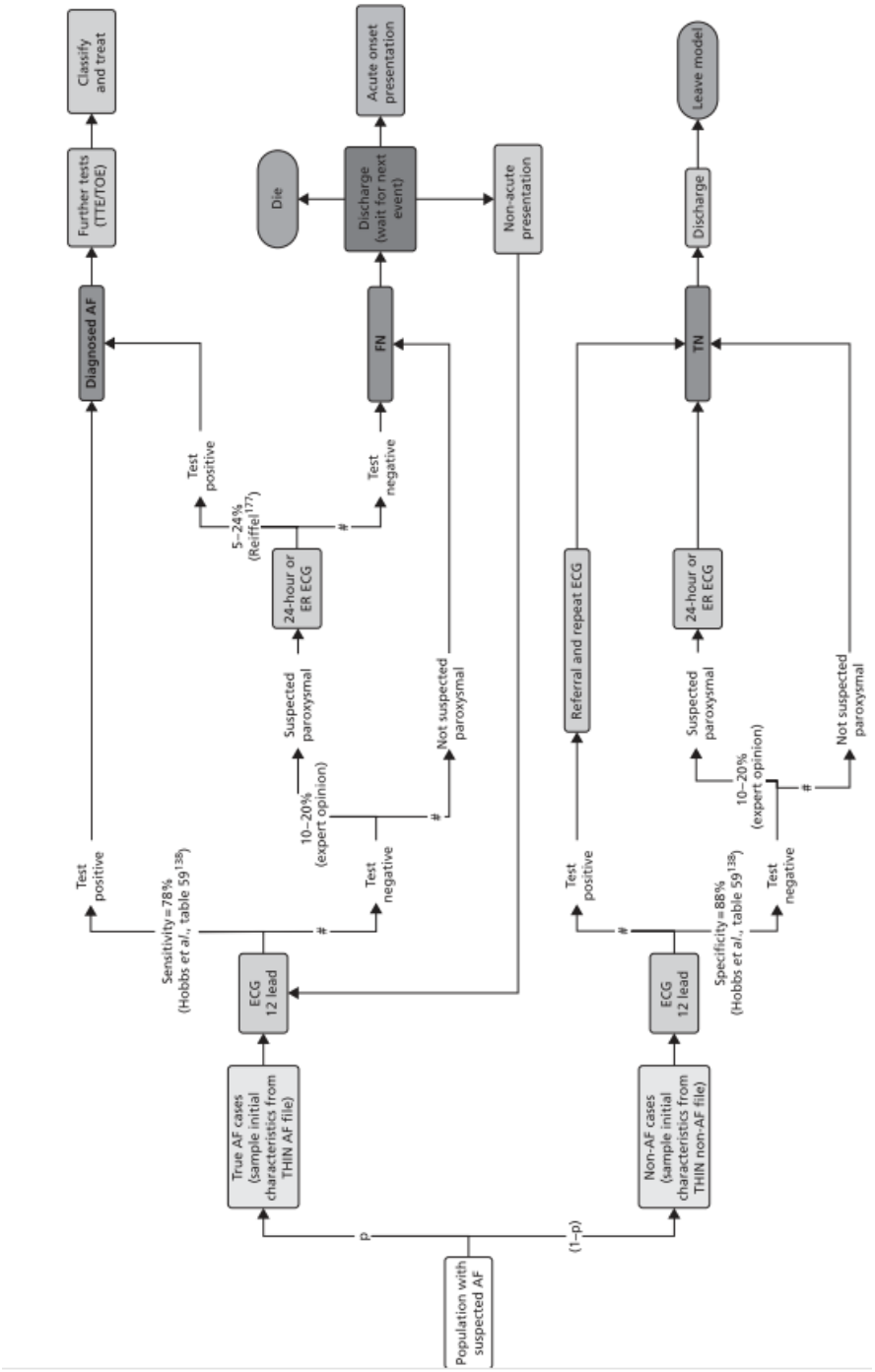
For the longer-term cost-effectiveness analysis, a discrete event simulation model was used. The model-based analysis compared screening strategies differing with respect to intervals between screening tests, type of screening test, interpreters and screening method (systematic opportunistic or systematic population screening) for 65-year-old persons. Patients that are not identified through screening may in the model be diagnosed at a later stage through routine care or after an event (e.g. ischemic stroke). In the model, data or assumptions on the following aspects were incorporated:

- AF incidence data
- Sensitivity and specificity of the screening tests
- The uptake of screening
- The costs of screening

If detected with AF patients were assumed to be prescribed warfarin. In a sensitivity analysis, patients instead received aspirin. Results of the analyses showed that QALYs gained were very similar for all strategies (also the no screening strategy). Small differences in costs were found, with slightly lower costs for systematic opportunistic screening compared to no screening.

Lord et al

Lord et al.[3] developed a model to show the course of a cohort of patients diagnosed with AF and treated according to the NICE clinical guidelines. The target group for community screening was persons ≥ 65 years with unknown AF and the screening method was iPhone ECG. In the model care pathways for AF were incorporated and the risk for ischemic stroke was a central parameter. The study, however, did not include any cost-effectiveness comparisons between screening strategies. What might be useful with respect to future modelling is that the model presented by Lord et al. includes a diagnostic pathway with outcomes modelled separately for true positives, true negatives, and false negatives. Models of the diagnostic pathway and disease process are shown in Figures 3 and 4.



FN, false-negative; p, prevalence of AF in patients tested for suspected AF; THIN, The Health Improvement Network; TN, true-negative.

Figure 3. Decision tree showing detail of diagnostic pathway, from Lord et al.

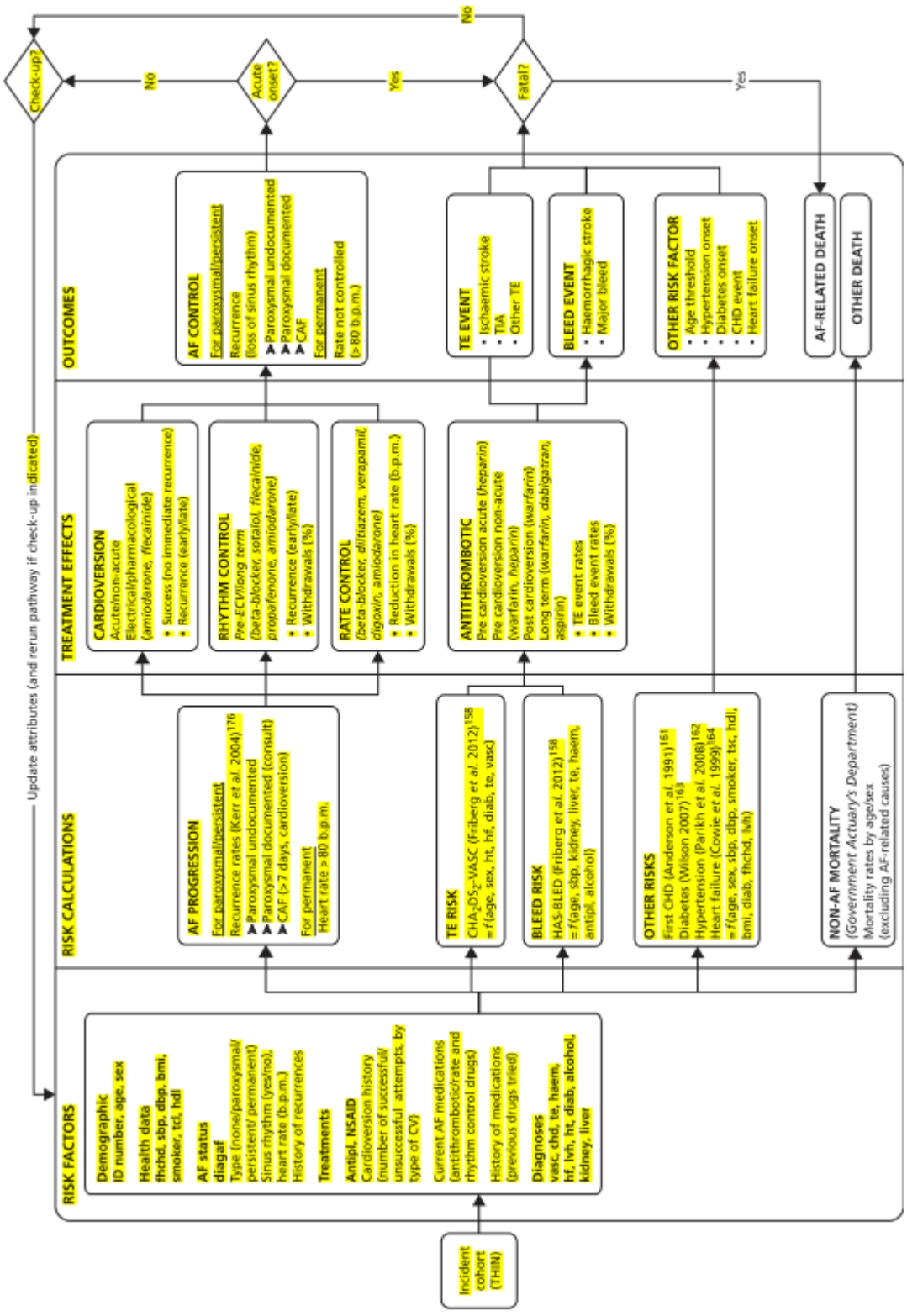


Figure 4. Atrial fibrillation disease process model, from Lord et al.

Lowres et al

A prospective study was performed and reported by Lowres et al. [4]. The effectiveness and cost-effectiveness of community screening for AF were evaluated. The target group for AF-screening was people ≥65 years visiting one of ten pharmacies in Sydney, Australia. The systematic opportunistic screening strategy was compared to a no-screening strategy. The screening method used was pulse palpation and hand-held iPhone-based single-lead ECG interpreted by a nurse and a cardiologist. If AF was suspected individuals were referred to their GP. Costs and outcomes were followed for 10 years for a cohort of 65- to 84-year old. Stroke risk information retrieved from previous studies was a very important factor for the health economic evaluation. Patients detected with AF were assumed to be treated with warfarin. The economic model used was not clearly reported, but assumedly it consisted of an initial decision-tree followed by a longer-term Markov model (as do most models in this area). Compared to no screening ICERs from a health care perspective were €3,142 per QALY and €15,993 per stroke prevented. Sensitivity analyses showed that results were most sensitive to assumptions on treatment adherence.

Aronsson et al

Aronsson et al. [5] analyzed the cost-effectiveness of systematic population screening for AF in 75- and 76-year-olds in Sweden. The screening method for detection of asymptomatic AF was intermittent ECG recording for two weeks (data from the STROKESTOP study). Following an initial decision tree, a Markov model was applied that tracked future consequences over the patients' lifetimes and with a societal perspective. Structure of the model and states included are described in Figure 5.

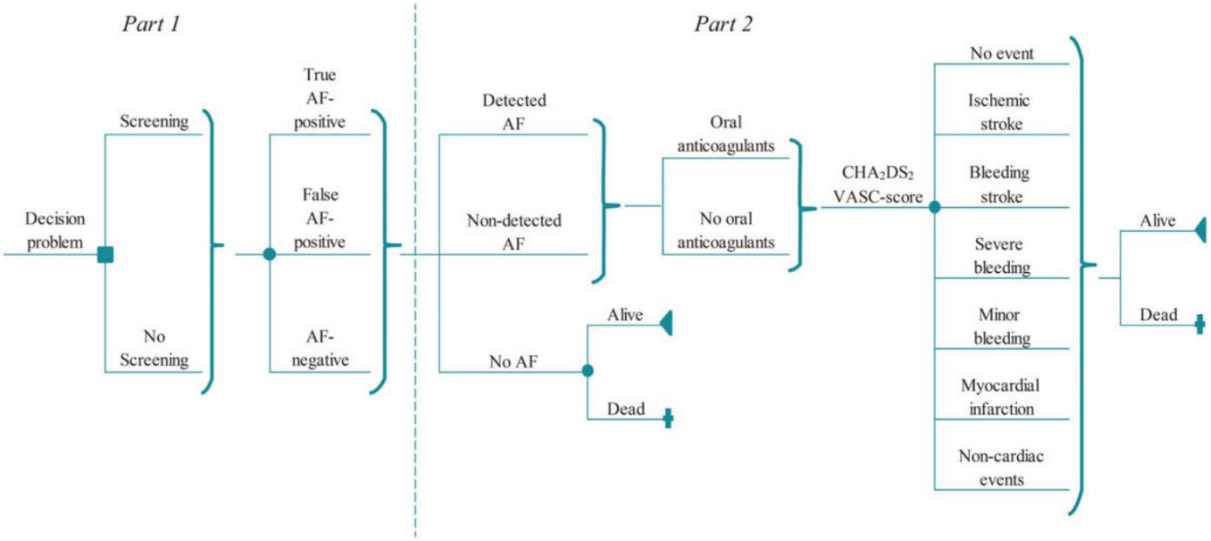


Figure 5. A basic description of the structure in the decision analytic Markov model, from Aronsson et al.

The decision problem and screening procedure is described in Part 1 of the model, while Part 2 shows how the risk of thrombo-embolic events and bleedings depends on AF-status and CHA2DS2-VASC score. All individuals may also suffer death from non-cardiac reasons. Part 2 was repeated every month for the rest of the life of the hypothetical individuals. Some of the patients detected with AF were assumed to be contraindicated for anticoagulation therapy, and the remainder were assumed to

use a DOAC (apixaban). In a sensitivity analysis, patients were instead assumed to use warfarin. ICERs reported from the base case model analysis were, for screening compared with no screening, €4,313 per QALY gained and €6,583 per stroke avoided.

Moran et al

The study by Moran et al. [6] assessed from a societal perspective the cost-effectiveness of a primary care based national screening program for AF in Ireland. An annual systematic opportunistic screening strategy was compared to no screening in people ≥65 years. The screening method used was pulse palpation followed by an ECG interpreted by a GP and an algorithm in cases where an irregular pulse was detected. Data were taken from a variety of sources for instance the SAFE study and the Irish Longitudinal Study on Ageing (TILDA). A model was used including an initial decision tree followed by a Markov model to capture long-term (until the age of 90 years) costs and benefits from treatment. The structure of and states included in the Markov model is described in Figure 6.

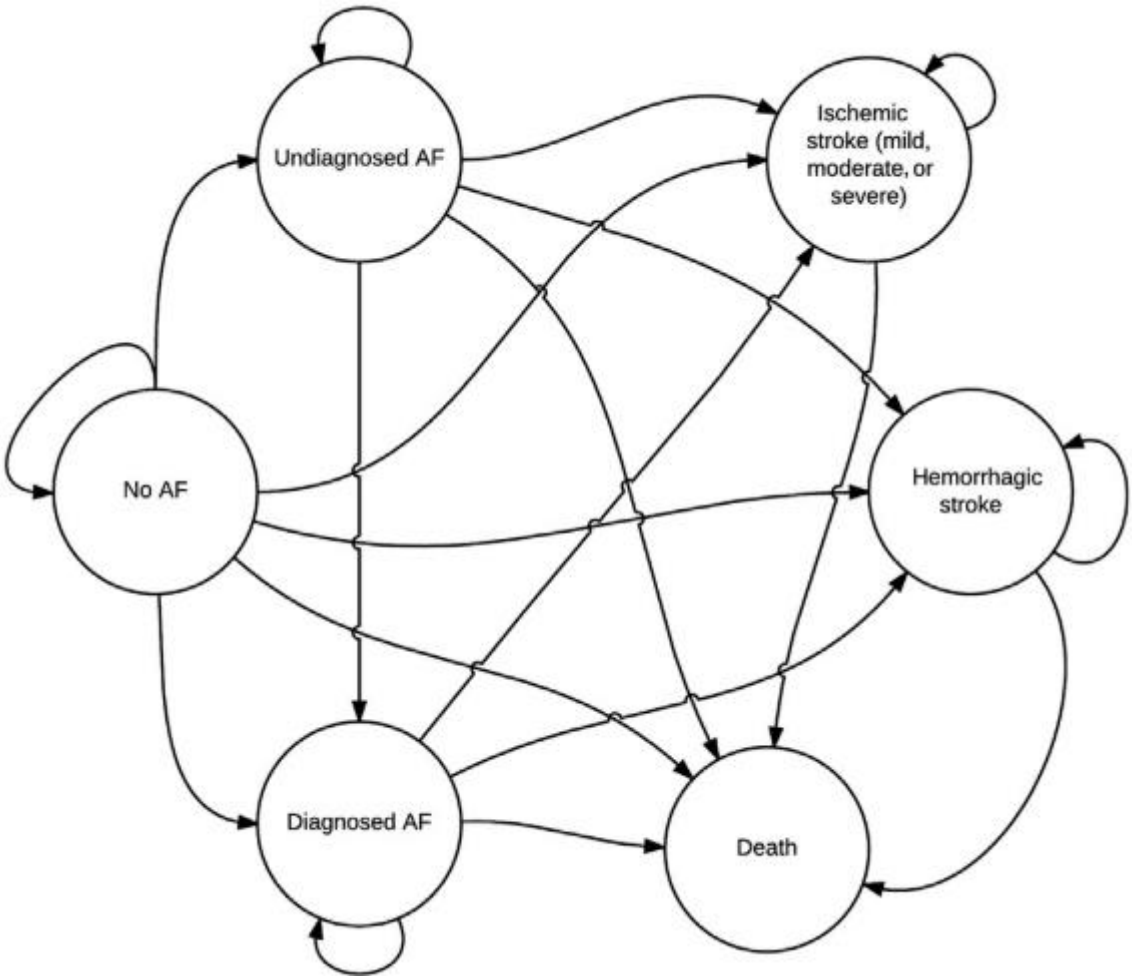


Figure 6. Model structure, from Moran et al.

Patients diagnosed with AF were assumed to be treated with DOACs, warfarin, antiplatelets, or no treatment. The distribution of different treatments was taken from TILDA and other routine sources. The analysis of screening compared with no screening resulted in an ICER of €20,271 per QALY. The result was sensitive to the start age of screening (€50,578 if screening were to start at the age of 50

years and €14,594 with 70 years as start age. Sensitivity analyses also showed that the result was sensitive to screening interval, with shorter intervals leading to increasing ICERs.

Levin et al

The study by Levin et al. [7] was a cost-effectiveness study, from a societal perspective, of screening for asymptomatic AF in 75-year old patients with a recent ischemic stroke. The screening strategies compared were intermittent ECG recordings using a handheld recording device at regular time intervals for 30 days, short-term 24 hours continuous Holter ECG, and a no-screening strategy. For the initial time period a decision tree was used and for the long-term (20 years) tracking of consequences a Markov model was used. Figure 7 describes states and events in the Markov model.

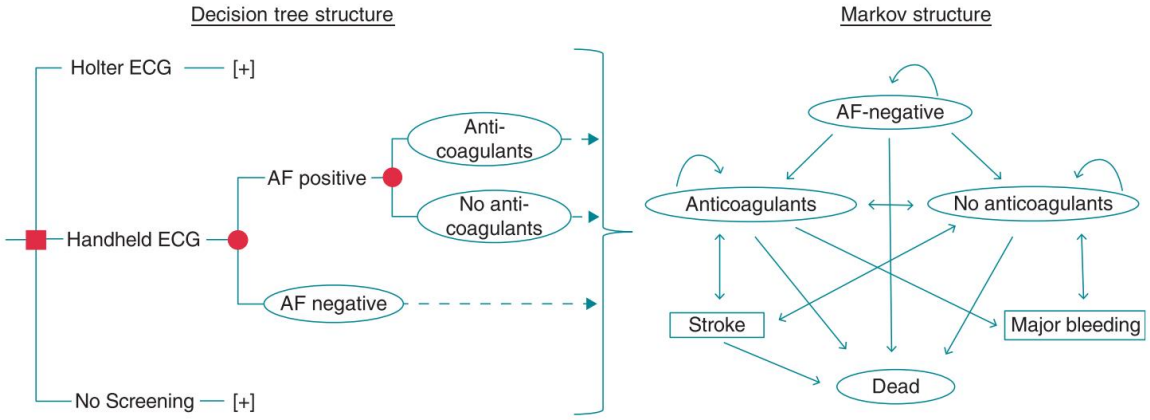


Figure 7. The structure of the decision analytic model, from Levin et al.

The initial decision tree represents the screening outcome. The Markov structure tracks patients' costs and effects for the analysed horizon. Ellipses represent health states and squares represent events.

The results of the model analysis were that Holter ECG was dominated (higher costs and less QALYs gained) by intermittent ECG screening. In a cohort analysis (1000 patients) over a 20-year period intermittent ECG screening compared to no screening resulted in 11 avoided strokes, 23 QALYs gained, and cost savings of €55,400.

Welton et al

In an HTA report by Welton et al. [8] a comprehensive literature review of economic evaluations of screening for AF was undertaken. They found only six studies reporting cost per QALY results of screening for AF (refs 1-6 in this document). Based on the review of previous literature a model was created to compare the cost-effectiveness of population-based screening programs. The model consists of an initial decision tree followed by a Markov model to track long-term costs and benefits. The decision tree describes the screening part including screening attendance, screening tests and findings, and diagnostic test results. The Markov model tracks AF-related events and mortality conditional on anticoagulant therapy. A previously published network meta-analysis of trials comparing DOACs with warfarin (INR range 2-3) was used to capture cost and benefits of anticoagulant therapy in AF over a lifetime perspective. The Markov model is described in Figure 8.

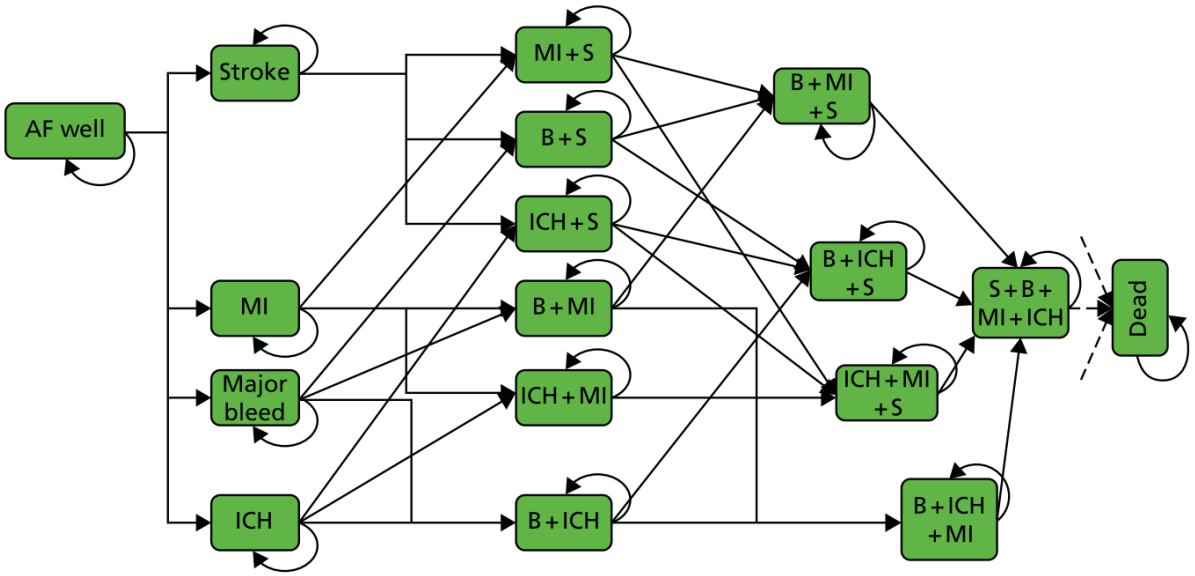


Figure 8. Discrete-time Markov model structure for screen-detected AF patients, from Welton et al.

B, major bleed; ICH, intracranial haemorrhage; S, stroke; MI, Myocardial Infarction.

The base-case results reported concern single screen invitation at different ages: 55, 60, 65, 70, 75 and 80 years. Both systematic population and systematic opportunistic screening strategies were considered and a number of different screening tests were analyzed: photoplethysmography, modified blood pressure monitor, pulse palpation (nurse), single-lead ECG (automatic/algorithm or nurse or GP or cardiologist), > 1- and < 12-lead ECG (cardiologist or automatic/algorithm), 12-lead ECG (nurse or GP or automatic/algorithm) Both ICERs and Incremental Net Benefits (INBs) were presented. In nearly all cases screening for AF had an ICER below £20,000, or a positive INB at a willingness-to-pay threshold of £20,000. Throughout the analyses, systematic opportunistic screening was cost-effective compared to systematic population screening and compared to no screening. The most cost-effective screening test was photoplethysmography. Results were sensitive to start age of screening, repeated screening and intervals

Jacobs et al

Jacobs et al. [9] used a societal perspective and a life time horizon when analyzing the cost-effectiveness of screening for AF in people 65 years and older in the Netherlands. The strategy analyzed was opportunistic screening of people coming to the primary care for influenza vaccination, and the screening test used was a handheld single-lead ECG. The screening strategy was compared to no screening. The model used for the analysis consisted of an initial decision tree and for the long-term analysis a Markov model with 3-months cycles was used. A schematic description of the Markov model is described in Figure 9.

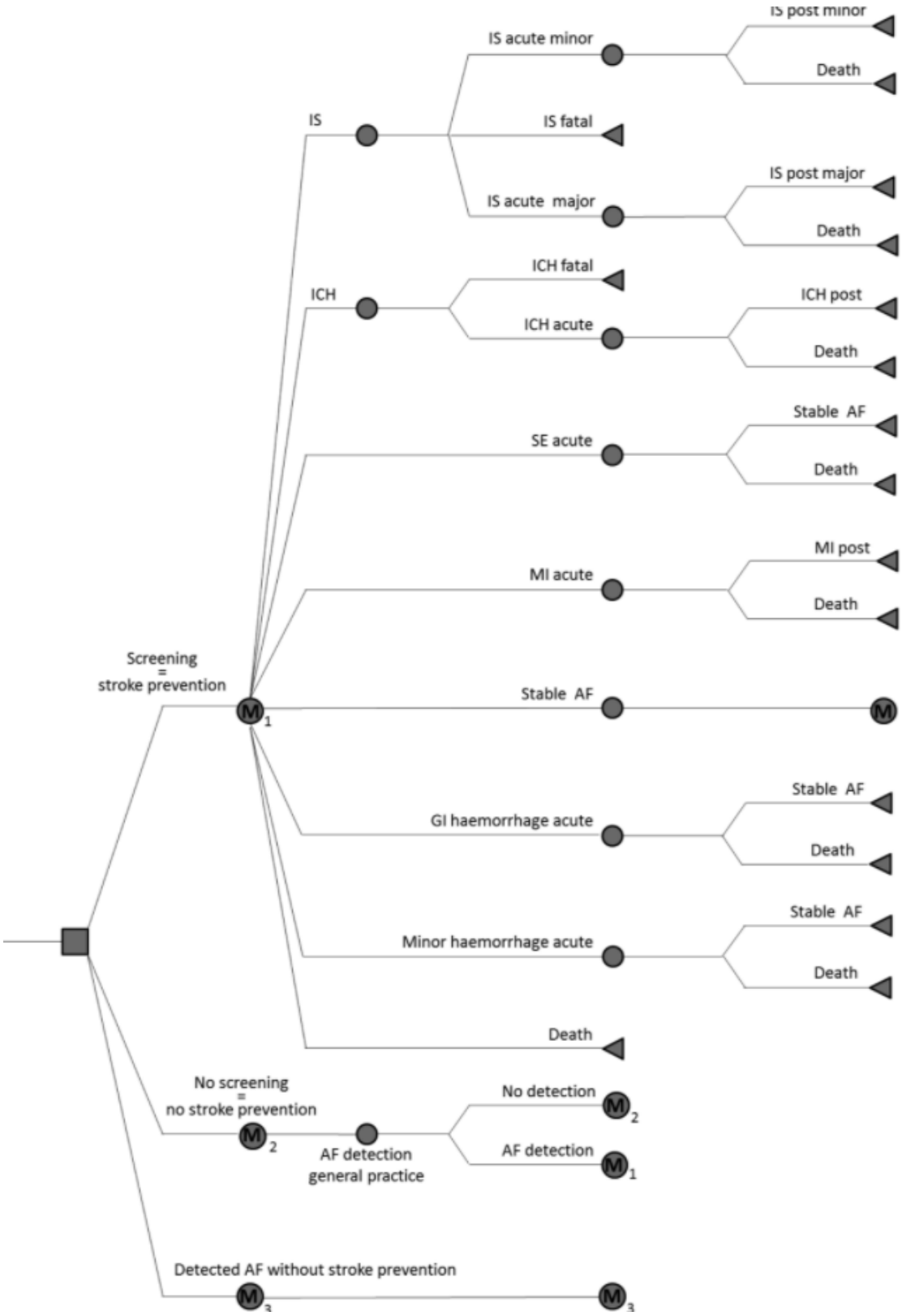


Figure 9. A schematic representation of the Markov structure, from Jacobs et al.

Event probabilities were derived from clinical trials. In comparison with a no screening strategy the handheld test analyzed in this study proved both to reduce overall costs by €764 and to increase benefits by 0.27 QALYs per patient. Results were robust with a slight sensitivity to costs for stroke and NOACs.

Tarride et al

The study by Tarride et al. [10] presents an economic evaluation of a cohort screened for AF in family practices in Canada. The cohort consisted of 2054 individuals 65 years or older from 22 family practices. A Markov model was used for tracking lifetime consequences and the analysis had a public payer perspective. Four strategies were analyzed:

- Screen with a 30-second radial manual pulse check (pulse check)
- Screen with a blood pressure machine with AF detection (BP-AF)
- Screen with a single-lead electrocardiogram (SL-ECG)
- No screening

Individuals detected with AF were assumed to receive oral anticoagulants (OACs). In the Markov model with 3-month cycles were incorporated risks for *ischemic stroke*, *intracranial haemorrhage (ICH)*, *non-ICH major bleeding*, and *death*. AF patients treated with OACs are assumed to be at lower risk for ischemic stroke but at higher risk of ICH and non-ICH major bleeding, compared to those not receiving OACs.

Compared to no screening both pulse check and BP-AF were dominant strategies (i.e. cost saving and generated more QALYs), while SL-ECG should be considered a cost-effective strategy with a cost per QALY of CAD$4,788. Comparing the different screening strategies, pulse check was the strategy associated with lowest expected costs ($202) and SL-ECG with the highest expected costs ($222). SL-ECG was the strategy resulting in highest expected number of QALYs (8.74362), and no screening resulted in the lowest expected number of QALYs (8.74195). So, effects on both costs and QALYs of AF screening were quite marginal. Results were robust according to sensitivity analyses performed.

Conclusions from the literature review

Economic evaluations of AF screening found in the literature have a lot of features in common. The most relevant features are summarized below.

The cost-effectiveness of screening

- AF screening is in principle cost-effective regardless of strategy and method. Opportunistic screening (lower costs) seems to be most cost-effective (uptake of screening is a possible problem). However population screening programs find more AF and saves more QALYs.
- Simply put, the results are driven by: 1) How effective are the program at discovering new AF cases? 2) How well are newly discovered AF patients treated concerning compliance?

Simulation model attributes

- All models identified have similar approaches, consisting of two parts – one decision-tree describing the initial screening procedure and its' results, thereafter a Markov model (or Discrete Event Simulation model) to trace long-term costs and benefits (QALYs).

- In later models, shorter cycle length has been used in the analysis (3 months instead of 12 months)
- The same health states reoccur in the different model studies. In the first part: screening or no screening (uptake), thereafter detected/undetected AF or No AF (dependent on sensitivity and specificity – i.e.. True/False AF-positive and AF-negative)
- Long-term model: Important health states/events are (risk for) stroke, bleeding, MI
- The most common target group is ≥ 65 years
- The most common, and due to gain in survival most sensible time perspective is lifetime
- Production loss is not included (considering the patients' age)

(Cost-effectiveness) results have been reported to be sensitive to:

- Stroke risk in patients with asymptomatic AF which is also largely based on some form of assumption
- Short term and long-term costs in the event of stroke
- Anticoagulant treatment adherence
- Time horizon
- Uptake of systematic opportunistic screening

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Appendix 1. Description of literature searches.

Web of Science (as shown in the Methods section)

Search no.	References found	Search terms
# 36	111	#35 AND #34 AND #4
# 35	4,461	#33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21
# 34	10,464,861	TS=((cost OR "cost benefit analysis" OR "health economics" OR pharmacoeconomics OR "cost analysis" OR cost-analysis OR "cost effectiveness analysis" OR "cost effective" OR cost-effective OR "cost utility analysis" OR "cost utility" OR cost-utility OR modeling OR modelling OR "economic model" OR "cost minimization analysis" OR costminimization OR costminimisation OR cost-minimisation OR cost-minimization OR "cost minimization" OR (model AND (cost OR economy OR economics OR pharmacoeconomic)) OR "economic model" OR "statistical model" OR "budget impact analysis" OR "budget impact" OR econometrics OR econometric OR markov OR "decision analysis" OR "discrete event simulation" OR "economic evaluation" OR "cost control" OR cost AND (effective OR utility OR benefit OR minimization OR minimisation)))
# 33	679	#20 AND #5
# 32	1,944	#19 AND #5
# 31	187	#18 AND #5
# 30	33	#17 AND #5
# 29	14	#16 AND #5
# 28	11	#15 AND #5
# 27	186	#14 AND #5
# 26	84	#13 AND #5
# 25	82	#12 AND #5
# 24	515	#11 AND #5
# 23	205	#10 AND #5
# 22	956	#9 AND #5
# 21	22	#8 AND #5
# 20	11,307	TS=(((mobile OR i-phone) AND app))
# 19	93,507	TS=(((reveal OR implantable) AND device))
# 18	4,698	TS=(photoplethysmograph*)
# 17	211	TS=(((modified OR “atrial fibrillation” OR PAF OR AF) AND (“BP monitor” OR “blood pressure monitor” OR sphygmomanometer)))
# 16	307	TS=((Sphygmomanometers OR “Blood pressure monitoring”, ambulatory/) AND (modified OR “atrial fibrillation” OR PAF OR AF))
# 15	44	TS=(Watchbp)
# 14	2,22	TS=(finger probe)
# 13	568	TS=((pulse AND (finger-tip or palpation)))

Search no.	References found	Search terms
# 12	499	TS=(pulse AND palpation)
# 11	14,08	TS=(((holter OR “cardiac event” OR R-test OR 7-day) AND monitor))
# 10	3,975	TS=(((ECG OR iECG OR electrocardiography OR EKG) AND (ELR OR holter OR “event monitor” OR “event record” OR “loop record”)))
# 9	13,708	TS=(((ECG OR iECG OR electrocardiography OR EKG) AND (“single lead” OR serial OR intermittent OR bipolar OR bi-polar OR thumb OR short-term OR 12-lead OR ambulatory OR portable)))
# 8	340	#7 AND #6
# 7	19,151	TS=(holter OR “single lead” OR 12-lead OR “event monitor” OR “event record” OR “loop record” OR ELR)
# 6	1,116	TS=(Electrocardiography, Ambulatory)
# 5	937,259	TS=(Screening)
# 4	102,587	#3 OR #2 OR #1
# 3	5,01	TS=(supraventricular arrhythmia)
# 2	191	TS=(auricular fibrillation)
# 1	99,422	TS=(Atrial fibrillation)

PubMed

AF Disease terms

(("Atrial Fibrillation"[Title/Abstract]) OR ("auricular fibrillation"[Title/Abstract]) OR ("supraventricular arrhythmia"[Title/Abstract]))

73,933 references

AF Screening interventions

(((screening[Title/Abstract]) AND ((Electrocardiography, Ambulatory[Title/Abstract]) AND (holter[Title/Abstract] OR "single lead"[Title/Abstract] OR 12-lead[Title/Abstract] OR "event monitor"[Title/Abstract] OR "event record"[Title/Abstract] OR "loop record"[Title/Abstract] OR ELR[Title/Abstract]))) OR ((screening[Title/Abstract]) AND (((ECG[Title/Abstract] OR iECG[Title/Abstract] OR electrocardiography[Title/Abstract] OR EKG)[Title/Abstract] AND ("single lead"[Title/Abstract] OR serial[Title/Abstract] OR intermittent[Title/Abstract] OR bipolar[Title/Abstract] OR bi-polar[Title/Abstract] OR thumb[Title/Abstract] OR short-term[Title/Abstract] OR 12-lead[Title/Abstract] OR ambulatory[Title/Abstract] OR portable))[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((ECG[Title/Abstract] OR iECG[Title/Abstract] OR electrocardiography[Title/Abstract] OR EKG)[Title/Abstract] AND (ELR[Title/Abstract] OR holter[Title/Abstract] OR "event monitor"[Title/Abstract] OR "event record"[Title/Abstract] OR "loop record"))[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((holter[Title/Abstract] OR "cardiac event"[Title/Abstract] OR R-test[Title/Abstract] OR 7-day)[Title/Abstract] AND monitor)[Title/Abstract])) OR ((screening[Title/Abstract]) AND

(pulse[Title/Abstract] AND palpation[Title/Abstract])) OR ((screening[Title/Abstract]) AND ((pulse[Title/Abstract] AND (finger-tip[Title/Abstract] OR palpation))[Title/Abstract])) OR ((screening[Title/Abstract]) AND ("finger probe"[Title/Abstract])) OR ((screening[Title/Abstract]) AND (Watchbp[Title/Abstract])) OR ((screening[Title/Abstract]) AND ((Sphygmomanometers[Title/Abstract] OR "Blood pressure monitoring", ambulatory/)[Title/Abstract] AND (modified[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR PAF[Title/Abstract] OR AF)[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((modified[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR PAF[Title/Abstract] OR AF)[Title/Abstract] AND ("BP monitor"[Title/Abstract] OR "blood pressure monitor"[Title/Abstract] OR sphygmomanometer))[Title/Abstract])) OR ((screening[Title/Abstract]) AND (photoplethysmograph[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((reveal[Title/Abstract] OR implantable)[Title/Abstract] AND device)[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((mobile[Title/Abstract] OR i-phone)[Title/Abstract] AND app)[Title/Abstract])))

3,616 references

AF Economic evaluations

(((((("Atrial Fibrillation"[Title/Abstract]) OR ("auricular fibrillation"[Title/Abstract]) OR ("supraventricular arrhythmia"[Title/Abstract])) AND (((screening[Title/Abstract]) AND ((Electrocardiography, Ambulatory[Title/Abstract]) AND (holter[Title/Abstract] OR "single lead"[Title/Abstract] OR 12-lead[Title/Abstract] OR "event monitor"[Title/Abstract] OR "event record"[Title/Abstract] OR "loop record"[Title/Abstract] OR ELR[Title/Abstract]))) OR ((screening[Title/Abstract]) AND (((ECG[Title/Abstract] OR iECG[Title/Abstract] OR electrocardiography[Title/Abstract] OR EKG)[Title/Abstract] AND ("single lead"[Title/Abstract] OR serial[Title/Abstract] OR intermittent[Title/Abstract] OR bipolar[Title/Abstract] OR bi-polar[Title/Abstract] OR thumb[Title/Abstract] OR short-term[Title/Abstract] OR 12-lead[Title/Abstract] OR ambulatory[Title/Abstract] OR portable))[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((ECG[Title/Abstract] OR iECG[Title/Abstract] OR electrocardiography[Title/Abstract] OR EKG)[Title/Abstract] AND (ELR[Title/Abstract] OR holter[Title/Abstract] OR "event monitor"[Title/Abstract] OR "event record"[Title/Abstract] OR "loop record"))[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((holter[Title/Abstract] OR "cardiac event"[Title/Abstract] OR R-test[Title/Abstract] OR 7-day)[Title/Abstract] AND monitor)[Title/Abstract])) OR ((screening[Title/Abstract]) AND (pulse[Title/Abstract] AND palpation[Title/Abstract])) OR ((screening[Title/Abstract]) AND ((pulse[Title/Abstract] AND (finger-tip[Title/Abstract] OR palpation))[Title/Abstract])) OR ((screening[Title/Abstract]) AND ("finger probe"[Title/Abstract])) OR ((screening[Title/Abstract]) AND (Watchbp[Title/Abstract])) OR ((screening[Title/Abstract]) AND ((Sphygmomanometers[Title/Abstract] OR "Blood pressure monitoring", ambulatory/)[Title/Abstract] AND (modified[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR PAF[Title/Abstract] OR AF)[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((modified[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR PAF[Title/Abstract] OR AF)[Title/Abstract] AND ("BP monitor"[Title/Abstract] OR "blood pressure monitor"[Title/Abstract] OR sphygmomanometer))[Title/Abstract])) OR ((screening[Title/Abstract])

AND (photoplethysmograph[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((reveal[Title/Abstract] OR implantable)[Title/Abstract] AND device)[Title/Abstract])) OR ((screening[Title/Abstract]) AND (((mobile[Title/Abstract] OR i-phone)[Title/Abstract] AND app)[Title/Abstract]))))) AND (cost[Title/Abstract] OR "cost benefit analysis"[Title/Abstract] OR "health economics"[Title/Abstract] OR pharmacoeconomics[Title/Abstract] OR "cost analysis"[Title/Abstract] OR cost-analysis[Title/Abstract] OR "cost effectiveness analysis"[Title/Abstract] OR "cost effective"[Title/Abstract] OR cost-effective[Title/Abstract] OR "cost utility analysis"[Title/Abstract] OR "cost utility"[Title/Abstract] OR cost-utility[Title/Abstract] OR modeling[Title/Abstract] OR modelling[Title/Abstract] OR "economic model"[Title/Abstract] OR "cost minimization analysis"[Title/Abstract] OR costminimization[Title/Abstract] OR costminimisation[Title/Abstract] OR cost-minimisation[Title/Abstract] OR cost-minimization[Title/Abstract] OR "cost minimization"[Title/Abstract] OR (model[Title/Abstract] AND (cost[Title/Abstract] OR economy[Title/Abstract] OR economics[Title/Abstract] OR pharmacoeconomic))[Title/Abstract] OR "economic model"[Title/Abstract] OR "statistical model"[Title/Abstract] OR "budget impact analysis"[Title/Abstract] OR "budget impact"[Title/Abstract] OR econometrics[Title/Abstract] OR econometric[Title/Abstract] OR markov[Title/Abstract] OR "decision analysis"[Title/Abstract] OR "discrete event simulation"[Title/Abstract] OR "economic evaluation"[Title/Abstract] OR "cost control"[Title/Abstract] OR cost[Title/Abstract] AND (effective[Title/Abstract] OR utility[Title/Abstract] OR benefit[Title/Abstract] OR minimization[Title/Abstract] OR minimisation))[Title/Abstract])) NOT ((animal NOT human[Title/Abstract]) OR (comment[Publication Type] OR letter[Publication Type] OR editorial[Publication Type] OR "case report"[Publication Type] OR "case study"[Publication Type] OR "case report" OR"case series"[Publication Type])))

24 references

Scopus

Type of studies	**Search terms**	**References found**
Disease terms	(TITLE-ABS-KEY ("Atrial fibrillation")) OR (TITLE-ABS-KEY ("auricular fibrillation")) OR (TITLE-ABS-KEY ("supraventricular arrhythmia"))	111,992
Screening interventions	((TITLE-ABS-KEY (screening)) AND ((TITLE-ABS-KEY (electrocardiograph* AND ambulatory)) AND (TITLE-ABS-KEY (holter OR "single lead" OR 12-lead OR "event monitor" OR "event record" OR "loop record" OR elr)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((ecg OR iecg OR electrocardiograph* OR ekg) AND ("single lead" OR serial OR intermittent OR bipolar OR bi-polar OR thumb OR short-term OR 12-lead OR ambulatory OR portable))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((ecg OR iecg OR electrocardiography OR ekg) AND (elr OR holter OR "event monitor" OR "event record" OR "loop record"))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((holter OR "cardiac event" OR r-test OR 7-day) AND monitor)))) OR ((	3,543

	TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (pulse AND palpation))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ((pulse AND (finger-tip OR palpation))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ("finger probe"))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (watchbp))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ((sphygmomanometers OR "Blood pressure monitoring" , AND ambulatory/) AND (modified OR "atrial fibrillation" OR paf OR af)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((modified OR "atrial fibrillation" OR paf OR af) AND ("BP monitor" OR "blood pressure monitor" OR sphygmomanometer))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (photoplethysmograph*))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((reveal OR implantable) AND device)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((mobile OR i-phone) AND app))))	
Economic evaluations	((TITLE-ABS-KEY ("Atrial fibrillation")) OR (TITLE-ABS-KEY ("auricular fibrillation")) OR (TITLE-ABS-KEY ("supraventricular arrhythmia"))) AND (((TITLE-ABS-KEY (screening)) AND ((TITLE-ABS-KEY (electrocardiograph* AND ambulatory)) AND (TITLE-ABS-KEY (holter OR "single lead" OR 12-lead OR "event monitor" OR "event record" OR "loop record" OR elr)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((ecg OR iecg OR electrocardiograph* OR ekg) AND ("single lead" OR serial OR intermittent OR bipolar OR bi-polar OR thumb OR short-term OR 12-lead OR ambulatory OR portable))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((ecg OR iecg OR electrocardiography OR ekg) AND (elr OR holter OR "event monitor" OR "event record" OR "loop record"))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((holter OR "cardiac event" OR r-test OR 7-day) AND monitor)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (pulse AND palpation))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ((pulse AND (finger-tip OR palpation))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ("finger probe"))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (watchbp))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY ((sphygmomanometers OR "Blood pressure monitoring" , AND ambulatory/) AND (modified OR "atrial fibrillation" OR paf OR af)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((modified OR "atrial fibrillation" OR paf OR af) AND ("BP monitor" OR "blood pressure monitor" OR sphygmomanometer))))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (photoplethysmograph*))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((reveal OR implantable) AND device)))) OR ((TITLE-ABS-KEY (screening)) AND (TITLE-ABS-KEY (((mobile OR	42

	i-phone) AND app))))) AND (TITLE-ABS-KEY ((cost OR "cost benefit analysis" OR "health economics" OR pharmacoeconomics OR "cost analysis" OR cost-analysis OR "cost effectiveness analysis" OR "cost effective" OR cost-effective OR "cost utility analysis" OR "cost utility" OR cost-utility OR modeling OR modelling OR "economic model" OR "cost minimization analysis" OR costminimization OR costminimisation OR cost-minimisation OR cost-minimization OR "cost minimization" OR (model AND (cost OR economy OR economics OR pharmacoeconomic)) OR "economic model" OR "statistical model" OR "budget impact analysis" OR "budget impact" OR econometrics OR econometric OR markov OR "decision analysis" OR "discrete event simulation" OR "economic evaluation" OR "cost control" OR cost AND (effective OR utility OR benefit OR minimization OR minimisation))))	

Appendix 2. Quality Assessment of Included Economic Analyses.

Column1	**Column2**	**Column3**
Study assessed		
	Yes/No/Not clear/NA	Comments
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		

Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		

NA=Not applicable.

Adapted from Drummond and Jefferson [40].