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Review Article

Cost-Effectiveness of Atrial Fibrillation Screening Strategies: A Systematic Review

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Abstract

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia. AF is associated with an increased risk of stroke. We aimed to review systematically the cost-effectiveness of screening strategies for patients with AF.

Methods: To find related research and articles, articles published in Iranian and international databases by using a combination of MeSH (Medical Subject Headings) terms and based on inclusion and exclusion criteria were searched and reviewed until Dec 2020. The main outcome measures of the final articles were incremental cost-effectiveness ratios (ICER) per gained or additional quality-adjusted life years (QALYs), additional case detected, and avoided stroke.

Results: Out of 3,360 studies found, finally, fifteen studies were included in the research. The lowest ICER numerical value was 78.39 for AF screening using ECG for 65-85 yr old Japanese women. The highest value of this index is equal to 70864.31 for performing ECG monitoring for more than 60 d for Canadians over 80 yr without AF history. In two studies, the results were expressed with the years of life gained (YLG measure. Of course, in one study, the results were not reported with this measure, and in one study, the results were reported with ICER.

Conclusion: Most of the studies acknowledged the cost-effectiveness of different AF screening strategies. However, studies that confirmed the cost-effectiveness of population-based screening were more than studies that confirmed the cost-effectiveness of other screening strategies.

Keywords: Cost-effectiveness; Economic evaluation; Atrial fibrillation screening

Introduction

AF is the most common cardiac arrhythmia that occurs in more than 10% of patients 75 yr and older (1-3). The incidence and prevalence of AF are increasing worldwide, growing threefold over the past 50 yr and becoming the epidemic of cardiovascular disease in the 21st century (1, 4-6). The prevalence of this complication increases with being more grown, from about 1% to 5% of the total population of people over 65 yr of age (7). In recent years, AF has become a health and

economic issue, with 33 million people worldwide being infected in 2010, and that number is expected to double by 2050 (8).

AF is associated with an increased risk of stroke. However, the disease is often asymptomatic and may not be known before a stroke (9-11). People with asymptomatic AF may be up to three times more likely to have a stroke before being diagnosed with AF (2). Early detection and management of AF prophylactic treatments such as oral anticoagulants can decrease the risk of stroke; As a result, patient health outcomes (e.g., quality of life and life expectancy) improve (12, 13) and the economic burden on health care providers reduce (14).

Despite all the research efforts in the field of AF, the prevention of this disease and its associated complications remains a challenge (15). Due to its cost and lack of evidence and more effective than conventional care for AF, international groups continue to oppose the use of systematic population-based screening in asymptomatic patients (16, 17). Currently, the importance of screening to detect asymptomatic AF has been realized in collaboration with the Medical Association. Opportunistic screening for AF is also recommended by international guidelines. Screening may reduce the risk of death and complications from a stroke, but its widespread implementation is costly. Judging whether spending money for clinical gain is still a matter of debate (18). In Canada, AF screening strategies with pulse screening were less expensive and more QALYs compared to no screening. Moreover, screening usage of a blood pressure monitor by AF detection algorithm was superior to the no screening strategy. The incremental cost of QALYs single-lead electrocardiogram (SL-ECG) was $4788 compared to no screening (1, 2).

In general, two potential population-screening strategies include opportunistic case detection and systematic screening. In finding patients' opportunistic cases, a health professional takes the patient's pulse during the consultation. If the pulse is irregular, an ECG is taken from the patient as a confirmatory test; But in systematic screening, the entire target population is called in for ECG testing (19).

Considering the upward trend in the incidence and prevalence of AF in different parts of the world and its significant economic burden at the individual, social and national levels, this study by searching international scientific and specialized databases and also by reviewing articles extracted from these databases, the cost-effectiveness of the AF screening program systematically reviewed and analyzed.

Methods

We aimed to review systematically the cost-effectiveness of screening strategies for patients with AF.

Search strategy

To find related research and articles, articles published in Iranian databases including SID, Magiran, Irandoc, ISC, Iranmedix, and also international databases including Web of Science, Medline, Pubmed, Embase, Scopus, National Health Services Evaluation Database, Cochrane of Reviewed Systematic Database: DAHTA-Database were searched and reviewed by using a combination of MeSH terms until Dec 2020. Furthermore, Google Scholar site were also used to complete the search.

Ethics declarations

The authors declare that due to no containment of clinical studies and patient data in this manuscript, there was no contrast with ethical standards.

Inclusion Criteria

The population in this study includes all patients with AF used screening strategies to diagnose the disease early. Intervention includes recurrent ECG recording, continuous Holter ECG, use of manual ECG devices, etc. Comparators are all screening strategies that can be substituted. The measurement of the results of the final articles was based on ICER per gained or additional QALYs, additional cases detected and avoided stroke.

Exclusion Criteria

1- Items such as review articles, abstracts, protocols, letters to the editor, etc.

2- Articles whose full text was published other than in English and Persian.

3- Studies in which full text was not available.

Procedure

All studies related to the cost-effectiveness of atrial fibrillation screening strategies were selected according to the inclusion and exclusion criteria mentioned above and duplicate cases were removed using Endnote 20 software. In the first stage, the title and summary of the remaining studies were studied independently by two researchers. If there was a disagreement, the third researcher reviewed the studies to avoid any bias. In the next stage, the full text of the studies was carefully examined by two researchers separately. Any disagreements between the researchers were addressed by the third person. Moreover, by referring to the list of included study sources, we tried to include qualified articles that were related to the study. Potential studies and researches eligible for inclusion in this study were retrieved and duplicates were removed using Endnote software ver. 20. Then screening studies based on title and abstract and based on inclusion and exclusion criteria were evaluated and reviewed by two people, at this stage, the principles of PRISMA were followed. Moreover, to make cost comparisons easier, all costs were converted to 2021 US dollars based on the purchasing power parity (PPP) index using the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Converter.

In terms of statistical analysis, the extracted articles were compared with each other based on indicators such as incremental cost-effectiveness ratios (ICER) per gained or additional quality-adjusted life years (QALYs).

Results

Based on the PRISMA flowchart in Fig. 1, the initial search results produced 3,360 records, and finally, 15 studies were included in the research.

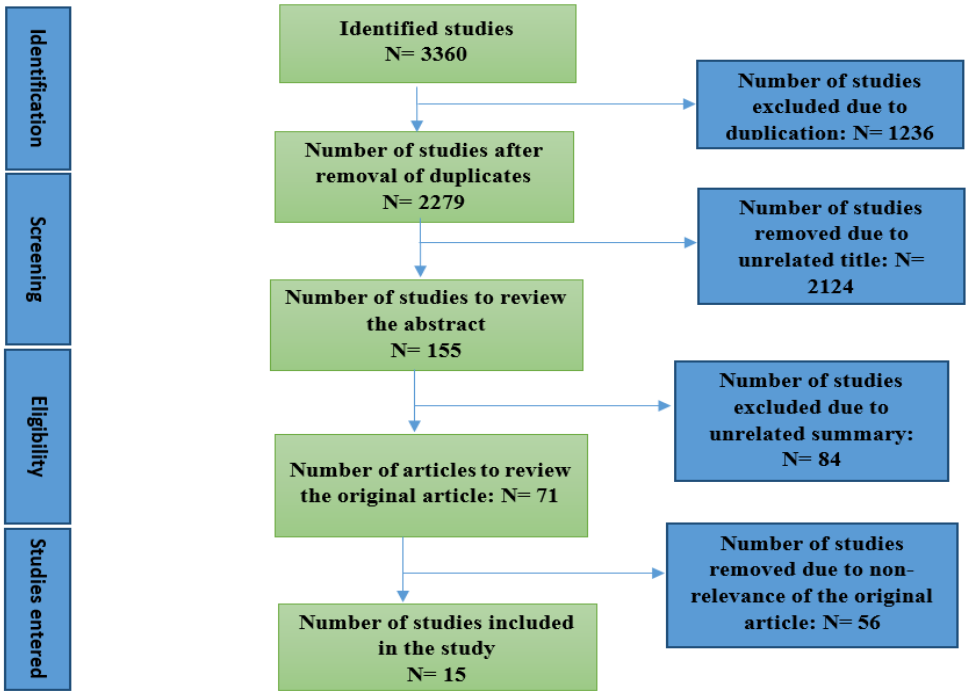

Fig. 1: PRISMA flowchart

The specifications and results of the studies are presented in Tables 1 and 2.

Study characteristics (Table 1)

Location: Netherlands, Canada, Ireland, Japan, Denmark, and the United States have published one study, Germany, the United Kingdom, and Australia two studies, and finally, Sweden three studies.

Perspective: In terms of study perspective, three studies were from the patient perspective, six studies were from the social perspective, three studies were from the health system perspective, and finally, two studies did not mention the study perspective.

Sensitivity analysis methods: In terms of uncertainty and sensitivity analysis method, three studies used only definitive sensitivity analysis (one and two way), two studies only probabilistic sensitivity analysis, and finally, four studies jointly used sensitivity and probability analysis. Other studies did not provide a clear report.

Type of AF screening method: Based on different AF screening strategies, out of fifteen final studies, eight studies analyzed the cost-effectiveness of systematic population screening strategy, three articles on targeted screening strategy, and two articles on opportunistic screening strategy. Finally, two studies analyzed all three screening strategies.

Type of economic evaluation: 13 studies merely analyzed the cost-effectiveness of AF screening strategies, and two studies evaluated these methods in terms of cost-effectiveness and cost-effectiveness.

Model Structures: The majority of the articles (nine articles) used Markov model, either alone or in combination with other models, to conduct cost-effectiveness and sensitivity analyses. Decision tree and decision analytic model were used in four articles. A simulation model, a multicenter randomized controlled trial, and a Monte Carlo simulation based on developed state-transition model, were each used in three different articles. In two articles, the model used was not reported.

Table 1: Characteristics of the final studies extracted

Study	*Country*	*Main result*	*Perspective*	*Interventions and comparator*	*Participant age (sex)*
Ralf Birkemeyer 2020 (20)	German	Systematic screening on AF with pretentious Heartbeats was associated with the health benefits and economic effects	Statutory sick funds	Pretentious Heartbeats screening, Non-screening	75-year-old
Hobbs 2005 (21)	West Midlands, UK	Opportunistic screening being cost-effective	Patient perspective	The targeted screening of people at higher risk of AF, Total population screening, Opportunistic AF screening	65 yr and over
Godwin D Giebel 2020 (22)	German	The mHealth devices to screen for AF leads to increased costs but also a reduction in the incidence of stroke	Patient-oriented perspective	ECG diagnosis positive and negative	Age 65-74 yr, age≥75 yr, female
Nathan R. Hill 2020 (14)	UK	Targeted screening being cost-effective	The UK NHS perspective	Targeted screening, Systematic screening, Opportunistic AF screening	Adults >= 50 yr
Maartje S. Jacobs	Netherlands	Population screening being cost-effective	Societal perspective	Not Reported	All patients older than 65

2018 (23)					yr
Mattias Aronsson 2015 (18)	Sweden	Screening for asymptomatic AF is cost-effective	Public health perspective	Asymptomatic AF screening, Non-screening	75-year-old individuals
Mattias Aronsson 2017 (24)	Sweden	Opportunistic screening being cost-effective	A health care payer perspective	Repeated screening, One-off screening	The ages of 65, 75, 78, 80, and 82 yr
Mustafa Oguz 2019 (25)	USA	Population screening being cost-effective	The US healthcare system perspective	Single 12-lead ECG, 14-day extended screening with Zenicor single-lead ECG, Z14, No screening	75-year-old individuals
Jessica Orchard 2020 (26)	Australia	Population screening being cost-effective	Not Reported	Using the Health Tracker app, Treatment rates before and during the study period AF, Metropolitan and Nonrandomized Control Groups	People ≥65 yr
Marco Proietti 2019 (27)	Danmark	Population screening being cost-effective	Not Reported	Screening performance analysis using a population-wide screening model	People ≥65,75 yr
Maeda 2004 (28)	Japan	Population screening being cost-effective	Societal perspective	Annual screening with ECG, Annual screening with pulse palpation, No screening	65-year-old
Lowres 2014 (29)	Australia	Screening with ECG and an automated algorithm is both feasible and cost-effective	Health funder perspective	Pulse palpation and ECG, No screening	People aged 65-84
Levin 2014 (30)	Sweden	Screening of silent AF by intermittent ECG recordings is cost-effective	Societal perspective	Screening using handheld ECG, Screening using 24 hour Holter ECG, No screening	75–85 yr
Moran 2016 (31)	Ireland	Opportunistic screening being cost-effective	Societal perspective	Annual opportunistic AF screening, No Screening	People aged 65 yr or older
McIntyre 2020 (32)	Canada	Targeted screening being cost-effective	Payer perspective	ECG monitoring (30 d and more if no AF was detected), No Screening	Individuals ≥ 80 yr

Outcome (Table 2)

The main outcome measures of the final articles were ICER per gained or additional QALYs, additional case detected, and avoided stroke. The lowest ICER numerical value was 78.39 for AF screening using ECG for 65-85 yr old Japanese women (28). Moreover, the highest value of this index is equal to 70864.31 for performing ECG monitoring for more than 60 d for Canadians

over 80 yr without AF history referred to outpatient clinics (32). The measurement of results in a study was expressed with the YLG measure (22). In a study, the measurement of results was expressed with YLG together with QALY (18).

Table 2: Characteristics of the final studies extracted

Study	*Outcome measure*	*QALY/YLG*			*Incremental costs $ (95% CrI)*	*Incremental QALYs (95% CrI)*	*ICER $ (95% CrI)*	*threshold of willingness to pay*	*discount rate*	*Sensitivity Analysis Method*
		YLG	*QALY*	*DALY*						
Ralf Birkemeyer 2020 (20)	Cost per QALY		✓		144.39	65 yr old: 0.008 75 yr old: 0.018 85 yr old 0.021	ICER ratio of 5663.57 per additional QALY	Not Reported	3%	Deterministic and probabilistic
Hobbs 2005 (21)	ICER		✓		Opportunisti: 18394.04 Systematic high risk: 41198.84 Systematic population: 79752.39	Not Reported	11738.31 per QALY in men and 14672.89 in women	Not Reported	3.5%	Probabilistic and one-way
Godwin D Giebel 2020 (22)	Costs per prevented stroke	✓			Not Reported	Not Reported	Not Reported	Not Reported	3%	Sensitivity analysis for values of device sensitivity (86%, 93%, 100%)
Nathan R. Hill 2020 (14)	Cost per QALY gained		✓		Systematic Screening (per 1,000 patients): –7211.52 Events: –12442.95 Treatment: 43812.49 Opportunistic Screening: –2255.43 Events –7511.76 Treatment: 26450.06	Systematic: patients with AF diagnosed through screening (per 1,000 patients): 34.71 Patients not diagnosed thorough screening: –31.31 Opportunistic: patients diagnosed through screening: 20.95 Patients not diagnosed thorough screening:	Systematic: 7098.75 Opportunistic: 8119.55	29291.32	3.5%	Univariate

					–18.90				
Maartje S. Jacobs 2018 (23)	Overall costs to QALYs per patient		✓	Overall costs by 1016.64	QALYs by 0.27 yr per patient	448.44 per additional case detected up to 5739.22 per QALY gained	26613.58 per QALY gained	Health gains: 1.5%, all unit costs: 4%	Probabilistic and univariate
Mattias Aronsson 2015 (18)	Cost per gained QALY &avoided stroke	✓	✓	6377.66	No screening: 6646 Screening: 6657	Cost of 550 per gained QALY and 839.48 per avoided stroke	Higher than 637.61	0%	Deterministic and probabilistic sensitivity analysis
Mattias Aronsson 2017 (24)	Cost per gained QALY		✓	588.88	Per QALY	588.88 cost per gained QALY	Not Reported	3%	Deterministic two-way and probabilistic
Mustafa Oguz 2019 (25)	Cost per QALY		✓	1884860.08 with ECG 12-lead 6548194.57 with Z14	$58,728 with ECG 12-lead $47,949 with Z14	61200.59 with12-lead ECG and 49967.77 with Z14	104210.25	3%	Deterministic
Jessica Orchard 2020 (26)	1. Cost per QALY 2. Cost-saving		✓	Not Reported	Not Reported	Not Reported	Not Reported	5%	Not Reported
Marco Proietti 2019 (27)	Cost per QALY		✓	Not Reported	Not Reported	3465.71	Higher than 569.44	Not Reported	Probabilistic
Maeda 2004 (28)	Cost per QALY		✓	1. ECG: Male: 1.29 Female: 1.54 2. Pulse Palpation: Male: 1.23 Female: 1.5	Incremental QALYs: ECG Male: 5.86 Female: 5.37 Pulse Palpation Male: 5.83 Female: 5.35	1. CG Male: 80.37 Female: 78.39 2. Pulse Palpation Male: 593.71 Female: 102.32	Not Reported	3%	Markov model
Lowres 2014 (29)	ICER per QALY gained, ICER per stroke avoided		✓	Not Reported	Not Reported	ICER per QALY gained: 4677.94 ICER per stroke avoided: 23812.34	Not Reported	5%	Not Reported
Levin	Cost		✓	Not Report-	Not Report-	Cost per	Not	3%	One-way sensitivity

2014 (30)	per life-year gained, cost per QALY gained		ed	ed	QALY gained: 338.4	Report-ed		
Moran 2016 (31)	Cost per QALY	✓	110	0.0036441	30124.31	58928.63 /QALY	5%	Not Reported
McIntyre 2020 (32)	Cost per QALY	✓	1. 7 d monitoring: 231981.13 2. Up to 30 d monitoring: 416550.06 3. Up to 60 d monitoring: 645991.25	1. 7 d monitoring: 5 2. Up to 30 d monitoring: 7 3. Up to 60 d monitoring: 9	1. 7 d monitoring: 42247.66 2. Up to 30 d monitoring: 59095.92 3. Up to 60 d monitoring: 70864.31	Not Report-ed	1.5%	One-way

Discussion

This study is the first systematic review study in the last five years that comprehensively evaluates the cost-effectiveness of various AF screening strategies (33). All studies had been conducted in high-income and middle-income countries. As noted in the findings, of all the studies found, most studies considered the systematic population screening strategy. Although most studies have considered screening strategies based on designated people to diagnose AF, the NICE guidelines recommend opportunistic case finding and not screening strategies. In addition, this guideline has been emphasized the use of clinical judgments of health care professionals when examining irregular heart rhythms and possible diagnosis of AF and providing standard care. Furthermore, the wearable device is recommended as an effective factor to follow up with a health care professional; however, this issue has been addressed in a study reviewed in this study (34).

According to the studies reviewed, various screening methods have been performed mainly on people in the age range of 65-75 yr. Of course, a number of these studies have been conducted outside this age range, and presenting the results and analyzing them in this age range is more documented and evidence-based. Moreover, a review of the extracted studies showed that economic evaluation of each of the three AF screening strategies with the comparator of no screening, each of the strategies was cost-effective, which indicates the importance of screening to identify and diagnose people at risk of AF. (18,20,25,28-32) For example, Aronsson et al. examined asymptomatic intermittent screening AF with asymptomatic screening conditions using the analytical decision-making simulation model. In this study, a cost of $550 per gained QALYs and $839.48 per avoided stroke, and the incremental cost was reported to be $6377.66. This study has acknowledged that screening for asymptomatic AF in the elderly was cost-effective and that the effectiveness of AF screening, despite its cost, was higher than no screening (18).

In Mustafa Oguz's study, non-valvular AF (NVAF) screening through single 12-lead ECG and single 12-lead ECG compared with 14-day extensive screening through the hand-held ECG device (Zenicor single-lead ECG, Z14) and no screening. ICER in this study reported $58,728 in the 12-lead ECG mode and $47,949 in the Z14. Screening the general population at age 75 for

NVAF was cost-effective on the threshold of willingness to pay of $100,000 (25).

In addition, in two studies, one of the screening strategies as an intervention was compared with the other two strategies as a comparator. In Hill et al.'s study (14), Targeted screening was compared with opportunistic AF screening and population screening strategies. The final QALYs for every 1000 patients diagnosed through targeted screening is 34.71 compared to population screening and 20.95 compared to opportunistic screening, which refers to the cost-effectiveness of the targeted screening strategy. Also, In Hobbs et al.'s study (21), opportunistic screening was compared with systematic screening (targeted and total population screening). The incidence and prevalence of the disease in the control population compared to both populations are a systematic intervention. In addition, the systematic or opportunistic intervention population is higher, which is also logical because the control population includes a group of people with a higher risk of AF and the prevalence rate is higher among such people. In this study, model-based analyzes showed small differences in cost and quality of life with different methods and severity of screening, but opportunistic annual screening resulted in the lowest number of ischemic strokes and the highest incidence of AF. Sensitivity results showed that screening for AF in men and women 65 yr of age was about 60% more cost-effective. In the implementation of the opportunistic screening strategy, 243 patients had irregular pulse without an initial diagnosis of AF, and in the ECG examination of 177 patients, 31 new cases were identified, which showed a prevalence of 0.69%. Overall, 44 new cases were identified without a screening program. In addition, in the implementation of the systematic screening strategy, by performing ECG on 2357 patients, 52 new cases were identified with an incidence of 1.1% per year. Of these, 31 were diagnosed by targeted screening and another 21 by total population screening. Another 22 cases were diagnosed outside the screening program. Typically, systematic high risk cost $21,119 and Systematic population $40,882, which is higher than opportunistic screening due to the size of the target community, the way it is run, and the variety of screening programs. Therefore, considering the number of people diagnosed and identified without a screening program, for economic justification, planning should be done in such a way that all people with AF are identified under a screening program (21).

Limitations

Despite some measures such as converting different currencies in the articles into a single currency and unifying them to facilitate calculations and validate comparisons between studies, because of the heterogeneity and differences between the final studies in terms of model structure, different study time intervals, comparative interventions and cases, different screening strategies and tests, and different outcome indicators, etc., cannot provide a comprehensive and conclusive conclusion. In addition, in this systematic review study and based on the designed search approach, only studies published in English and Persian were considered.

Conclusion

Related to high-income and middle-income countries, most of the studies acknowledged the cost-effectiveness of different AF screening strategies. However, studies confirming the cost-effectiveness of population-based screening were more than studies that confirmed the cost-effectiveness of strategies other than population-based screening. In general, this can be attributed to lower costs and higher effectiveness of this type of screening strategy due to earlier detection of AF disease, which in total can reduce direct costs from out-of-pocket and third party payers and can lead to an increase in the number of timely diagnoses of patients with AF. In addition, the implementation of AF screening strategies can be a good alternative to clinical delayed assessments and diagnoses and the subsequent expensive diagnostic and treatment methods.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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