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

Hassan Abolghasem Gorji 1, *Majid Khosravi 1, Razieh Mahmoodi 1, Mojtaba Hasoumi 1, Aghdas Souresrafil 1, Vahid Alipour 1, Aziz Rezapour 1, Marjan Hajahmadi 2, Samad Azari 1

1. Health Management and Economics Research Center, Health Management Research Institute, Iran University of Medical Sciences, Tehran, Iran
2. Cardiovascular Department, Rasoul Akram General Hospital, Iran University of Medical Sciences, Tehran, Iran

*Corresponding Author: Email: khosravi.m1@gmail.com

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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 Adults ≥ 50 yr |
| 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 |

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| Year | Country | Study Description | Perspective | Additional Details |
|------|---------|-------------------|-------------|--------------------|
| 2018 | Sweden  | Screening for asymptomatic AF is cost-effective | Public health perspective | Asymptomatic AF screening, Non-screening |
| 2015 | Sweden  | Opportunistic screening being cost-effective | A health care payer perspective | Repeated screening, One-off screening |
| 2017 | Sweden  | 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 Using the Health Tracker app, Treatment rates before and during the study period AF, Metropolitan and Nonrandomized Control Groups Screening performance analysis using a population-wide screening model Annual screening with ECG, Annual screening with pulse palpation, No screening |
| 2019 | Australia | Population screening being cost-effective | Societal perspective | People ≥65 yr |
| 2014 | Japan | Population screening being cost-effective | Not Reported | 65-year-old |
| 2014 | Australia | Screening with ECG and an automated algorithm is both feasible and cost-effective | Health funder perspective | People aged 65-84 |
| 2014 | Sweden | Screening of silent AF by intermittent ECG recordings is cost-effective | Societal perspective | 75-85 yr |
| 2016 | Ireland | Opportunistic screening being cost-effective | Societal perspective | People aged 65 yr or older |
| 2020 | Canada | Targeted screening being cost-effective | Payer perspective | Individuals ≥ 80 yr |
| 2018 | Canada | Screening with ECG and an automated algorithm is both feasible and cost-effective | Health funder perspective | People aged 65-84 |
| 2020 | Canada | Screening of silent AF by intermittent ECG recordings is cost-effective | Societal perspective | 75-85 yr |
| 2016 | Ireland | Opportunistic screening being cost-effective | Societal perspective | People aged 65 yr or older |
| 2020 | Canada | Targeted screening being cost-effective | Payer perspective | 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 7064.31 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 |
|--------------------------------|-----------------|----------|-------------------------------|-------------------------------|-----------------|---------------------------------|---------------|-----------------------------|
| Ralf Birkenmeyer 2020 (20)    | Cost per QALY   | ✔        | 144.39                        |                               | ICER ratio of 5663.57 per additional QALY | Not Reported | 3%                          | Deterministic and probabilistic |
| Hobbs 2005 (21)               | ICER            | ✔        | Opportunistic: 18394.04        | Systematic high risk: 41198.84 | Systematic population: 79752.39 | 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: 29291.3 | Systematic: 7098.75 Opportunistic: 8119.55 | 29291.3 | 3.5%                        | Univariate |

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| Author                  | Year | Costs          | Cost per additional QALY gained | Health gains | Probabilistic and univariate analysis |
|-------------------------|------|----------------|----------------------------------|--------------|--------------------------------------|
| Maartje S. Jacobs       | 2018 | Overall costs to 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 | 1.5%, all unit costs: 4% |
| Mattias Aronsson        | 2015 | Cost per gained QALY and avoided stroke | 6377.66 | Higher than 637.61 | 0% |
| Mattias Aronsson        | 2017 | Cost per gained QALY | 588.88 cost per gained QALY | Not Reported | 3% |
| Mustafa Oguz            | 2019 | Cost per QALY | 1884860.08 with ECG 12-lead 6548194.57 with Z14 | Not Reported | Not Reported |
| Jessica Orchard         | 2020 | Cost per QALY | Not Reported | Not Reported | Not Reported |
| Marco Proietti          | 2019 | Cost saving Cost per QALY | Not Reported | Not Reported | Not Reported |
| Maeda                   | 2004 | 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 | Not Reported | 3% |
| Lowres                  | 2014 | ICER per QALY gained, ICER per stroke avoided | Not Reported | Not Reported | Not Reported |
| Levin                   |      | Cost | Not Reported | Cost per | Not | 3% |

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### 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

| Year | Screening Method | Cost per QALY gained | Cost per life-year gained, per QALY gained | QALY gained | Cost per QALY gained | Report- ed | Moran 2016 | McIn- tyre 2020 |
|------|------------------|----------------------|-------------------------------------------|-------------|----------------------|------------|------------|--------------|
| 2014 | (30)             |                      |                                            | 338.4       |                      |            | ✔          |              |
| 2016 | (31)             |                      |                                            | 58928.6     | 5%                   | Not Report- ed |            |              |
| 2020 | (32)             |                      |                                            | 70864.31    |                      | One-way    |            |              |
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 opportunistc 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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