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Understanding the Burden of Atrial Fibrillation and Importance of Screening: A Global Perspective and Recommendations for Turkey

REVIEW

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ABSTRACT

Considering the aging population, the increase in predisposing factors, and the improvement in healthcare with increased survival rates, atrial fibrillation has been the most common cardiac arrhythmia in adults with a rise in the estimated lifetime risk over recent years. While aging is a powerful risk factor for atrial fibrillation, the leading prevalent comorbidities are hypertension, heart failure, obesity, obstructive sleep apnea, diabetes mellitus, and chronic kidney disease. Atrial fibrillation is associated with substantial morbidity, impaired quality of life, and increased mortality and healthcare costs. As a significant proportion of the total atrial fibrillation population is asymptomatic or mildly symptomatic, early identification and initiation of appropriate treatment for atrial fibrillation may prevent potentially detrimental outcomes such as stroke and heart failure and decrease all-cause mortality. Although screening via evolving health technologies has recently been emerging, verification of the electrocardiogram track recording over at least 30 seconds by a physician with expertise is still required for a definite diagnosis. Based on the global and national data and the current healthcare environment in Turkey, this targeted review with cardiology, neurology, and family physicians' perspectives highlights the importance of early detection by implementing the advancing screening modalities as well as the need for raised awareness of both patients and healthcare professionals and establishment of a multidisciplinary clinical approach for a better outcome in atrial fibrillation management.

Keywords: Atrial fibrillation, burden of disease, stroke, screening, morbidity, mortality

INTRODUCTION

Atrial fibrillation (AF) is the most common recurrent adult arrhythmia of clinical significance, and the current worldwide epidemiological data show that it is a global epidemic with remarkable mortality and morbidity. European Society of Cardiology (ESC) defined AF as the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing with an irregular ventricular response.[1] Atrial fibrillation is associated with a transient ischemic attack, ischemic stroke, systemic embolism, heart failure (HF), cognitive decline, and dementia.[2] Stroke risk has been successfully predicted by the CHA_2DS_2-VASc score based on a 9-point scale including congestive HF, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65-74 years, and sex (female). Although the most common symptoms are dyspnea, chest pain, dizziness, fatigue, and palpitations, a remarkable proportion of patients stay completely asymptomatic during each presentation of AF, and most of them remain underdiagnosed in clinical practice.[3] Therefore, the true prevalence of AF is suspected to be higher when these subclinical or "silent" AF cases are included.[4]

While AF is a complex problem that causes a significant burden to patients, caregivers, and healthcare systems, management of AF patients requires a miscellaneous, comprehensive, and multidisciplinary approach. As a continuum of this approach, early detection of AF has become more important and recent, significant progress has been made for this by implementing advancing technologies

for diagnosis and screening. However, there is still a lack of evidence for the sufficiency of screening programs and the impact of early detection in AF on its clinical outcomes. Therefore, in this review, we aimed to look into the global and national current disease burden of AF from multiple perspectives such as epidemiology, modifiable, and nonmodifiable risk factors, as well as to understand the current global screening efforts in order to improve the clinical outcomes of AF and provide specific recommendations for future diagnostic landscape in Turkey.

METHOD

In the preparation phase of this review, 3 cardiologists and 3 neurologists with proven experience in AF and stroke prevention working in university and training and research hospitals in Turkey gathered along with 2 family physicians, who are board members of the Family Physician's Association, in a meeting to identify the scope of the review article and literature search, evaluate the resources, and develop recommendations related to the investigation topics.

HIGHLIGHTS

- Early detection of atrial fibrillation (AF) has become more important, and significant progress has been made for this by implementing advancing technologies for diagnosis and screening. However, there is still a lack of evidence for the sufficiency of screening programs and the impact of early detection in AF on its clinical outcomes.
- While this study highlighted that current screening methods require extensive monitoring and are limited by low cost-effectiveness, a variety of new technologies and machine learning were found to be helpful to develop rapid, cheap, and accurate diagnosing tools which can easily be used at home. However, again more data are needed as evidence for their effectiveness.
- Family physicians (FP) in Turkey will be able to monitor and manage their patients with chronic diseases including AF soon by the recently introduced "Disease Management Platform" initiative. Therefore, this new era on how FP will operate can be an opportunity to identify AF patients in the primary care setting in a timely manner.
- In order to achieve timely AF diagnosis, we believe that FPs' awareness of AF symptoms and electrocardiogram assessment abilities should be improved, family medicine, cardiology, and neurology societies/associations should work together to optimize educational content for continuous FP training programs, and interdisciplinary communication between these specialties should be improved via integrated electronic records system to provide sufficient disease management after the initial diagnosis.
- Finally, the targeted screening population needs to be defined and prioritized carefully to establish time and cost-effective screening programs for AF in the Turkish primary care setting.

The main literature search was performed in English and Turkish by searching MEDLINE, EMBASE, and PubMed databases for the 2010-2022 period in order to utilize the most recent data. Literature dating back to previous periods was reviewed only for the purpose of evaluating the historical evolution of treatments. The main literature search was done by using AF, disease burden, mortality, morbidity, risk factors, and screening as fixed terms. The citations of references were reviewed when relevant and finally, most recent, related guidelines were also assessed.

Epidemiology

The absolute number of AF cases has almost doubled from 1990 to 2017 due to population growth and aging. Access to advanced screening techniques for patients with a risk of AF and increased awareness might also been contributed to this rise. More asymptomatic cases have been diagnosed. The estimated global number of individuals with AF in 2010 was 33.5 million [(20.9 million males (uncertainty interval (UI), 19.5-22.2 million) and 12.6 million females (UI, 12.0-13.7 million)].[5] In 2017, global data revealed that there were 37.57 million (95% UI, 32.55-42.59) prevalent cases and 3.05 million (95% UI, 2.61-3.51) incident cases of AF. The age-standardized prevalence and incidence of AF were 481.5 (95% UI, 416.5-546.2) per 100 000 people and 38.2 (95% UI, 32.6-43.9) per 100 000 people, respectively. The number of AF-associated deaths has also more than doubled in this 20-year period. The age-standardized mortality rate of AF was 4.0 (95% UI, 3.9-4.2) per 100 000 people in 2017.[6]

The estimated prevalence of AF in the United States of America varies from approximately 2.7 million to 6.1 million in 2010, and AF prevalence is predicted to increase to 12.1 million in 2030.[7] In the European Union, the prevalence of AF in adults >55 years of age was calculated to be 8.8 million (95% CI, 6.5-12.3 million) in 2010 and was estimated to reach 17.9 million in 2060 (95% CI, 13.6-23.7 million).[8] Age- and gender-adjusted prevalence of AF varied 12-fold between regions, with the highest in North America, Europe, China, and Southeast Asia (270-360 cases per 100 000 persons) and the lowest in the Middle East, Africa, and South Asia (30-60 cases per 100 000 persons) ($P < .001$). Atrial fibrillation prevalence was 7-fold higher in middle-income countries (MICs) and 11-fold higher in high-income countries (HICs) ($P < .001$) than in low-income countries (LICs). These variations in AF prevalence in different regions are explained by traditional AF risk factors that are tied to economic development. However, the low number of AF cases may also be related to the difficulties in the diagnosis of AF, and further studies are needed.[9]

Although the lifetime risks of AF have been demonstrated as 1 in 4 in individuals from the Framingham Heart Study (FHS) and Rotterdam Study, more recent studies from Framingham and the European BiomarCaRE Consortium illustrated that the lifetime risk for AF in European ancestry has increased to 1 in 3.[10-12] The lifetime risk of AF in the Atherosclerosis Risk in Communities (ARIC) study cohort was approximately 1 in 3 among Whites and 1 in 5 among African Americans.[13]

Although the epidemiology of AF has been extensively reported in the United States and Europe, there is not enough data reported from the developing countries. More recently, several epidemiological studies have been performed in Turkey, a country with a younger population. As a part of the Turkish Adult Risk Factor Study, cohorts from 1990 to 1997/1998 and 2002/2003 have been followed up until 2006/2007 screening and 3450 participants (1707 men, 1743 women; mean age 52 ± 13 years) have been involved. In Turkish adults, the current incidence and prevalence of chronic AF were anticipated to be 35 000 per year (22 000 in women) and 310 000 (200 000 in women), respectively.[14] Data from the population-based TuRkish Atrial Fibrillation (TRAF) cohort from 2008 to 2012 suggest that the estimated prevalence of AF in Turkey was 1.08%.[15]

Risk Factors

Unmodifiable Risk Factors

There are some differences between men and women in terms of AF epidemiology. The Olmsted County Minnesota and the Rotterdam studies showed that the AF incidence (per 1000 person-years) was 4.7 and 11.5 in men and 2.7 and 8.9 in women, respectively.[11,16] A higher incidence of AF in men was also reported in Asian populations while some showed differences.[5,17] Similarly, the age-adjusted prevalence of AF is higher in men than in women in North American and European populations. The higher prevalence of AF in men is also stated in both HICs and LICs and MICs.[5] However, a database study from China reported that the estimated lifetime risk of AF at the age of 55 was 21.1% (95% CI, 19.3%-23.0%) for females and 16.7% (95% CI, 15.4%-18.0%) for males.[17] According to the Global Burden of Disease Study 2017, AF cases were also more in males compared to females, with a higher age-standardized incidence rate. Conversely, age-standardized mortality rate was higher in females [4.1 (95% UI 3.9-4.2) per 100 000 people] than in males [3.9 (95% UI 3.5-4.4) per 100 000 people].[6]

It has been proven that there is an increasing trend for the incidence of AF with advancing age. Global Burden of Disease Study 2017 revealed that the number of AF prevalent and incident cases peaked at the ages of 75-79 and 65-69 in both sexes, respectively.[6] In the BiomarCaRE study, the incidence increased after age 50 years in males and 60 years in females, but the cumulative incidence of AF was similar, at >30%, by age 90 years.[12] According to the FHS, there was a 4.98-, 7.35-, and 9.33-fold risk of AF in the age groups of 60-69, 70-79, and 80-89 years, respectively, compared with the 50-59 years group.[18] Similar to that, in a Turkish cohort, the prevalence rates were 0.46%, 2.09%, and 2.49%, and the incidence rates were 0.31, 1.98, and 3.50 per 1000 person-years in the age groups 32-59, 60-69, and ≥70 years, respectively.[14] However, 43.4% of the Turkish cohort involved in GARFIELD-AF registry was under 65 years of age, possibly due to a younger population presence in Turkey compared to the other participating countries in this registry.[19] While the frequency in females was higher than in males (56% vs. 44%) in Atrial Fibrillation in Turkey: Epidemiologic Registry, 50.5% of the patients were women in another cohort from Turkey.[19,20]

Racial differences were shown in the incidence of AF. In the UK Clinical Practice Research Datalink study which had a cohort of ≥45 years of age, the incidence rates per 1000 person-years standardized to the UK population were 8.1 (95% CI, 8.1-8.2) in Whites vs. 5.4 (95% CI, 4.6-6.3) in Asians and 4.6 (95% CI, 4.05.3) in Black patients.[21] Moreover, the lifetime risk of AF recently has been estimated to be approximately 1 in 3 among Whites and 1 in 5 among Blacks in the United States.[7] The lifetime risk of AF was 36% and 30% in white men and women, 21% and 22% in African American men and women, retrospectively.[13] In addition, family history was found to be associated with an increased risk of developing AF. Fourteen genetic loci have shown to be related to AF inheritance.[22]

Modifiable Risk Factors

Physical activity is associated with AF, not only sedentary lifestyle causes a higher risk of AF but also excessive physical activity is also related with increased AF risk.[23] While a sedentary lifestyle directly increases systemic inflammation and causes autonomic dysfunction, it also induces other risk factors such as hypertension, obesity, and diabetes. On the other hand, excessive exercise may also promote AF by both increasing the vagal tone and causing cardiac remodeling.[22]

Smoking is an important risk factor for AF. The Rotterdam Study found that both former and current smoking were equally associated with increased AF risk.[24] In the ARIC study, the multivariable-adjusted incidence of AF was 1.5- and 2-fold higher in ever-smokers and current smokers, respectively.[25] Exposure during gestational development or early childhood is associated with an approximately 40% increased risk of AF.[26]

There has been a significant association between elevated body mass index and AF by causing left atrial enlargement, increased left ventricular mass, and diastolic dysfunction. A meta-analysis stated that obesity enhances AF risk by almost 50% in a gradual manner.[27]

The FHS illustrated that diabetic men and women had a 40% and 60% increased risk of AF, respectively.[28] Patients with diabetes or impaired glucose homeostasis had a 34% greater risk of AF than individuals without diabetes.[29] Worse glycemic control and a longer duration of diabetes are associated with increased AF risk. The predicted risk of AF increases by 3% per additional year of diabetes. The risk of AF in patients with diabetes for >10 years was almost 10-fold higher than in those with diabetes less than 5 years.[30]

Obstructive sleep apnea (OSA) has also been associated with risk of developing AF. The Sleep Heart Health Study showed that AF prevalence was 4 times higher in the OSA cohort, and almost one-third of participants experienced arrhythmia during sleep.[31] The Olmsted County Study confirmed the higher AF rates in the individuals with OSA and revealed that the magnitude of nocturnal oxygen desaturation was predictive for AF.[32] The Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) registry showed that patients with OSA had more severe symptoms and hospitalization

need was higher than those without OSA but had similar mortality, risk of stroke, or myocardial infarction. Treatment of OSA with continuous positive airway pressure prevents the progress to developing permanent AF.[33]

High blood pressure is also suspected to be a risk factor of AF. While there was a minor association with mean arterial pressure, pulse pressure was highly predictive of AF risk.[34] The CHARGE-AF consortium found that both higher systolic and diastolic blood pressure were significantly associated with AF.[35] Fifty-year follow-up of the FHS revealed that being under anti-hypertensive treatment does not completely clear off the elevated AF risk associated with hypertension.[18]

There are several other potentially modifiable risk factors for AF such as coronary artery disease, HF, hyperlipidemia, chronic kidney disease, and alcohol and tobacco usage.[36,37] Moreover, psychological stress might lead to a higher incidence of AF. In a national study among young veterans from the United States, posttraumatic stress disorder was associated with a 13% higher risk of incident AF.[38] It has been also proven that psychological relaxation methods transiently modify autonomic regulation and improve the quality of life in AF patients.[39] The most common modifiable risk factors for AF are summarized in Table 1.

A prospective cohort from the Turkish Adult Risk Factor Study revealed that hypertension was the most common risk factor followed by advanced age, whereas the most common comorbid disorder was also reported as hypertension (73%) in the prospective, multicentric Atrial Fibrillation in Turkey: Epidemiologic Registry.[14,20] Data from the GARFIELD-AF registry revealed that in Turkey, even if the patients were younger compared to the global data, they had a burden of concomitant diseases such as acute coronary syndrome, a history of systemic embolization, congestive HF, and coronary artery disease.[19]

Table 1. Modifiable and Unmodifiable Risk Factors for the Development of Atrial Fibrillation

Unmodifiable risk factors
Age
Sex
Ethnicity
Family history
Modifiable risk factors
Physical activity
Smoking
Obesity
Diabetes mellitus/impaired glucose tolerance
Obstructive sleep apnea
Hypertension
Coronary artery disease
Heart failure
Hyperlipidemia
Chronic kidney disease
Alcohol consumption
Psychological stress

Clinical Outcome and Burden of the Disease

Patients with AF may have various symptoms such as chest tightness and pain, exercise intolerance, dizziness, syncope, and sleep disturbances, whereas a significant part of patients is initially asymptomatic, with a possibly fatal or debilitating prognosis.

Atrial fibrillation is firmly associated with an elevated risk of transient ischemic attack and stroke, and anticoagulation reduces stroke risk in patients with AF. According to the FHS, the associated risk of AF for stroke was 1.5% among 50-59 years old, whereas it was 23.5% in the 80-89-year-old group.[40] Age, female sex, hypertension, and prior stroke/transient ischemic attack/thromboembolism are the other independently associated risk factors for stroke in patients with AF.[41] The incidence of silent atrial fibrillation in patients with a recent stroke was 23.7% in a cohort of more than 11 000 patients.[42] The guidelines of the European Society of Cardiology recommend using the CHA_2DS_2-VASc score to estimate the risk for stroke in the presence of AF and to use anticoagulation therapy if the CHA_2DS_2-VASc score is ≥1 in men and ≥2 in women to prevent stroke.[43] Atrial fibrillation may lead to cognitive impairment varying from mild dysfunction to dementia via apparent or silent stroke or unclear stroke-independent pathways.[44]

Strokes in AF patients are associated with increased morbidity and mortality. Stroke occurring with AF was nearly twice as likely to be fatal as non-AF stroke. Stroke recurrence was more frequent, and functional deficits were more likely to be severe among survivors.[45] The Copenhagen Stroke Study showed that patients with AF had a poorer neurological and functional outcome with higher rates of in-hospital death (odds ratio (OR), 1.7; 95% CI, 1.2-2.5) and longer hospital stay (50 days vs. 40 days, $P < .001$) compared with the stroke patients without AF. Moreover, there was a larger infarct particularly in the cerebral cortex in patients with AF.[46]

Age was found to be the only independent predictor of stroke among the factors in CHA_2DS_2-VASc score (OR 1.026, $P < .001$) in Atrial Fibrillation in Turkey: Epidemiologic Registry. Stroke prevalence in AF patients was 15%, and all of these patients were included in the high-risk group according to the CHA_2DS_2-VASc score.[20] Stroke incidence was 7.04% at diagnosis and 6.87% during the follow-up in the population-based TRAF cohort.[15]

Ege Stroke Registry, the first systematic epidemiologic report on the stroke profile of Turkish people, presented the profile of risk factors and etiologic and clinical data of 2000 patients with first-ever-in-a-lifetime stroke between 1991 and 1995. The major risk factor of ischemic stroke was atrial fibrillation in one-fifth of the cases.[47] Retrospective analysis of 611 ischemic stroke patients revealed that 39% of these patients had evidence of persistent or paroxysmal AF (≥30 seconds) detected either by electrocardiogram (ECG), inpatient routine cardiac monitoring, or 24-hour Holter ECG. On

the other hand, 21% of them had no arrhythmia on ECG or cardiac monitoring, while episodes of AF lasting <30 seconds were present on 24-hour Holter monitoring.[48]

Multiple AF-associated mechanisms and myocardial alterations may lead to left ventricular dysfunction and HF in AF patients. Atrial fibrillation and HF often coexist and have the same risk factors and share clinical findings. They may aggregate and exacerbate each other which is difficult to find out which occurs first and may cause significantly greater mortality than either condition alone. The PREVEND (Prevention of Renal and Vascular End-Stage Disease) from the Netherlands found the incidence of HF as 4.90 and 0.85 per 1000 person-years for patients with or without AF, respectively.[49] While HF has been determined a potent risk factor for AF, AF was also identified as a major risk factor for new-onset HF.[50]

Data from AF patients in the ORBIT-AF revealed that more than 60% of AF patients were symptomatic with a decreased quality of life, but only one-third of them had severe disabling symptoms.[51] Patients with AF experience anxiety disorders and depressive symptoms more often which also decreases their quality of life.[52] A cross-sectional study analyzing the impact of AF on frailty and functionality in older adults in Turkey showed that AF is associated with poor quality of life with severe clinical outcomes including falls, disability, and mortality.[53]

Approximately 30% of AF patients have at least 1 and 10% have more than 1 hospitalization per year, and the most common hospitalization cause was cardiovascular problems.[54] It was estimated to be 2-times higher compared to their age- and sex-matched non-AF controls (37.5% vs. 17.5%, respectively), whereas inpatient costs of an AF patient are 3-fold higher vs. controls.[55] A German-wide, multi-center database found that AF was the main reason for hospitalization in 14% of patients but their in-hospital mortality was less than 1%.[56]

Atrial fibrillation also causes a significant economic burden; a nationwide study from the United States showed that emergency visits and hospital admissions for AF increased remarkably between 2007 and 2014, whereas the annual charges for admitted AF patients increased by 37% from $7.39 billion in 2007 to $10.1 billion in 2014.[57] The individual incremental cost of AF was $8705 per year in the United States, while the national incremental cost related to AF was annually estimated at $6-26 billion in 2011.[55]

Atrial fibrillation is related to a 2-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men, with an overall 3.5-fold mortality risk increase.[12] In a recent study, the most common causes of death among AF patients were malignancy (23.1%), HF (14.5%), and infection/sepsis (17.3%), whereas stroke-related mortality was only 6.5%.[58]

In a Turkish cohort, survival after onset of AF was 5-9 years, and overall mortality was 6.8 per 100 person-years.[14] GARFIELD-AF large-scale registry revealed that although the mean risk score values were lower, the all-cause mortality rate was higher in Turkey compared to the global data.[19] Another retrospective study from Turkey evaluating the role of AF on mortality and morbidity in patients with ischemic stroke reported that AF affected the prognosis of ischemic stroke adversely in terms of mortality and morbidity.[59]

Screening for AF

Global Efforts

Due to the increasing number of cases, high prevalence of asymptomatic patients, and strong association with stroke, screening strategies have been developed and implemented in clinical usage. As there is a potential to prevent AF-related strokes with effective treatment, early detection of AF, particularly the asymptomatic ones, and elimination of risk factors to reduce complications have become an important target in the management. Advances in technology such as artificial intelligence and wearable devices have facilitated this research in the past decade.[60]

Pulse palpation, automated blood pressure monitors, single-lead ECG devices, photoplethysmography (PPG) devices, other sensors (using seismocardiography, accelerometers, and gyroscopes, etc.) used in applications for smartphones, wrist bands, and watches are the tools used for AF screening. Intermittent smartwatch detection of AF is possible through PPG or ECG recordings. Smartwatches and other wearables can passively measure pulse rate from the wrist using an optical sensor for PPG and alert the consumer of a pulse irregularity (based on a specific algorithm for AF detection analyzing pulse irregularity and variability). Pulse palpation has a high number of false positives but is the cheapest method. Screening by the self-pulse assessment has been recommended by the National Stroke Association; however, this attempt has only shown scarce success, with a sensitivity and specificity of 70% in the elderly.[61] As hypertension is a potent risk factor for AF, blood pressure monitorization has been used to detect AF in several studies and showed higher accuracy than pulse palpation.[62,63] Hand-held single-lead ECG devices were found to be cost-effective for AF screening in hospital settings and can be implemented in primary care during seasonal vaccination programs.[64-66]

Mobile health technologies are currently emerging for AF screening. Machine learning and artificial intelligence may lead to a breakthrough in AF detection by ECG recording in the last decade. More than 400 000 smartwatch app users were enrolled in the Apple Heart Study, and 0.52% of them received an irregular pulse notification whereas, among the participants 65 years of age and older, the notification ratio was 3.2%. Electrocardiogram patch confirmed that 84% (95% CI, 76-92) of the participants who had initial notifications experienced AF in their subsequent notifications.[67,68] About 0.23% of the participants of the Huawei Heart Study received a "suspected AF," and 87% of these were confirmed as having AF, with a positive predictive value of 91.6% [95% CI, 91.5-91.8].[69] The Fitbit Heart Study (NCT04380415), enrolled a greater proportion of older individuals and women than prior studies, examined a novel PPG-based software algorithm for detecting AF. Participants who had an irregular heart rhythm were invited to a telehealth visit, and eligible participants were then mailed a 1-week single-lead ECG patch monitor. While the analysis of the results is in progress,

this study will possibly bring significant enlightenment to the use of wearable technology for AF detection.[70]

Although mobile health technologies revolutionize the diagnosis and screening of AF, there are several limitations. While AF detection algorithms have a high sensitivity and specificity in a controlled research environment, they can cause unnecessary anxiety and additional tests for false-positive cases. Also, the devices may be difficult to use in older individuals or in those with physical disabilities. In addition, the cost may be a challenge as further widening the socioeconomic healthcare gap. Cybersecurity is an important concern that should be addressed with security measures. Moreover, clinicians may feel exhausted as the volume of data continues to increase.[71]

The success of the screening for AF mainly depends on the screened population and the intensity of screening. Therefore, there are 2 types of strategies established for AF screening including opportunistic or systematic screening of individuals above a certain age (usually ≥65 years) or with higher stroke risk.[43] Primary care, pharmacies, or community screening during special events are good settings for AF screening. There was no significant difference between systematic vs. opportunistic or general practice vs. community screening in a meta-analysis; however, recurrent heart rhythm monitoring was found to be more effective than a single assessment. [60]

Single-timepoint screening of a cohort over 65 years of age found the incidence of undiagnosed AF as 1.4%, and 67% of them had a high risk of stroke.[4] An intense 2-week screening using twice-daily intermittent hand-held ECG recordings in a 75-76-year-old cohort found AF in 3% of them. When the cohort was stratified to those with ≥1 additional stroke risk factor, AF incidence was increased to 7.4%.[72] Silent AF is more frequent than symptomatic AF in patients with a pacemaker or during external continuous rhythm monitoring. Several studies such as ASSERT-II (Subclinical AF in older asymptomatic patients, NCT01694394), REVEAL-AF (Incidence of AF in high-risk patients, NCT01727297), GRAF (Graz study on the Risk of Atrial Fibrillation, NCT01461434), and Danish Loop study (NCT02036450) using subcutaneous long-term continuous monitoring in people at risk of AF provided a relatively more accurate estimate for silent AF incidence.[60] Among 256 patients with an implantable cardiac loop recorder, the rate of asymptomatic AF detection for episodes persisting over 5 minutes was 34% per year.[73]

The adjusted stroke and all-cause mortality rates over 1.5 years of follow-up were 4% and 7% in untreated silent AF patients compared with 1% and 2.5%, respectively, in matched controls without AF.[74] Similar to that, in the EORP AF registry (Eurobservational Research Programme), first-year mortality was 2 times higher in asymptomatic AF cohort vs symptomatic ones (9.4% vs. 4.2%, $P < .0001$).[75] In the Belgrade AF study, AF progression or ischemic stroke development rates were much higher in those with an asymptomatic presentation.[76]

According to the STROKESTOP study, screening can also find out suboptimally managed AF cases as intermittent ECG recording can increase the detection of new AF.[77] The REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) study comparing a smartphone/tablet-based single-lead ECG system twice weekly over 12 months with routine care revealed an almost 4-fold increase in AF detection in patients aged ≥65 years.[78] While some of the selected studies focused on AF screening are summarized in Table 2, more studies have been established and some of them are still ongoing. The sensitivity and specificity of the screening methods are given in Table 3.

Opportunistic screening in all patients visiting the health system ≥65 years of age by pulse-taking or ECG rhythm strip has been recommended in the ESC AF guidelines; however, if an older age threshold is chosen (aged ≥75 years) or an additional stroke risk factor is present, the guideline states that screening should be advanced with a systematic ECG screening to be more efficient. A definite diagnosis should be confirmed by a single-lead ECG recording of ≥30 seconds or a 12-lead ECG reviewed by an experienced physician.[43] Hence, this rapid ECG clarification may reduce the anxiety and prevent misdiagnosis and its consequences.

Atrial fibrillation causes a significant economic burden for healthcare systems; therefore, screening should be cost-effective for wider usage. Opportunistic AF screening seems to be cheaper than systematic screening. Appropriate choice of the screening tool and setting is important; several cost-effective algorithms have been established based on pulse palpation, hand-held ECG devices, and smartphones and watches with pulse PPG applications.[60] Both systematic and opportunistic screening was found to be more cost-effective than routine practice for patients ≥65 years.[79]

Challenges and Opportunities in Atrial Fibrillation Screening in Turkey with Future Directions

As in any other country, AF is an emerging public health problem in Turkey due to its increasing incidence and prevalence in the aging population.[14] The significant burden of AF has been illustrated in multiple large observational cohort studies including increased stroke, morbidity, and mortality.[16] Contradictory to the global data, female to male ratio, number of patients under 65 years, and all-cause mortality rate were higher in the Turkish cohort.[19] Current predictions report that 15% of people with AF are currently undiagnosed and up to 75% may be eligible for anticoagulation treatment to prevent stroke.[67] Primary prevention by reducing modifiable risk factors and early initiation of anticoagulation therapy in high-risk individuals by extensive screening are needed in Turkey for a better outcome.

Atrial fibrillation diagnosis in Turkey is mostly achieved by the cardiology clinics in secondary or tertiary care since there is no mandatory referral system from primary care to hospitals and patients are free to enter the healthcare system at whatever point they choose and to use hospitals' ambulatory outpatient services without needing a referral.[80,81] While primary care had been observed to be a good setting for AF screening in other countries, family physicians (FP) in Turkey rarely perform an ECG in their daily routine.

Table 2. Studies Focused on AF Screening and Their Outcomes

Study	Participants (Number)	Intervention	Outcome
Prevalence of Sub-Clinical Atrial Fibrillation Using and Implantable Cardiac Monitor (ASSERT-II) (NCT01694394)	65 years and older with an increased risk of AF and cardiovascular events but without prior history of AF or implanted pacemaker or defibrillator (n=256)	ICM	Frequent detection of subclinical AF
Incidence of AF in High-Risk Patients (REVEAL AF) (NCT01727297)	18 years and older with a CHADS2 score ≥3 (or 2 with at least 1 additional risk factor) (n=446)	Reveal ICM	AF remains undetected in patients monitored less than 30 days, ICMs can detect AF episodes which cannot be found with conventional short-term monitoring strategies.
Atrial Fibrillation Detected by Continous ECG Monitoring (LOOP) (NCT02036450)	70-90 years olds with at least 1 additional stroke risk factor but without prior history of AF (n=6000)	ILR	ILR screening resulted in a 3-time increase in AF detection in individuals with stroke risk factors.
Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland, Sweden (STROKESTOP) (NCT01593553)	75-76 years olds (n=7173)	ECG screening for AF using intermittent ECG recorder	The use of intermittent ECGs increased new AF detection 4-fold indicating that screening is safe and beneficial in older populations.
Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study	65 years and older with a CHADS-VASc score ≥2 (n=1001)	AliveCor Kardia monitor attached to a WiFi-enabled iPod to obtain ECGs (iECGs)	iECG screening is very effective in identifying incident AF cases in patients ≥65 years of age with an increased risk of stroke.
Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older (SCREEN-AF) (NCT02392754)	75 years and older with hypertension and without known AF (n=856)	Screening: Intervention-AF screening (ECG patch monitor)	Screening with a ECG patch monitor among older patients with hypertension led to a 10-fold increase in AF detection.
The Apple Heart Study (NCT03335800)	22 years and older without AF (n=419 297)	Smartphone application and ECG patch monitor	Among participants who had an irregular pulse notification, 34% had AF on subsequent ECG patch readings and 84% of notifications were concordant with AF. Irregular pulse notification rate is significantly higher in ≥65 years old.
The Huawei Heart Study	18 years and older (n=644 124)	PPG-based smart devices	The positive predictive value of detecting AF was 91.6% with periodic measurements in every 10 minutes.
The Fitbit Heart Study (NCT04380415)	22 years and older without AF (n=644 124)	PPG-based smart devices and ECG patch monitor	Analysis is in progress.
Prevalence of Sub-Clinical Atrial Fibrillation Using and Implantable Cardiac Monitor (ASSERT-II)	NCT01694394	Implantable cardiac monitor	Detection rate for subclinical AF ≥5 minutes 34.4%/y (95% CI, 27.7-42.3)
Incidence of AF in High-Risk Patients (REVEAL AF)	NCT01727297	Reveal implantable cardiac monitor	The detection rate of AF lasting 6 or more minutes at 18 months was 29.3%. Detection rates at 30 days and 6, 12, 24, and 30 months were 6.2%, 20.4%, 27.1%, 33.6%, and 40.0%, respectively.

(*Continued*)

Table 2. Studies Focused on AF Screening and Their Outcomes (*Continued*)

Study	Participants (Number)	Intervention	Outcome
Atrial Fibrillation Detected by Continous ECG Monitoring (LOOP)	NCT02036450	Implantable loop recorder	A single 10-second ECG yielded a sensitivity (and negative predictive value) of 1.5% (66%) for AF detection, increasing to 8.3% (67%) for twice-daily 30-second ECGs during 14 days and to 11% (68%), 13% (68%), 15% (69%), 21% (70%), and 34% (74%) for a single 24-hour, 48-hour, 72-hour, 7-day, or 30-day continuous monitoring, respectively.
Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland, Sweden (STROKESTOP)	NCT01593553	ECG screening for atrial fibrillation using intermittent ECG recorder	AF was found in 0.5% of the screened population on their first ECG. The use of intermittent ECGs increased new AF detection 4-fold. A previous diagnosis of AF was known in 9.3% (n = 666; 95% CI, 8.6-10.0). Total AF prevalence in the screened population was 12.3%.
Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study	N/A	AliveCor Kardia monitor attached to a WiFi-enabled iPod to obtain ECGs (iECGs)	19n patients in the iECG group were diagnosed with AF over the 12-month study period vs 5 in the RC arm (hazard ratio, 3.9; 95% CI = 1.4-10.4; P = .007) at a cost per AF diagnosis of $10 780 (£8255).
Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older (SCREEN-AF)	NCT02392754	Screening: Intervention-AF screening (ECG patch monitor)	AF was detected in 5.3% in the screening group vs. 0.5% in the control group (relative risk, 11.2; 95% CI, 2.7-47.1; P = .001; absolute difference, 4.8%; 95% CI, 2.6%-7.0%; P < .001; number needed to screen, 21). Twice-daily AF screening using the home BP monitor had a sensitivity of 35.0% (95% CI, 15.4%-59.2%), specificity of 81.0% (95% CI, 76.7%-84.8%), positive predictive value of 8.9% (95% CI, 4.9%-15.5%), and negative predictive value of 95.9% (95% CI, 94.5%-97.0%).

PPG, photoplethysmography; ILR, implantable loop recorder; ICM, implantable cardiac monitor; AF, atrial fibrillation; RC, routine care; ECG, electrocardiogram. AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiogram.

While immunization and monitoring of pregnant women and infants were stated to be well-coordinated services by FPs, chronic disease management was said to be neglected in an exploratory-descriptive study that aimed to explore primary care workers' perspectives whether the current model could achieve the cardinal functions of primary care and have an integrative position in the healthcare system. The reason behind this negligence being reported as chronic disease management was not included in the performance targets systems. Recently "The Disease Management Platform" initiative has been introduced by the Minister of Health to allow FPs to identify and manage diabetes, hypertension, comprehensive geriatric care, obesity, and chronic disease risk assessment.[82] By this new initiative, FPs will be able to monitor and manage their patients with chronic diseases including AF. Therefore, this new era on how FP will operate can also be an opportunity to identify AF patients in the primary care setting in a timely manner. However, in order to establish time- and cost-effective screening programs for AF in the Turkish primary care setting, the targeted screening population needs to be defined and prioritized carefully. While opportunistic screening in all patients visiting the health system ≥65 years of age by pulse-taking or ECG rhythm strip has been recommended by the ESC guideline,

Table 3. Sensitivity and Specificity of Various AF Screening Tools

Screening Tool	Sensitivity	Specifity
Pulse taking[60]	87%-97%	70%-81%
Automated BP monitors[61, 62]	93%-100%	86%-92%
Single lead ECG[63-65]	94%-98%	76%-95%
Mobile health technologies[66-68]	91.5%-98.5%	91.4%-100%

BP, blood pressure; ECG, electrocardiogram; AF, atrial fibrillation.

this age limit may be reduced since the Turkish AF population under 65 years of age is found to be at a higher proportion than the global average.[19] However, age is an important factor in the CHA_2DS_2-VASc score, and targeting younger patients will reduce the risk profile of patients screened. Therefore, screening younger than 65 years of age approach will need a validation interms of cost-effectiveness.

Additionally, in order to bring these screening programs to life, FPs' awareness on AF symptoms and ECG assessment abilities should be improved accordingly. Family medicine and cardiology and neurology societies/associations should work together to optimize educational content for continuous FP training programs. Interdisciplinary communication between these specialties should be improved via an integrated electronic records system to provide sufficient disease management after the initial diagnosis. Although there is a national electronic healthcare records platform in Turkey (E-Pulse) where patients and their physicians can access records such as disease and prescription history with performed tests and imaging, it is not fully integrated within the healthcare providers and physicians still do not have full access to patients' records in different clinics.[83] Therefore, completion of this integration will significantly contribute to the sufficient management of AF patients as in all other chronic diseases.

Current screening methods require extensive monitoring and are limited by low cost-effectiveness.[84] A variety of new technologies and machine learning have been utilized to develop a rapid, cheap, accurate diagnosing tool which can be used at home. Although advanced technologies such as smartphones with PPG or accelerometer sensors, smart bands, and external electrodes that can provide a smartphone single-lead electrocardiogram (iECG) are growing in popularity, more data are needed as evidence for their effectiveness. Despite being unproven if these devices may replace the current screening modalities, innovations in technology may help to increase awareness and allow self-diagnosis/suspicion and better follow-up through smart devices. As of 2018, there were 41.9 million smartphone users in Turkey. This number is expected to rise to 52.8 million users by 2021 and 56.4 million users by 2023. During the second quarter of 2018, 71% of Turkish inhabitants connecting to the internet using a mobile were doing so at 4G speeds, and it is anticipated that 13% of connections will be made over 5G by 2025.[85] Despite the lower usage of smartphones and the internet among the elderly, the current high percentage of smartphone penetration rate in Turkey should be seen as a futuristic opportunity to assess the effectiveness of these technologies in detecting AF.

CONCLUSION

The incidence and prevalence of AF are rising globally, and increased awareness and enhanced detection have become more important as a significant proportion of the cases remains asymptomatic. While the average age of the AF population is lower in younger nations like Turkey, more targeted screening programs should be initiated in primary and secondary care by pulse-taking or ECG rhythm checking. Referral to specialists should also be strongly recommended after the first diagnosis of AF in order to achieve effective primary prevention and management. Additionally, advancing technology should be assessed and implemented in these programs, and self-management through patient education should be combined with a multidisciplinary clinical approach to improve the patient outcome and reduce the disease burden.

Ethics Committee Approval: Since this is a narrative review article with expert opinions, this study didn't need ethical approval by any means.

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