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Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, characterised by irregularly irregular ventricular pulse and loss of association between the cardiac apex beat and radial pulsation [1]. Loss of active ventricular filling is associated with:

- Stagnation of blood in the atria, leading to thrombus formation and a risk of embolism, increasing the risk of stroke.
- Reduction in cardiac output (especially during exercise) which may lead to heart failure.

Terminology^[2]

- Acute: onset within the previous 48 hours.
- Paroxysmal: spontaneous termination within seven days and most often within 48 hours. Paroxysmal AF may degenerate into a sustained form of AF.
- Recurrent:
 - Two or more episodes, which may be defined as paroxysmal if they terminate spontaneously or persistent if the arrhythmia requires electrical or pharmacological cardioversion for termination.
 - Successful termination of AF does not alter the classification of persistent AF.
- Persistent: not self-terminating; lasting longer than seven days, or prior cardioversion. Persistent AF may degenerate into permanent AF.

- Permanent:
 - Long-standing AF (defined as over a year) that is not successfully terminated by cardioversion, when cardioversion is not pursued or has relapsed following termination.
 - Reversion of permanent AF to normal sinus rhythm is possible, particularly in those cases where the AF is caused by an underlying disease process which is successfully treated (eg, thyroid disease) or where a specialist procedure is performed that modifies the electrophysiological properties of the heart.

Epidemiology

- AF is the most common sustained cardiac arrhythmia and estimates suggest its prevalence is increasing [3].
- Currently, the estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to the ageing of the general population and a reduction in undiagnosed AF. There is a greater prevalence in older people and in patients with conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus or chronic kidney disease [2]

It is more common in males than in females [4].

Aetiology^[5]

- Most people with AF have an identifiable cause. Lone AF (no obvious cause and all investigations are normal) occurs in up to 11% of people with AF. It is more common in people with paroxysmal AF (occurring in 30-40%).
- The most common causes of AF are coronary heart disease, hypertension, valvular heart disease and hyperthyroidism.

- Other factors thought to cause or be associated with AF include:
 - Cardiac or valve conditions eg, rheumatic heart disease, sick sinus syndrome, pre-excitation syndromes (such as Wolff-Parkinson-White syndrome) and heart failure.
 - Less common cardiac causes include cardiomyopathy, pericarditis, myocarditis, atrial septal defect, congenital heart disease and atrial myxoma.
 - Non-cardiac causes include drugs (eg, thyroxine or bronchodilators), acute infection (including COVID-19 infection), electrolyte depletion, lung cancer, pulmonary embolism, thyrotoxicosis and diabetes mellitus.
 - Dietary and lifestyle factors include excessive caffeine intake, excessive alcohol intake and obesity.

Presentation

Perform manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying AF in people presenting with any of the following ^[3]:

- Breathlessness/dyspnoea.
- Palpitations.
- Syncope/dizziness.
- Chest discomfort.
- Stroke/transient ischaemic attack (TIA).

The WatchBP® Home A device (Microlife) is an oscillometric blood pressure monitor. While recording blood pressure, it automatically detects pulse irregularity that may be caused by symptomatic or asymptomatic AF. The device reliably detects AF and may increase the rate of detection when used in primary care. WatchBP® Home A should be considered for use in people with suspected hypertension and those being screened or monitored for hypertension in primary care [6].

Differential diagnosis

- Atrial flutter.
- Atrial extrasystoles.
- Supraventricular tachyarrhythmias.
- Atrioventricular nodal re-entrant tachycardia.
- Wolff-Parkinson-White syndrome.
- Ventricular tachycardia.

Associated diseases

- AF is often associated with other arrhythmias eg, atrial flutter or supraventricular tachycardia.
- AF can alternate with atrial flutter, atrial flutter may develop into AF and atrial flutter may occur during treatment of AF with antiarrhythmic drugs.
- In patients with Wolff-Parkinson-White syndrome, AF can lead to rapid ventricular rates and ventricular fibrillation, especially when atrioventricular nodal blocking agents are used.

Investigations^{[3] [7]}

Editor's note

Dr Sarah Jarvis, 12th January 2022

KardiaMobile for detection of AF [8]

NICE has issued new guidance on the detection of AF using the portable ECG recorder, KardiaMobile. They note that:

Detection of AF in people with suspected paroxysmal AF usually involves wearing a continuous ECG monitor, such as a Holter monitor.

Clinical evidence shows that significantly more people had AF detected using the KardiaMobile single-lead device compared with a Holter monitor.

Cost modelling shows that KardiaMobile is cost saving over two years compared with Holter monitor for symptomatic patients.

Consequently, it concludes that KardiaMobile should be recommended as an option for detecting AF in symptomatic patients (eg, with palpitations) suspected of having paroxysmal AF, who are referred for ambulatory ECG monitoring by a clinician.

Further assessment is focused on identifying any underlying cause, and assessment of cardiac function:

- A 12-lead ECG should be performed in all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected:
 - An ECG is diagnostic except in paroxysmal AF between attacks.
 The distinguishing feature of AF is variability in the R-R intervals.
 - If paroxysmal AF is suspected and has not been detected by standard 12-lead ECG recording:
 - Use a 24-hour ambulatory ECG monitor if asymptomatic episodes are suspected or if episodes are less than 24 hours apart.
 - Use an ambulatory ECG monitor, event recorder or other ECG technology for a period appropriate to detect atrial fibrillation if symptomatic episodes are more than two hours apart.

- In people with suspected paroxysmal AF undetected by standard ECG recording: use a 24-hour ambulatory ECG monitor in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart. Use an ambulatory ECG monitor, event recorder or other ECG technology in those with symptomatic episodes more than 24 hours apart.
- Blood tests: TFTs, FBC (anaemia may precipitate heart failure), renal function and electrolytes (abnormal serum potassium levels can potentiate arrhythmias, especially if the patient is taking, or about to start, digoxin), LFTs and coagulation screen (pre-warfarin).
- CXR (may indicate cardiac structural causes of AF, such as mitral valve disease or heart failure).

- Echocardiogram:
 - Transthoracic echocardiography (TTE) should be performed in people with AF:
 - For whom a baseline echocardiogram is important for longterm management.
 - For whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered.
 - In whom there is a high risk or a suspicion of underlying structural/functional heart disease (eg, heart failure or heart murmur) that influences subsequent management (eg, choice of antiarrhythmic drug).
 - In whom refinement of clinical risk stratification for antithrombotic therapy is needed.
 - TTE should not routinely be performed solely for the purpose of further stroke risk stratification in people with AF for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria.
 - Perform transoesophageal echocardiography (TOE) in people with AF:
 - When TTE demonstrates an abnormality (such as valvular heart disease) that warrants further specific assessment in those in whom TTE is technically difficult and/or of questionable quality and where there is a need to exclude cardiac abnormalities.
 - For whom TOE-guided cardioversion is being considered.
- CT or MRI scan of the brain: should be performed if there is any suggestion of stroke or TIA.

Management^[3]

• The management of AF involves **control of the arrhythmia** (by rhythm or rate control) and **thromboprophylaxis** to prevent strokes.

- Treat any underlying cause eg, acute infection, hyperthyroidism. AF may revert on treatment or resolution of an associated problem eg, acute infection or alcohol intoxication.
- Treat associated heart failure.

No further intervention may be required; lifestyle changes, such as avoiding the precipitating factor (eg, alcohol or caffeine), may suffice.

Referral

Urgent admission to hospital may be indicated when [5]:

- There is a very rapid pulse (greater than 150 bpm) and/or low blood pressure (systolic blood pressure less than 90 mm Hg).
- There is loss of consciousness, severe dizziness, ongoing chest pain, or increasing breathlessness.
- There is a complication of AF, such as stroke, TIA or acute heart failure.

Routine referral to a cardiologist should be considered when:

- The person is young eg, less than 50 years of age.
- Paroxysmal AF is suspected.
- There is uncertainty regarding whether rate or rhythm control should be used.
- Drug treatments that can be used in primary care are contraindicated or have failed to control symptoms.
- The person is found to have valve disease or left ventricular systolic dysfunction on echocardiography.
- Wolff-Parkinson-White syndrome or a prolonged QT interval is suspected on the ECG.

Refer people promptly at any stage if treatment fails to control the symptoms of AF and more specialised assessment and management are required [3].

Rate or rhythm control^[3]

Offer rate control as the first-line strategy to people with AF, except in people:

- Whose AF has a reversible cause.
- Who have heart failure thought to be primarily caused by AF.
- With new-onset AF.
- For whom a rhythm control strategy would be more suitable based on clinical judgement.

Rate control

- Offer either a standard beta-blocker (a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy, unless digoxin monotherapy is more appropriate (see following bullet point).
- Consider digoxin monotherapy for people with non-paroxysmal AF only if they are sedentary (do no or very little physical exercise) or other rate-limiting drug options are ruled out because of comorbidities or the person's preferences.
- If monotherapy does not control symptoms and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any two of the following: betablocker, diltiazem (currently unlicensed use), digoxin.
- For people with AF and concomitant heart failure, follow the recommendations on theuse of beta-blockers and avoiding calcium-channel blockers in the National Institute for Health and Care Excellence (NICE) guideline on chronic heart failure [9].
- Do not offer amiodarone for long-term rate control.

Rhythm control

Consider pharmacological and/or electrical rhythm control for people with AF whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful.

Cardioversion

- For people having cardioversion for AF that has persisted for longer than 48 hours, offer electrical (rather than pharmacological) cardioversion.
- Consider amiodarone therapy starting four weeks before and continuing for up to twelve months after electrical cardioversion to maintain sinus rhythm.
- For people with AF greater than 48 hours of duration, in whom elective cardioversion is indicated:
 - Both TOE-guided cardioversion and conventional cardioversion should be considered equally effective.
 - A TOE-guided cardioversion strategy should be considered where experienced staff and appropriate facilities are available and where a minimal period of pre-cardioversion anticoagulation is indicated due to the person's choice or bleeding risks.

Drug treatment for long-term rhythm control

- Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment and likelihood of recurrence of AF.
- If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (a beta-blocker other than sotalol) as firstline treatment unless there are contra-indications.
- If beta-blockers are contra-indicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account.

- Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent AF [10]:
 - Whose AF is not controlled by alternative treatment options including beta-blockers.
 - Who have at least one of the following cardiovascular risk factors:
 - Hypertension requiring drugs of at least two different classes, diabetes mellitus, previous TIA, stroke or systemic embolism, left atrial diameter of 50 mm or greater, or age 70 years or older.
 - And, who do not have left ventricular systolic dysfunction.
 - And, who do not have a history of, or current, heart failure.
- Consider amiodarone for people with left ventricular impairment or heart failure.
- Do not offer class Ic antiarrhythmic drugs such as flecainide or propafenone to people with known coronary or structural heart disease.
- Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (eg, alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy should be considered. In people with paroxysmal AF, a 'pill-in-the-pocket' strategy should be considered for those who:
 - Have no history of left ventricular dysfunction, or valvular or coronary heart disease; and
 - Have a history of infrequent symptomatic episodes of paroxysmal AF; and
 - Have a systolic blood pressure greater than 100 mm Hg and a resting heart rate above 70 bpm and are able to understand how to, and when to, take the medication.

Left atrial ablation

If drug treatment is unsuccessful, unsuitable or not tolerated in people with symptomatic paroxysmal or persistent atrial fibrillation:

- Offer radiofrequency point-to-point ablation; or
- If radiofrequency point-by-point ablation is assessed as being unsuitable, consider cryoballoon ablation or laser balloon ablation.
- When considering left atrial ablation, discuss the risks and benefits
 and take into account the person's preferences. It is important to
 explain that the procedure is not always effective and that resolution
 of symptoms may not be permanent.
- Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic AF.

Preventing recurrence after ablation

- Consider antiarrhythmic drug treatment for three months after left atrial ablation to prevent recurrence of AF. The person's preferences, and the risks and potential benefits should be taken into account.
- The requirement for antiarrhythmic drug treatment should be reassessed at three months after left atrial ablation.

Pace and ablate strategy

- Consider pacing and atrioventricular node ablation for people with permanent AF with symptoms or left ventricular dysfunction thought to be caused by high ventricular rates.
- When considering pacing and atrioventricular node ablation, reassess symptoms and the consequent need for ablation after pacing has been carried out and drug treatment further optimised.
- Consider left atrial catheter ablation before pacing and atrioventricular node ablation for people with paroxysmal AF or heart failure caused by non-permanent (paroxysmal or persistent) AF.

Thromboprophylaxis

See also the separate Stroke Prevention article.

Assessment of stroke risk [3]

Use the CHA₂DS₂-VASc stroke risk score to assess stroke risk in people with symptomatic or asymptomatic paroxysmal, persistent or permanent AF, or a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm or catheter ablation [11].

Patients with AF who are clearly low-risk, (age <65 and lone AF) do not require antithrombotic therapy. This applies to male patients with CHA₂DS₂-VASc score = 0 and female patients with CHA₂DS₂-VASc score = 1 in whom the single point is allocated due to female sex.

Bleeding risk [3]

NICE advises using the ORBIT risk score because evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools. Accurate knowledge of bleeding risk improved patient concordance with respect to treatment and risk reduction. NICE acknowledges that other risk scores may be used until ORBIT is built into clinical pathways and electronic systems ^[12]. Offer modification and monitoring of the following risk factors:

- Uncontrolled hypertension.
- Poor control of international normalised ratio (INR) ('labile INRs').
- Concurrent medication for example, concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID).
- Harmful alcohol consumption.
- Reversible causes of anaemia.

Editor's note

Dr Sarah Jarvis, 30th June 2021

The link above to the ORBIT risk calculator was included in the original NICE update of April 2021 [3]. It was replaced with another tool on 10th June 2021 but reinstated on 30th June 2021.

The ORBIT risk calculator linked to in the NICE guidance shows the score of 2 for low haematocrit (<36% for women or <40% for men) or low haemoglobin (<120 g/L for women or <130 g/L for men) only on clicking male/female sex. [13]

Anticoagulation [3]

- Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or edoxaban.
- Offer a vitamin K antagonist (eg, warfarin) to people with AF if direct-acting oral anticoagulants are contra-indicated, not tolerated or not suitable.
- Offer anticoagulation to people with a CHA₂DS₂-VASc score of 2 or above, taking bleeding risk into account. Whilst the benefit of anticoagulation will outweigh the bleeding risk in most people, it may not do so for those with an increased risk of bleeding. Careful monitoring of bleeding risk is important.
- Consider anticoagulation with a direct-acting oral anticoagulant for men with AF and a CHA2DS2-VASc score of 1, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options, when used in line with the criteria specified in the relevant NICE technology appraisal guidance - see References, below.
- Take into account any contra-indications for each drug and follow the guidance in the British National Formulary and the MHRA advice on direct-acting oral anticoagulants, in particular for advice on dosages in people with renal impairment, reversal agents and monitoring [14] [15].
- GP prescribing data from 648 practices across the UK between 2000 and 2015 showed that in 2000, patients with paroxysmal AF were half as likely to be prescribed anticoagulants as patients with other forms of AF and by 2015 these patients were approximately 20% less likely to be offered anticoagulants. Although a much greater proportion of patients with paroxysmal AF received anticoagulants in the latter years of the study, a significant treatment gap persists ^[16].
- For adults with AF who are stable and already taking a vitamin K antagonist, advise them to continue with their current medication and discuss the option of switching treatment at their next routine appointment, taking into account the person's time in therapeutic range.
- Do not withhold anticoagulation solely because of a person's age or their risk of falls.

- If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies.
- Do not offer aspirin monotherapy solely for stroke prevention to people with AF.

Editor's note

Dr Sarah Jarvis, 10th August 2021

NICE updates for DOACs

NICE has updated its technological appraisal documents for apixaban $^{\left[17\right]}$, dabigatran $^{\left[18\right]}$, edoxaban $^{\left[19\right]}$ and rivaroxaban $^{\left[20\right]}$. The indications for individual treatments as below are unchanged.

However, NICE stresses for each option the importance of having an informed discussion with the person about the risks and benefits of each DOAC compared with warfarin and the other DOACs. For people taking warfarin, they recommend considering the potential risks and benefits of switching to any given DOAC, taking into account their level of international normalised ratio (INR) control.

Apixaban^[17]

Apixaban is recommended as an option for preventing stroke and systemic embolism in people with non-valvular AF with one or more risk factors such as prior stroke or TIA, age 75 years or older, hypertension, diabetes mellitus, and symptomatic heart failure.

Dabigatran etexilate [18]

Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism in people with non-valvular AF with one or more of the following risk factors:

- Previous stroke, TIA or systemic embolism.
- Left ventricular ejection fraction below 40%.
- Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above.
- Age 75 years or older.
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Idarucizumab may be used when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding but studies assessing efficacy and safety are ongoing [21].

Rivaroxaban^[20]

Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism in people with non-valvular AF with one or more risk factors such as:

- Congestive heart failure.
- Hypertension.
- Age 75 years or older.
- Diabetes mellitus.
- Prior stroke or TIA.

Edoxaban [19]

Edoxaban is recommended as an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, with one or more risk factors:

- Previous stroke or TIA.
- Congestive heart failure.
- Age ≥75 years.
- Diabetes mellitus.
- Hypertension.

Assessing anticoagulation control with vitamin K antagonists, including warfarin

See the separate Oral Anticoagulants article.

Left atrial appendage occlusion

Should be considered if anticoagulation is contra-indicated or not tolerated [22].

Management of acute atrial fibrillation [3]

Rate and rhythm control

- Emergency electrical cardioversion, without delaying to achieve anticoagulation, is required for people with life-threatening haemodynamic instability caused by new-onset AF.
- In people with AF presenting acutely with haemodynamic instability, offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and start rate control if it is more than 48 hours or is uncertain.
- Senior specialist input should be obtained on the use of betablockers In people with atrial fibrillation presenting acutely with suspected concomitant acute decompensated heart failure.
 Calcium-channel blockers should not be given.
- Consider either pharmacological or electrical cardioversion depending on clinical circumstances and resources in people with new-onset AF who will be treated with a rhythm control strategy.
- If pharmacological cardioversion has been agreed on clinical and resource grounds for new-onset AF, offer flecainide or amiodarone if there is no evidence of structural or coronary heart disease, or amiodarone if there is evidence of structural heart disease.
- In people with AF in whom the duration of the arrhythmia is greater than 48 hours or uncertain and considered for long-term rhythm control, delay cardioversion until they have been maintained on therapeutic anticoagulation for a minimum of three weeks. During this period offer rate control as appropriate.
- Do not offer magnesium or a calcium-channel blocker for pharmacological cardioversion.

Anticoagulation

In people with new-onset AF who are receiving no or subtherapeutic anticoagulation therapy: in the absence of contra-indications, offer heparin at initial presentation and continue heparin until a full assessment has been made and appropriate antithrombotic therapy has been started, based on risk stratification.

In people with a confirmed diagnosis of AF of recent onset (less than 48 hours since onset), offer oral anticoagulation if stable sinus rhythm is not successfully restored within the same 48-hour period following onset of AF, or there are factors indicating a high risk of AF, or it is recommended following assessment using the CHA₂DS₂-VASc score.

In people with new-onset AF where there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent AF.

Stopping anticoagulation

- In people with a diagnosis of AF, anticoagulation should not be stopped solely because AF is no longer evident.
- Decisions to stop anticoagulation should be based on a reassessment of stroke and bleeding risk using CHA2DS2-VASc and ORBIT and a discussion of the person's preferences.

Other management options

- Cryoablation or high-intensity focused ultrasound (HIFU) ablation may be used in the management of AF for patients undergoing concomitant open-heart surgery - eg, mitral valve replacement or repair [23] [24].
- Microwave ablation of the atria for patients with AF can be performed via a catheter introduced through a femoral vein or by surgical microwave ablation in patients undergoing concomitant open-heart surgery [25].
- Thoracoscopic epicardial radiofrequency ablation has been shown to be effective, at least in the short term ^[26].

- Percutaneous endoscopic laser balloon pulmonary vein isolation for $AF^{[27]}$:
 - NICE recommends that current evidence on the safety of percutaneous endoscopic laser balloon pulmonary vein isolation for AF shows there are serious but well-recognised complications but evidence on efficacy is adequate to support the use of this procedure.
 - Percutaneous endoscopic laser balloon pulmonary vein isolation aims to maintain a normal heart rhythm. It uses laser ablation to isolate the electrical impulses originating in the pulmonary veins, which are thought to be responsible for triggering AF.
 - The procedure is performed with the patient under general anaesthesia or sedation.

Complications

- AF increases risk of stroke six-fold (much more in patients with rheumatic heart disease) and becomes increasingly important as a risk factor for stroke with increasing age. Paroxysmal as well as persistent AF increases risk of stroke.
- The risk of stroke is less in patients with no other structural heart disease ('lone AF').
- AF can also precipitate acute heart failure and aggravate established heart failure.
- Chronic atrial tachyarrhythmia may lead to cardiomyopathy.
- AF is associated with an approximate doubling of the risk of premature death.
- There may be implications for the patient's fitness to drive. Check with the Driver and Vehicle Licensing Agency (DVLA).

Prognosis

- AF is associated with reduced life expectancy in older patients.
- People with AF have double the mortality and a five-fold higher risk of stroke than those without fibrillation ^[5].

- Prognosis depends on the patient's underlying medical condition.
- Any atrial arrhythmia can cause a tachycardia-induced cardiomyopathy.

Prevention

- Smoking cessation: smoking is a risk factor for coronary heart disease as well as a precipitating factor for AF.
- Alcohol moderation or avoidance: acute alcoholic intoxication or alcohol withdrawal may precipitate paroxysmal AF.
- Diet: caffeine may induce paroxysmal AF in susceptible individuals.

Further reading

- Assessing fitness to drive: guide for medical professionals; Driver and Vehicle Licensing Agency
- Aboyme A, Nehass M, Coromilas J. Arrhythmia and myocardial infarction incidence in 904 patients diagnosed with novel coronavirus and an academic centre. J Am Coll Cardiol. 2021 May 11;77(18):3147. doi: 10.1016/S0735-1097(21)04502-2. Epub 2021 May 3. PMCID: PMC8091354.
- Doshi RN; The State of Atrial Fibrillation in 2020. J Innov Card Rhythm Manag. 2021 Jan 15;12(1):4350-4353. doi: 10.19102/icrm.2021.120105. eCollection 2021 Jan.

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