ATRIAL FIBRILLATION

CHI Formulary Development Project

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Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
CHI	Council of Health Insurance
DOAC	Dual Oral Anticoagulant
ESC	European Society of Cardiology
HR	Heart Rate
IDF	CHI Drug Formulary

LMWH	Low Molecular Weight Heparin
NICE	National Institute for Health and Care Excellence
NOAC	New Oral Anticoagulant
SFDA	Saudi Food and Drug Authority
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist

Executive Summary

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The electrocardiographic characteristics of AF include[1]:

- Irregularly irregular R-R intervals
- Absence of distinct repeating P waves
- Irregular atrial activations

The global prevalence of AF has increased substantially over the past three decades and is currently at approximately 60 million cases. The highest burden is seen in countries with high socio-demographic index, though the largest recent increase occurred in middle socio-demographic index countries[2].

AF is the most common sustained cardiac arrhythmia, with a prevalence of 1 to 2% of the general population in western countries. In Saudi Arabia, a retrospective study was conducted in King Abdul-Aziz Hospital in Jeddah during the period 2010-2017 to study the risk factors, etiologies, comorbidities, and outcomes of AF. It found that AF was

more prevalent among females, and that hypertension, valvular heart disease, and type 2 diabetes mellitus were the most prevalent risk factors of AF in Saudi Arabia[3]. Additionally, a scoping review published in 2021 looked at the characteristics of AF in patients from the Middle East and South Asia. In the middle eastern countries, there were considerable variations in the epidemiological data reported in the included studies, with incidence/prevalence rates ranging from 2.8 to 17.8%, and the reported age range of patients was 58.8–68.4 years. Finally, the leading prevalent AF-associated co-morbidities included hypertension, diabetes mellitus, heart failure, valvular heart diseases and stroke, and this was consistent with studies in other ethnicities from around the world[4]. A cross-sectional study found a prevalence of 4% among the medical admissions in a hospital in Kuwait. Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% if other risk factors are present[5].

The most common clinical manifestations include general fatigue, rapid and irregular heartbeat, fluttering or "thumping" in the chest, dizziness, shortness of breath, anxiety, weakness, faintness, confusion, fatigue when exercising, sweating, chest pain or pressure[6].

The main goals of AF drug treatment include controlling the heart rate, regaining a normal heart rhythm, and reducing the risk of having a stroke. Drug therapy is an integral component for the management of AF, which is categorized into rate control and rhythm control, in addition to an anticoagulant. Rate control medications can span from beta blockers, non-dihydropyridines (non-DHP) calcium channel blockers (CCBs) to digoxin. Rhythm control covers antiarrhythmics medications. Anticoagulants, including new oral anticoagulants or NOACs (apixaban, dabigatran, rivaroxaban, edoxaban), warfarin, low molecular weight heparin (LMWH) or heparin are the main stay for stroke prevention[1].

CHI issued Atrial Fibrillation guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report provides an update on the Atrial Fibrillation Guidelines for CHI Formulary with the ultimate objective of updating the IDF- *CHI Drug Formulary* all while addressing and incorporating the best available and emerging clinical and economic evidence regarding the drug therapies used in the management of Atrial Fibrillation.

Main Triggers of AF Update include **a new updated 2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC** which tackled a specific population: pregnancy and **a new updated 2021 National**

Institute for Health and Care Excellence (NICE) Atrial fibrillation: diagnosis and management which introduced a new assessment tool for bleeding, named ORBIT, which has a higher accuracy in predicting absolute bleeding risk.

Some missed guidelines such as **The Saudi Center for Evidence Based Health Care Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-valvular Atrial Fibrillation (2014)** which included the use of aspirin as antithrombotic therapy rather than an anticoagulant, **the CHEST Guideline and Expert Panel Report on Antithrombotic Therapy for Atrial Fibrillation (2018)** which re-emphasized the recommendation about duration of anticoagulation specified in other guidelines, **the Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation (2020),** which included the SFDA-registered antidote for dabigatran called **idarucizumab** (Praxbind), as well as andexanet alfa, antidote for rivaroxaban and apixaban, which is not yet SFDA registered. Finally, **the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation (2018)** included the goal of maintaining levels of <1.2 ng/ml for digoxin when used as rate control.

In the final section of the document, an array of appendices can be found, encompassing treatment algorithms specifically tailored for atrial fibrillation patients.

Table 1. Major Updates in the Management of Atrial Fibrillation

New AF Guidelines Released	Major Updates
2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC update from 2016[1]	The 2020 ESC recommendations represent an update of the 2016 ESC recommendations for the management of Atrial Fibrillation in Adults. The update includes **anticoagulation use post catheter ablation and atrial fibrillation management in pregnancy.**
The National Institute for Health and Care Excellence (NICE) Atrial fibrillation: diagnosis and management update from 2014[7]	The 2021 NICE recommendations represent an update of the 2014 NICE recommendations for the management of Atrial Fibrillation in Adults.

	The update includes **the introduction of a new assessment tool for bleeding that is very precise and yields better results. The name of this assessment tool is ORBIT.**
The Saudi Center for Evidence Based Health Care Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-Valvular Atrial Fibrillation (Added)[5]	The Saudi clinical practice guideline elaborates on the use of antithrombotic treatment in non-valvular atrial fibrillation. It does mention **the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation.**
Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report (2018) (Added)[8]	The CHEST guideline highlights **the superiority of NOACs over warfarin as well as the switching from warfarin to NOACs in unprovoked bleeding is favored too.**
The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation (Added)[9]	The 2020 Canadian guidelines mention **the use of antidote for specific NOACs in case of life-threatening bleeding. It does introduce two drugs: idarucizumab and andexanet alfa.**
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018 (Added)[10]	The Australian and New Zealand association guidelines for the diagnosis of atrial fibrillation mentions **the serum concentration goal of digoxin to not exceed 1.2 ng/ml for toxicity control**.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of idarucizumab were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 2. New SFDA Registered Drugs for the Management of Atrial Fibrillation

MAJOR CHANGES		
Addition of New Molecules	**Drug Class**	**HTA Recommendations**

Idarucizumab	Humanized monoclonal antibody fragment (Fab)	Positive Recommendation from NICE[7]

Table 3. Non-SFDA Registered Drugs for the Management of Atrial Fibrillation

Non-SFDA Registered New Molecules	Drug Class	HTA Recommendations
Andexanet Alfa	Recombinant Factor Xa	Positive recommendation from NICE[8], IQWIG[9] and CADTH[10]

At the end of the report, a key recommendation synthesis section is added highlighting the use of each drug class in specific group of patients. Table 4 is a summary of the general recommendations for the management of AF.

Table 4. General Recommendations for the Management of Atrial Fibrillation

Patient Population	Recommendations	GOR LOE/SOA	Reference Guidelines
Post catheter ablation	Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.	Class 1	2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[11]
Special population: pregnancy	In pregnant women with HCM, cardioversion should be considered for persistent AF.	Class 2a	2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[11]
Special population: pregnancy	Ibutilide or flecainide IV may be considered for termination of AF in stable patients with structurally normal hearts of acute management.	Class 2b	2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[11]

Special population: pregnancy	For the long-term management Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. Digoxin or verapamil should be considered for rate control if beta-blockers fail.	Class 2a	2020 ESC Guidelines for the diagnosis and management of atrial fibrillation[11]
AF diagnosed patients	Use the ORBIT bleeding risk score because evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools.	Strong recommendation	NICE Atrial fibrillation: diagnosis and management (2021)[12]
AF diagnosed patients	Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation.	Strong recommendation	NICE Atrial fibrillation: diagnosis and management (2021)[12]
Patients who choose antithrombotic therapy	The Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation.	Weak recommendation, moderate quality evidence	The Saudi Center for Evidence Based Health Care Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-valvular Atrial Fibrillation[5]
Patients who choose antithrombotic therapy	For patients with AF, the guideline recommends against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke	Strong recommendation, moderate quality evidence	CHEST Guideline and Expert Panel Report (2018)[13]

	prevention alone, regardless of stroke risk.		
Potentially life-threatening bleeding and patients who need urgent surgery and are on Dabigatran	Administration of idarucizumab for emergency reversal of dabigatran's anticoagulant for which normal hemostasis is necessary.	Strong Recommendation; Moderate-Quality Evidence.	2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society[14]
Potentially life-threatening bleeding and patients who need urgent surgery and are on Apixaban/Rivaroxaban/ Edoxaban	Administration of andexanet alfa (once available) for emergency reversal of the anticoagulant effect of apixaban, edoxaban, and rivaroxaban.	Strong Recommendation; Low-Quality Evidence.	2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society[14]
Patients who are using digoxin for rate control for atrial fibrillation	When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of < 1.2 ng/ml.	Strong Recommendation; moderate - Quality Evidence.	National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand 2018[15]

Updates were reflected throughout the document as per the below:

- **All Additions** are emphasized using a green font.
- **All Updates** are emphasized using an orange font.
- **All modifications or information** subject to re-phrasing are highlighted in yellow.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

The purpose of this document is to update the "2014 AHA/ ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation". The areas of the 2014 AF Guideline that were updated were limited to those for which important new data from clinical trials had emerged and/or new U.S. Food and Drug Administration (FDA) indications for thromboembolism protection devices have appeared in the data available to the writing group up to August 2018. Please consult the full-text version of the 2014 AF Guideline for text and evidence tables supporting the unchanged recommendations and for clinical areas not addressed in this focused update.

Recommendations for selecting anticoagulant regimen: [3, p 110]

- For patients with AF and an elevated CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. (Class I)

Options include:

- Warfarin (LOE: A)
- Dabigatran (LOE: B)
- Rivaroxaban (LOE: B)
- Apixaban (LOE: B)

- Edoxaban (LOE: B-R)

- NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve.
- In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA2DS2-VASc score is recommended for assessment of stroke risk.
- For patients with AF who have mechanical heart valves, warfarin is recommended Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.
- Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually.
- In patients with AF, anticoagulant therapy should be individualized based on shared decision making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences. A
- For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF.
- For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.
- For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.
- For patients with AF who have a CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.
- For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered.
- In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran, or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk (No Benefit) Class III

- The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve (Harm) (Class III)

Recommendations for Prevention of Thromboembolism:

1- For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least 3 weeks before and at least 4 weeks after cardioversion, regardless of the CHA2DS2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm. However, this approach is associated with a higher risk of stroke than TEE-guided cardioversion. TEE is recommended.

2- For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated.

3- After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile**.**

4- For patients with AF or atrial flutter of less than 48 hours' duration with a CHA2DS2-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy.

5- For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the LAA, if anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least 4 weeks. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of atrial fibrillation (AF) recommend that transesophageal echocardiography (TEE) be performed prior to cardioversion in patients with AF of more than 48 hours duration.

6- For patients with AF or atrial flutter of less than 48 hours' duration with a CHA2DS2-VASc score of 0 in men or 1 in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, versus no anticoagulant therapy, may be considered before cardioversion, without the need for post cardioversion oral anticoagulation. In the absence of a strong contraindication,

all patients undergoing cardioversion of AF/AFL receive at least four weeks of therapeutic anticoagulation (Canadian Guidelines).

1.2 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

Essential information from the patient's history, physical examination, electrocardiogram, and a transthoracic echocardiogram should be obtained at the time of diagnosis and periodically during the disease. Additional laboratory testing, such as thyroid stimulating hormone assay, and ambulatory ECG monitoring may be necessary.

The two principal management decisions for patients are:

1- *Need for antithrombotic therapy to prevent systemic embolization.*

- Every patient with AF should be evaluated for the need of antithrombotic therapy to prevent systemic embolization even for the first AF episode.
- This is accomplished by use of the CHA_2DS_2-VASc score.
- All patients whose risk of embolization exceeds the risk of bleeding are candidates for long-term antithrombotic therapy.
- Recommendations regarding prevention of thromboembolism have been updated and mentioned in 2019 focused update of atrial fibrillation management.

2- *Rate versus a rhythm control strategy*

This should be determined based on severity of symptoms, presence of structural heart disease, adequacy of rate control during episodes of atrial fibrillation, and the patient's preference for using antiarrhythmic drug therapy or undergoing ablation-based interventions.

Rate control strategy: generally uses drugs that slow conduction across the atrioventricular (AV) node, such as beta blockers, non-dihydropyridine calcium channel blockers, digoxin and amiodarone.

A rhythm control strategy uses either antiarrhythmic drug therapy, percutaneous catheter ablation, and/or a surgical procedure. Electrical cardioversion may be necessary to restore sinus rhythm. Antiarrhythmic medications are generally started before cardioversion and continued to maintain sinus rhythm (in the event of AF recurrence)

Factors that may favor attempts at rhythm control include difficulty in achieving adequate rate control, younger patient age, tachycardia-mediated cardiomyopathy, first episode of AF, AF precipitated by an acute illness, and patient preference.

Most important RATE CONTROL recommendations: *Appendix1*

- Control ventricular rate using a beta blocker or non-dihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF (Class I LOE B)
- IV beta blocker or non-dihydropyridine calcium channel blocker is recommended to slow ventricular has in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Class I LOE B)
- For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary (Class I LOE C)
- A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF (Class IIa LOE B)
- IV amiodarone can be useful for rate control in critically ill patients without pre-excitation (Class IIa LOE B)
- AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological therapy is inadequate and rhythm control is not achievable (Class IIa LOE B)
- A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable when patients remain asymptomatic, and LV systolic function is preserved (Class IIb LOE B)
- Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Class IIb LOE C)
- AV nodal ablation should not be performed without prior attempts to achieve rate control with medications (Class III: Harm LOE C)
- Non dihydropyridine calcium channel antagonists should not be used in decompensated HF (Class III: Harm LOE C)
- With pre-excitation and AF, digoxin, non-dihydropyridine calcium channel antagonists, or amiodarone should not be administered (Class III: Harm LOE B)
- Dronedarone should not be used to control ventricular rate with permanent AF (Class III LOE B)

Recommendations for Electrical and Pharmacological Cardioversion of AF and Atrial Flutter *Appendix2*

Direct-current cardioversion

- Cardioversion is recommended for AF or atrial flutter to restore sinus rhythm. If unsuccessful, cardioversion attempts may be repeated. (Class I LOE B)

- Cardioversion is recommended for AF or atrial flutter with RVR, that does not respond to pharmacological therapies (Class I LOE C)
- Cardioversion is recommended for AF or atrial flutter and pre-excitation with hemodynamic instability (Class I LOE C)
- It is reasonable to repeat cardioversion in persistent AF when sinus rhythm can be maintained for a clinically meaningful period between procedures (Class IIa, LOE C)

Pharmacological cardioversion

- Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Class I LOE A)
- Amiodarone is reasonable for pharmacological cardioversion of AF(Class IIa LOE A)
- Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting (Class IIa LOE B)
- Dofetilide should not be initiated out of hospital (Class III: Harm LOE B)

1.3 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC). (Updated from 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS)

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world.

Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or non- VKA oral anticoagulants (NOACs) markedly reduces stroke and mortality in AF patients.

Other interventions such as rhythm control and rate control improve AF-related symptoms and may preserve cardiac function.

A summary of the management diagnosis of atrial fibrillation patients:

- Use ECG screening in at-risk populations for AF, especially stroke survivors and the elderly.

- Evaluate all AF patients by clinical evaluation, ECG, and echocardiogram for underlying cardiovascular conditions such as hypertension, heart failure, valvular heart disease, and others.
- Propose lifestyle changes to all suitable AF patients to make their management more effective.
- Treat underlying cardiovascular conditions adequately, e.g. valve repair or replacement in AF patients with significant valvular heart disease, treatment of heart failure, or management of hypertension, among others.
- Use oral anticoagulation in all AF patients unless they are at low risk for stroke based on the CHA2DS2VASc score or have true contraindications for anticoagulant therapy.
- Check ventricular rate in all AF patients and use rate control medications to achieve lenient rate control.
- Evaluate AF-related symptoms in all AF patients using the modified EHRA symptoms scale. Whenever patients have AF-related symptoms, aim to improve symptoms by adjustment of rate control therapy and by offering antiarrhythmic drugs cardioversion, or catheter or surgical ablation.
- Select antiarrhythmic drugs based on their safety profile and consider catheter or surgical ablation when antiarrhythmic drugs fail.
- Do not use antiplatelet therapy for stroke prevention in AF.
- Do not use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.
- Do not perform cardioversion or catheter ablation without anticoagulation unless an atrial thrombus has been ruled out transesophageal echocardiogram.

The 2016 ESC guidelines were updated in 2020. New recommendations were issued for the diagnosis and management of AF and are summarized below[11]:

Table 5. Classes of Recommendations in ESC Guidelines

Class	Definition	Recommendation
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	**Is recommended or is indicated**
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	

Class IIa	Weight if evidence/opinion is in favor of usefulness/efficacy	**Should be considered**
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	**May be considered**
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	**Is not recommended**

Table 6. Levels of Evidence in ESC Guidelines

Level of Evidence	Definition
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of the experts and/or small studies, retrospective studies, registries.

The HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score >_3) for early and more frequent clinical review and follow-up. (Class 2a)

Table 7. HAS-BLED Bleeding Risk Score

Letter	Risk factor	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65 years)	1

D	Drugs or alcohol (1 point each)	1 or 2

In patients with a definite duration of AF < 24h and a very low stroke risk (CHA2DS2-VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted. (Class 2b)

Table 8. CHA2DS2-VASc Score

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age >= 75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thrombo-embolism	2
V	Vascular disease	1
A	Age 65-74	1
S	Sex category (female sex)	1
Maximum score		9

- For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended. (Class 1)
- In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmic risk factors is recommended. (Class 1)
- Opportunistic screening for AF is recommended in hypertensive and OSA patients. (Class 1 and 2a)
- In AF patients with ACS undergoing an uncomplicated PCI, early cessation (< 1week) of aspirin and continuation of dual therapy with an OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used. (Class 1)

Post catheter ablation:

- Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. (Class 1)

Special population: pregnancy

- In pregnant women with HCM, cardioversion should be considered for persistent AF. (Class 2a)
- Ibutilide or flecainide IV may be considered for termination of AF in stable patients with structurally normal hearts of acute management. (Class 2b)
- For the long-term management flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. Digoxin or verapamil should be considered for rate control if beta-blockers fail. (Class 2a)

1.4 2021 NICE Atrial Fibrillation: Diagnosis and Management. (Updated from NICE guidelines: Atrial fibrillation: management Clinical guideline Published: 18 June 2014)

Atrial fibrillation is the most common sustained cardiac arrhythmia. The aim of treatment is to prevent complications, particularly stroke, and alleviate symptoms

Drug treatments include:

- Anticoagulants to reduce the risk of stroke and
- Antiarrhythmics to restore or maintain the normal heart rhythm or to slow the heart rate in people who remain in atrial fibrillation

Non-pharmacological management includes:

- Electrical cardioversion, which may be used to 'shock' the heart back to its normal rhythm, and catheter or
- Surgical ablation to create lesions to stop the abnormal electrical impulses that cause atrial fibrillation
- Asses risk of stroke using the CHA_2DS_2-VASc stroke risk score and bleeding risks using the HAS-BLED score
- Offer anticoagulation to people with a CHA2DS2-VASc score of 2 or above, taking bleeding riskinto account. Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist.

Rate and rhythm control:

Offer rate control as the first-line strategy to people with atrial fibrillation except in people:

- whose atrial fibrillation has a reversible cause
- who have heart failure thought to be primarily caused by atrial fibrillation.
- with new-onset atrial fibrillation
- with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm
- for whom a rhythm control strategy would be more suitable based on clinical judgement

Left atrial ablation:

- If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:
- offer left atrial catheter ablation to people with paroxysmal atrial fibrillation
- consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation
- discuss the risks and benefits with the person

Rate control:

- Offer either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy.
- Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise
- 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 2 of the following: a beta-blocker, diltiazem, digoxin.
- Do not offer amiodarone for long-term rate control.

Rhythm control:

- Consider pharmacological and/or electrical rhythm control for people with atrial fibrillation whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful.
- For people having cardioversion for atrial fibrillation that has persisted for longer than 48 hours, offer electrical (rather than pharmacological) cardioversion.

- Consider amiodarone therapy starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm and discuss the benefits and risks of amiodarone with the person.

Drug treatment for long-term rhythm control:

- If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindications.
- Dronedarone second-line treatment option and after alternative options have been considered
- If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account
- Consider amiodarone for people with left ventricular impairment or heart failure.
- Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to

people with known ischaemic or structural heart disease.

The 2014 NICE guideline was updated in 2021. New recommendations were issued for the management of AF and are summarized below[12]:

- Use the ORBIT bleeding risk score because evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools.
- Offer monitoring and support to modify risk factors for bleeding, including reversible causes of anemia.
- If direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist.
- For adults with atrial fibrillation who are already taking a vitamin K antagonist and are stable, continue with their current medication and discuss the option of switching treatment.
- Do not offer amiodarone for long-term rate control.
- Consider antiarrhythmic drug treatment for 3 months after left atrial ablation to prevent recurrence of atrial fibrillation, considering the person's preferences, and the risks and potential benefits.
- Reassess the need for antiarrhythmic drug treatment at 3 months after left atrial ablation.
- Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation.

1.5 The Saudi Center for Evidence Based Health Care Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-valvular Atrial Fibrillation 2014

The Saudi center on antithrombotic treatment of patients with non-valvular atrial fibrillation 2014 issued the below recommendations[5]:

Table 9. Interpretation of Strong and Conditional (Weak) Recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Antithrombotic treatment of patients with non-valvular atrial fibrillation at **low risk of stroke:**

- For patients with non-valvular atrial fibrillation at low risk of stroke (e.g., CHADS2 score = 0), the Ministry of Health of Saudi Arabia guideline panel suggests no antithrombotic therapy rather than aspirin [weak recommendation, moderate quality evidence] or oral anticoagulation (weak recommendation, moderate quality evidence)
- For patients who choose antithrombotic therapy, the Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation. (Weak recommendation, moderate quality evidence)

Antithrombotic treatment of patients with non-valvular atrial fibrillation at **intermediate risk of stroke**:

- For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g., CHADS2 score = 1), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence) or aspirin. (Strong recommendation, moderate quality evidence)

Antithrombotic treatment of patients with non-valvular atrial fibrillation at **high risk of stroke:**

- For patients with non-valvular atrial fibrillation at high risk of stroke (e.g., CHADS2 score = 2 or greater), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence), aspirin (strong recommendation, moderate quality evidence) or aspirin plus clopidogrel (strong recommendation, moderate quality evidence).

Use of Novel Oral Anticoagulants (NOAC) versus Vitamin K Antagonists (VKA):

- For patients with non-valvular atrial fibrillation in whom oral anticoagulation is recommended (or suggested), the Ministry of Health of Saudi Arabia guideline panel suggests the use of Novel Oral Anticoagulants (dabigatran 150 mg bid, rivaroxaban 20 mg once a day or apixaban 5 mg bid) rather than Vitamin K antagonists (weak recommendation, moderate quality evidence)

1.6 Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report (2018)

The CHEST guideline focusing on antithrombotic therapy for atrial fibrillation issued the below recommendations[13]:

- In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, the guideline suggests using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low-quality evidence.)
- In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for recurrent ACS and/or stent thrombosis, the guideline suggests triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (weak recommendation, low quality evidence).
- In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED ≥3), the guideline suggests triple therapy for one month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (weak recommendation, low quality evidence).
- In AF patients taking warfarin without high risk of thromboembolism or who do not have a mechanical valve, the guideline suggests pre-operative management without bridging (Weak recommendation, low quality evidence).
- In AF patients on antithrombotic prophylaxis with warfarin with a high risk of thromboembolism or with a mechanical valve, the guideline suggests pre-operative management with bridging (Weak recommendation, low quality evidence).
- In AF patients on antithrombotic prophylaxis with a NOAC, the guideline suggests pre-operative management without bridging (Weak recommendation, low quality evidence).
- For patients with AF of documented duration of 48 hours or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (weak recommendation, low quality evidence.)
- For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality evidence).

- For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible, but that initiation of anticoagulation must not delay any emergency intervention (weak recommendation, low quality evidence).
- For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality evidence).

1.7 The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation

The 2020 Canadian cardiovascular society for the management of atrial fibrillation issued the below recommendations[14]:

- In the absence of a strong contraindication, all patients undergoing cardioversion of AF/AFL receive at least four weeks of therapeutic anticoagulation.
- The guideline recommends that patients with AF who are receiving OAC should have their renal function assessed at baseline and at least annually to detect latent kidney disease, determine OAC eligibility, and to support drug dosing (Strong Recommendation; Moderate-Quality Evidence)
- The guideline recommends that Creatinine Clearance, as estimated by the Cockcroft–Gault method, be used to support dosing decisions of anticoagulant medications (Strong Recommendation, High-Quality Evidence)
- The guideline recommends that OAC not be routinely prescribed for patients with AF and advanced liver disease (Child-Pugh C or liver disease associated with significant coagulopathy) (Strong Recommendation; Low-Quality Evidence).
- When an OAC is indicated in the presence of active malignancy, the guideline suggests a DOAC in preference to VKA (Weak Recommendation; Low-Quality Evidence).
- The guideline suggests that interruption of OAC is not necessary for most procedures with a minimal risk of bleeding (Weak Recommendation; Moderate Quality Evidence).

- The guideline recommends interruption of OAC for most procedures with a low/moderate- or high risk of bleeding, or where the bleeding risk associated with the procedure is uncertain (Strong Recommendation, Low-Quality Evidence)
- When a decision to interrupt VKA therapy for an invasive procedure has been made, the guideline suggests that the interruption begins 5 days prior to the procedure, that a procedure with a low bleeding risk may proceed when the INR is ≤1.5, and a procedure with an intermediate or high bleeding risk may proceed when the INR is ≤1.2 (Weak Recommendation; Low-Quality Evidence)
- The guideline recommends immediate electrical cardioversion for patients whose recent-onset AF is the direct cause of instability with hypotension, acute coronary syndrome, or pulmonary edema (Strong Recommendation, Low-Quality Evidence)
- The guideline recommends evidence-based beta-blockers (bisoprolol, carvedilol, metoprolol) be first-line agents for rate-control of hemodynamically stable AF in the acute care setting in patients with significant left-ventricular dysfunction (LVEF ≤40%) (Strong Recommendation; Moderate-Quality Evidence).
- The guideline recommends titrating rate-controlling agents to achieve a heart rate target of ≤100 bpm at rest for patients presenting with a primary diagnosis of AF in the acute care setting. (Strong Recommendation, Low-Quality Evidence)

Addition of Drugs Within Classes:

- The guideline recommends administering idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary. (Strong Recommendation; Moderate-Quality Evidence.
- The guideline recommends administering andexanet alfa (once available) for emergency reversal of the anticoagulant effect of apixaban, edoxaban, and rivaroxaban in patients presenting with uncontrollable or potentially life-threatening bleeding who have received any of these agents within the preceding 18 hours. (Strong Recommendation; Low-Quality Evidence).

1.8 The national heart foundation of Australia and cardiac society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018

The 2018 national heart foundation of Australia and New Zealand for the management of atrial fibrillation issued the below recommendations[15]:

- When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of <1.2 ng/ml (moderate, strong)
- Calcium channel antagonists should be avoided in patients with left ventricular systolic dysfunction (ejection fraction <40%). (Low, strong)
- Amiodarone should not be administered as a first-line agent for chronic rate control, given its toxicity profile. (low, strong)
- Membrane-active antiarrhythmic agents (e.g., sotalol or flecainide) should not be used in patients managed with a rate-control strategy. (low, strong)

Section 2.0 Drug Therapy

2.1 Class I (voltage-gated Na+ channel blockers)

2.1.1.a Saudi FDA Indications:

Drug	Class	Disease
a- Quinidine	Class Ia	Atrial fibrillation
b- Flecainide	Class Ic, IVb	

a- Quinidine:

2.1.2.a Clinical guidelines recommendations and Efficacy:

Quinidine has been associated with an increase in all-cause mortality likely due to ventricular arrhythmias (torsades de pointes). It is no longer recommended for patients with AF and may be an alternative treatment for AF when other, newer antiarrhythmic drugs cannot be used. [1, p42] [2, p40]

Conclusion: it is used only when flecainide and newer antiarrhythmic drugs cannot be used in rhythm control. N.B: newer antiarrhythmic drugs include sotalol, dronedarone, dofetilide, ibutilide & propafenone (not available in KSA).

2.1.3.a Safety profile:[5]

US Boxed Warning

Mortality:

In many trials of antiarrhythmic therapy for non–life-threatening arrhythmias, active antiarrhythmic therapy has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease.[5]

It prolongs the QT interval, can cause torsades de pointes. [2, p42]

Conclusion: box warning of increased mortality rendering last choice after flecainide

2.1.4 a Drug-Drug interactions profile [5]

Class	Drug		
X **(Avoid combination)**	Aclidinium Ajmaline Cimetropium Citalopram Clarithromycin Conivaptan Domperidone Eluxadoline Entrectinib Enzalutamide Erythromycin (Systemic) Fexinidazole [INT] Fingolimod Mefloquine Mequitazine Mifepristone	Fluconazole Flupentixol Fusidic Acid (Systemic) Gemifloxacin Glycopyrrolate (Oral Inhalation) Glycopyrronium (Topical) Grapefruit Juice Idelalisib Ipratropium (Oral Inhalation) Itraconazole Ketoconazole (Systemic) Lasmiditan Lefamulin Levofloxacin-Containing Products (Systemic) Levosulpiride Lopinavir Oxatomide	Revefenacin Ribociclib Ritonavir Saquinavir Sparfloxacin Tamoxifen Thioridazine Tiotropium Pazopanib Pimozide Piperaquine Posaconazole Potassium Chloride Potassium Citrate Probucol QT-prolonging Class IA Antiarrhythmics (Highest Risk)

	Moxifloxacin (Systemic) Nelfinavir Nilotinib Tipranavir Topotecan Umeclidinium Vincristine (Liposomal) Voriconazole		QT-prolonging Class III Antiarrhythmics (Highest Risk) Quetiapine

Conclusion: Quinidine has a lot of drugs- drug interactions category X which makes infrequently used.

2.1.5.a Contraindications Profile [5]

- Hypersensitivity to quinidine or any component of the formulation.
- thrombocytopenia; thrombocytopenic purpura.
- myasthenia gravis.
- heart block greater than first degree; idioventricular conduction delays (except in patients with a functioning artificial pacemaker).
- those adversely affected by anticholinergic activity.
- concurrent use of quinolone antibiotics which prolong QT interval, cisapride, amprenavir, or ritonavir.

Conclusion: it is recommended to carefully reviewing contraindications before starting quinidine

➔ **Quinidine use is not recommended in light of the above information, mainly the contraindications and black box warning.**

2.1.6.a Dosage and administration [5]:

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dosage and administration	Maximum Daily Dose
Quinidine sulfate	200 mg	Oral	Adult: Pharmacological conversion: 400 mg/dose every 6 hours Maintenance of sinus rhythm: 200 mg every 6 hours	2,400 mg/day
			Pediatrics: 30 mg/kg/day in divided doses every 6 hours	60 mg/kg/day

2.1.7.a Therapeutic designation and suggested prescribing edits

Table 10. Therapeutic Designation

Drug	*Strength*	*Dosage Form*	*Therapeutic Designation*	*Prescribing Edits*
Quinidine sulfate	*200 mg*	*Oral*	*Essential*	*ST*

Therapeutic designation: Although it is non preferred by guidelines, but it is recommended to be used as an alternative treatment for AF when other, newer antiarrhythmic drugs cannot be used. [1, p42] [2, p40]

N.B: other antiarrhythmic drugs include flecainide, sotalol and other agents not available in KSA such as dronedarone, dofetilide, ibutilide & propafenone.

Prescribing edits are:

ST: used after flecainide in rhythm control strategy.

b- Flecainide:

2.1.2.b Clinical guidelines recommendations and Efficacy:

Flecainide is an antiarrhythmic drug (Class Ic, IVb) recommended for rhythm control strategy.

- Flecainide is effective for pharmacological cardioversion of AF or atrial flutter & for prevention of recurrent symptomatic AF in patients without structural heart disease & pathological left ventricular hypertrophy (classI,A)[1, 40] [1, p 61] [2, p 32, 38]
- A single oral dose ("pill-in-the-pocket") of Flecainide can be used to terminate AF out of hospital once observed to be safe in a monitored setting. (Class IIa,B) [2, p 32]

(*'pill-in-the-pocket' strategy is defined as the person managing paroxysmal atrial fibrillation themselves by taking antiarrhythmic drugs only when an episode of atrial fibrillation starts.)*

- Pre-treatment with flecainide, enhances the efficacy of electrical cardioversion and prevent recurrent AF. (IIa,b)[1,p45]
- Flecainide can be used for conversion of fetal arrhythmias without major adverse effects, and thus are likely to be safe to treat maternal symptomatic AF [1, p 54]
- High ventricular rates resulting from the conversion of AF into atrial flutter with 1:1 conduction by flecainide can be prevented by pre-administering a beta-blocker, verapamil, or diltiazem. [1, p42]
- **Conclusion: effective drug for cardioversion of AF or atrial flutter in patients without structural heart disease, can be used in *'pill-in-the-pocket' strategy***

2.1.3.b Safety profile:[5]

- US Boxed Warning

Mortality:

An excessive mortality or nonfatal cardiac arrest rate was seen in patients (with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously) treated with flecainide compared with that seen in placebo-treated patients. (CAST trail)

Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter:

A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such

as digoxin or beta-blockers may lower the risk of this complication. Therefore, Flecainide is not recommended for use in patients with chronic atrial fibrillation.

- ADRs >10%:

1. Central nervous system: Dizziness (19% to 30%)
2. Ocular: Visual disturbances (16%)
3. Respiratory: Dyspnea (~10%)

- Adverse reactions mentioned in guidelines:

1. Do not offer class 1c antiarrhythmic drugs such as flecainide to people with known ischemic or structural heart disease [2, p38] [4, p 20]
2. Hypotension [2, p35]

Conclusion: should not be used in patients with structural heart disease.

Expert's opinion: It's mandatory to follow up ECG Baseline, day 1, day 2–3 after start of therapy to be stopped if QRS duration increases >25% above baseline.

2.1.4 b Drug-Drug interactions profile [5]:

Category of interactions	Drug
X	Asunaprevir Fexinidazole Fosamprenavir Pimozide Ritonavir Tipranavir

Conclusion: no significant DDI

2.1.5.b Contraindications Profile: [5]

- Hypersensitivity to flecainide or any component of the formulation

- Pre-existing second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block) (except in patients with a functioning artificial pacemaker)
- Cardiogenic shock
- Concurrent use of ritonavir
- Patients with structural heart disease

Conclusion: should not be used in patients with structural heart disease.

2.1.6.a Dosage and administration [5]:

- Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dosage and administration	Maximum Daily Dose
Flecainide acetate	100 mg	Oral	Adult: Paroxysmal atrial fibrillation/flutter(prevention): Initial: 50 mg every 12 hours; increase by 50 mg twice daily at 4-day intervals Atrial fibrillation or flutter (pharmacological cardioversion) <70 kg: 200 mg ≥70 kg: 300 mg	400 mg
			Pediatrics: Weight-based dosing: Oral: Initial: 1 to 3 mg/kg/day divided every 8 hours usual maintenance range: 3 to 6 mg/kg/day BSA-directed dosing. Infants ≤6 months: Oral: Initial: 50 mg/m2/day divided every 8 to 12 hours; may titrate dose at	8 mg/kg/day

			4-day intervals; maximum daily dose: 200 mg/m2/day. Infants >6 months, Children, and Adolescents: Oral: Initial: 100 mg/m2/day divided every 8 to 12 hours; may titrate dose at 4-day intervals; maximum daily dose: 200 mg/m2/day	

Table 11. Therapeutic Designation

Drug	***Strength***	***Dosage Form***	***Therapeutic Designation***	***Prescribing Edits***
Flecainide acetate	*100 mg*	*Oral*	*Essential*	------

N.B. Usually, the safety of antiarrhythmic drug therapy determines the initial choice of antiarrhythmic drugs. Flecainide among other antiarrhythmic drugs (Dronedarone, propafenone & sotalol not in KSA list) are recommended for rhythm control in patients without structural heart disease.

Therapeutic Designation: essential as first line in case of rhythm control of AF without structural heart disease before amiodarone.

2.2 Class II (autonomic inhibitors and activators)

Drug	**Disease 1**
Class IIa (beta blockers)	Nonselective: carvedilol, propranolol Selective: atenolol, bisoprolol, betaxolol, esmolol, metoprolol
Class IId (muscarinic M2 receptor activators):	digoxin

2.2 Class IIa B-Blockers

2.2.1.a Saudi FDA Indications

Drug	**Disease**

Beta blocker, cardio selective: Atenolol Betaxolol Bisoprolol Metoprolol Esmolol Nebivolol (mentioned in European guidelines only)	AF
Beta blocker, non-cardio selective: Propranolol Carvedilol	AF

2.2.2 Clinical guidelines recommendations and Efficacy:

- Beta blockers are the most effective and commonly used drug class for rate control. [2, p 29]
- Beta blockers are recommended to control heart rate in AF patients with LVEF ≥40% or LVEF <40%. (ClassI,LOE B) [1,p61]
- According to American & European guidelines beta blockers are usually not considered effective for maintaining sinus rhythm in patients with AF. It can be used as add on therapy to certain antiarrhythmic drugs Vaughan Williams class IC agent to prevent a rapid ventricular response due to 1:1 AV conduction during atrial flutter [2, p 35,40]
- According to NICE guidelines: "If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindication." [4, p19]
- IV beta blockers (esmolol, propranolol, and metoprolol) are recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. (In hemodynamically stable patients). [2, p 29]
- Orally administered beta blockers, including atenolol, metoprolol, nadolol, propranolol have all been effectively used for ongoing ventricular rate control in patients with chronic AF. 2, p 29]

Conclusion: most effective drug class for rate control in acute and chronic setting.

According to EMC beta blockers mentioned in guidelines are not labelled for AF.

According to European guidelines atenolol and propranolol are not recommended for AF but are mentioned in American guidelines. Nebivolol is mentioned in European guidelines only. The rest of beta blockers are recommended in both American and European guidelines with high level of evidence (Class I LOE B)

2.2.3 Safety profile [5]

- US Boxed Warning (Atenolol – Bisoprolol- Betaxolol -Metoprolol)
- Cessation of therapy:
- Advise patients with coronary artery disease who are being treated with beta blocker against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction (MI) and ventricular arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with beta-blockers. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly, even in patients treated only for hypertension.

➢ **Esmolol:** >10%

Cardiovascular: Asymptomatic hypotension (25%), symptomatic hypotension (12%)

➢ **Carvedilol:** >10%:

- Cardiovascular: Hypotension (≤20%), orthostatic hypotension (≤20%)
- Central nervous system: Dizziness (2% to 32%), fatigue (24%)
- Endocrine & metabolic: Weight gain (10% to 12%), hyperglycemia (5% to 12%)
- Gastrointestinal: Diarrhea (1% to 12%)
- Neuromuscular & skeletal: Asthenia (11%)

Most common reported adverse symptoms are lethargy, headache, peripheral oedema, upper respiratory tract symptoms, gastrointestinal upset, and dizziness. Adverse effects include bradycardia, atrioventricular block, and hypotension. [1, p37]

Conclusion: not problematic, require monitoring of blood pressure and heart rate to avoid bradycardia.

2.2.4 Drug-Drug interactions profile [5]:

Class	Drug	Effect
X **(Avoid combination)** **For all beta blockers**	Floctafenine	Floctafenine may enhance the adverse/toxic effect of Beta-Blockers.
	Bromperidol	May diminish the hypotensive effect of Blood Pressure Lowering Agents. Blood Pressure Lowering Agents may enhance the hypotensive effect of Bromperidol.
	Rivastigmine	Rivastigmine may enhance the bradycardic effect of Beta-Blockers.
	Fexinidazole [INT]	Bradycardia-Causing Agents may enhance the arrhythmogenic effect of Fexinidazole [INT].
	Specific to propranolol & carvedilol: Beta2-Agonists	Beta-Blockers (Nonselective) may diminish the bronchodilator effect of Beta2-Agonists.

Conclusion: not problematic DDI however it is recommended to review DDI when prescribing this class.

2.2.5 Contraindications Profile [5]:

Drug	Contraindication
All beta blockers	Hypersensitivity to drug or any component of the formulation, severe sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated heart failure
	Canadian labeling: Pheochromocytoma (in the absence of alpha-blockade); hypotension
Esmolol	IV administration of calcium channel blockers (e.g., verapamil) near esmolol (i.e., while cardiac effects of another

	drug are still present); pulmonary hypertension. Canadian labeling: Patients requiring inotropic agents and/or vasopressors to maintain cardiac output and systolic blood pressure; right ventricular failure secondary to pulmonary hypertension
Atenolol – Bisoprolol-propranolol	Canadian labeling: cor pulmonale; severe peripheral arterial disorders; anesthesia with agents that produce myocardial depression; metabolic acidosis
Metoprolol	**Immediate-release tablets/injectable formulation:** ➢ Hypertension and angina (oral only): Sinus bradycardia; cardiogenic shock; overt heart failure; sick sinus syndrome; severe peripheral arterial circulatory disorders ➢ Myocardial infarction (oral and injection): Severe sinus bradycardia (heart rate <45 beats/minute); significant first-degree heart block (P-R interval ≥0.24 seconds); systolic blood pressure <100 mm Hg; moderate to severe cardiac failure
Propranolol:	bronchial asthma

Conclusion: should be avoided in bradycardia, heart block, cardiogenic shock; uncompensated heart failure.

2.2.6 Dosage and administration [5]:

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dosage and administration	Maximum Daily Dose
Carvedilol	*3.125 mg* *6.25 mg* *12.5 mg* *25 mg*	*Tablet*	*3.125–25 mg BID*	*50 mg*
propranolol	*10 mg* *40 mg* *80 mg*	*Tablet*	*Adult: Maintenance of ventricular rate control: 10–40 mg TID or QID*	*160 mg*
			Pediatric: usual daily dose: 2 to 4 mg/kg/day	*16 mg/kg/**day*** *or 60 mg/**day***
	1mg/ml	*Injection*	*Adult: Acute ventricular rate control:* *IV: 1 mg over 1 minute; repeat as needed every 2 minutes up to a maximum of 3 doses*	*3 mg*
			Pediatrics: 0.01 to 0.15 mg/kg/dose slow IV over 10 minutes; may repeat every 6 to 8 hours as needed	*Infants: 1 mg/dose; children and adolescents: 3 mg/dose*
Atenolol	*25mg* *50 mg* *100 mg*	*Tablet* *Injection*	*Po:25–100 mg QD* *IV Initial: 2.5 mg bolus administered over 2.5 minutes, followed by additional 2.5 mg doses at 5-minute intervals until a response is observed*	*100 mg* *maximum cumulative dose: 10 mg*
Bisoprolol	*2.5, 5, 10 mg*	*Tablet*	*2.5 to 10 mg once daily*	*20 mg [1, p37]*
Esmolol	*10 mg/ml*	*Injection*	*500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV*	*300 mcg/kg/min*

				[2, p29]
Metoprolol tartrate [6]	*50 ,100 ,200 mg*	*Tablet*	*50mg two or three times daily. If necessary, the dose may be increased to 300mg daily in divided doses*	*300 mg/day*
Betaxolol	*20 mg*	*Tablet*	*20 mg once daily*	*20 mg*
Nebivolol	*5mg*	*Tablet*	*2.5–10 mg once daily* *(Mentioned in European guidelines only)*	*10 mg*

2.2.7 Therapeutic designation and suggested prescribing edits

Table 12. Therapeutic Designation

Drug	***Strength***	***Dosage Form***	***Therapeutic Designation***	***Prescribing Edits***
Carvedilol	*3.125 ,6.25 ,12.5* *25 mg*	*Tablet*	*Essential*	
propranolol	*10 ,40,80 mg*	*Tablet*	*Essential*	----------
	1mg/ml	*Injection*		
Atenolol	*25,50,100 mg*	*Tablet*	*Essential*	
Bisoprolol	*2.5,5,10 mg*	*Tablet*	*Essential*	
Esmolol	*10mg/ml*	*Injection*	*Essential*	*EU*
Metoprolol tartrate	*50 ,100 ,200 mg*	*Tablet*	*Essential*	
Betaxolol	*20 mg*	*Tablet*	*Essential*	
Nebivolol	*5mg*	*Tablet*	*Essential*	

Therapeutic Designation:

Beta blockers are first line in rate control strategy of AF in acute and long-term therapy [1, p36] **According to EMC beta blockers mentioned in guidelines are not labelled for AF.**

According to European guidelines atenolol and propranolol are not recommended for AF but are mentioned in American guidelines. Nebivolol is mentioned in European guidelines only. The rest of beta blockers are recommended in both American and European guidelines with high level of evidence (Class I LOE B).

Prescribing Edits:

EU: Esmolol should be used in emergency settings only.

2.2.b Digoxin Class IId (Muscarinic M2 Receptor Activators):

2.2.1.b Saudi FDA Indications

Drug	Disease
Digoxin	Atrial fibrillation

2.2.2.b Clinical guidelines recommendations and Efficacy:

- Digoxin is recommended to control heart rate in AF patients with LVEF ≥40% or LVEF <40%. [1, p 60] (class I, LOE B).
- Digoxin is recommended to control heart rate in acute setting or as a long-term pharmacological rate control therapy. [1, p 36]
- Digoxin is not usually first-line therapy for ventricular rate control in patients with AF. [2, p29][4,p18]
- For acute rate control, beta-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone. [1, p36]

Conclusion: digoxin is effective in rate control of AF in acute and long-term setting after beta-blockers and diltiazem/verapamil

2.2.3.b Safety profile: [5]

The major adverse effects include:

- Cardiac arrhythmias (e.g., ectopic, and re-entrant cardiac rhythms and heart block)
- Gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting)
- Neurological complaints (e.g., visual disturbances, disorientation, and confusion).

In toxic states (serum levels >2 ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with co-existent hypokalemia. [1, p37]

Conclusion: digoxin has narrow therapeutic index so monitoring of its serum level or symptoms of toxicity should be considered.

2..2.4 Drug-Drug interactions profile [5]

Category	Drug
X	Benznidazole Fexinidazole [INT] Lasmiditan Metronidazole (Systemic)

Conclusion: few DDI, but should be considered due to narrow therapeutic index

2.8.5 Contraindications Profile [5]

Hypersensitivity to digoxin, other forms of digitalis, or any component of the formulation; ventricular fibrillation.

Do **NOT** use it in patients with preexcitation associated with an accessory pathway, as this can lead to ventricular arrhythmias. [1, p30]

Conclusion: DDI should be reviewed carefully when recommending digoxin due to its narrow therapeutic index.

2.8.6 Dosage and administration

Table 1: Dosage and Administration

Drug	***Strength***	***Dosage form***	***Dosage and administration***	***Maximum daily dose***
Digoxin	*0.1mg,* *0.0625mg,* *0.25mg,*	*Tablet*	*0.125 to 0.25 mg once daily*	*0.25 mg*

	0.125 mg			
	0.5 MG/2ML *0.125 MG/ML* *0.1 MG/ML*	*IM, IV* *IV* *[IV BOLUS]*	*Adult: 0.25 to 0.5 mg over several minutes, with repeat doses of 0.25 mg every 6 hours to a maximum of 1.5 mg over 24 hours*	*1.5 mg*

2.8.7 Therapeutic designation and suggested prescribing edits

Table 13. Therapeutic Designation

Drug	***Strength***	***Dosage form***	***Therapeutic Designation***	***Prescribing Edits***
digoxin	*0.1 mg* *0.0625 mg* *0.25 mg* *0.125 mg*	*Tablet*	*Essential*	*ST*
	0.5 MG/2ML	*IM, IV*		
	0.125 MG/ML	*IV*		
	0.1 MG/ML	*[IV BOLUS]*		

Therapeutic designation: essential in rate control strategy of AF patients in acute setting or long-term control.

Prescribing edits:

ST: digoxin is used after beta blockers and diltiazem/verapamil in acute rate control strategy in AF

2.3 Class III (K+ channel blockers and openers)

2.3.1.a Saudi FDA Indications

Drug	Disease

Amiodarone	Atrial fibrillation

2.3.2.a Clinical guidelines recommendations and Efficacy:

Rate control:

- Amiodarone is an option for acute control of heart rate in patients with hemodynamic instability or severely reduced LVEF (Class IIb,LOE B) [1, P40]
- Suggested as adjunctive therapy in patients where heart rate control cannot be achieved using combination therapy e (e.g., beta-blocker or verapamil/ diltiazem combined with digoxin). [1, p37]

Rhythm control:

- In patients with ischemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF (rhythm control). (Class I, LOE A) [1,61]
- Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure. (Class I, LOE B) [1,61]
- Pre-treatment with amiodarone (requiring a few weeks of therapy), can improve the efficacy of electrical cardioversion [1,41]

Conclusion: In rate control strategy: amiodarone is used after beta-blockers, verapamil, diltiazem. In rhythm control strategy in AF without structural heart disease: amiodarone is used after flecainide. In rhythm control strategy in AF with heart disease amiodarone is used as first line.

2.3.3.a Safety profile: [5]

US Black Box Warning:

Life-threatening arrhythmias (tablet):

Amiodarone is intended for use only in patients with indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

- **Pulmonary toxicity (tablet):**

Amiodarone can cause pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 17% in some series of patients. Pulmonary toxicity has been fatal about 10% of the time. Obtain a baseline chest X-ray and pulmonary function tests, including diffusion capacity, when amiodarone therapy is initiated. Repeat history, physical exam, and chest X-ray every 3 to 6 months.

- **Hepatotoxicity:**

Amiodarone can cause hepatotoxicity, which can be fatal. Obtain baseline and periodic liver transaminases and discontinue or reduce dose if the increase exceeds 3 times normal or doubles in a patient with an elevated baseline. Discontinue amiodarone if the patient experiences signs or symptoms of clinical liver injury.

- **Worsened arrhythmia (tablet):**

Amiodarone can exacerbate arrhythmias. Initiate amiodarone in a clinical setting where continuous ECGs and cardiac resuscitation are available.

ADR >10%:

Cardiovascular: Hypotension (intravenous: 20%; oral: <1%; refractory in rare cases)

Endocrine & metabolic: Phospholipidemia (pulmonary phospholipidosis; oral: 50%; intravenous: <1%)

Gastrointestinal: Nausea (oral: 10% to 33%; intravenous: 4%), vomiting (10% to 33%; intravenous: <2%)

Ophthalmic: Epithelial keratopathy (98% to 99%)

Respiratory: Pulmonary toxicity (oral: 2% to 17%; intravenous: <1%)

ADR (mentioned in guidelines): Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), constipation, increased INR. [2, p35]

Conclusion: amiodarone has low safety profile and requires monitoring.

Expert's Opinion:

ECG is mandatory in Baseline, 1 week, 4 weeks to measure QT interval as it must be stopped if QT prolongation >500 ms.

Thyroid Dysfunction is one of the most common side effects in clinical practice specially with maintenance therapy.

2.1.4.a Drug-Drug interactions profile:[5]

Category of Interactions	Drug

X	Agalsidase Alfa Agalsidase Beta Aminolevulinic Acid (Systemic) Bromperidol Citalopram Clarithromycin Conivaptan Daclatasvir Domperidone Entrectinib Erythromycin (Systemic) Fexinidazole [INT] Fingolimod Flupentixol Fusidic Acid (Systemic) Gemifloxacin Grapefruit Juice Idelalisib Indinavir Lasmiditan Lefamulin Levofloxacin-Containing Products (Systemic) Lofepramine Lopinavir	Moxifloxacin (Systemic) Nelfinavir Nilotinib Pazopanib Pimozide Piperaquine Posaconazole Probucol Quetiapine Ribociclib Ritonavir Saquinavir Sofosbuvir Sparfloxacin Thioridazine Tipranavir Topotecan Vincristine (Liposomal) Voriconazole

Conclusion:

- **Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated.**
- **Although it is the most effective available antiarrhythmic drug for maintenance of sinus rhythm in patients with paroxysmal or persistent AF. Drug interactions and toxicities, however, are sufficient to preclude its routine use as a rate controlling agent**. [2, p38]

2.3.5 Contraindications Profile [5]:

Hypersensitivity to amiodarone, iodine, or any component of the formulation; sick sinus syndrome, second- or third-degree atrioventricular block, bradycardia leading to syncope without a functioning pacemaker; cardiogenic shock.

Canadian labeling (oral formulation): Additional contraindications (not in US labeling): Evidence of hepatitis; pulmonary interstitial abnormalities; thyroid dysfunction.

2.3.6.a Dosage and administration [5]:

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dosage and administration	Maximum Daily Dose
Amiodarone	200 mg	Tablet	Loading dose: 600 to 800 mg daily in divided doses for a total load of up to 10 g Maintenance dose of 100 to 200 mg once daily	Loading: 800 mg Maintenance:200 mg
	50mg/ml	injection	Initial: 150 mg over 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute for 18 hours Continue for a total load of up to 10 g	10g

2.3.7 Therapeutic designation and suggested prescribing edits:

Table 14. Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic Designation	Prescribing Edits
Amiodarone	200 mg	Tablet	Essential	ST (except in rhythm control in case of heart failure
	50mg/ml	injection		

Therapeutic designation: essential drug for rate control and rhythm control strategies of AF

Prescribing edits:

ST: In rate control strategy amiodarone is used after beta-blockers, verapamil, diltiazem.

ST: In rhythm control strategy in AF without structural heart disease, amiodarone is used after flecainide, Propafenone, dronedarone, dofetilide & sotalol (only flecainide is available in KSA, sotalol not sure if available in KSA).

ST: In rhythm control strategy of AF with CAD amiodarone is used after dronedarone, dofetilide & sotalol (if available in KSA)

In rhythm control strategy of AF with heart failure: amiodarone is first line.

2.4 Class IV (Ca++ handling modulators)

2.4.1 Saudi FDA Indications:

Subclass	Drugs
Class IVa (surface membrane Ca++ channel blockers)	diltiazem, verapamil
Class IVb (intracellular Ca++ channel blockers)	Flecainide

2.4.1 Saudi FDA Indications

2.4.1. (A) Class IV a (surface membrane Ca++ channel blockers):

2.4.1 Saudi FDA Indications:

Drug	Disease
Diltiazem (off-label)	AF
Verapamil (IV only is labeled for AF)	AF

2.4.2 Clinical guidelines recommendations and Efficacy:

- Diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%. (Class I, LOE B) [1, p 60]

Conclusion: diltiazem and verapamil are first line before amiodarone in rate control with hypertension, COPD, and no cardiovascular disease,

2.4.3 Safety profile [5]:

Verapamil	Diltiazem
>10%: Gastrointestinal: Gingival hyperplasia (≤19%), constipation (7% to 12%)	**1% to 10%:** Gastrointestinal: Dyspepsia (1% to 6%), abdominal enlargement (2%), nausea (2%), diarrhea (1% to 2%), anorexia (<2%), constipation (<2%), dysgeusia (<2%), vomiting (<2%), xerostomia (<2%)
>10%: Central nervous system: Headache (1% to 12%)	**1% to 10%:** Central nervous system: Dizziness (2% to 10%), headache (2% to 8%), pain (6%), fatigue (5%)
1% to 10%: Cardiovascular: Peripheral edema (1% to 4%), hypotension (3%) cardiac failure (≤2%) atrioventricular block (1% to 2%) bradycardia (heart rate <50 bpm: 1%)	**>10%** Cardiovascular: Peripheral edema (5% to 15%) 1% to 10%: Cardiovascular: Lower extremity edema (5% to 8%) bradycardia (3% to 4%) first-degree atrioventricular block (3% to 4%) hypotension (3% to 4%), edema (2% to 3%) cardiac failure (<2%) complete atrioventricular block (<2%)
Concerns related to adverse effects [mentioned in guidelines]	

Conduction abnormalities: May cause first-, second-, and third-degree AV block or sinus bradycardia; risk increases with agents known to slow cardiac conduction.

Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.

Disease-related concerns:

Accessory bypass tract (e.g., Wolff-Parkinson-White [WPW] syndrome): During an episode of atrial fibrillation or flutter in patients with an accessory bypass tract or preexcitation syndrome, use has been associated with increased anterograde conduction down the accessory pathway leading to ventricular fibrillation; avoid use in such patients.

Left ventricular dysfunction: Use with caution in left ventricular dysfunction; due to negative inotropic effects, may exacerbate condition. Avoid use in patients with heart failure due to lack of benefit and/or worse outcomes with calcium channel blockers in general.

Conclusion: should not be used in patients with heart failure due to negative inotropic effects.

2.4.4 Drug-Drug interactions profile [5]:

INTERACTING
Aprepitant
Asunaprevir
Bosutinib
Bromperidol
Budesonide
Cobimetinib
Conivaptan
Dantrolene *Depen*
Dofetilide
Disopyramide
Domperidone
Fexinidazole [INT]
Flibanserin
Fosaprepitant
Fusidic Acid
Idelalisib
Ivabradine
Lasmiditan
Lomitapide
Naloxegol
Neratinib
Pimozide
Rifampin
Simeprevir
Ulipristal *Depends*
Pazopanib
Topotecan Depend
Vincristine

DILTIAZE	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
VERAPAMIL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	...	X	X	X	X	X

Conclusion: There are a lot of drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor) but more with verapamil

2.4.5 Contraindications Profile [5]:

Contraindication	Drug
Oral & IV: Hypersensitivity to diltiazem or any component of the formulation; sick sinus syndrome (except in patients with a functioning artificial pacemaker); second- or third-degree AV block (except in patients with a functioning artificial pacemaker hypotension (systolic pressure <90 mm Hg) or cardiogenic shock IV ONLY: severe heart failure (unless secondary to a supraventricular tachycardia amenable to verapamil); concurrent use of IV beta blocking agents; atrial fibrillation or flutter associated with accessory bypass tract (e.g., Wolff-Parkinson-White syndrome, short PR syndrome); ventricular tachycardia (with wide-complex tachycardia [QRS ≥0.12 seconds], must determine whether origin is supraventricular or ventricular)	Verapamil, diltiazem
ORAL: severe left ventricular dysfunction, atrial flutter or fibrillation and an accessory bypass tract (Wolff-Parkinson-White [WPW] syndrome, Lown-Ganong-Levine syndrome). Canadian labeling: Additional contraindications (not in US labeling): Pregnancy; use in women of childbearing potential; concurrent use with IV dantrolene; concurrent use with ivabradine; severe bradycardia (<40 beats per minute).	VERAPAMIL
ORAL: acute MI and pulmonary congestion Canadian labeling: Additional contraindications (not in US labeling): Complicated myocardial infarction (MI) (ventricular failure manifested by pulmonary congestion); marked bradycardia; concurrent use of	DILTIAZEM

ivabradine or flibanserin, breastfeeding, severe left ventricular dysfunction	

Conclusion: it is recommended to carefully review contraindications before starting this class.

2.4.6 Dosage and administration:[5]

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dosage and administration	Maximum Daily Dose
Diltiazem [1, p37]	Tablets (30mg-60mg-90mg-120mg) Sustained release capsule (200mg-300 mg)	Immediate release tablet Sustained release capsule	60 mg 3 times daily up to 360 mg total daily dose Immediate release was [mentioned only in ESC guidelines] (120–360 mg once daily modified release).	360 mg
Verapamil	Immediate release Tablet (40mg 80mg-120mg)	Immediate release tablet	40–120 mg 3 times daily	480 mg
	Sustained release tablets 240 mg	Sustained release tablet	(180–480 mg once daily modified release).	
	IV for injection 5mg/2ml	Injection	2.5–10 mg intravenous bolus (Repeated as required). 0.075-0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg.	Based on cardiac response

			after 30 min if no response, then 0.005 mg/kg/min infusion [2, p29]	

2.4.7 Therapeutic designation and suggested prescribing edits

Table 15. Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic Designation	Prescribing Edits
Diltiazem	Tablets (30mg-60mg-90mg-120mg)	Immediate release tablet	Essential	----------
	Sustained release capsule (200mg-300 mg)	Sustained release capsule		
Verapamil	Immediate release Tablet (40mg 80mg-120mg)	Immediate release tablet	Essential	--------
	Sustained release tablets 240 mg	Sustained release tablet		
	IV for injection 5mg/2ml	Ampoule		EU

Therapeutic designation:

Diltiazem and Verapamil are Essential to be on Formulary as first line therapy for rate control before amiodarone in patients with no cardiovascular disease or heart failure. This class is not approved by EMC for AF except verapamil injection but is

recommended by American and European guidelines with high level of evidence. (Class I LOE B). NICE guidelines recommended diltiazem only.

Prescribing Edits:

EU: intravenous form of verapamil should be used in emergency setting.

2.5 Oral Anticoagulants

2.5.1 Saudi FDA Indications:

Drug	Disease
Apixaban	AF
Dabigatran	
Edoxaban	
Rivaroxaban	
Warfarin sodium	

2.5.2. Clinical guidelines recommendations and Efficacy: [1, p 60] [3, p110]

- Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more & all female AF patients with a CHA2DS2-VASc score of 3 or more. [1, p 60] (Class I LOE A]
- When oral anticoagulation is initiated in a patient with AF who is eligible for a non-vitamin K antagonist oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist. (Class I LOE A] [1, p 60]
- Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to severe mitral stenosis or mechanical heart valves. (Class I LOE B)
- NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are NOT recommended in patients with 100 heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C). (Class III)
- Patient age, weight, renal function & drug-drug interactions and other comorbidities influence the choice of NOAC.

- Head-to-head prospective RCT data for NOACs are needed for further evaluation of comparative bleeding risk and effectiveness. [3, p 114]

Conclusion: oral anticoagulation therapy is essential to prevent thromboembolism in AF patients according to CHA_2DS_2-VASc score. Vitamin K antagonist are recommended in AF patients with moderate-to severe mitral stenosis or mechanical heart valves otherwise NOACs are preferred.

2.5.3 Safety profile:[5]

- Apixaban, Dabigatran, Edoxaban, Rivaroxaban:

US Boxed Warning

▼ Discontinuation:

Premature discontinuation of any oral anticoagulant, including apixaban, increases the risk of thrombotic events. If anticoagulation with apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Spinal/Epidural hematoma:

Epidural or spinal hematomas may occur in patients treated with apixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; a history of spinal deformity or spinal surgery; optimal timing between the administration of apixaban and neuraxial procedures is not known.

Monitor patients frequently for signs and symptoms of neurologic impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

- **Edoxaban:**

US Boxed Warning

Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 mL/minute:

Edoxaban should not be used in patients with CrCl >95 mL/minute. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCl >95 mL/minute had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.

- Warfarin:

US Boxed Warning

Bleeding risk:

Warfarin can cause major or fatal bleeding. Perform regular monitoring of international normalized ratio (INR) on all treated patients. Drugs, dietary changes, and other factors affect INR levels achieved with warfarin therapy. Instruct patients about prevention measures to minimize the risk of bleeding and to report immediately to their health care provider signs and symptoms of bleeding.

Adverse reactions >10%

- Apixaban, Dabigatran, Edoxaban, Rivaroxaban:

ADRs >10%: Hematologic & oncologic: Hemorrhage

- **Dabigatran**:

>10%:

Gastrointestinal: Gastrointestinal symptoms (eg, dyspepsia, gastritis-like symptoms; 25% to 40%; dose dependent)

Conclusion: main ADR is increased risk of bleeding.

2.5.4 Drug-Drug interactions profile [5]

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Anticoagulants	X	X	X	X	
Cobicistat				X	
Dabigatran	X		X	X	

Edoxaban	X	X		X	
Hemin	X	X	X	X	X
CYP3A4 Inducers (Strong)				X	
Inducers of CYP3A4 (Strong) And P-Glycoprotein	X			X	
Mifepristone	X	X	X	X	X
Omacetaxine	X	X	X	X	X
Oxatomide					X
Rivaroxaban	X	X	X		
Streptokinase					X
St John's Wort	X			X	
Tamoxifen					X
Urokinase	X	X	X	X	X
Apixaban		X	X	X	
Vorapaxar	X	X	X	X	X
Lasmiditan		X	X		
P-Glycoprotein/ABCB1 Inducers		X			
Sulfinpyrazone		X			
Rifampin			X		

Conclusion: Similar drug-drug interaction profile in NOAC class, DDI should be reviewed carefully.

2.5.5 Contraindications Profile: [5]

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Severe hypersensitivity reaction (i.e., anaphylaxis) to drug or any component of the formulation	✓	✓	✓	✓
Active pathological bleeding	✓	✓	✓	✓
Lesions or conditions at increased risk of clinically significant bleeding	✓	✓	✓	✓
Active peptic ulcer disease with recent bleeding	✓	✓	✓	✓
Concomitant use with any other anticoagulant including unfractionated heparin (except at doses used to maintain central venous or arterial catheter patency), low molecular weight heparins or heparin derivatives and oral anticoagulants except during switching between anticoagulants	✓	✓ +antithrombin agents (e.g., bivalirudin),	✓	✓
Patients with mechanical prosthetic heart valve(s)		✓		
Pregnancy				✓
Lactation		✓		✓
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	✓			✓
Concomitant systemic treatment with strong cyp3a4	✓			✓
Concomitant therapy with strong p-glycoprotein inhibitors	✓	✓		✓
Severe renal impairment (crcl <30 ml/minute)		✓		

Bleeding diathesis		✓		

Warfarin contraindication: Hypersensitivity to warfarin or any component of the formulation; hemorrhagic tendencies (eg, active GI ulceration, patients bleeding from the GI, respiratory, or GU tract; cerebral aneurysm; CNS hemorrhage; dissecting aortic aneurysm; spinal puncture and other diagnostic or therapeutic procedures with potential for significant bleeding); recent or potential surgery of the eye or CNS; major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces; blood dyscrasias; malignant hypertension; pericarditis or pericardial effusion; bacterial endocarditis; unsupervised patients with conditions associated with a high potential for noncompliance; eclampsia/preeclampsia, threatened abortion, pregnancy (except in women with mechanical heart valves at high risk for thromboembolism

Conclusion: high risk medications, should be used cautiously.

2.5.6 Dosage and administration:[5]

Table 1: Dosage and Administration

Drug	***Strength***	***Dosage Form***	***Dosage and administration***	***Maximum Daily Dose***
Apixaban	*2.5 mg and 5mg*	*Tablet*	*Oral:* ✓ *5 mg twice daily* ✓ *2.5 mg twice daily patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL*	*10 mg*
Dabigatran	*75, 110 and 150 mg*	*Capsule*	*110 mg or 150 mg twice daily.* *Acc. to risk of bleeding*	*300 mg*
Edoxaban	*15, 30 and 60 mg*	*Tablet*	*60 mg once daily*	*120 mg*

Rivaroxaban	*10, 15 and 20 mg*	*Tablet*	*Oral: 20 mg once daily with the evening meal.* *Post-PCI with stent placement and nonvalvular atrial fibrillation Oral: 15 mg once daily with food*	*20 mg*
Warfarin sodium	*1,2,2.5,3,5,7.5 and 10 mg*	*Tablet*	*Initial: 5 mg once daily for most patients* *Maintenance: Usual maintenance dose: 2 to 10 mg once daily.* *Dosing must be individualized*	*Adjusted according to INR*

2.5.7 Therapeutic designation and suggested prescribing edits:

Table 16. Therapeutic Designation

Non–vitamin K oral anticoagulant:

Drug	***Strength***	***Dosage Form***	***Therapeutic Designation***	***Prescribing Edits***
Apixaban	*2.5 mg and 5mg*	*Tablet*	*Essential*	----------
Dabigatran	*75, 110 and 150 mg*	*Capsule*	*Essential*	
Edoxaban	*15, 30 and 60 mg*	*Tablet*	*Essential*	
Rivaroxaban	*10, 15 and 20 mg*	*Tablet*	*Essential*	

Vitamin K antagonist:

Drug	*Strength*	*Dosage Form*	*Therapeutic Designation*	*Prescribing Edits*
Warfarin sodium	*1,2,2.5,3,5,7.5 and 10 mg*	*Tablet*	*Essential*	------

Therapeutic Designation: Essential drugs for preventing thromboembolism in AF patients.

Conclusion:

- **Vitamin K antagonists are recommended in AF patients with moderate-to severe mitral stenosis or mechanical heart valves.**
- **NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).**

2.6 Antidotes

2.6.1 Drug Classification

Table 17. Pharmacological Classification of Antidotes

Drug	Class
Idarucizumab	Monoclonal antibody
Andexanet alfa	Coagulation Factor Xa [Recombinant], Inactivated

2.6.2 SFDA Registration Status

Table 18. SFDA Registration Status of Antidotes

Drug	Class
Idarucizumab	SFDA registered
Andexanet alfa	Not SFDA registered

2.6.3 Saudi FDA Approved Indications

Table 19. SFDA Approved Indications for Idarucizumab

Drug	Indication
Idarucizumab	Atrial fibrillation – reversal of bleeding caused by Dabigatran anticoagulant

2.6.4 Clinical Guidelines Recommendations and Efficacy

The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation recommends the below[14]:

The guideline recommends administering idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary (Strong Recommendation; Moderate-Quality Evidence)

Conclusion: If a patient presents with life-threatening bleeding and is using dabigatran, idarucizumab should be used to reverse the effect of the anticoagulant.

2.6.5 Safety Profile

The adverse reactions for idarucizumab are listed below[16]:

- 1% to 10%:
    - Central nervous system: Headache (5%)
    - Gastrointestinal: Constipation (7%), nausea (5%)
- Frequency not defined:
    - Hypersensitivity: Hypersensitivity reaction (including bronchospasm, fever, hyperventilation, pruritus, skin rash)
- <1%, post marketing, and/or case reports: Acute ischemic stroke, circulatory shock, deep vein thrombosis, intracardiac thrombus (left atrium), multiorgan failure, myocardial infarction (NSTEMI), pulmonary edema, pulmonary embolism, right heart failure, thromboembolic complications

Conclusion: Idarucizumab does not have a big list of adverse drug reactions.

2.6.6 Drug-Drug Interaction Profile

The drug interaction with Idarucizumab is listed below[16]:

- Efgartigimod Alfa: May diminish the therapeutic effect of Fc Receptor-Binding Agents. Risk C: Monitor therapy.
- The mechanism of this interaction is likely efgartigimod alfa binding to the neonatal Fc receptor, which reduces the ability of other agents to bind the Fc receptor and exert their therapeutic effect.
- Patient management: Monitor for reduced efficacy of agents that bind to the Fc receptor (eg, monoclonal antibodies, immune globulins, agents containing the human Fc domain) during coadministration with efgartigimod alfa. If chronic use of such agents is required, consider therapeutic alternatives to efgartigimod alfa.

2.6.7 Contraindication Profile

There are no contraindications listed in the manufacturer's labeling[16].

Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to idarucizumab or any component of the formulation.

2.6.8 Dosage and Administration

The dosage and administration of idarucizumab is presented in the table below[16]:

Table 20. Dosage and Administration of Idarucizumab

Drug	Dosage and administration
Idarucizumab	IV: 5 g (administered as 2 separate 2.5 g doses no more than 15 minutes apart).

Note: Repeat dosing is not usually required. However, another dose may be considered (despite limited data) if bleeding continues and there is laboratory evidence of persistent dabigatran effect or before an emergent invasive procedure if there is concern for a persistent anticoagulant effect.

2.6.9 Prescribing Edits

Table 21. Prescribing Edits for Idarucizumab

Drug	Prescribing edits	Justification
Idarucizumab	QL	Coverage is limited to specific time: administered as 2 separate 2.5 g doses **no more than 15 minutes apart**)

	EU	This drug status on Formulary is only for Emergency use: when life-threatening bleeding because of dabigatran

2.6.10 Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations for Idarucizumab by the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 22. Health Technology Assessment (HTA) Recommendation for Idarucizumab

	Idarucizumab
NICE[7]	Idarucizumab (Praxbind, Boehringer Ingelheim Limited) was launched in the UK in December 2015. It is licensed for use in adults treated with dabigatran etexilate (Pradaxa, Boehringer Ingelheim Limited) when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding. The committee considered that Idarucizumab costs £2,400 per 5 g (2×2.5 g/50ml) dose excluding VAT.
CADTH[17]	The population chosen are adult patients treated with dabigatran → no economic studies were identified that met the selection criteria.
HAS	Not available
IQWIG	Not available
PBAC	Not available.

Section 3.0 Key Recommendations Synthesis

- Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. (Class 1)
- In pregnant women with HCM, cardioversion should be considered for persistent AF. (Class 2a)
- Ibutilide or flecainide IV may be considered for termination of AF in stable patients with structurally normal hearts of acute management. (Class 2b)
- For the long-term management Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. Digoxin or verapamil should be considered for rate control if beta-blockers fail. (Class 2a)
- Use the ORBIT bleeding risk score because evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools. (Strong recommendation)
- Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation. (Strong recommendation)
- The Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation. (Weak recommendation, moderate quality of evidence)
- For patients with AF, the guideline recommends against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk. (Weak recommendation, moderate quality of evidence)
- Administration of idarucizumab for emergency reversal of dabigatran's anticoagulant for which normal hemostasis is necessary. (Strong recommendation, moderate quality of evidence)
- Administration of andexanet alfa (once available) for emergency reversal of the anticoagulant effect of apixaban, edoxaban, and rivaroxaban. (Strong recommendation, low quality of evidence)
- When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of <1.2 ng/ml. (Strong recommendation, moderate quality of evidence)

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Atrial Fibrillation. These recommendations should be used to support and not replace clinical decision-making in individual patient management. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual patients' needs, preferences and values.

Section 5.0 References

[1] Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., ... & Hindricks, G. (2016). 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European journal of cardio-thoracic surgery*, *50*(5), e1-e88.

[2January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., ... & Murray, K. T. (2014). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*, *64*(21), e1-e76.

[3] January, C. T., Wann, L. S., Calkins, H., Chen, L. Y., Cigarroa, J. E., Cleveland, J. C., ... & Heidenreich, P. A. (2019). 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*, *74*(1), 104-132.

[4] Jones, C., Pollit, V., Fitzmaurice, D., & Cowan, C. (2014). The management of atrial fibrillation: summary of updated NICE guidance. *Bmj*, *348*, g3655.

[5] Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; April 27, 2020

[6] Metoprolol Tartrate 100 mg tablets - Summary of Product Characteristics (SmPC) - (emc). (n.d.). Www.Medicines. Org.Uk. Retrieved May 3, 2020, from https://www.medicines.org.uk/emc/product/5344/smpc#INDICATIONS

Updated References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612
2. Adrian D Elliott, Prashanthan Sanders. worldwide prevalence of atrial fibrillation. Published 2023. Accessed June 13, 2023. https://pubmed.ncbi.nlm.nih.gov/36600003/
3. Mashat AA, Subki AH, Bakhaider MA, et al. Atrial fibrillation: risk factors and comorbidities in a tertiary center in Jeddah, Saudi Arabia. *Int J Gen Med*. 2019;Volume 12:71-77. doi:10.2147/IJGM.S188524
4. Salam AM, Kaddoura R, Salih V, Asopa S. Atrial fibrillation in Middle Eastern Arabs and South Asians: a scoping review. *Rev Cardiovasc Med*. 2021;22(4):1185. doi:10.31083/j.rcm2204127

5. Hersi Ahmad Al Fagih Abdulmohsin Almusaad Bandar Alghamdi Fayez Bokhari Ghadah Bawazeer Hind Al Modaimegh Ihab Suliman AS, Neumann I, Brignardello-Petersen R, et al. *Atrial Fibrillation Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-Valvular Atrial Fibrillation i Allergic Rhinitis in Asthma Antithrombotic Treatment of Patients with Non-Valvular Atrial Fibrillation Antithrombotic Treatment of Patients with Non-Valvular Atrial Fibrillation Antithrombotic Treatment of Patients with Non-Valvular Atrial Fibrillation Guideline Adaptation Panel Members Saudi Expert Panel McMaster Working Group Acknowledgements We Acknowledge Dr.*; 2014.

6. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: Relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. 2014;114(9):1453-1468. doi:10.1161/CIRCRESAHA.114.303211

7. *Atrial Fibrillation: Diagnosis and Management NICE Guideline.*; 2021. www.nice.org.uk/guidance/ng196

8. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;154(5):1121-1201. doi:10.1016/j.chest.2018.07.040

9. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Canadian Journal of Cardiology*. 2020;36(12):1847-1948. doi:10.1016/j.cjca.2020.09.001

10. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Heart Lung Circ*. 2018;27(10):1209-1266. doi:10.1016/j.hlc.2018.06.1043

11. *Reversal of the Anticoagulant Effect of Dabigatran: Idarucizumab Evidence Summary Key Points from the Evidence.*; 2016. www.nice.org.uk/guidance/esnm73

12. *Andexanet Alfa for Reversing Anticoagulation from Apixaban or Rivaroxaban.*; 2021. www.nice.org.uk/guidance/ta697

13. for Quality I, in Health Care E. *Extract 1 Translation of Sections 2.1 to 2.6 of the Dossier Assessment Andexanet Alfa (Akute Schwere Blutungen)-Nutzenbewertung Gemäß § 35a SGB V Andexanet Alfa (Acute Severe Bleeding)-Benefit Assessment According to §35a Social Code Book V 1.* www.iqwig.de

14. andexanet alfa cadth hta . Accessed June 14, 2023. https://www.cadth.ca/andexanet-alfa

15. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612

16. lexicomp. idarucizumab drug therapy . Published online 2023. Accessed June 14, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/doc/retrieve/docid/multinat_f/5900955?cesid=3YIfaGwRgUr&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3DidaruCIZUmab%26t%3Dname%26acs%3Dtrue%26acq%3Didaruci#adr

17. *Idarucizumab for Reversing Anticoagulation 2*.

18. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Journal of Cardio-thoracic Surgery*. 2016;50(5):E1-E88. doi:10.1093/ejcts/ezw313

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Atrial Fibrillation Scope

Section	Rationale/Updates
Section 1.3 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS [18]	**2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC** [11] Updated Recommendations: - The HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score >_3) for early and more frequent clinical review and follow-up (class 2a) - In patients with a definite duration of AF < 24h and a very low stroke risk (CHA2DS2-VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted. (Class 2b) - For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended. (class 1) - In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmic risk factors is recommended. (Class 1) - Opportunistic screening for AF is recommended in hypertensive and OSA patients. (Class 1 and 2a) - In AF patients with ACS undergoing an uncomplicated PCI, early cessation (< 1week) of aspirin and continuation of dual therapy with an OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used. (Class 1) Post catheter ablation: - it is recommended that: systemic anticoagulation with warfarin or a NOAC is continued for at least 2

	months post ablation, and long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. (Class 1) <u>Special population: pregnancy</u> - In pregnant women with HCM, cardioversion should be considered for persistent AF. (Class 2a) - Ibutilide or flecainide IV may be considered for termination of AF in stable patients with structurally normal hearts of acute management. (Class 2b) - For the long-term management Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. Digoxin or verapamil should be considered for rate control if beta-blockers fail. (Class 2a)
Section 1.4 NICE guidelines: Atrial fibrillation: management Clinical guideline Published: 18 June 2014	**NICE Atrial fibrillation: diagnosis and management (2021)**[12] <u>Updated Recommendations:</u> - Use the ORBIT bleeding risk score because evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools. - Offer monitoring and support to modify risk factors for bleeding, including reversible causes of anemia. - If direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist. - For adults with atrial fibrillation who are already taking a vitamin K antagonist and are stable, continue with their current medication and discuss the option of switching treatment. - Do not offer amiodarone for long-term rate control. - Consider antiarrhythmic drug treatment for 3 months after left atrial ablation to prevent recurrence of atrial fibrillation, considering the person's preferences, and the risks and potential benefits. - Reassess the need for antiarrhythmic drug treatment at 3 months after left atrial ablation. - Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation.
Addition of a new section:	**<u>Missing Recommendations:</u>**

The Saudi Center for Evidence Based Health Care Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-valvular Atrial Fibrillation[5]	- For patients who choose antithrombotic therapy, the Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation. (weak recommendation, moderate quality evidence) - For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence) or aspirin. (strong recommendation, moderate quality evidence) - For patients with non-valvular atrial fibrillation in whom oral anticoagulation is recommended (or suggested), the Ministry of Health of Saudi Arabia guideline panel suggests the use of Novel Oral Anticoagulants (dabigatran 150 mg bid, rivaroxaban 20 mg once a day or apixaban 5 mg bid) rather than Vitamin K antagonists (weak recommendation, moderate quality evidence)
Addition of a new section: Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report (2018) [13]	- For patients with AF, the guideline recommends against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk (Strong recommendation, moderate quality evidence). - In patients with AF who are eligible for OAC, we recommend NOACs over VKA (strong recommendation, moderate quality evidence). - In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, the guideline suggests using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low-quality evidence.) - For patients with AF of documented duration of 48 hours or less undergoing elective cardioversion (electrical or pharmacologic), the guideline suggests starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (weak recommendation, low quality evidence). - In AF patients requiring OAC undergoing elective

	PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for recurrent ACS and/or stent thrombosis, the guideline suggests triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (weak recommendation, low quality evidence). - In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED ≥3), the guideline suggests triple therapy for one month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (weak recommendation, low quality evidence). - In AF patients taking warfarin without high risk of thromboembolism or who do not have a mechanical valve, the guideline suggests pre-operative management without bridging (Weak recommendation, low quality evidence). - In AF patients on antithrombotic prophylaxis with warfarin with a high risk of thromboembolism or with a mechanical valve, the guideline suggests pre-operative management with bridging (Weak recommendation, low quality evidence). - In AF patients on antithrombotic prophylaxis with a NOAC, the guideline suggests pre-operative management without bridging (Weak recommendation, low quality evidence).
Addition of a new section: **The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation**[14]	- The guideline recommends that patients with AF who are receiving OAC should have their renal function assessed at baseline and at least annually to detect latent kidney disease, determine OAC eligibility, and to support drug dosing (Strong Recommendation; Moderate-Quality Evidence) - The guideline recommends that Creatinine Clearance, as estimated by the Cockcroft–Gault method, be used to support dosing decisions of anticoagulant medications (Strong Recommendation, High-Quality Evidence) - The guideline recommends that OAC not be routinely prescribed for patients with AF and advanced liver disease (Child-Pugh C or liver disease associated with significant coagulopathy) (Strong Recommendation; Low-Quality Evidence). - When an OAC is indicated in the presence of active

	malignancy, the guideline suggests a DOAC in preference to VKA (Weak Recommendation; Low-Quality Evidence). - The guideline suggests that interruption of OAC is not necessary for most procedures with a minimal risk of bleeding (Weak Recommendation; Moderate Quality Evidence). - The guideline recommends interruption of OAC for most procedures with a low/moderate- or high risk of bleeding, or where the bleeding risk associated with the procedure is uncertain (Strong Recommendation, Low-Quality Evidence) - When a decision to interrupt VKA therapy for an invasive procedure has been made, the guideline suggests that the interruption begins 5 days prior to the procedure, that a procedure with a low bleeding risk may proceed when the INR is ≤1.5, and a procedure with an intermediate or high bleeding risk may proceed when the INR is ≤1.2 (Weak Recommendation; Low-Quality Evidence) - The guideline recommends immediate electrical cardioversion for patients whose recent-onset AF is the direct cause of instability with hypotension, acute coronary syndrome, or pulmonary edema (Strong Recommendation, Low-Quality Evidence) - The guideline recommends evidence-based beta-blockers (bisoprolol, carvedilol, metoprolol) be first-line agents for rate-control of hemodynamically stable AF in the acute care setting in patients with significant left-ventricular dysfunction (LVEF ≤40%) (Strong Recommendation; Moderate-Quality Evidence). - The guideline recommends titrating rate-controlling agents to achieve a heart rate target of ≤100 bpm at rest for patients presenting with a primary diagnosis of AF in the acute care setting (Strong Recommendation, Low-Quality Evidence) - The guideline recommends dronedarone not be used for AF rate-control or in patients with HF (Strong Recommendation; High-Quality Evidence). - The guideline recommends intermittent antiarrhythmic drug therapy (“pill-in-the-pocket”) as an alternative to daily antiarrhythmic therapy in patients with infrequent, symptomatic episodes of AF (Strong Recommendation, Low-Quality Evidence) <u>Addition of Drugs Within Classes:</u> - The guideline recommends administering

	idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary (Strong Recommendation; Moderate-Quality Evidence. - The guideline recommends administering andexanet alfa (once available) for emergency reversal of the anticoagulant effect of apixaban, edoxaban, and rivaroxaban in patients presenting with uncontrollable or potentially life-threatening bleeding who have received any of these agents within the preceding 18 hours (Strong Recommendation; Low-Quality Evidence). - The guideline suggests that patients who have a contraindication to beta-blocker therapy and to amiodarone be considered for prophylactic therapy to prevent post-operative AF with IV magnesium, bi-atrial pacing, colchicine, and/or posterior pericardiotomy (Weak Recommendation; low quality of evidence)
Addition of a new section: **National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand:** **Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018**[15]	<u>Missing Recommendations:</u> - When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of <1.2 ng/ml (moderate, strong) - Calcium channel antagonists should be avoided in patients with left ventricular systolic dysfunction (ejection fraction <40%). (Low, strong) - Amiodarone should not be administered as a first-line agent for chronic rate control, given its toxicity profile (low, strong) - Membrane-active antiarrhythmic agents (e.g. sotalol or flecainide) should not be used in patients managed with a rate-control strategy (low, strong) - Flecainide can be considered in the maintenance of sinus rhythm in patients without left ventricular systolic dysfunction, moderate left ventricular hypertrophy or coronary artery disease.

Appendix C. MeSH Terms Pubmed

Query	Filters	Search Details	Results
((((((((((((((((((((((Atrial Fibrillation[MeSH Terms]) OR (Atrial Fibrillations[Title/Abstract])) OR (Fibrillation, Atrial[Title/Abstract])) OR (Fibrillations, Atrial[Title/Abstract])) OR (Auricular Fibrillation[Title/Abstract])) OR (Auricular Fibrillations[Title/Abstract])) OR (Fibrillation, Auricular[Title/Abstract])) OR (Fibrillations, Auricular[Title/Abstract])) OR (Persistent Atrial Fibrillation[Title/Abstract])) OR (Atrial Fibrillation, Persistent[Title/Abstract])) OR (Atrial Fibrillations, Persistent[Title/Abstract])) OR (Fibrillation, Persistent Atrial[Title/Abstract])) OR (Fibrillations, Persistent Atrial[Title/Abstract])) OR (Persistent Atrial Fibrillations[Title/Abstract])) OR (Familial Atrial Fibrillation[Title/Abstract])) OR (Atrial Fibrillation, Familial[Title/Abstract])) OR (Atrial Fibrillations, Familial[Title/Abstract])) OR (Familial Atrial Fibrillations[Title/Abstract])) OR (Fibrillation, Familial	Guideline, in the last 5 years	("atrial fibrillation"[MeSH Terms] OR "atrial fibrillations"[Title/Abstract] OR "fibrillation atrial"[Title/Abstract] OR "fibrillations atrial"[Title/Abstract] OR "auricular fibrillation"[Title/Abstract] OR "auricular fibrillations"[Title/Abstract] OR (("fibril"[All Fields] OR "fibril s"[All Fields] OR "fibrilation"[All Fields] OR "fibrilization"[All Fields] OR "fibrilized"[All Fields] OR "fibrillate"[All Fields] OR "fibrillated"[All Fields] OR "fibrillates"[All Fields] OR "fibrillating"[All Fields] OR "Fibrillation"[All Fields] OR "Fibrillations"[All Fields] OR "fibrillization"[All Fields] OR "fibrillize"[All Fields] OR "fibrillized"[All Fields] OR "fibrillizes"[All Fields] OR "fibrillizing"[All Fields] OR "fibrillous"[All Fields] OR "fibrills"[All Fields] OR "fibrils"[All Fields]) AND "Auricular"[Title/Abstract]) OR "fibrillations auricular"[Title/Abstract] OR "persistent atrial fibrillation"[Title/Abstract] OR "atrial fibrillation persistent"[Title/Abstract] OR (("atrial	30

Atrial[Title/Abstract])) OR (Fibrillations, Familial Atrial[Title/Abstract])) OR (Paroxysmal Atrial Fibrillation[Title/Abstract])) OR (Atrial Fibrillation, Paroxysmal[Title/Abstract])) OR (Atrial Fibrillations, Paroxysmal[Title/Abstract])) OR (Fibrillation, Paroxysmal Atrial[Title/Abstract])) OR (Fibrillations, Paroxysmal Atrial[Title/Abstract])) OR (Paroxysmal Atrial Fibrillations[Title/Abstract])		fibrillation"[MeSH Terms] OR ("Atrial"[All Fields] AND "Fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields] OR ("Atrial"[All Fields] AND "Fibrillations"[All Fields]) OR "atrial fibrillations"[All Fields]) AND "Persistent"[Title/Abstract]) OR "fibrillation persistent atrial"[Title/Abstract] OR (("fibril"[All Fields] OR "fibril s"[All Fields] OR "fibrilation"[All Fields] OR "fibrilization"[All Fields] OR "fibrilized"[All Fields] OR "fibrillate"[All Fields] OR "fibrillated"[All Fields] OR "fibrillates"[All Fields] OR "fibrillating"[All Fields] OR "Fibrillation"[All Fields] OR "Fibrillations"[All Fields] OR "fibrillization"[All Fields] OR "fibrillize"[All Fields] OR "fibrillized"[All Fields] OR "fibrillizes"[All Fields] OR "fibrillizing"[All Fields] OR "fibrillous"[All Fields] OR "fibrills"[All Fields] OR "fibrils"[All Fields]) AND "persistent atrial"[Title/Abstract]) OR "persistent atrial fibrillations"[Title/Abstract] OR "familial atrial fibrillation"[Title/Abstract] OR "atrial fibrillation familial"[Title/Abstract] OR (("atrial fibrillation"[MeSH Terms] OR ("Atrial"[All	

		Fields] AND "Fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields] OR ("Atrial"[All Fields] AND "Fibrillations"[All Fields]) OR "atrial fibrillations"[All Fields]) AND "Familial"[Title/Abstract]) OR (("familialities"[All Fields] OR "familiality"[All Fields] OR "familially"[All Fields] OR "familials"[All Fields] OR "familie"[All Fields] OR "family"[MeSH Terms] OR "family"[All Fields] OR "Familial"[All Fields] OR "families"[All Fields] OR "family s"[All Fields] OR "familys"[All Fields]) AND "atrial fibrillations"[Title/Abstract]) OR (("fibril"[All Fields] OR "fibril s"[All Fields] OR "fibrilation"[All Fields] OR "fibrilization"[All Fields] OR "fibrilized"[All Fields] OR "fibrillate"[All Fields] OR "fibrillated"[All Fields] OR "fibrillates"[All Fields] OR "fibrillating"[All Fields] OR "Fibrillation"[All Fields] OR "Fibrillations"[All Fields] OR "fibrillization"[All Fields] OR "fibrillize"[All Fields] OR "fibrillized"[All Fields] OR "fibrillizes"[All Fields] OR "fibrillizing"[All Fields] OR "fibrillous"[All Fields] OR "fibrills"[All Fields] OR "fibrils"[All	

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Appendix D. Treatment Algorithm