Advanced

CARDIOVASCULAR MEDICINE

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Editors

Ashok Seth
FRCP (London, Edin, Irel) FACC FESC FSCAI (USA)
FCSI DSc (Honoris Causa) DLitt (Honoris Causa)
Chairman
Fortis Escorts Heart Institute
Chairman
Cardiology Council
Fortis Group of Hospitals
New Delhi, India

Sameer Shrivastava
MD DM FISCU FESC FIAE FISC
Director
Noninvasive Cardiology
Fortis Escorts Heart Institute and
Research Center
New Delhi, India

Upendra Kaul
MD DM FCSI FICC FACC FSCAI FAMS
Executive Director
Interventional Cardiology
Fortis Escorts Heart Institute and
Research Center
New Delhi, India

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Headquarters
Jaypee Brothers Medical Publishers (P) Ltd.
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E-mail: jaypee@jaypeebrothers.com

Overseas Offices
J.P. Medical Ltd.
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Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld 235, 2nd Floor
Clayton, Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
E-mail: cservice@jphmedical.com

Jaypee Medical Inc.
325, Chestnut Street
Suite 412
Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
E-mail: support@jpmedus.com

Jaypee Brothers Medical Publishers (P) Ltd.
17/1-B, Babar Road, Block-B
Shaymali, Mohammadpur
Dhaka-1207, Bangladesh
Mobile: +08801912003485
E-mail: jaypeedhaka@gmail.com

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and well-wishers

CONTRIBUTORS

Ajay Kaul MCH
Chairman and Head
Department of Cardiothoracic and Vascular Surgery
BLK Center for Cardiac Sciences
BLK Super Specialty Hospital
New Delhi, India

AK Khera MD DNB MNAMS
Principal Consultant in Non-invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

AK Singh MD (Respiratory Medicine)
Consultant
Department of Pulmonology
Sleep Medicine and Critical Care
Fortis Escorts Heart Institute
New Delhi, India

Amit Varma MBBS MD
Director
Department of Critical Care Medicine
Fortis Escorts Heart Institute
New Delhi, India

Amitesh Chakravarty MD
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Anil Karlekar MD
Executive Director and Head
Department of Cardiac Anesthesiology and Critical Care
Fortis Escorts Heart Institute
New Delhi, India

Ankush Sachdeva MD
Associate Consultant
Department of Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Anumeha Omar MBBS
Resident
Non-invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Aparna Jaswal MD DNB CCDS FHRS FACC
Heart Rhythm Society-IBHRE World Ambassador
Senior Consultant Electrophysiologist
Fortis Escorts Heart Institute
New Delhi, India

Arvind Sethi MD DNB
Chairman
Interventional Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Aseem Dhall MD DM (Cardiology)
Senior Intervention Cardiologist
Department of Cardiology
Fortis Escorts Heart Institute and
Research Center
New Delhi, India

Ashok K Omar MD FESC FIAE FASE FCSI
Director
Non-invasive Cardiology
Head
Heart Command and Emergency
Fortis Escorts Heart Institute
New Delhi, India

Ashok Seth FRCP (London, Edin, Irel) FACC FESC
FSCAI (USA) FCSI DSc (Honoris Causa) DLitt (Honoris Causa)
Chairman
Fortis Escorts Heart Institute
Chairman, Cardiology Council
Fortis Group of Hospitals
New Delhi, India

Ashutosh Marwah MD FNB
Principal Consultant
Department of Pediatric and
Congenital Heart Diseases
Fortis Escorts Heart Institute
New Delhi, India

Atul Verma MBBS DRM
Principal Consultant and Head
Nuclear Medicine
Fortis Escorts Heart Institute
New Delhi, India

Avinash Verma MD DNB
Junior Consultant
Department of Electrophysiology
Fortis Escorts Heart Institute
New Delhi, India

Bhumika S Anand
Physician Assistant
Fortis Escorts Heart Institute
New Delhi, India

Biswajit Paul MD DNB
Consultant Cardiologist
Department of Non-invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Devesh Dutta MD FNB
Junior consultant
Department of Anesthesia and
Critical Care Medicine
Fortis Escorts Heart Institute
New Delhi, India

Dheeraj Gandotra MD DNB (Cardiology)
Junior Consultant
Interventional Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Kenneth Lee Harris MS
Fortis Totipotent RX Center for Cellular Medicine
Fortis Memorial Research Institute
Gurgaon, Haryana, India

Khushboo Choudhury MSc
Fortis Totipotent RX Center for Cellular Medicine
Fortis Memorial Research Institute
Gurgaon, Haryana, India

KK Sharma MD
Anesthesiologist
Department of Anesthesiology and Intensive Care
Fortis Escorts Heart Institute
New Delhi, India

Krishna S Iyer MBBS MS MCH
Executive Director
Pediatric and Congenital Heart Surgery
Fortis Escorts Heart Institute
New Delhi, India

Lal C Daga DNB (Fellow) DNB (Cardiology)
Junior Consultant
Fortis Escorts Heart Institute
New Delhi, India

Malay Shukla MD DM
Junior Consultant
Fortis Escorts Heart Institute
New Delhi, India

Mitu A Minocha MD
Associate Consultant
Department of Cardiology
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Mona Bhatia MD
Head
Department of Radiodiagnosis and Imaging
Fortis Escorts Heart Institute
New Delhi, India

N Dalal MBBS MD
Associate Consultant
Department of Pulmonology, Sleep Medicine and Medical Critical Care
Fortis Hospital, Vasant Kunj, New Delhi, India
Fortis Escorts Heart Institute
New Delhi, India

Neel Bhatia MD
Junior Consultant
Fortis Escorts Heart Institute
New Delhi, India

Neeraj Awasthy MD DM
Associate Consultant
Department of Pediatric Cardiology and
Congenital Heart diseases
Fortis Escorts Heart Institute
New Delhi, India

Nishant Kumar MBBS PGDCC
Clinical Assistant
Non-invasive Cardiology
Fortis Escort Heart Institute
New Delhi, India

Nishith Chandra MD DM
Director
Interventional Cardiology
Fortis Escort Heart Institute
New Delhi, India

Niti Chadha MD DM (Cardiology)
IBHRE Certified EP Specialist
Department of Pacing and Electrophysiology
Fortis Escorts Heart Institute
New Delhi, India

Parvathi U Iyer MBBS MD FICU
Director
Pediatric Intensive Care
Fortis Escorts Heart Institute
New Delhi, India

Peeyush Jain MD (Med) DM (Cardiology)
Head
Department of Preventive and Rehabilitative Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Poonam Khurana MD
Principal Consultant
Department of Radiodiagnosis and Imaging
Fortis Escorts Heart Institute
New Delhi, India

Pradyut Bag MD IDCCM FNB EDIC
Consultant
Critical Care Medicine
Fortis Escorts Heart Institute
New Delhi, India

Pramod Joshi MD DNB
Junior Consultant
Fortis Escorts Heart Institute
New Delhi, India

Rajat Agrawal MBBS MD
Senior Consultant
Critical Care Medicine
Fortis Escorts Heart Institute
New Delhi, India

Rajat Gupta DNB FNB
Associate Consultant
Fortis Escorts Heart Institute
New Delhi, India

Rajeev Dhalwani MD
Junior Consultant
Non-invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Rajesh Chauhan MD (Anesthesia)
Principal Consultant Anesthesia
Department of Cardiac Anesthesiology
Fortis Hospital, Vasant Kunj
New Delhi, India

RC Khurana MD
Head
Transfusion Medicine
Fortis Escorts Heart Institute
New Delhi, India

Rishabh Khurana MD
Postgraduate student
Department of Radiodiagnosis
Maulana Azad Medical College
New Delhi, India

RS Chatterji MD DNB
Senior Consultant
Department of Pulmonology
Critical Care and Sleep Medicine
Fortis Escorts Heart Institute
New Delhi, India

S Radhakrishnan MD DM
Director and Head
Department of Pediatric and
Congenital Heart Disease
Fortis Escorts Heart Institute
New Delhi, India

S Yadav MBBS PGDCC
Senior Resident
Fortis Escorts Heart Institute
New Delhi, India

Sachin V Chaudhary DNB Fellow (Cardiology)
Department of Cardiology
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Sameer Shrivastava MD DM FISCU FESC FIAE FISC
Director
Non-invasive Cardiology
Fortis Escorts Heart Institute and
Research Center
New Delhi, India

Sanjay Gupta MD DNB
Associate Director
Department of Cardiac Anesthesiology
Principal Consultant
Department of Cardiac Surgery
Fortis Flt Lt Rajan Dhal Hospital, Vasant Kunj
New Delhi, India

Sanjeev Pandey MBBS DRM
Consultant
Nuclear Medicine
Fortis Escorts Heart Institute
New Delhi, India

Sanjiv Bharadwaj MD DM
Senior Consultant
Invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Saramma Thomas MRS
Head
Regional Nursing
Fortis Escorts Heart Institute
New Delhi, India

Satyendra Kumar Tiwari DNB Fellow (Cardiology)
Department of Cardiology
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Savitri Srivastava MD (Med) DM (Card) FAMS FACC
Director
Pediatric and Congenital Heart Disease
Fortis Escorts Heart Institute
New Delhi, India

Seema Thakur DM (Medical Genetics)
Senior Consultant
Genetics and Fetal Medicine
Fortis Hospitals
New Delhi, India

Smita Mishra MD (Pediatrics) FDNB (Ped Cardiology)
Senior Consultant
Pediatric Cardiologist
Fortis Escorts Heart Institute
New Delhi, India

Subhash Chandra MD DM (AIIMS) DNB
Associate Director
Interventional Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Sujeet Narain MD DNB (Cardiology)
Junior Consultant
Fortis Escorts Heart Institute
New Delhi, India

Suman Bhandari MD DM FSCAI
Chairman
Interventional Cardiology
Saket City Hospital
New Delhi, India

Syed Asrar Ahmed Qadri MCH
Department of Cardiovascular Surgery
Escorts Heart Institute and Research Center
New Delhi, India

TS Kler MD DM (Cardiology)
Executive Director and Head
Department of Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Upendra Kaul MD DM FCSI FICC FACC FSCAI FAMS
Executive Director
Interventional Cardiology
Fortis Escorts Heart Institute and
Research Center
New Delhi, India

V Nangia MD FCCP
Fellowship in Sleep Medicine (Standford) (USA)
Diploma in Interventional Bronchoscopy (Spain)
MSc in Infectious Diseases (UK)
Director and Head
Pulmonology
Sleep Medicine and Medical Critical Care
Fortis Hospital, Vasant Kunj
Fortis Escorts Heart Institute
New Delhi, India

Venkatesh Ponemone PhD
Director
Laboratory and Clinical Research Affairs
Fortis Totipotent RX Center for
Cellular Medicine
Fortis Memorial Research Institute
Gurgaon, Haryana, India

Vibhu Ranjan Gupta MBBS MPhil
Medical Director
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Vijay Kumar MD DNB (Cardiology)
Senior Consultant Cardiologist
Fortis Escorts Heart Institute and Research Center
New Delhi, India

Vinay Kumar Sharma MD DM
Senior Consultant
Department of Non-invasive Cardiology
Fortis Escorts Heart Institute
New Delhi, India

Vinay Sanghi MD DM
Associate Director
Department of Interventional Cardiology
Fortis Hospital, Shalimar Bagh
New Delhi, India

Vishal Rastogi MD DM FSCAI
Senior Interventional Cardiologist
Fortis Escorts Heart Institute
New Delhi, India

Vivek Kumar MD
Principal Consultant Cardiologist
Fortis Escorts Heart Institute
New Delhi, India

Yugal K Mishra MBBS MS PhD
Director
Department of Cardiovascular Surgery
Fortis Escorts Heart Institute and Research Center
New Delhi, India

PREFACE

The last 25 years have witnessed unprecedented scientific advancements in the field of cardiology. Every year, new drugs, new devices and new technologies continue to improve outcomes and prolong lives of our patients with heart disease. Every year, robust clinical trials influence our management of life-threatening cardiac conditions to save lives. To the extent that the way, we practice cardiology today, is distinctly superior and different from what we practiced even 3–5 years ago.

'Staying updated' with the present knowledge has become never as more important than before to benefit our patients and do justice to our profession and receive satisfaction in doing so.

Advanced Cardiovascular Medicine brings you the 'up-to-date' knowledge of the art and science of management of the most important cardiac conditions, we face in our clinical practice. We have ensured that the book covers a vast variety of relevant topics, which would be very useful to all physicians and cardiologists in their daily care of patients. Each chapter has been written by acknowledged international and national authorities in the field, who have ensured that their presentation of advanced science and technology is combined with their own vast experience of its applications to the Indian Clinical Scenario.

As we continue to look beyond the horizon and strive for the ultimate advancements of *gene therapies and genomics*, *artificial blood*, *organ regeneration in laboratory*, etc. We believe that this book will become an inseparable companion to us for delivering our best to our patients in 2016 and beyond.

Wish you a very successful and fruitful professional journey with *Advanced Cardiovascular Medicine*.

Ashok Seth
Sameer Shrivastava
Upendra Kaul

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11

Drug Management of Arrhythmias: Newer Insights

Aseem Dhall, Satyendra Kumar Tiwari

INTRODUCTION

Tachyarrhythmias are broadly characterized as supraventricular tachycardia (SVT), defined as a tachycardia in which the driving circuit or focus originates, at least in part, in tissue above the level of the ventricle [i.e. sinus node, atria, atrioventricular (AV) node, or His bundle], and ventricular tachycardia (VT), defined as a tachycardia in which the driving circuit solely originates in ventricular tissue or Purkinje fibers. Because of differences in prognosis and management, the distinction between SVT and VT is critical early in the acute management of a tachyarrhythmia. In general (with the exception of idiopathic VT), VT often carries a much graver prognosis, usually implies the presence of significant heart disease, and therefore requires immediate attention to revert to sinus rhythm. However, SVT is usually not lethal and often does not result in hemodynamic collapse; therefore, more conservative measures can be applied initially to convert to sinus rhythm.

There have been several breakthroughs in the management of arrhythmias in the recent past.

- Persistent imperfections of currently available antiarrhythmic drugs and rapidly expanding technologies have led to continued explosion in the use of devices and ablative techniques for both supraventricular and ventricular arrhythmias.
- Atrial fibrillation (AF) has become active focus of research with the recognition that with our aging population it is now a major health hazard.
- Stroke is recognized as complication of AF, and with the introduction of new antithrombotic agents, stroke prevention has become important consideration in AF management.
- There has been increasing interest in the use of so-called upstream therapy in arrhythmia management. Upstream therapy targets the process leading to arrhythmia development (primary prevention) or reducing the arrhythmia recurrence after initial presentation (secondary prevention).

Antiarrhythmic drugs are important components of any therapeutic strategy even after the advances seen in ablation techniques and device based therapies. Antiarrhythmic drugs could be used for prevention of sudden cardiac death, ventricular tachycardia, or supraventricular tachyarrhythmia. Currently, the implantable cardioverter–defibrillator therapy is being used as the mainstay of treatment for most lethal ventricular tachyarrhythmias, and antiarrhythmic drugs for these arrhythmias are presently used as acutely to terminate or as adjuncts to device therapy. It has been seen that drugs used for atrial tachyarrhythmias are often limited by the effect of drug on the ventricles that led to development of drugs acting on ion channels located in the atria. The outward K current, the acetylcholine-activated outward K current, and both peak and late atrial Na currents have become principal targets for antiarrhythmic drugs.[1-4] Another strategy is to use such agents that affect multiple channels at the same time, while minimizing the toxicity. In this review, the properties and evidence-based future uses of these drugs will be discussed.

NEWER INSIGHTS IN ANTIARRHYTHMIC TREATMENT OF ATRIAL FIBRILLATION

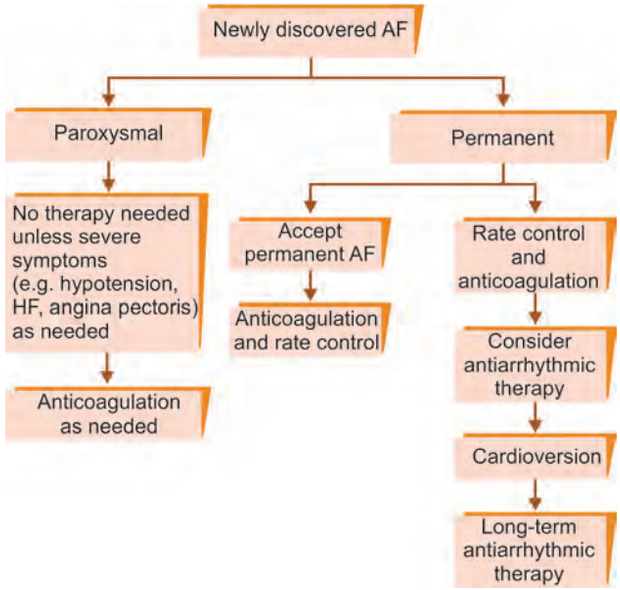
Goals of therapy with the use of these drugs include a reduction in the frequency and duration of episodes of arrhythmia as well an emerging goal of reducing mortality and hospitalizations associated with AF. The use of these drugs has been limited by both proarrhythmic and noncardiovascular toxicities as well as often modest antiarrhythmic efficacy. Despite these limitations, antiarrhythmic drugs remain widely prescribed for the management of symptomatic AF, and a host of new antiarrhythmic drugs are in various stages of clinical development.

Goals of therapy in AF are as follows:

- Rate and rhythm control
- Prevention of thromboembolism

The outline of management of patients with newly diagnosed AF is outlined in Flow chart 11.1.

Flow chart 11.1 Pharmacological management of patients with newly discovered atrial fibrillation



Abbreviations: AF, atrial fibrillation; HF, heart failure.

Rate Versus Rhythm Control

A multitude of studies have evaluated the health-related outcomes associated with a strategy of rate compared with rhythm control in patients with AF.[5-7] These studies, which included primarily patients aged >60 years with at least one risk factor for stroke, failed to demonstrate a mortality benefit associated with a rhythm control strategy. This equivalence in outcome was in part related to toxicities associated with antiarrhythmic drug therapy as well as excess stroke risk in patients in whom anticoagulation was discontinued.[8] At present, practice guidelines recommend antiarrhythmic therapy for patients with significant symptoms despite adequate rate control.[9]

How strict should the rate control be? Optimal criteria for rate control are presently unknown. Excess bradycardia may lead to syncope or fatigue; whereas consistently faster rate may result in tachycardia-induced cardiomyopathy. Strict rate control is a resting heart rate of <80 bpm and <110 bpm with exercise. RACE 2 (rate control versus electrical cardioversion for persistent atrial fibrillation) trial[10] showed that strict rate control is not essential, and that in selected patients a target heart rate <100 bpm may suffice.

Drugs for Cardioversion of AF (Rhythm Control)

It has been seen that rhythm conversion of AF while using antiarrhythmic drug therapy is much more for acute AF (<7 days) as compared to long-standing AF.

- *Ibutilide* is intravenous IKr channel blocking agent that is also known to enhance the late inward sodium current.[11] The drug is 50% effective to restore sinus rhythm and is more effective for atrial flutter than for AF.[11] Ibutilide causes QT prolongation and Torsdes de Points (TDP), so patients should be monitored for at least approximately 2 hours after drug infusion has been given.
- *Amiodarone* can be used intravenously as rhythm converting agent; but it is weak agent for rhythm control.[12] Intravenous amiodarone is also having rate-controlling effects and amiodarone while used orally can convert AF to sinus rhythm with conversion rate of 27% over time course of 3 weeks.
- *Propafenone and Flecainide* can be used as oral and intravenous agents. Flecainide (200–300 mg) or propafenone (450–600 mg) orally has been given for patients who present within 30 minutes approximately of arrhythmia onset and this approach is popularized as "pill in the pocket" approach. The conversion rate for AF was found to be approximately 85%.[13] The drugs should be used in patients with structurally normal heart.
- *Vernakalant* is a novel agent that has been tested in various trials for the rhythm control of AF.[14,15] In one of the study where intravenous amiodarone was compared with vernakalant, it was shown that there was 50% conversion rate of AF at 90 minutes with vernakalant while only 5% with amiodarone.[16]
- *Dronedarone* is an amiodarone analog. As compared to amiodarone, it is less lipophilic and without iodine moieties that cause thyroid dysfunction. Like amiodarone, dronedarone has multichannel blocker and antiadrenergic properties. It prolongs action potential duration and decreases heart rate, while lower potential of polymorphic ventricular tachycardia. Plasma level of dronedarone are reached to maximum within 1–4 hours and its plasma protein binding is around 98%, but oral bioavailability is about 15%. Mean concentrations of dronedarone are reached within 1 week of 400 mg twice daily. Dronedarone is metabolized by cytochrome P450 (CYP3A4) enzymes, with excretion of small amount of unchanged drug in bile and urine. The elimination half-life (about 24 hours) is shorter than that for the amiodarone. It is contraindicated in symptomatic heart failure.

A study was designed to see the effect of dronedarone on mortality in patients with congestive heart failure (CHF) and results showed a greater mortality in the dronedarone-treated group.[17] It was concluded that drug should not be used in patients with decompensated heart failure. A Placebo-Controlled, Double-Blind, Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter (ATHENA) showed reduction in cardiovascular accidents while using dronedarone.[18] Dronedarone is the only antiarrhythmic drug that has shown a decrease risk of stroke in AF patients.

In the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), effect of dronedarone was evaluated in patients having permanent AF and it was concluded that there was more risk of stroke, cardiovascular death, and hospitalizations.[19]

Antiarrhythmic Efficacy of Dronedarone

A meta-analysis from various randomized controlled trials (DAFNE, EURIDIS, ADONIS, ATHENA, DIONYSOS trials). In all trials, dronedarone delayed the time to first recurrence of arrhythmia and decreased recurrence of these events and had modest antiarrhythmic efficacy. Also, dronedarone was found to have reduced efficacy in maintaining sinus rhythm, but only being modestly better tolerated than amiodarone.

Rate Control

Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation (ERATO) trial was designed to see the efficacy of dronedarone 400 mg bid given for 6 months to control ventricular rate in permanent AF and dronedarone was found to reduce the ventricular rate of permanent AF and other types of AF patients as well. So, it can be concluded that dronedarone is having potential to control both rhythm and rate in patients with AF/AFL. But the antiarrythmic efficacy is half as compared with amiodarone.

Dronedarone safety has been evaluated in ANDROMEDA trial in which patients with symptomatic decompensated heart failure were enrolled with or without AF.[17] Due to increased mortality among dronedarone-treated patients, the trial was terminated prematurely. Excess mortality was probably due to decompensated heart failure, arrhythmia, and sudden cardiac death (SCD). Long-term effect of dronedarone was evaluated in ATHENA study, where dronedarone 400 mg bid was used against placebo for all-cause mortality in patients with a recent or current history of nonpermanent AF/AFL and additional risk factors.[20] The trial excluded the patients who were clinically decompensated. After the results of ATHENA trial, the FDA approved dronedarone in the treatment of AF/AFL so as to reduce the risk of cardiovascular hospitalization. Dronedarone use is contraindicated in decompensated heart failure, as a boxed warning issued by the FDA.[21]

Adverse Event Profile

- Nausea, vomiting, diarrhea, and rash can be seen with dronedarone.
- Sometimes transient elevation in serum creatinine can be seen with dronedarone that returns to baseline within a week after discontinuation of drug.[22]
- Dronedarone has no proarrhythmic effect and there is no data with oral anticoagulation therapy.

Recently, guidelines from American College of Cardiology/Heart Rhythm Society and European Society of Cardiology for selection of drugs in AF focused on the use of flecainide, propafenone, sotalol, dronedarone, or amiodarone in patients without underlying heart disease (i.e. coronary artery disease, heart failure, or left ventricular hypertrophy). Guidelines also agree on the use of amiodarone, sotalol, and dronedarone for patients with coronary artery disease and amiodarone for patients with symptomatic CHF. As per guidelines, for patients having left ventricular hypertrophy, same drugs should be used as in those with structurally normal heart (Flow chart 11.2).

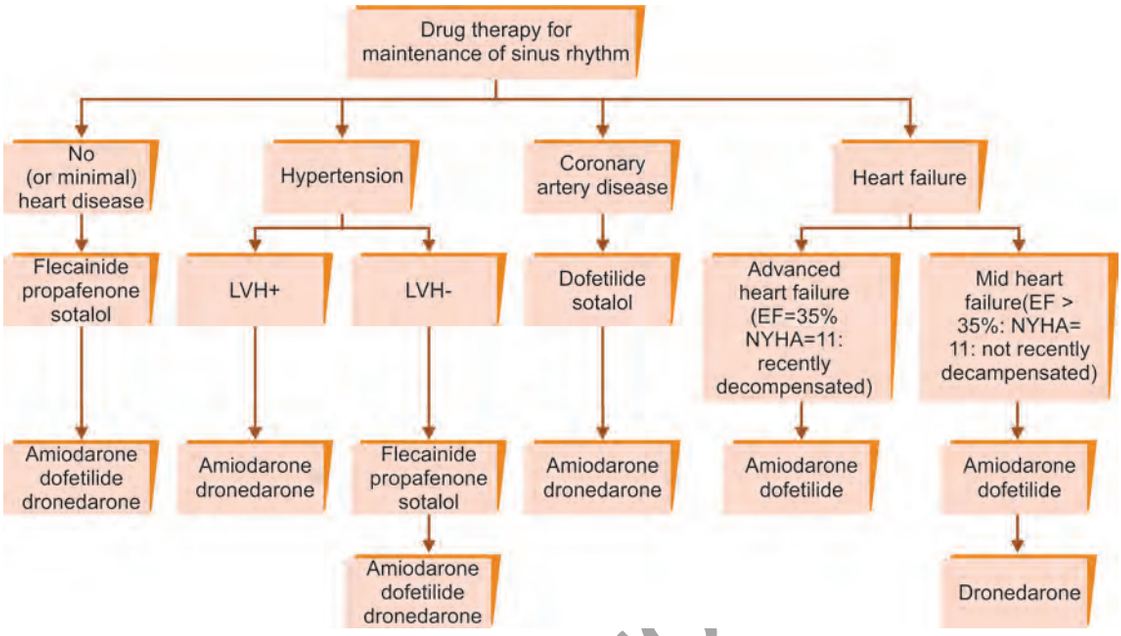
Anticoagulation for AF

Atrial fibrillation is associated with an increased risk for stroke in significant proportion of patients. Loss of atrial systolic function results in sluggish blood flow in the atrium. Atrial distention disturbs the atrial endothelium and activates hemostatic factors leading to a hypercoagulable state. Several factors increase the risk for stroke in patients with AF. The primary risk factors are increased age, history of stroke or transient ischemic attack, hypertension, left atrial enlargement, diabetes, and CHF. The CHADS2 scoring system is now widely used and forms the basis for current guidelines. In CHADS2, one point is given for the following risk factors: recent CHF, hypertension, age older than 75 years, and diabetes: two points are given for a prior stroke. Patients with a CHADS2 score of 0 should not require antithrombotic therapy. Considering conventional treatment by warfarin, patients with a CHADS2 score of 1 may be treated with either aspirin or warfarin. Patients with a CHADS2 score of 2 or more should be treated with warfarin with a target international normalized ratio (INR) of 2–3. Regarding patients >75 years old, the Birmingham Atrial Fibrillation treatment of the Aged Study supported the use of warfarin, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.

Newer Antithrombotics

In general, antithrombotics have either been approved or are likely to be approved by the FDA and European authorities for stroke prevention in nonvalvular AF. The current recommendations are that when oral anticoagulant therapy is indicated, the new anticoagulants are preferable to warfarin for most patients. The major problem with all three drugs is the risk of rare but potentially fatal uncontrollable bleeding. No studies in patients have yet assessed the ability of prohemostatic drugs to antagonize excess anticoagulant effects. Regardless of the relatively short half-life of these agents, immediate reversal of the anticoagulant effect may be needed in case of major bleeding or emergency surgery. The major positive aspects of these agents include the following: (1) no need for monitoring of INR, as required for warfarin: (2) reduced risk of adverse interactions following a change in diet or concomitant drugs: and (3) an enhanced ability to prevent strokes.

Flow chart 11.2 Potential role for dronedarone in atrial fibrillation for the maintenance of sinus rhythm



Abbreviations: EF, ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

Apixaban

Apixaban, a factor Xa inhibitor was superior to aspirin in patients with AF. The AVERROES trial study, which compared apixaban with aspirin, was terminated early because of a clear difference in favor of apixaban. Primary outcomes events (stroke) were reduced without any increase in major bleeding [hazard ratio (HR) 0.45: $P < 0.001$]. The decisive ARISTOTLE trial evaluated apixaban against warfarin in > 18,000 patients with AF. Apixaban was clearly superior to warfarin in preventing stroke or systemic embolism (HR, 0.79: $P = 0.01$ for superiority), caused less bleeding, and resulted in lower mortality ($P = 0.047$).

Dabigatran Etexilate (Pradaxa) and Rivaroxaban

Dabigatran etexilate is a prodrug that is converted to the active moiety dabigatran[23] (direct thrombin inhibitor). The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a large, open-label, randomized trial in which dabigatran was compared with warfarin (goal INR 2.0–3.0) in 18,113 patients with nonvalvular AF. Primary outcome rate of all stroke or systemic embolism was found to be 1.71% per year in the warfarin group.[24,25] FDA, on October 19, 2010, approved dabigatran 150 mg orally twice daily for stroke prevention and prevention of peripheral embolism in patients with nonvalvular AF.[23] A dose of 75 mg twice daily was approved if creatinine clearance was 15–30 mL/min.

FDA approved rivaroxaban (Xarelto) 20 mg orally once daily for prevention of stroke in AF patients in 2011, after the results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial[26] (ROCKET AF). Rivaroxaban is contraindicated in patients with creatinine clearance < 15 mL/min, and dose reduction to 15 mg once daily has been recommended. Dabigatran and rivaroxaban should not be used in patients with acute kidney injury. The 2011 American Heart Association/Heart Rhythm Society (ACCF/AHA/HRSA) Guidelines recommended dabigatran as an alternative to warfarin therapy for the prevention of stroke and systemic thromboembolism in patients with paroxysmal and permanent AF and with risk factors for stroke or systemic embolization.[27] As per guidelines, dabigatran should not be given to patients with prosthetic heart valve or significant valve disease, significant renal dysfunction (creatinine clearance < 15 mL/min), or chronic liver disease. Recently, the 2012 American College of Chest Physicians (ACCP) guidelines stated that anticoagulation or antiplatelet therapy should be offered to patients with a CHADS2 score of ≥1.[28]

Newer Antiarrhythmic Therapy for Supraventricular Arrhythmias and Ventricular Arrhythmias

Celivarone

Celivarone is benzofuran-derivative devoid of iodine with similar electrophysiological properties to amiodarone.[29] Efficacy of celivarone was tested at 300 mg or 600 mg daily doses for conversion of AF and atrial flutter (CORYFEE) and

a dose-related study compared celivarone at 50, 100, 200, or 300 mg once daily with amiodarone for the maintenance of sinus rhythm (MAIA) have already been completed. Results showed the lowest rate of AF recurrence at the 50 mg dose without increased efficacy at the higher doses.[30]

Vernakalant

Vernakalant is an atrial depolarizing agent, acting on multiple ion channels, which has its major target IKur. It also blocks Ito and INa, but there is little effect on IKr or IKs.[31] The drug has been used in a multicenter, randomized trial, the CRAFT trial (conversion of rapid atrial fibrillation trial) that was performed in patients with AF to establish the safety and efficacy of intravenous vernakalant.[32] A 2-mg/kg vernakalant infusion over 10 minutes was given in AF patients and second dose was repeated at a dose of 3-mg/kg infusion if normal sinus rhythm was not restored within a period of 15 minutes and there was found a statistically significant difference in conversion to sinus rhythm when compared with placebo group (61% vs. 5%; $P = 0.0005$).

Vernakalant has its modest effect for rhythm conversion of recently detected AF with maintenance of sinus rhythm approximately 24 hours. Oral vernakalant can be useful alternative for maintenance of sinus rhythm, but phase 3 trials are still underway. If drug is found efficacious in these trials, then probably it would have more potential for clinical application while conversion attempts could be undertaken so as to restoration of long-term sinus rhythm. Adverse effects seen with vernakalant might be cough and dysgeusia.

Ivabradine

Ivabradine is selective 1f channel blocker (f denotes funny channel, so called because it had unusual properties compared with other current systems known at the time of its discovery) and inhibits the spontaneous pacemaker activity of the sinus node.[33] As a result, there is reduction in the heart rate without affecting myocardial contractility.[34] The blockage of 1f channel is dependent on heart rate and dose. Electrophysiological studies of ivabradine have already shown very little effect on conduction system or atrial and ventricular refractoriness. The drug is metabolized 80% in liver by CYP3A4 enzyme, so cannot be used if drugs inhibiting the same enzyme, such as macrolide and ketoconazole are being used simultaneously. Data analysis has shown that most of the side effects of ivabradine are dose related. Ivabradine also affects the ion channels in the retina that could be the mechanism for ivabradine's side effect, a visual luminous phenomenon, which is also known as phosphenes (14.5%). Visual luminous phenomenon generally abates over time while treatment is not interrupted. Significant sinus bradycardia is seen in approximately 3.3% of patients. Sometimes palpitations, nausea, headaches, vertigo, muscle cramps, hyperuricemia can be noted. There is not much trial data on the treatment of atrial tachyarrhythmias with ivabradine. Ivabradine is used off-label in Europe for the treatment of inappropriate sinus tachycardia.

Adenosine A1 Receptor Agonists

As we know, intravenous adenosine terminates AV nodal re-entry tachycardia or AV re-entry after stimulating the A1 adenosine receptor by creating transient AV block. Sometimes adenosine can give rise to serious adverse effect profile[35] like flushing (18%), dyspnea (12%), and chest pain (7%), and it has been correlated with activity of adenosine on the receptors A2A, A2B, and A3 adenosine receptor subtypes. Studies have been done to identify A1 receptor–selective agonists for SVT termination and control of rate in AF. Some of these agents are under trials presently, including tecadenoson and selodenoson. Tecadenoson is currently being tested in TEMPEST trial[36] that is a multicenter, double-blinded, placebo-controlled trial that randomly assigned 181 patients to receive placebo versus tecadenoson for SVT termination. Conversion rates were found to be 73.5% in the tecadenoson-treated patients and 6.7% in the placebo group. Side effects were mild and found to be dose-related, like 12 patients had second-degree heart block and two patients developed complete heart block. In few patients, flushing, dyspnea, and chest pain were reported.

Ranolazine

Ranolazine is piperazine-derivative having chemical structure similar to lidocaine while blocking multiple ion channels. It is new agent having the antianginal and antiarrhythmic activity. Its most potent ion channel blocking effect is seen on late sodium current.[37-40] Ranolazine belongs to Vaughan Williams Class IB agent and prolongs action potential duration, with QT interval prolongation. Experiments done on animals have shown antiarrhythmic effects in the ventricle also.[39,40] Ranolazine has shown clinically to reduce arrhythmic episodes, in patients presenting with acute coronary syndrome[38] in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 trial (MERLIN-TIMI 36) and despite causing QT prolongation, ranolazine was not found to be associated with increased risk of SCD compared with placebo.[41] Based on limited experience but often good clinical results, it appears that ranolazine can be used as add-on therapy to Class III antiarrhythmic agent in patients with recurrent VT.

Upstream Therapies for AF

The concept of preventing the development of atrial electric and mechanical remodeling and thereby reducing the likelihood of AF is referred to as "upstream" therapy. It is

now recognized that AF originates from atrial tissue that has altered structure or function. Fibrosis within the atrium is one of the major mechanisms of atrial remodeling, which provide the substrate for AF generation and maintenance.[42] Potential agents in this category include blockers of the renin-angiotensin axis, aldosterone inhibitors, polyunsaturated fatty acids, and statins.[43] It is likely that agents in this category of upstream therapy will be most effective when administered before the development of significant atrial fibrosis.

Targets of Future Antiarrhythmic Agents

The commonly used antiarrhythmic for treatment of ventricular tachycardia/ventricular fibrillation acts on sodium channels (Class I agents) or potassium channels (Class III agents), but efficacy has not been constant and there is always risk for drug-related ventricular proarrhythmia. Newer targets for the treatment of ventricular arrhythmia are being explored and newer pharmacologic agents will be tested in future clinical trials in upcoming years. Newer targets have focused on the roles of sodium–calcium exchange, intracellular calcium, gap junctions, and adenosine triphosphate (ATP)-sensitive potassium channel blockade.[44] Altered intracellular calcium homeostasis has been implicated in development of ventricular arrhythmias.[45] Pharmacotherapies to normalize intracellular calcium handling by either stabilizing RyR2 activity or modulating associated proteins involved in diastolic SR calcium leakage so as to prevent ventricular arrhythmia may be a future insight in development of antiarrhythmic agents in this regard.

Gap Junctions

When cell–cell coupling is disrupted in the heart, it results in arrhythmogenesis since synchronization of depolarization and repolarization is lost. It has been suggested that restoration of coupling via gap junctions could be an effective antiarrhythmic target approach.[44] Connexin 43 has been implicated as the principal gap junction protein that maintains cell to cell coupling in ventricles, and its function is impaired during episodes of ischemia.[46]

Sodium–calcium Exchange

The sodium–calcium exchanger (NCX) is a cell membrane protein that removes a single calcium ion in exchange for the import of three sodium ions in the cardiomyocyte. It has been seen that increased expression of NCX is associated with cardiac contractile dysfunction, so an increased risk of arrhythmias in congestive cardiac failure.[47] Findings are promising but it has to be tested in clinical trials and larger studies.

Blockade of ATP-Sensitive Potassium Channel

During ischemia, there is increase in extracellular potassium, most probably that causes development of ventricular arrhythmias. In fact, ATP-sensitive potassium channels during ischemia cause potassium efflux and action potential duration is reduced along with impaired function of the sodium/potassium ATPase have also been postulated.[48] Ischemia causes potassium distribution heterogeneously that leads to dispersion of repolarization and thus creating availability of a substrate for re-entrant arrhythmias. Glibenclamide is an ATP-sensitive potassium channel inhibitor that reduces action potential duration in models of ischemia, and suppresses episodes of extrasystoles and ventricular fibrillation.[48]

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