New Arrhythmia Technologies
To our families and the memories of all those who have inspired us to look toward the future.
Part I Advances in antiarrhythmic pharmacologic therapy
Gerald V. Naccarelli (Section Editor)

1 New antiarrhythmic pharmacologic therapies and regulatory issues in antiarrhythmic drug development, 3
Heather M. Ross, Peter R. Kowey, Gerald V. Naccarelli

2 New frontiers in antithrombotic therapy for atrial fibrillation, 14
James A. Reiffel

Part II Future of antiarrhythmic therapy
Michael R. Rosen (Section Editor)

3 Principles of pharmacogenomics: Focus on arrhythmias, 31
Dan M. Roden

4 The cardiac sodium-channel carboxy terminus: predicted and detected structure provide a novel target for antiarrhythmic drugs development, 36
Robert S. Kass, Joseph W. Cormier, Ian W. Glaaser

5 Embryonic stem-cell-derived cardiomyocytes as a model for arrhythmia, 48
J. Hescheler, M. Halbach, Z.J. Lu, H. Bohlen, B.K. Fleischmann, M. Reppel

6 Gene and cell therapy for sinus and AV nodal dysfunction, 54
Peter Danilo, Jr., Steven Girouard, Peter R Brink, Ira S. Cohen, Richard B. Robinson, Michael R. Rosen

7 Gene therapy for cardiac tachyarrhythmias, 65
J. Kevin Donahue, Amy D. McDonald, Alexander Bauer, Kan Kikuchi, Tetsuo Sasano

Part III Monitoring, noninvasive mapping, risk assessment, and external defibrillation
N.A. Mark Estes III (Section Editor)

8 New developments in noninvasive rhythm monitoring, implantable hemodynamic monitoring, functional status monitoring, and noninvasive mapping, 75
Jonathan Weinstock, Munther K. Homoud, Mark S. Link, N.A. Mark Estes III

9 Techniques of prediction of arrhythmia occurrence and stratification for sudden cardiac death, 84
Aseem D. Desai, Bradley P. Knight

10 Beta-blocker efficacy in long-QT syndrome patients with mutations in the pore and nonpore regions of the hERG potassium-channel gene, 91
Arthur J. Moss, Derick R. Peterson, Wojciech Zareba, Rahul Seth, Scott A. McNitt, Mark L. Andrews, Ming Qi, Michael J. Ackerman, Jesaia Benhorin, Elizabeth S. Kaufman, Jennifer L. Robinson, Jeffrey A. Towbin, G. Michael Vincent, Li Zhang
11 New developments in out-of-hospital cardiac defibrillation: evaluation of AED strategies, 95
Robert J. Myerburg, Shuertelle Elliot, Donald G. Rosemberg, Alberto Interian Jr., Agustin Castellanos

Part IV Advances in pacing
David L. Hayes (Section Editor)

12 Sensor and sensor integration, 111
Robert F. Rea

13 New electrode and lead designs for pacemakers, 119
Charles J. Love

14 Current concepts in intravascular pacemaker and defibrillator lead extraction, 124
Dhanunjaya R. Lakkireddy, Atul Verma, Bruce L. Wilkoff

15 Left ventricular epicardial lead implantation: Anatomy, techniques, and tools, 134
Jennifer Cummings, William Belden, Bruce L. Wilkoff

16 New resynchronization lead systems and devices, 145
Robert F. Rea

17 New indications for pacing, 154
David L. Hayes

Part V Advances in implantable defibrillators
Paul J. Wang (Section Editor)

18 Implantable defibrillator sensing and discrimination algorithms, 163
Kelly Richardson, Amin Al-Ahmad, Paul J. Wang

19 Arrhythmia prevention and termination algorithms, 178
Gregory Engel, Paul J. Wang, Amin Al-Ahmad

20 New lead designs and lead-less systems, 187
Kenneth A. Ellenbogen, Bruce D. Gunderson, Mark A. Wood

21 Optimization of defibrillation function, 197
Michael R. Gold, Paul J. DeGroot

22 Remote web-based device monitoring, 206
Edmund Keung, Yang Xue

23 New ICD indications, 219
Erik Sirulnick, Amin Al-Ahmad, Paul J. Wang

Part VI Advances in catheter surgical ablation
David E. Haines (Section Editor)

24 Advances in surgical ablation devices for atrial fibrillation, 233
Spencer J. Melby, Anson M. Lee, Ralph J. Damiano, Jr.

25 Epicardial access: present and future applications for interventional electrophysiologists, 242
Robert A. Schweikert, Andre Natale

26 Advances in catheter control devices, 257
Girish Narayan, Paul J. Wang, Amin Al-Ahmad

27 Advances in energy sources in catheter ablation, 262
David E. Haines

28 New ablation paradigms: Anatomic ablation of complex arrhythmia substrates, 274
David J. Callans

Index, 283
Contributors

**Michael J. Ackerman, MD, PhD**  
Director, LQTS Clinic and Sudden Death Genomics Laboratory,  
Mayo Clinic, Rochester, MN, USA

**Amin Al-Ahmad, MD**  
Associate Director of Cardiac Arrhythmia Service  
Cardiac Arrhythmia Service,  
Stanford University Medical Center  
Stanford, CA, USA

**Mark L. Andrews, BBS**  
Analyst/Programmer  
University of Rochester Medical Center  
Rochester, NY, USA

**Alexander Bauer, MD**  
Johns Hopkins University School of Medicine  
Baltimore, MD, USA

**William Belden, MD**  
Fellow in Electrophysiology,  
Cleveland Clinic Foundation, Cleveland Clinic  
Cleveland, OH, USA

**Jesaia Benhorin, MD**  
Professor of Medicine  
The Heiden Department of Cardiology,  
Bikur Cholim Hospital  
Jerusalem, Israel

**Heribert Bohlen, PhD**  
Director of Axiogenesis AG  
Axiogenesis AG  
Cologne, Germany

**Peter R. Brink, PhD**  
Professor and Chairman,  
Department of Physiology and Biophysics  
Health Sciences Center,  
Stony Brook University  
Stony Brook, NY, USA

**David J. Callans, MD**  
Professor of Medicine, University of Pennsylvania Hospital of the University of Philadelphia, PA, USA

**Agustin Castellanos, MD**  
Professor of Medicine, Division of Cardiology  
Miller School of Medicine,  
University of Miami  
Miami, FL, USA

**Ira S. Cohen, PhD**  
Leading Professor of Physiology and Biophysics;  
Director of the Institute of Molecular Cardiology  
Health Sciences Center, Stony Brook University  
Stony Brook, NY, USA

**Joseph W. Cormier, PhD**  
Graduate Research Assistant  
Department of Pharmacology,  
Columbia University  
New York, NY, USA

**Jennifer Cummings, MD**  
Associate Staff  
Cleveland Clinic Foundation  
Cleveland, OH, USA

**Ralph J. Damiano, Jr, MD**  
John M. Shoenberg Professor of Surgery,  
Chief of Cardiac Surgery,  
Washington University School of Medicine at Barnes Jewish Hospital  
St Louis, MO, USA

**Peter Danilo, Jr, PhD**  
Senior Research Scientist  
Department of Pharmacology,  
Center for Molecular Therapeutics,  
Columbia University  
New York, NY, USA
Contributors

Paul J. DeGroot, MS
Senior Principal Scientist and Bakken Fellow,
Cardiac Rhythm Management Research,
Medtronic Inc.
Minneapolis, MN, USA

Aseem D. Desai, MD
Assistant Professor of Medicine, Cardiac
Electrophysiology, University of Chicago Hospitals;
Director, Implantable Device Therapy
Cardiac Electrophysiology,
University of Chicago Hospitals
Chicago, IL, USA

J. Kevin Donahue, MD
Associate Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Kenneth A. Ellenbogen, MD
Director, Electrophysiology and Pacing
VCU School of Medicine
Richmond, VA, USA

Shauntelle Elliott, RN
Clinical Research Coordinator
Jackson Memorial Medical Center
Cardiac Arrhythmia Service,
Miami, FL, USA

Gregory Engel, MD
Cardiac Electrophysiology Fellow
Cardiac Arrhythmia Service,
Stanford University Medical Center
Stanford, CA, USA

N. A. Mark Estes III, MD
Director, Cardiac Arrhythmia Service,
Tufts New England Medical Center;
Professor of Medicine,
New England Medical Center
Boston, MA,
USA

Bernd Fleischmann
Director, Institute of Physiology
University of Bonn
Bonn, Germany

Steven Girouard, PhD
Director, Basic Research
Guidant Corporation
St Paul, MN, USA

Ian W. Glaaser, PhD
Graduate Research Assistant
Department of Pharmacology,
Columbia University
New York, NY, USA

Michael R. Gold, MD
Chief of Cardiology and Director of
Heart and Vascular Center
Medical University of South
Carolina
Charleston, SC, USA

Bruce D. Gunderson, MS
Principal Scientist, Medtronic Inc.
Minneapolis, MN,
USA

David E. Haines, MD
Director, Heart Rhythm Center,
Cardiology Division,
William Beaumont Hospital
Royal Oak, MI,
USA

M. Halbach, PhD
Institute of Neurophysiology,
University of Cologne
Cologne, Germany

David L. Hayes, MD
Chair, Division of Cardiovascular
Diseases
Mayo Clinic
Rochester, MN, USA

Jurgen Hescheler, MD, PhD
Director, Institute of Neurophysiology
University of Cologne
Cologne, Germany

Munther K. Homoud, MD
Assistant Professor of Medicine,
Tufts University School of Medicine
Tufts New England Medical Center
Boston, MA, USA

Alberto Interian Jr, MD
Professor of Medicine; Interim Chief,
Division of Cardiology;
Director, Electrophysiology
Miller School of Medicine,
University of Miami
Miami, FL, USA

Robert S. Kass, PhD
David Hossack Professor of Pharmacology
(in the Center of Neurobiology and Behavior)
and Chairman
Department of Pharmacology,
Columbia University
New York, NY, USA
Contributors

Elizabeth S. Kaufman, MD
Associate Professor of Medicine
MHMC Arrhythmia Service
Cleveland, OH, USA

Edmund Keung, MD
Director, VA National ICD Surveillance Center and
Western Pacemaker Surveillance Center
Associate Chief, Cardiology Section
San Francisco VA Medical Center
San Francisco, CA, USA

Kan Kikuchi, PhD
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Bradley P. Knight, MD
Director of Cardiac Electrophysiology
Cardiac Electrophysiology,
University of Chicago Hospitals
Chicago, IL, USA

Peter R. Kowey, MD
Chief of Cardiology, Main Line Health System
Professor of Medicine, Jefferson Medical College
Wynnewood, PA, USA

Dhanunjaya R. Lakkireddy, MD
Fellow in Electrophysiology
Cleveland Clinic Foundation
Cleveland, OH, USA

Anson M. Lee, BS
Medical Student
Washington University School of Medicine
at Barnes Jewish Hospital
St Louis, MO, USA

Mark S. Link, MD
Assistant Professor of Medicine
Tufts University School of Medicine
Tufts New England Medical Center
Boston, MA, USA

Charles J. Love, MD
Professor of Clinical Medicine
Director, Arrhythmia Device Services
Director, Electrophysiology Section and Laboratory
OSU Division of Cardiovascular Medicine
Columbus, OH, USA

Amy D. McDonald, BS
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Scott A. McNitt, MS
Associate Professor
University of Rochester Medical Center
Rochester, NY, USA

Spencer J. Melby, MD
Washington University School of Medicine
St Louis, MO, USA

Arthur J. Moss, MD
Professor of Medicine
University of Rochester Medical Center
Rochester, NY, USA

Robert J. Myerburg, MD
Professor of Medicine and Physiology; American Heart
Association Chair in Cardiovascular Research
Miller School of Medicine,
University of Miami
Miami, FL, USA

Gerald V. Naccarelli, MD
Bernard Trabin Chair in Cardiology
Professor of Medicine
Chief, Division of Cardiology
Director, Cardiovascular Center
Penn State University College of Medicine
Hershey, PA, USA

Girish Narayan, MD
Falk Cardiovascular Center,
Stanford University Hospital
Stanford, CA, USA

Andrea Natale, MD
Co-Section Head, Electrophysiology and Pacing
Director, Center for Atrial Fibrillation and
EP Laboratories
Cleveland Clinic Foundation
Cleveland, OH, USA

Derick R. Peterson, PhD
Associate Professor, Biostatistics and
Computational Biology
University of Rochester Medical Center
Rochester, NY, USA

Ming Qi, PhD
Research Assistant Professor, Pathology and Lab Medicine
University of Rochester Medical Center
Rochester, NY, USA
Robert F. Rea, MD
Associate Professor of Medicine,
Mayo Clinic
Rochester, MN, USA

James A. Reiffel, MD
Professor of Clinical Medicine
Columbia University
New York, NY, USA

M. Reppel, PhD
Group Leader
Institute of Neurophysiology,
University of Cologne
Cologne, Germany

Kelly Richardson, MD & Jennifer L. Robinson, MS
Electrophysiology Fellow
Stanford Hospital
Stanford, CA, USA

Richard B. Robinson, PhD
Professor of Pharmacology
Department of Pharmacology,
Center for Molecular Therapeutics,
Columbia University
New York, NY, USA

Jennifer Robinson
Research Associate
University of Rochester Medical Center
Rochester, NY, USA

Dan M. Roden, MD
Professor of Medicine and Pharmacology;
Director, Oates Institute for Experimental Therapeutics
Vanderbilt University School of Medicine
Nashville, TN, USA

Michael R. Rosen, MD, PhD
Gustavus A. Pfeiffer Professor of Pharmacology;
Professor of Pediatrics; Director, Center for Molecular Therapeutics
Columbia University
New York, NY, USA

Donald G. Rosenberg, MD
Professor of Clinical Medicine,
Division of Cardiology
Miller School of Medicine,
University of Miami
Miami, FL, USA

Heather M. Ross, MS, APRN
Nurse Practitioner
Center for Adult Congenital Heart Disease,
St Joseph’s Hospital and Medical Center
Phoenix, AZ, USA

Tetsuo Sasano, MD
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Robert A. Schweikert, MD
Staff Physician
Department of Cardiovascular Medicine,
Cleveland Clinic
Cleveland, OH, USA

Rahul Seth, BS
University of Rochester Medical Center
Rochester, NY, USA

Erik Sirulnick, MD
Electrophysiology Fellow
Falk Cardiovascular Center,
Stanford University Hospital
Stanford, CA, USA

Jeffrey A. Towbin, MD
Professor of Pediatrics
Texas Children’s Hospital
Houston, TX, USA

Atul Verma, MD
Fellow in Electrophysiology
Cleveland Clinic Foundation
Cleveland, OH, USA

G. Michael Vincent, MD
Professor of Medicine
Department of Medicine, LDS Hospital
Salt Lake City, UT, USA

Paul J. Wang, MD
Professor of Medicine,
Stanford University School of Medicine;
Director, Cardiac Arrhythmia Service and Cardiac Electrophysiology Laboratory,
Stanford Hospital and Clinics
Stanford University Medical Center
Stanford, CA, USA

Jonathan Weinstock, MD
Assistant Professor of Medicine,
Tufts University School of Medicine
Tufts New England Medical Center
Boston, MA, USA
Bruce L. Wilkoff, MD
Director of Cardiac Pacing and Tachyarrhythmia Devices, Department of Cardiovascular Medicine, Cleveland Clinic Foundation
Cleveland, OH, USA

Mark A. Wood, MD
Professor of Medicine
Virginia Commonwealth University Medical Center
Richmond, VA, USA

Yang Xue, BS
University of Michigan Medical School
Fremont, CA, USA

Wojciech Zareba, MD, PhD
Associate Professor of Medicine
University of Rochester Medical Center
Rochester, NY, USA

Li Zhang, MD
Assistant Professor of Medicine
Department of Medicine, LDS Hospital
Salt Lake City, UT, USA
New Arrhythmia Technologies is designed to serve as an up-to-date text on the rapidly advancing field of arrhythmia innovations. The breadth of the topics covered mirrors the expansive nature of the growing field of arrhythmia evaluation and therapy. The text begins with a comprehensive discussion of new pharmacologic agents for arrhythmia management and new antithrombotic agents, particularly for atrial fibrillation, and proceeds to include chapters on future arrhythmia therapies utilizing pharmacogenomics, structural approaches to novel antiarrhythmic drug therapy, embryonic stem cell-derived cardiomyocytes, and gene and cell therapy for sinus node and A-V nodal dysfunction and cardiac tachyarrhythmias. The numerous advances in noninvasive rhythm monitoring, implantable hemodynamic monitoring, functional status monitoring, and non-invasive mapping are discussed. There have been important advances in risk stratification for sudden death and the identification of relationships between the gene defect and the response to therapy. Because of the central role that out-of-hospital cardiac defibrillation has played in improving survival of sudden cardiac death, a chapter has been devoted to this topic.

In the exploding field of new arrhythmia devices, the text covers sensors and sensor algorithms, new electrode and lead designs for both pacing and defibrillation, advances in lead extraction, new resynchronization devices and left ventricular lead delivery systems for cardiac venous and epicardial placement, and new pacing indications. In the field of defibrillation, chapters are devoted to important advances in arrhythmia prevention and termination algorithms, sensing and discrimination algorithms, new ICD lead design and lead-less systems, optimization of defibrillator waveforms, new ICD indications, and web-based monitoring.

There have been remarkable advances in the development of techniques and devices for the surgical and catheter ablation of arrhythmias. A series of chapters are devoted to the explosion in surgical devices and techniques for atrial fibrillation, novel epicardial access techniques, innovative catheter control devices, new energy sources for catheter ablation, and new ablation paradigms.

We believe that New Arrhythmia Technologies provides a unique view into the latest in arrhythmia innovations through the eyes of the experts in the field.

PW
We wish to thank the contributors who have generously provided their expertise and time to this project. We would like to thank the efforts of Vicki Donald and Gina Almond of Blackwell Publishing for making this dream a reality. We wish to thank Michael Homer, BS for his administrative assistance. We also wish to thank all of the many unacknowledged assistants and colleagues who have been critical to the editing of each manuscript. Finally, we wish to thank the families of all the editors and contributors who tolerated us as we completed these chapters and this project.
PART I

Advances in antiarrhythmic pharmacologic therapy
CHAPTER 1

New antiarrhythmic pharmacologic therapies and regulatory issues in antiarrhythmic drug development

Heather M. Ross, MS, APRN, Peter R. Kowey, MD, & Gerald V. Naccarelli, MD

Introduction

Until the 1980s, the majority of approved antiarrhythmic drugs were developed for use in the treatment of ventricular arrhythmias. Since that time, antiarrhythmic drug development has concentrated on the management of atrial fibrillation. Antiarrhythmic drugs that have proven useful in cardioversion and maintenance of sinus rhythm include Class IA sodium channel blockers: quinidine, procainamide, and disopyramide; Class IC sodium channel blockers: flecainide and propafenone; and the Class III agents: sotalol, dofetilide, and amiodarone. In addition, intravenous ibutilide is effective in the termination of atrial fibrillation. Quinidine, flecainide, propafenone-IR and -SR, sotalol, dofetilide, and ibutilide have FDA approval in the United States for the treatment of atrial fibrillation. Due to subjective adverse symptoms, end-organ toxicity, proarrhythmic potential, and lack of safety data in structural heart disease, Class IA agents are being used less frequently than in the past. Class IC drugs have been limited to use in patients with minimal or no structural heart disease. Sotalol and dofetilide can provoke torsade de pointes, and amiodarone use is often limited due to potential end-organ toxicity. In response to these limitations, the pharmaceutical industry has pursued the development of more effective and safer antiarrhythmic drugs for the treatment of atrial fibrillation. Drug development to treat ventricular arrhythmias continues as well, though to a lesser extent than for atrial fibrillation.

Theoretically, an ideal antiarrhythmic drug for the treatment of atrial fibrillation would have the following characteristics: (1) suppress phase 4 automaticity and thus atrial triggers; (2) prolong atrial refractory periods in a use-dependent fashion; (3) slow intraatrial conduction; (4) atrial selectivity to minimize ventricular proarrhythmic effects; (5) prolong AV nodal refractoriness and slow AV nodal conduction for the purpose of rate control; (6) a half-life long enough for once a day usage; (7) low potential for subjective, end-organ and proarrhythmic side effects; (8) safety for use in patients with structural heart disease, incorporating no significant negative inotropic effects or drug interactions.

Antiarrhythmic pharmaceutical development is currently moving in two general directions. First, efforts are being made to modify existing agents in an attempt to ameliorate safety and efficacy concerns. Second, pharmaceutical companies are working to develop agents with novel therapeutic
mechanisms in an effort to achieve more effective drug therapy than is offered by existing compounds. Dofetilide and propafenone-SR are the most recently approved antiarrhythmic agents for the treatment of atrial fibrillation. In addition, new data suggest that carvedilol may have a role in treating atrial fibrillation. Investigational antiarrhythmic drugs abound. Non-antiarrhythmic drugs, such as ACE inhibitors, angiotensin receptor blockers, and HMG CoA enzyme inhibitors, also appear to have a role in suppressing atrial fibrillation in certain patient subtypes. This chapter will review the efficacy of the newly approved and currently investigational antiarrhythmic drugs that hold promise in the treatment of atrial fibrillation and other arrhythmias.

Newly approved agents

Termination of atrial fibrillation

In patients with more persistent atrial fibrillation, only oral dofetilide has a Class I indication for the termination of atrial fibrillation, based on the results of SAFIRE-D (Symptomatic Atrial Fibrillation Investigative REsearch on Dofetilide) and EMERALD (European and Australian Multicenter Evaluative Research on Atrial fibrilation Dofetilide) clinical trials. Dofetilide prolongs action potential duration nearly twofold more in the atria than in the ventricles. This may explain the drug’s effectiveness in converting atrial fibrillation to sinus rhythm. Both studies tested doses of 125, 250, and 500 μg of dofetilide twice daily compared with placebo. In EMERALD, sotalol 80 mg twice daily was also tested [1–6]. SAFIRE-D included 325 patients with persistent atrial fibrillation. The majority of patients had structural heart disease and 40% had a depressed ejection fraction. In SAFIRE-D, a 32% conversion rate by day three was noted, superior to the 1% placebo conversion rate (p < .001) [1]. EMERALD included 535 patients with persistent atrial fibrillation or atrial flutter. In EMERALD, 500 μg of dofetilide twice daily achieved a 29% rate of converting atrial fibrillation to sinus rhythm, proving more efficacious than sotalol (6%; p < .05) [2].

Further data regarding the efficacy of dofetilide in terminating atrial fibrillation come from the DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) trial in which 391 patients who had atrial fibrillation at baseline had more frequent spontaneous conversion to sinus rhythm with dofetilide (12% at 1 month and 44% at 12 months) compared with placebo (1% at 1 month and 13% at 12 months; p < .001) [4, 5].

Suppression of atrial fibrillation

Oral procainamide, disopyramide, flecainide, propafenone, and sotalol are as effective as quinidine for the prevention of atrial fibrillation with efficacy rates averaging about 50%. Comparative trials have demonstrated that Class IC drugs and sotalol are better tolerated than Class IA agents. Recent data suggest that amiodarone is the most effective agent for maintaining sinus rhythm [7]. The Canadian Trial of Atrial Fibrillation (CTAF) demonstrated that patients treated with amiodarone had a lower recurrence rate (35%) versus sotalol or propafenone (63%) (p < .001). However, side effects requiring drug withdrawal was higher (p = .06) in the amiodarone-treated group [7, 8].

Dofetilide blocks the rapid potassium delayed rectifier current (\(I_{Kr}\)). Reverse use-dependent effects may minimize its electrophysiologic effects at rapid rates, such as those occurring with supraventricular tachyarrhythmias. By prolonging action potential duration, dofetilide has no negative inotropic effects and may even be a positive inotropic agent [3]. In addition to being an effective agent for medical conversion of atrial fibrillation to sinus rhythm, dofetilide (500 μg twice daily) had a 58% efficacy in maintaining sinus rhythm at 1 year postcardioversion compared with only 25% in a placebo group in the SAFIRE-D trial (p < .001) [1]. Results of maintaining sinus rhythm in the EMERALD trial were similar [2]. In both studies, efficacy appeared to be dose related. In DIAMOND-AF, 1 year efficacy rates for maintaining sinus rhythm was superior in the dofetilide treated patients at 79%, compared with 42% in placebo patients (p < .001) [6]. DIAMOND-CHF found that dofetilide was superior to placebo in maintaining sinus rhythm after conversion from atrial fibrillation (HR 0.35; CI = 0.22–0.57; p < .001) [5].

Prospective trials of dofetilide did not demonstrate efficacy high enough to attain FDA approval.
in the suppression for paroxysmal atrial fibrillation; however, clinical experience suggests efficacy rates similar to other Class III, IA and IC drugs. Dose adjustment based on creatinine clearance and in-hospital initiation under telemetry conditions has been shown to decrease the incidence of drug-induced torsade de pointes [6].

For the suppression of recurrent paroxysmal atrial fibrillation, comparative trials have demonstrated that Class IC drugs and sotalol are equally effective and better tolerated than Class IA drugs [7]. Although these drugs have reported efficacy rates of about 50% at 1 year, up to 70% of patients who have remained on Class IC drugs after a year of treatment experience rare recurrences and minimal side effects that do not require drug discontinuation [7, 9].

In early 2004, a twice-daily formulation of propafenone became available in the United States. In the RAFT and ERAFT trials, propafenone-SR demonstrated statistical dose-related efficacy that was at least as effective as the immediate release form of the drug [10, 11]. In RAFT, propafenone-SR significantly lengthened the time to the first symptomatic atrial arrhythmic recurrence at all doses tested, compared with placebo [10]. These studies yielded a very favorable dose–response curve. The findings from ERAFT were consistent with RAFT, although the 225 mg twice-daily dose was not tested [11]. Plasma levels of propafenone were more likely to maintain therapeutic levels with the sustained formulation of the drug. The sustained release formulation is available in 225, 325, and 425 mg tablets, dosed twice daily rather than three times daily as with the immediate release formulation. The 325 mg twice-daily dose of sustained release of propafenone appears to be roughly equivalent to the 150 mg three times a day dose of the immediate release formulation [10].

Carvedilol possesses complex electrophysiologic properties, related to its Vaughan Williams Class II dose-related antiadrenergic (β1, β2, and α) effects. In addition, carvedilol has direct membrane-stabilizing activity (Class IA), prolongs repolarization by blocking potassium channels (Class III), and inhibits L-type calcium channels (Class IV). Carvedilol carries no known proarrhythmic activity. Carvedilol inhibits several native potassium channels responsible for repolarization in cardiomyocytes, including the rapidly and slowly activating components of the delayed rectifier current (I_Kr and I_Ks) and the transient outward current (I_TO). Carvedilol does not affect the inward rectifier current (I_K1) which prolongs the action potential duration and effective refractory period to repeat excitability [12–14].

In a post-cardioversion trial comparing carvedilol to bisoprolol, carvedilol had a 14% lower rate of atrial fibrillation relapse during the 1 year period following cardioversion [15]. Carvedilol was also compared with two other β1 selective blockers, metoprolol and atenolol, in a study of postoperative atrial fibrillation as a complication of cardiac surgery. Postoperative atrial fibrillation occurred in 8% of carvedilol-treated patients, versus 32% of patients receiving metoprolol or atenolol, for a 75% risk reduction. This occurred despite significantly poorer baseline left ventricular function in the carvedilol group [16].

Carvedilol was compared with amiodarone in a placebo-controlled trial of patients with chronic atrial fibrillation undergoing electrical cardioversion. Patients were randomized to receive carvedilol, amiodarone, or no antiarrhythmic drug for 6 weeks before and after external transthoracic cardioversion. Successful cardioversion was achieved with carvedilol and amiodarone pretreatment (87% and 94%), versus no antiarrhythmic prophylaxis (69%). Patients in both drug-treated groups immediately had longer fibrillatory cycle length intervals preconversion and longer atrial effective refractory periods 5 min post-conversion than unprotected patients. More patients who experienced a relapse of atrial fibrillation within 7 days were untreated (44%), compared with those receiving either carvedilol (29%) or amiodarone (19%) treatment [17].

**Approaches to new antiarrhythmic drugs**

**Modifications: targeted improvements with new antiarrhythmic drugs**

The pharmaceutical industry is currently devoting notable attention to the development of improved Class III antiarrhythmic drugs with enhanced efficacy and safety profiles. These agents are among the most effective currently available antiarrhythmic
drugs for the suppression or cardioversion of atrial fibrillation and ventricular tachycardia [7]. Unfortunately, many patients and healthcare providers find the adverse effects associated with these agents, particularly the risks of end-organ toxicity and proarrhythmia, to be untenable.

There are currently more than a dozen new Class III compounds in development [18–23]. These are targeted to various potassium channels, with varying degrees of specificity or breadth. Some agents additionally block calcium channels, and others have beta blockade or sodium channel-blocking capacity (Table 1.1).

Within this category of new antiarrhythmic drugs as improved versions of existing potassium channel-blocking compounds, there are two particularly novel developments to note. Scientists have been able to target blockade of the ultrarapid potassium rectifier current ($I_{\text{Kr}}$), which exists only in atrial tissue, thereby affording atrial specificity and theoretically eliminating the risk of torsade de pointes as a result of ventricular action potential delay. Second, the ability to block the acetylcholine-dependent potassium current ($I_{\text{KAch}}$) offers another new specificity in targeting antiarrhythmic drug effects to the atria [18].

### Cardioversion of atrial fibrillation
Tedisamil is currently in Phase III trials in the United States to evaluate for an indication for cardioversion of atrial fibrillation. Tedisamil is a Class III agent with blockade of $I_{\text{Kr}}$, $I_{\text{to}}$, $I_{\text{Ks}}$, $I_{\text{Kur}}$, and $I_{\text{KAch}}$, as well as sodium-channel-blocking properties. This new compound will theoretically offer an alternative to intravenous ibutilide, without risk of torsade de pointes [19, 20, 27].

<table>
<thead>
<tr>
<th>Modifications of existing compounds</th>
<th>Novel mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azimilide ($I_{\text{Kr}}, I_{\text{Ks}}$)</td>
<td>Piboserod (5-HT4)</td>
</tr>
<tr>
<td>Dronedarone ($I_{\text{Kr}}, I_{\text{to}}, I_{\text{to}}, I_{\text{WA}}$)</td>
<td>ZP-123 (GAP 486)</td>
</tr>
<tr>
<td>RSD-1235 ($I_{\text{Kur}}, I_{\text{to}}, I_{\text{WA}}, I_{\text{KAch}}$)</td>
<td>AAP10 (connexin modulator)</td>
</tr>
<tr>
<td>GYKI-16638 ($I_{\text{Kr}}, I_{\text{KS}}, I_{\text{WA}}$)</td>
<td>GsMtx4 (stretch receptor antagonist)</td>
</tr>
<tr>
<td>AZD7009 (atrial repolarization delay)</td>
<td></td>
</tr>
<tr>
<td>AVE1213 (atrial repolarization delay)</td>
<td></td>
</tr>
<tr>
<td>ATI-2042 ($I_{\text{Kr}}, I_{\text{to}}, I_{\text{to}}, I_{\text{to}}, I_{\text{WA}}$)</td>
<td></td>
</tr>
<tr>
<td>Tedisamil ($I_{\text{Ks}}, I_{\text{to}}, I_{\text{KAch}}, I_{\text{WA}}, I_{\text{Kur}}$)</td>
<td></td>
</tr>
<tr>
<td>AVE-0118 ($I_{\text{to}}$, $I_{\text{to}}$, $I_{\text{to}}$, $I_{\text{to}}$, $I_{\text{WA}}$)</td>
<td></td>
</tr>
<tr>
<td>Ersentilide ($I_{\text{Kr}}, \beta$)</td>
<td></td>
</tr>
<tr>
<td>Trecetilide ($I_{\text{Kur}}, I_{\text{WA}}$)</td>
<td></td>
</tr>
<tr>
<td>Almokalant ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>Terikalant ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>SB237376 ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>HMR1402 ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>HMR1556 ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>L768673 ($I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>Ambasilide ($I_{\text{to}}, I_{\text{Kt}}, I_{\text{KAch}}, I_{\text{Kur}}, I_{\text{WA}}$)</td>
<td></td>
</tr>
<tr>
<td>NIP142 ($I_{\text{Kur}}, I_{\text{KAch}}$)</td>
<td></td>
</tr>
<tr>
<td>CP0605 ($I_{\text{WA}}, I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>KB-R7943 ($I_{\text{WA}}, I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>Cariporide ($I_{\text{WA}}, I_{\text{to}}$)</td>
<td></td>
</tr>
<tr>
<td>DTI0009 (adenosine A1 blocker)</td>
<td></td>
</tr>
<tr>
<td>Tecadenoson (CVT-510) (long-acting adenosine A1 blocker)</td>
<td></td>
</tr>
<tr>
<td>Abanoquil ($\alpha_{1a}$ blocker)</td>
<td></td>
</tr>
<tr>
<td>E3174 (angiotensin II blocker)</td>
<td></td>
</tr>
<tr>
<td>KB130015 (thyroid antagonist)</td>
<td></td>
</tr>
</tbody>
</table>
Suppression of atrial fibrillation

Azimilide is an $I_{Kr}$ and $I_{Ks}$ blocker that does not appear to have any reverse use dependence. Thus, azimilide maintains its electrophysiologic effects over both slow and fast heart rates. Azimilide, similar to amiodarone, blocks both $I_{Kr}$ and $I_{Ks}$, which is thought to minimize the risk of torsade de pointes compared with only $I_{Kr}$ blockade. Azimilide has demonstrated efficacy in treating atrial fibrillation based on clinical trials in the Azimilide Supraventricular Arrhythmia Program (ASAP). The most effective dose appears to be 125 mg daily, averaging about 50% suppression of paroxysmal atrial fibrillation. Lower doses have produced inconsistent effects in suppressing atrial fibrillation compared with placebo. One pivotal study of 125 mg daily did not show statistical benefit in suppressing paroxysms of atrial fibrillation [28].

Because of this, ongoing trials include A-STAR (Azimilide Supraventricular Tachy-Arrhythmia Reduction) to further assess the efficacy of azimilide in suppressing paroxysmal atrial fibrillation and A-COMET (Azimilide CardiOversion Maintenance Trial) to assess its role in maintaining sinus rhythm in persistent atrial fibrillation post-cardioversion [29]. In A-COMET II, azimilide will be compared with placebo and sotalol.

ALIVE (AzimiLide post-Infarction surVival Evaluation) found azimilide to have neutral effects in a placebo-controlled trial of post-myocardial infarction patients with a hazard ratio of 1.0 with a mortality rate of 11.6% in both the placebo and azimilide-treated groups. In addition, the time to the development of atrial fibrillation was longer ($p = .04$) in the azimilide group [30]. Safety data from trials thus far show that azimilide appears to have a low incidence of drug provoked torsade de pointes. Subjective toxicity is minimal, but a low incidence of drug-induced neutropenia has been reported [30, 31].

Dronedarone appears to slow sinus rates less than amiodarone. However, its AV nodal refractory period prolonging effect should confer some rate control benefits [32].

In the DAFNE (Dose Adjustment For Normal Eating) trial, dronedarone 400 mg twice daily was superior to placebo in preventing recurrent atrial fibrillation. The median time to recurrence was 59.9 days in the dronedarone group compared with 5.3 days in the placebo group ($p < .05; RR = 0.45; CI = 0.28–0.72$). Higher doses of dronedarone were ineffective and associated with a higher incidence of gastrointestinal subjective adverse effects [33]. Ongoing studies at the 400 mg twice-daily dose include ADONIS (American African trial with DrONnedarone In atrial fibrillation or flutter for the maintenance of Sinus rhythm) and EURIDIS (EURopean trial In atrial fibrillation or atrial flutter patients receiving Dronedaron for the main tenance of Sinus rhythm). Both of these studies have demonstrated that dronedarone suppresses recurrent atrial fibrillation at a dose of 400 mg twice daily [24].

Another novel compound group is the atrial repolarization delaying action agents, which will theoretically allow for adequate dosing to suppress atrial arrhythmias effectively, without risk of torsade de pointes due to concomitant repolarization delay in ventricular tissues. Drugs featuring $I_{Kur}$ blockade offer particular hope in this category [18].

RSD-1235 is an atrial selective potassium channel blocker with little effect on ventricular repolarization. In the CRAFT trial RSD-1235 was shown to have a dose-related ability to terminate atrial fibrillation [34].

AVE-0118 is a biphenyl derivative that blocks the atrial delayed rectifier current and $I_{ACH}$ with little effect on ventricular tissue. Early basic studies demonstrate that it prolongs the atrial effective refractory period, even after atrial remodeling has occurred from persistent atrial fibrillation [35].

Rate control of atrial tachyarrhythmias

Tecadenoson is an adenosine analog with selective $A_1$ receptor agonist activity. This avoids hypotension that is associated with stimulation of the $A_2$ receptor, and is commonly experienced with intravenous administration of adenosine. Tecadenoson has completed enrollment of phase III trials for
ventricular rate control in paroxysmal supraventricular tachycardia. Enrollment continues in trials to examine tecadenoson as an agent for ventricular rate control in atrial fibrillation. This drug will be indicated only for rate control and not suppression of atrial fibrillation [25].

**Treatment of ventricular arrhythmias**

Advances in cardiac care have significantly improved survival after myocardial infarction. Compared to the past, early revascularization and thrombolytic agents have minimized the size of myocardial scar compared to 20 years ago. However, a significant number of patients still carry myocardial scar, and thus border zone areas, prone to development of anisotropy and reentrant ventricular arrhythmia circuits. While catheter ablation for ischemic monomorphic ventricular tachycardia is relatively successful, it is a highly specialized procedure not accessible by all patients. As with atrial fibrillation, significant numbers of patients with ventricular tachycardia rely on pharmacologic therapies for arrhythmia suppression. Similar problems regarding safety and efficacy exist with preparations used to suppress ventricular arrhythmias in this growing population.

As there is more enthusiasm for developing antiarrhythmic drugs for the treatment of atrial fibrillation, very few drugs are being developed for the treatment of ventricular arrhythmias. Gap junction modulators may have use in treating ventricular tachyarrhythmias. Multiple new drugs, such as azimilide and dronedarone, are being studied in patients with ICDs to determine if they are effective in suppressing recurrent ICD shocks.

Early animal studies are examining new compounds with combined Class IB and Class III antiarrhythmic properties for the suppression of ventricular tachycardia. In vivo studies with dog and rabbit models have been encouraging, suggesting further development of the compound GYKI-16638. To date, however, human studies have not commenced [21].

**Innovations: compounds with novel antiarrhythmic mechanisms**

As our understanding of the wide range of etiologies for atrial fibrillation onset improves, scientists have begun to develop antiarrhythmic agents with entirely new mechanisms of action. Gap junction (connexin) modulators, such as AAP10 and ZP123, offer promise for the treatment of atrial fibrillation in the setting of dilated cardiomyopathies. Stretch receptor antagonists, including GsMtX4, may gain significant efficacy in the treatment of individuals with hypertrophic hearts, diastolic dysfunction, and valvular regurgitation [18].

There has been some indirect association that 5-hydroxytryptamine (5-HT) can cause atrial fibrillation. Piboserod (an atrial-selective 5-HT receptor antagonist) was developed as a result of this theory. Clinical results to date, however, have been disappointing [20].

Data exist from multiple studies that angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful for the suppression of atrial fibrillation, by mechanisms not previously thought to have any significant antiarrhythmic effects [23, 35, 36–38]. More recent data from AFFIRM suggest that these drugs may be particularly useful in as antiarrhythmic agents in patients with significant heart failure [39, 40].

**Antiarrhythmic therapy choice based on survival data from clinical trials**

DIAMOND-MI studied the effects of dofetilide compared with placebo in patients with post-myocardial infarction with ejection fraction of ≤ 35%. A total of 1510 patients were recruited (749 dofetilide; 761 placebo) with a minimum follow-up of 1 year. Dofetilide was titrated under telemetry conditions for the first 3 days of dosing. Dofetilide had neutral mortality effects when compared with placebo in the post-myocardial infarction setting (230 dofetilide versus 243 placebo deaths, HR = 0.94, p = .23). Dofetilide had no adverse or beneficial effect on cardiac mortality or arrhythmic death. Pharmacologic conversion of atrial fibrillation was more frequent in the dofetilide group (p = .002) [41].

The DIAMOND-CHF trial randomized 1518 patients admitted to the hospital with heart failure and an ejection fraction of ≤ 35% to dofetilide (n = 762) or placebo (n = 756). During follow-up, 311 (41%) died in the dofetilide arm, versus 317 (42%) deaths in the placebo arm (p = NS;
HR = 0.95; CI = 0.81–1.11). These results are noteworthy for 25 (3.3%) cases of torsade de pointes in the dofetilide group versus 0% in the placebo treated patients. Hospitalizations for heart failure were statistically lower ($p = .001$) in the dofetilide group (30%) than the placebo group (38%) [5, 6].

In DIAMOND-AF, total mortality was 44.6% in the dofetilide group, no different than the 45.1% mortality rate in the placebo group. DIAMOND-AF also demonstrated that heart failure hospitalizations were nonsignificantly lower ($p = .14$, HR = 0.69; CI = 0.51–0.93) in the dofetilide group (29.3%) versus the placebo group (39.7%) and in all cases hospitalizations were also lower in the dofetilide group ($p = .003$) [5, 6].

The ALIVE trial randomized patients to placebo versus 75–100 mg/day of azimilide. Key inclusion criteria included acute myocardial infarction within 6–21 days; ejection fraction 15–35%; and abnormal heart rate variability of $\leq 20$ U. Azimilide also appears to be safe to use in the post-myocardial infarction population since the demonstrated hazard ratio of mortality was 1.0 compared with placebo. In ALIVE, time to the development of atrial fibrillation was longer ($p = .04$) in the azimilide group [31].

The role of dronedarone in treating patients with left ventricular dysfunction will depend on the final results of the ANDROMEDA trial, which will have a combined primary endpoint of mortality and hospital admissions secondary to heart failure. The ANDROMEDA trial, studying the safety of dronedarone in patients with left ventricular dysfunction, was prematurely terminated due to statistically nonsignificant higher mortality in the antiarrhythmic treated arm of the study [27]. Further analyses of these data will determine if dronedarone will be safe to use in this patient population.

**Genetics and genomics**

With the mapping of the human genome, genetics and genomics are becoming increasingly well understood for their role in affecting drug metabolism. Humans are endowed with polymorphisms, relatively common expressions of specific patterns in genetic code [42]. For example, some individuals carry a genetically coded inability to metabolize compounds via the cytochrome P450 system. This genomic variation, or polymorphism, is significant in considering medications, such as amiodarone, that require this system for adequate metabolism and avoidance of lethal toxicities. As a poignant example, erythromycin, the commonly used antibiotic, may cause prolongation of the QT interval with resultant development of torsade de pointes when ingested by an individual who is also taking amiodarone [43].

In addition to effecting toxic drug responses, genomic variations may also affect therapeutic efficacy. This phenomenon is becoming understood with respect to several analgesic preparations, and is extended to other classes of drugs including antiarrhythmic agents. The pharmaceutical industry is on the cusp of understanding how to modify various preparations in an effort to tailor the effect to an individual’s specific genetic needs [26, 42].

**Regulatory issues**

The development of drugs for arrhythmia indications is tricky business. Evidence of efficacy constitutes a significant hurdle, but demonstration of safety is even more daunting. Multiple studies, which prove that the drug can be utilized safely in the appropriate patient population with an acceptable risk, are required for registration. In addition, studies must be designed and executed in such a way so as to extract relevant and useful information about how to dose the drug and how to monitor patients. There must be a safety experience that is at least large enough to identify adverse effects that will occur with moderate frequency when the drug is available for general use, recognizing that rare side effects may not be recognized even within a robust dataset.

The first step in antiarrhythmic drug development is a careful characterization of the drug’s electrophysiologic effects. This includes a full description of its activity at specific ion channels and other cell targets, followed by *in vivo* experiments to demonstrate a composite electropharmacologic profile. One would prefer to see how the drug performs in well-validated arrhythmia models as an index of its potential clinical utility, though the predictive value of animal models of this kind may be low.
It may at least be possible in this early phase to define an electrical effect as a function of blood or tissue concentration to begin to approximate a target dose in humans. It is important to understand that an excellent understanding of the drug’s actions in this early phase will facilitate development in later phases, both with regard to issues of efficacy and safety.

Most antiarrhythmic drugs have complex pharmacology. This fact places a significant burden on early phase clinical development to understand basic pharmacological principles, such as distribution, metabolism, and elimination. Such factors are especially important in this realm. Because most antiarrhythmic drugs have a relatively narrow toxic/therapeutic ratio, factors that increase or decrease drug exposure are very important to the drug’s safe use. The electrocardiogram provides a crude tool to delineate electrophysiologic effects in some, but not all, cases. For example, it is not possible to observe changes in atrial refractoriness on the surface electrocardiogram, greatly complicating the evaluation of atrial specific agents. It may be necessary to conduct invasive electrophysiologic studies to define the drug’s activity in these cases, or utilize previously implanted pacemakers for this purpose. With opportunities to develop and study parenteral as well as oral formulations, decisions about the best methods of drug delivery should be made in early stages so as to properly focus the overall development program.

The next phases of development are considered the critical path, for it is here that so-called “proof of concept” studies are devised and carried out. At this point, patients without significant comorbidities are exposed to the investigational drug at various doses with the goal of demonstrating activity in the target arrhythmia. Investigators face a fine line between recruiting too few patients in the interest of economy, and spending too much on what might not necessarily be a pivotal trial. Nevertheless, this phase of study must clearly demonstrate efficacy and safety at achievable drug concentrations to permit the program to go forward, and to generate the correct hypotheses for late-phase clinical development.

It is in this intermediary phase of development that many other things must be learned about the new agent. In addition to defining a useful dose range, drug and device interactions must be defined. Particular attention must focus on those agents, such as anticoagulants, that are used frequently in patients with cardiac arrhythmia. Safety issues must be more carefully defined to allow for proper focusing of later clinical development. Although longitudinal studies will follow, adequate exposures to define intermediate term tolerability are necessary to set the stage for those very important longer-term safety trials. It is in this stage of development that special populations, such as those with organ impairment or the elderly, may be studied to determine entry criteria for the pivotal trial experience.

Pivotal efficacy studies are tailored to study critical issues related to the putative safety and efficacy of the new chemical entity. It is important that these studies are designed creatively to maximize the yield of information and to allow for proper drug labeling if successful. Studies can be conducted for various indications. In the case of atrial fibrillation, the drug can be considered for conversion to, or maintenance of, sinus rhythm or both. Placebo-controlled studies may be used as long as the patient is protected against the complications of inordinately high heart rates and thromboembolic events. Studies of sufficient duration (at least 12 months) are necessary to assess chronic tolerance. The relevant patient population must be studied here, as inclusion and exclusion criteria for the trials will be used for product labeling.

The development of drugs for ventricular arrhythmia indications is much more difficult and challenging. In previous times, suppression of premature ventricular depolarizations or prevention of inducible ventricular tachycardia in the electrophysiology laboratory were accepted as surrogates of efficacy. This is no longer the case; direct suppression and/or prevention of sustained ventricular tachycardia/fibrillation (VT/VF) are now the gold standard. For parenteral compounds, the intravenous amiodarone development program sets the standard [44, 45]. In this program, patients with frequently recurring VT/VF, refractory to conventional agents, were treated in dose ranging and positive comparator studies. Prevention of recurrent sustained arrhythmia was the primary endpoint. Approval for prophylaxis of high-risk patients, such as those after myocardial infarction,
is a lofty goal that is unrealistic, short of conducting mega-trials, because of low event rates.

Oral drug development for ventricular arrhythmias may be less complex. Although prevention of inducibility can be used to “prove the concept,” a controlled study to assess sustained arrhythmia recurrence is expected for approval. The most expeditious and practical way to accomplish this is with placebo-controlled studies in patients with implantable defibrillators and a minimum baseline shock frequency. This also avoids the need for a positive comparator that greatly increases the complexity of blinding and multiplies the number of patients that need to be enrolled.

Longer-term safety data are desirable in the development of any antiarrhythmic agent, and particularly in patients with structural heart disease whose substrate and organ function can change over time. Although this may not be possible within the context of controlled trials, long-term extension and “compassionate use” experience may help to provide needed information. These experiences may also serve to increase the size of the overall database for regulatory review, expected to be in excess of 2000 patients for most drugs.

Approval of a potent antiarrhythmic drug in the modern era does not necessarily translate into widespread use. Restrictions may be placed on distribution and access based on safety issues. Dofetilide provides the most recent example in which concerns about adjustments for altered renal function and risk of torsade de pointes prompted the FDA to impose requirements for physician registration and central pharmacy distribution. One would expect that such measures would not be necessary for drugs devoid of major safety concerns. Nevertheless, we expect that there will be increasing emphasis on techniques of postmarketing surveillance so that major but unexpected safety issues can be identified and addressed as soon as possible in the drug’s real-world experience.

It is reasonable to assume that drugs with novel mechanisms of action and with new indications will be developed in years to come. For example, with the proliferation of ablation techniques and their wider application, drugs can be developed and studied that are intended to suppress the arrhythmias that develop postablation. We have already seen drugs come forward that have targets other than conventional ion channels. As this work progresses, it will be important to remain open to creative protocols and to innovative development programs that will facilitate bringing these new products to clinical use expeditiously. No matter how this is done, it is of paramount importance to emphasize the most fundamental treatment principle, that the benefit of the drug must clearly exceed the risk. Clinical trials preserve the ability to precisely determine the magnitude of both sides of the therapeutic equation.

Conclusion

The search for effective, safe antiarrhythmic drugs continues with constant development activities on the part of pharmaceutical corporations. Efforts to modify existing structures promise enhanced safety with established mechanisms of action. In particular, efforts to modify amiodarone to create a safe and well-tolerated Class III antiarrhythmic drug are driving the development of several new compounds currently in clinical trials and regulatory examination. The investigation and development of drugs with novel mechanisms of action holds the potential reward of enhanced antiarrhythmic efficacy, particularly for the control of atrial fibrillation and, to a lesser extent, ventricular tachycardia.

The continually evolving understanding of the role played by genetics in drug metabolism will yield additional improvements in antiarrhythmic drug efficacy in the future. Hopefully, today’s early stages of genomics research will result in the development of drugs that can play a role in an antiarrhythmic regimen specifically designed to fit a patient’s genetic structure, enhancing not only efficacy, but significantly, safety as well.

References


27 Hohnloser SH, Dorian P, Straub M, Beckmann K, Kowey P. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial


Atrial fibrillation (AF) is associated with alterations in atrial size (enlargement), mechanics (reduced emptying characteristics and flow velocity), and prothrombotic hemochemical changes [1–10]. These modifications can result in stagnant atrial flow (especially in the appendage) and in alterations of several coagulation factors, fibrinolytic balance, nitric oxide secretion in the atria and the consequences of its reduction, and, to a lesser extent, platelet derived factors [1–10]. These effects raise the probability of atrial clot formation. Some of the hemochemical alterations that contribute to thromboembolic risk in AF are aspirin sensitive, such as P-selectin, (β-thromboglobulin, and platelet factor 4. Most, however, are not affected by aspirin, but their procoagulant actions can be reduced by warfarin, including, for example, factor VII, fibrinogen, D-dimer, prothrombin fragment 1.2, thrombin–antithrombin complex, altered fibrinolytic balance, increased superoxides (which degrade NO).

Mobile atrial thrombi may produce systemic embolization, resulting in end-organ dysfunctional events, such as stroke, visual loss, coronary occlusion, and bowel or limb necrosis. Risk for embolism in AF is independent of whether or not rate-related, irregularity-related, or other AF-related symptoms are present. Importantly, it has been recently appreciated that risk for embolism in the AF patient at risk may persist, in at least some patients, even if (and after) sinus rhythm has been restored, as was clearly demonstrated in trials, such as RACE and AFFIRM [11, 12]. Possible explanations for persistent risk include (Table 2.1) recurrent episodes of unappreciated asymptomatic AF, incomplete reverse atrial remodeling in NSR with residual flow impairment, and negative atrial inotropic effects of drug or ablative therapy. Atrial size 6 months after cardioversion, for example, is reduced if NSR is maintained as compared with that seen if AF recurs, but atrial size is not necessarily reduced to normal [13]. Moreover, the longer AF persists prior to cardioversion, the slower and less extensive is the reduction in atrial size following cardioversion [14]. Atrial contractility may also be reduced by negative notropic effects of antiarrhythmic agents being used to maintain sinus rhythm [15]. Similarly, there data exists to suggest that following catheter ablative procedures for the cure of AF, significant atrial enlargement and mechanical dysfunction can persist or develop? [16].

Multiple clinical trials have increased our knowledge base about the risk factors for AF-associated thrombus formation and emboli, and about optimal preventative therapies [17–20]. The incidence of embolic risk has been shown to be low (<1–2%/year) in patients with AF who are >65 years of age and have no associated high-risk markers while the incidence is higher in patients with certain identified risk factors, including in most series.

Table 2.1 Possible reasons for persistent thromboembolic risk following restoration of sinus rhythm in patients with AF.

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic (undetected) AF recurrences</td>
</tr>
<tr>
<td>Persistence of atrial enlargement and/or atrial dysfunction (absence of complete reverse remodeling)</td>
</tr>
<tr>
<td>Atrial dysfunction induced by pharmacotherapy</td>
</tr>
<tr>
<td>Atrial dysfunction resulting from ablative injury</td>
</tr>
<tr>
<td>Concomitant, nonatrial sources of emboli</td>
</tr>
</tbody>
</table>