Hopes and Disappointments with Antiarrhythmic Drugs

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**Abstract**

Ventricular arrhythmias such as sustained ventricular tachycardia and ventricular fibrillation account for two thirds of sudden cardiac deaths. Most ventricular tachyarrhythmias have well understood mechanisms such that it is theoretically possible to conceive of an antiarrhythmic drug-based intervention that would prevent arrhythmias that cause sudden cardiac death. Pharmaceutical agents which interfere with ion channel activity are known as antiarrhythmic drugs.

Acute experiments showing antiarrhythmic effects in the basic science laboratory have often not translated into clinical effectiveness. Evidence of efficacy has been difficult to assess and appears to be sparse. However, proarrhythmia is common and complicates assessment of the potential value of antiarrhythmic drugs. Important studies such as the Cardiac Arrhythmia Suppression Trial and the Survival With ORal D-sotalol study confirmed that antiarrhythmic drugs could kill rather than cure patients at risk of sudden cardiac death, and spelled the death knell for widespread use of antiarrhythmic drugs for the primary prevention of sudden cardia death in high risk patients.

However, when the implantable cardioverter defibrillator was introduced into clinical practice the situation changed - a drug that generally supressed ventricular tachyarrhythmias was needed, but safety concerns were alleviated because the ICD could reverse proarrhythmic adverse effects. The accent changed towards the development of drugs that might reduce the prevalence or the symptomatic burden of ventricular arrhythmias. Similarly, antiarrhythmic drug development progressed towards finding an agent that might reduce symptoms associated with recurrent atrial fibrillation rather than for the treatment of ventricular arrhythmia.

In recent times the goal of antiarrhythmic therapy has changed again. No longer is it thought necessary to develop blockbuster therapies, but to concentrate on the specific mechanisms of cardiac arrhythmias in individuals and to develop therapies that can be specifically engineered to help carefully defined phenotypes. Personalised or precision medicine is now guiding the development of antiarrhythmics agents that are directed to very specific targets and arrhythmia mechanisms and are without off-target effects that may compromise their efficacy.

The value of antiarrhythmic medical therapy has raised great hopes which have been followed by disillusionment. Now hopes and needs are rising again, and we are better prepared to make this therapy successful. If we understand the arrhythmias we may be able to design effective and uncomplicated therapy.

Life-threatening ventricular arrhythmias such as sustained ventricular tachycardia and ventricular fibrillation are responsible for two thirds of sudden cardiac deaths. Since many ventricular tachyarrhythmias have well understood mechanisms it is theoretically possible to conceive of an antiarrhythmic drug-based intervention that would annul the arrhythmia and prevent sudden death. Furthermore, because most arrhythmogenesis are related to increased automaticity, conduction block, inhomogeneous repolarisation, re-entry, reflection and other electrophysiological abnormalities, drugs that directly affect cellular and tissue electrophysiology (antiarrhythmic agents) should offer an opportunity to prevent, terminate, slow or otherwise counter cardiac arrhythmia.

Traditionally antiarrhythmic agents are classified according to their effect on the action potential - the Vaughan Williams’ classification[[1]](#endnote-1). Class I drugs impair the fast sodium current and reduce myocardial conduction velocity with variable effects on repolarising currents (class IA lengthening the action potential duration (e.g, disopyramide and procainamide, class IB (e.g., lidocaine and mexiletine) shortening the action potential, and class IC (e.g., flecainide and propafenone) having little effect on repolarisation). Class III agents predominantly delay repolarisation without affecting the inward sodium current and conduction velocity. Sotalol, dronedarone and amiodarone are the main drugs in this category. Classes II, IV and V are not usually thought of as specific antiarrhythmic agents although all (Class II: beta blockers, Class IV: non-dihydropyridine calcium channel blockers, and Class V: glycosides) impair conduction in tissue with decremental conduction velocities such as the AV node. There have been other schemes suggested by which to classify antiarrhythmics, notably the Sicilian Gambit[[2]](#endnote-2), which in trying to bring order to chaos[[3]](#endnote-3) unfortunately proved to be clinically unwieldy and was never fully accepted.

Substantial research, mostly between the 1960’s and the 1980’s, demonstrated that antiarrhythmic agents had value in supressing symptomatic ventricular arrhythmias. However, it soon became apparent that antiarrhythmic drugs could kill rather than cure the patient. This should not have been a surprise since proarrhythmic effects of antiarrhythmic drugs had long been recognised, for example quinidine syncope had been documented two decades earlier to be due to drug-induced ventricular tachyarrhythmia[[4]](#endnote-4). Nevertheless, it took the Cardiac Arrhythmia Suppression Trial (CAST)[[5]](#endnote-5) published in 1989 (Vaughan Williams class 1 agents: flecainide and encainide, later moricizine), closely followed by the similarly adverse Survival with Oral d-Sotalol (SWORD) trial[[6]](#endnote-6) (Vaughan Williams Class III agents) to bring home the realisation that off-target electrophysiological effects of antiarrhythmic drugs might outweigh any positive effect related to arrhythmia suppression. A possible exception to this general rule appeared to be amiodarone[[7]](#endnote-7), which continued to be used in both primary and secondary prevention of sudden cardiac death in high risk populations and was shown by 1995 in several primary prevention studies[[8]](#endnote-8) and metanalyses[[9]](#endnote-9),[[10]](#endnote-10) to be life-saving.

However, during the early 1980’s therapy was being implemented with the implantable cardioverter defibrillator (ICD) and in 1997 the Amiodarone versus Implantable Defibrillator (AVID) trial was published showing that the ICD was far better than amiodarone for secondary prevention for patients who had already suffered a cardiac arrest, haemodynamically unstable ventricular or syncope related to ventricular arrhythmias[[11]](#endnote-11). This was confirmed within several years by the Canadian Implantable Defibrillator Study (CIDS)[[12]](#endnote-12) and the Cardiac Arrest Study Hamburg (CASH)[[13]](#endnote-13) trials. The Multi-center Autonomic Defibrillator Implantation Trial MADIT II[[14]](#endnote-14) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[[15]](#endnote-15) also established the value of ICD treatment over that of antiarrhythmic therapy for primary prevention in patients with poor left ventricular function related to both ischemic heart disease and dilated non-ischemic cardiomyopathy. By 2006 international guidelines firmly recommended ICD therapy over treatment with amiodarone for both primary and secondary prevention[[16]](#endnote-16). However, ICD therapy was expensive, with high up-front costs, and even guidelines in 2006 gave the option of reverting to less effective treatment with amiodarone when an ICD was not available. This option persists to this day[[17]](#endnote-17). Furthermore, results from old ICD studies are increasingly challenged because of the improvements in general management of myocardial infarction and heart failure. Recent studies such as the Defibrillator Implantation in Patients with Non-ischemic Systolic Heart Failure (DANISH) trial[[18]](#endnote-18) in patients with non-ischemic cardiomyopathy, a classic class I indication for an ICD, have given impetus to a more widespread assessment of the ICD versus antiarrhythmic therapy and for a search for novel methods of stratifying patients for their risk of sudden cardiac death.

The development of class I and Class III drugs for the treatment of ventricular arrhythmias / sudden cardiac death came to a complete halt in the 1990s - only Azimilide was continued in a development programme that might lead to its use as a ventricular antiarrhythmic drug. However, in 2004 it as reported that the AzimiLide post Infarct surVival Evaluation (ALIVE) trial in post myocardial infarction patients was negative[[19]](#endnote-19).

Despite these set-backs with attempts use antiarrhythmics for the prevention of sudden cardiac death and the recurrence of ventricular tachyarrhythmias an important new use for antiarrhythmic drugs was stimulating new research; a great interest was being taken in attempts to develop drugs that might safely suppress symptomatic recurrences of atrial fibrillation. Several new amiodarone analogues, such as budiodarone[[20]](#endnote-20) and dronedarone[[21]](#endnote-21) were developed, but concerns naturally persisted about ventricular proarrhythmia. Although dronedarone was approved for the management of recurrent atrial fibrillation, very negative results in patients with left ventricular impairment or permanent atrial fibrillation lead to it being little used.

A new tack was then taken, was it possible to develop drugs that were targeted much more at ion channels that were primarily located in the atrium? Such drugs were designed and investigated, most were ineffective – poor benefit-risk ratio (tedisamil)[[22]](#endnote-22), not sufficiently atrial specific (ibutilide)[[23]](#endnote-23) or valuable only in an intravenous formulation (vernakalant)[[24]](#endnote-24). In any case, pulmonary vein isolation for the suppression of atrial fibrillation recurrences had been introduced in 1998 and investigators were moving ahead with this radically new form of therapy – there was little incentive for pharma companies to continue to develop antiarrhythmic drugs.

Neither the ICD nor pulmonary vein isolation are completely successful therapies, now there is a clamour for adjuvant therapies. Amiodarone is often valuable in combination with left atrial ablation for atrial fibrillation, or together with an ICD for the treatment of symptomatic recurrences of ventricular arrhythmias. In recent years, only three drugs have been systematically investigated for the suppression of ventricular tachycardias and ICD interventions in patients fitted with ICDs for secondary prevention of sudden cardiac death. Studies with ranolazine, a late sodium current inhibitor initially introduced for the management of chronic stable angina[[25]](#endnote-25), eleclazine[[26]](#endnote-26), a highly specific late sodium current inhibitor and azimilide[[27]](#endnote-27) an iKr and IKs repolarising current inhibitor. The study with eleclazine was discontinued prematurely because of futility[[28]](#endnote-28), whilst the trial with ranolazine continues (RAID – Ranolazine And the Implantable DefibrillaTor)[[29]](#endnote-29), but results are not expected for a year or so. The SHIELD 2[[30]](#endnote-30) study with azimilide had only just got started when it was inexplicably stopped for commercial reasons. Interestingly, when the results of the terminated trial were published the point estimates were trending in the direction of efficacy. Unfortunately, there seem to be no plans to develop azimilide further.

A number of drugs have been developed for the management of atrial fibrillation that might also have been developed for treating ventricular arrhythmias, but for the clinical and commercial imperative to ignore ventricular antiarrhythmic approaches in favour of finding an effective agent to reduce the recurrence and complications of atrial fibrillation. Two analogues of amiodarone deserve particular mention, dronedarone and budiodarone. Although there seems to be no interest in pursuing the further investigation of dronedarone, budiodarone may be developed along these lines.

Ventricular tachycardia in patients with structurally normal hearts can be safely managed with antiarrhythmic agents. Class IC agents are widely and effectively used to manage right ventricular outflow tract tachycardias, the origin of many of these tachycardias can also be successfully dealt with by a single ablation procedure, this form of therapy is often preferred. The situation with left sided outflow tachycardia, again predominantly occurring in patients with otherwise structurally normal hearts are not so easy to manage with ablation because it may be difficult to reach the focus f the arrhythmia to allow successful ablation. For these patients class Ic antiarrhythmic agents are recommended[[31]](#endnote-31).

More than this, as we approach the era of personalised / precision medicine, the concept of blockbuster therapy, which achieves only a net population benefit, whilst causing harm to some, must give way to more carefully targeted treatment which specifically corrects underlying disorders rather than merely compensates for one abnormality by creating another. Selective therapy has been extensively explored for the management of atrial fibrillation. The idea was to choose agents that were active on ion channels that were largely confined to the atrium. Thus electrophysiological changes induced by drugs would not affect the ventricles and would not encourage ventricular proarrhythmia. But this approach was not aimed at specific mechanism of the arrhythmia under treatment. So many arrhythmias, especially atrial fibrillation remain clouded in uncertainty about the particular mechanism that is responsible for the arrhythmia, and we are therefore unable to be precise about the most direct and safe therapeutic agent to suppress the arrhythmia.

However, the knowledge base is progressively enlarging. We can measure the presence of normal or abnormal receptor function or ion channel activity. We understand that certain genotypes result in specific phenotypes, we understand how some drugs work better or worse in specific genotypic or epigenetic circumstances. Thus, we are not far from being able to approach the ideals of precision or personalised medicine.

A very good example of a precision approach to antiarrhythmic therapy can be found in the treatment of long QT syndrome. In long QT3 there is a genetically mediated gain of function of the slow sodium current leading to prolongation of the action potential and prolongation of the QT interval. Polymorphic ventricular tachycardia and sudden cardiac death may result. A variety of drugs inhibit the delayed (late or slow) sodium current and can therefore reverse the effects of the genetic abnormality. Some of these drugs also have “off-target” effects such as block of the fast or peak sodium current (flecainide or mexiletine)[[32]](#endnote-32) or the rapid inward rectifier potassium current iKr (ranolazine)[[33]](#endnote-33). Others have only isolated effects on the slow sodium current (eleclazine)[[34]](#endnote-34), and this represents the ideal agent for the treatment of long QT3. It is also interesting to note that eleclazine or ranolazine might also have a beneficial, but more non-specific effect on arrhythmias related to other causes of the long QT syndrome less specifically by stabilising the cardiac ryanodine receptor and suppression of afterdepolarisation responsible for torsades de pointes[[35]](#endnote-35). Other specific pathologies have also been identified in monogenic disorders, such as the Brugada syndrome, where defective trafficking can be restored with antiarrhythmic agents for example mexiletine[[36]](#endnote-36).

**Conclusion**

Although the mainstay of effective therapies for the ventricular tachyarrhythmias responsible for sudden cardiac death are nowadays the implantable cardioverter-defibrillator and ventricular ablation, it is well appreciated that biochemical, structural, neurohormonal and electrophysiological abnormalities underlie the instability of the ventricular rhythm. It seems unlikely that therapies that destroy more cardiac tissue or simply intervene to convert a sustained ventricular arrhythmia are the best approaches to restore sinus rhythm or prevent ventricular arrhythmias.

The ideal approach would to be to prevent abnormalities that eventually lead to electrophysiological changes that support sustained and potentially fatal ventricular arrhythmias. Failing that, adjustment of the electrophysiological milieu to prevent ventricular arrhythmogenesis seems intrinsically plausible, although dogged by off-target and unintentional on-target effects that have not allowed the development of blockbuster, or even more specific antiarrhythmic agents.

Increasingly the genetic and molecular basis for electrophysiological disturbances are becoming more understood and more easily recognisable. It is, therefore, perhaps possible to begin to design patient-specific pharmacological agents that will specifically correct or counteract abnormalities without producing unintentional adverse effects that limit the efficacy and safety of antiarrhythmic drugs. This new precision medicine approach is only just beginning but adds more hope and dispels disillusionment with the use of antiarrhythmic drug for the management of cardiac arrhythmias.

References

1. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol. 1984 Apr;24(4):129-47. Review. PubMed PMID: 6144698. [↑](#endnote-ref-1)
2. The 'Sicilian Gambit'. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Eur Heart J. 1991 Oct;12(10):1112-31. Review. PubMed PMID: 1723682. [↑](#endnote-ref-2)
3. Katritsis D, Camm AJ. Antiarrhythmic drug classifications and the clinician: a gambit in the land of chaos. Clin Cardiol. 1994 Mar;17(3):142-8. Review. PubMed PMID: 7513270. [↑](#endnote-ref-3)
4. Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhyhtmias. Circulation. 1964 Jul;30:17-26. PubMed PMID: 14197832. [↑](#endnote-ref-4)
5. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med. 1989 Aug 10;321(6):406-12. PubMed PMID: 2473403. [↑](#endnote-ref-5)
6. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet. 1996 Jul 6;348(9019):7-12. Erratum in: Lancet 1996 Aug 10;348(9024):416. PubMed PMID: 8691967. [↑](#endnote-ref-6)
7. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). The CASCADE Investigators. Am J Cardiol. 1993 Aug 1;72(3):280-7. PubMed PMID: 8342505. [↑](#endnote-ref-7)
8. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet. 1997 Mar 8;349(9053):675-82. Erratum in: Lancet 1997 Jun 14;349(9067):1776. PubMed PMID: 9078198. [↑](#endnote-ref-8)
9. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. Lancet. 1997 Nov 15;350(9089):1417-24. PubMed PMID: 9371164. [↑](#endnote-ref-9)
10. Boutitie F, Boissel JP, Connolly SJ, Camm AJ, Cairns JA, Julian DG, Gent M, Janse MJ, Dorian P, Frangin G. Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. The EMIAT and CAMIAT Investigators. Circulation. 1999 May 4;99(17):2268-75. PubMed PMID: 10226092. [↑](#endnote-ref-10)
11. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med. 1997 Nov 27;337(22):1576-83. PubMed PMID: 9411221. [↑](#endnote-ref-11)
12. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000 Mar 21;101(11):1297-302. PubMed PMID: 10725290. [↑](#endnote-ref-12)
13. Kuck KH, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000 Aug 15;102(7):748-54. PubMed PMID: 10942742. [↑](#endnote-ref-13)
14. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators.. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002 Mar 21;346(12):877-83. PubMed PMID: 11907286. [↑](#endnote-ref-14)
15. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators.. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005 Jan 20;352(3):225-37. PubMed PMID: 15659722. [↑](#endnote-ref-15)
16. European Heart Rhythm Association.; Heart Rhythm Society., Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; American College of Cardiology.; American Heart Association Task Force.; European Society of Cardiology Committee for Practice Guidelines.. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006 Sep 5;48(5):e247-346. PubMed PMID: 16949478. [↑](#endnote-ref-16)
17. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace. 2015 Nov;17(11):1601-87. doi: 10.1093/europace/euv319. Review. PubMed PMID: 26318695. [↑](#endnote-ref-17)
18. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016 Sep 29;375(13):1221-30. doi: 10.1056/NEJMoa1608029. PubMed PMID: 27571011. [↑](#endnote-ref-18)
19. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, Karam R, Sonnenblick EH, Brum JM; AzimiLide post Infarct surVival Evaluation (ALIVE) Investigators.. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation. 2004 Mar 2;109(8):990-6. PubMed PMID: 14967728. [↑](#endnote-ref-19)
20. Ezekowitz MD, Nagarakanti R, Lubinski A, Bandman O, Canafax D, Ellis DJ, Milner PG, Ziola M, Thibault B, Hohnloser SH; PASCAL Investigators.. A randomized trial of budiodarone in paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2012 Jun;34(1):1-9. doi: 10.1007/s10840-011-9636-3. PubMed PMID: 22205496. [↑](#endnote-ref-20)
21. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; ATHENA Investigators.. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009 Feb 12;360(7):668-78. doi: 10.1056/NEJMoa0803778. Erratum in: N Engl J Med. 2009 Jun 4;360(23):2487. N Engl J Med. 2011 Apr 14;364(15):1481. PubMed PMID: 19213680. [↑](#endnote-ref-21)
22. Hohnloser SH, Dorian P, Straub M, Beckmann K, Kowey P. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. J Am Coll Cardiol. 2004 Jul 7;44(1):99-104. PubMed PMID: 15234416. [↑](#endnote-ref-22)
23. Jin Q, Zhou J, Zhang N, Lin CJ, Pang Y, Gu G, Shen WF, Wu LQ. Ibutilide decreases defibrillation threshold by the reduction of activation pattern complexity during ventricular fibrillation in canine hearts. Chin Med J (Engl). 2012 Aug;125(15):2701-7. PubMed PMID: 22931978. [↑](#endnote-ref-23)
24. Frommeyer G, Ellermann C, Dechering DG, Kochhäuser S, Bögeholz N, Güner F, Leitz P, Pott C, Eckardt L. Ranolazine and Vernakalant Prevent Ventricular Arrhythmias in an Experimental Whole-Heart Model of Short QT Syndrome. J Cardiovasc Electrophysiol. 2016 Oct;27(10):1214-1219. doi: 10.1111/jce.13029. PubMed PMID: 27283775. [↑](#endnote-ref-24)
25. Karwatowska-Prokopczuk E, Wang W, Cheng ML, Zeng D, Schwartz PJ, Belardinelli L. The risk of sudden cardiac death in patients with non-ST elevation acute coronary syndrome and prolonged QTc interval: effect of ranolazine. Europace. 2013 Mar;15(3):429-36. doi: 10.1093/europace/eus400. PubMed PMID: 23258816. [↑](#endnote-ref-25)
26. Bacic D, Carneiro JS, Bento AA, Nearing BD, Rajamani S, Belardinelli L, Verrier RL. Eleclazine, an inhibitor of the cardiac late sodium current, is superior to flecainide in suppressing catecholamine-induced ventricular tachycardia and T-wave alternans in an intact porcine model. Heart Rhythm. 2017 Mar;14(3):448-454. doi: 10.1016/j.hrthm.2016.10.021. PubMed PMID: 27777148. [↑](#endnote-ref-26)
27. Robinson VM, Bharucha DB, Mahaffey KW, Dorian P, Kowey PR; SHIELD-2 Investigators. Results of a curtailed randomized controlled trial, evaluating the efficacy and safety of azimilide in patients with implantable

cardioverter-defibrillators: The SHIELD-2 trial. Am Heart J. 2017 Mar;185:43-51. doi: 10.1016/j.ahj.2016.10.025. PubMed PMID: 28267474. [↑](#endnote-ref-27)
28. <http://www.pharmalive.com/gilead-looking-even-weaker-on-the-rd-front-as-it-racks-up-some-more-clinical-failures-in-q3-report/> - accessed 1st March 2017 [↑](#endnote-ref-28)
29. RAID trial: https://clinicaltrials.gov/ct2/show/NCT01215253 [↑](#endnote-ref-29)
30. Robinson VM, Bharucha DB, Mahaffey KW, Dorian P, Kowey PR; SHIELD-2 Investigators. Results of a curtailed randomized controlled trial, evaluating the efficacy and safety of azimilide in patients with implantable cardioverter-defibrillators: The SHIELD-2 trial. Am Heart J. 2017 Mar;185:43-51. doi: 10.1016/j.ahj.2016.10.025. PubMed PMID: 28267474. [↑](#endnote-ref-30)
31. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016 Nov;18(11):1609-1678. PubMed PMID: 27567465. [↑](#endnote-ref-31)
32. Moss AJ, Windle JR, Hall WJ, Zareba W, Robinson JL, McNitt S, Severski P, Rosero S, Daubert JP, Qi M, Cieciorka M, Manalan AS. Safety and efficacy of flecainide in subjects with Long QT-3 syndrome (DeltaKPQ mutation): a randomized, double-blind, placebo-controlled clinical trial. Ann Noninvasive Electrocardiol. 2005 Oct;10(4 Suppl):59-66. PubMed PMID: 16274417. [↑](#endnote-ref-32)
33. Moss AJ, Zareba W, Schwarz KQ, Rosero S, McNitt S, Robinson JL. Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long-QT syndrome. J Cardiovasc Electrophysiol. 2008 Dec;19(12):1289-93. doi: 10.1111/j.1540-8167.2008.01246.x. PubMed PMID: 18662191; PubMed Central PMCID: PMC2614458. [↑](#endnote-ref-33)
34. Zablocki JA, Elzein E, Li X, Koltun DO, Parkhill EQ, Kobayashi T, Martinez R, Corkey B, Jiang H, Perry T, Kalla R, Notte GT, Saunders O, Graupe M, Lu Y, Venkataramani C, Guerrero J, Perry J, Osier M, Strickley R, Liu G, Wang WQ, Hu L, Li XJ, El-Bizri N, Hirakawa R, Kahlig K, Xie C, Li CH, Dhalla AK, Rajamani S, Mollova N, Soohoo D, Lepist EI, Murray B, Rhodes G, Belardinelli L, Desai MC. Discovery of Dihydrobenzoxazepinone (GS-6615) Late Sodium Current Inhibitor (Late I(Na)i), a Phase II Agent with Demonstrated Preclinical Anti-Ischemic and Antiarrhythmic Properties. J Med Chem. 2016 Oct 3. [Epub ahead of print] PubMed PMID: 27690427. [↑](#endnote-ref-34)
35. Parikh A, Mantravadi R, Kozhevnikov D, Roche MA, Ye Y, Owen LJ, Puglisi JL, Abramson JJ, Salama G. Ranolazine stabilizes cardiac ryanodine receptors: a novel mechanism for the suppression of early afterdepolarization and torsades de pointes in long QT type 2. Heart Rhythm. 2012 Jun;9(6):953-60. doi: 10.1016/j.hrthm.2012.01.010. PubMed PMID: 22245792; PubMed Central PMCID: PMC3335957. [↑](#endnote-ref-35)
36. Moreau A, Keller DI, Huang H, Fressart V, Schmied C, Timour Q, Chahine M. Mexiletine differentially restores the trafficking defects caused by two Brugada syndrome mutations. Front Pharmacol. 2012 Apr 20;3:62. doi: 10.3389/fphar.2012.00062. PubMed PMID: 22529811; PubMed Central PMCID: PMC3330751. [↑](#endnote-ref-36)