While this summary is intended to focus on the clinical aspects of the use of antiarrhythmic drugs, any meaningful discussion of antiarrhythmic drugs first requires a brief review of the basic mechanisms by which arrhythmias are generated. If you find the cellular electrophysiology of arrhythmias to be painfully dull, or if it elicits that same cold sweat I recall when learning it in medical school, by all means skip to the section on “clinical uses of antiarrhythmics!”

Essentially, all arrhythmias result from either an abnormality of impulse generation, an abnormality of impulse conduction, or a combination of the two. Abnormalities of impulse generation generally fall into one of two categories; either abnormal automaticity or “triggered activity”. Abnormal automaticity is thought to occur due to reduced resting membrane potential (more positive than normal) causing the membrane to be closer to the threshold for generating an action potential. Triggered activity, also known as after depolarizations, occur either during phase II or III of the action potential (early after depolarizations) or during phase IV of the action potential (delayed after depolarizations). In both forms of triggered activity, the abnormal depolarization requires a preceding impulse (the triggering beat). Disorders of impulse conduction on the other hand, generally result from either conduction block or “reentry”. Reentry is the most common mechanism for all arrhythmias.

The ultimate goal of antiarrhythmic therapy is to maintain normal rhythm and conduction in the heart. Antiarrhythmic drugs generally either decrease or increase conduction velocity, alter the excitability of cardiac cells by changing the duration of the refractory period, or suppress abnormal automaticity. All antiarrhythmic drugs alter membrane ion conduction which in turn alters the shape of the cardiac action potential.

Classes of Antiarrhythmic drugs

**Class I antiarrhythmics**
These drugs are generally considered sodium channel blockers. They act by reducing the rate of rise of phase 0 of the action potential and thus slow conduction. Because the class I-a antiarrhythmics also have some potassium channel blocking properties, they tend to increase action potential duration and the effective refractory period. The class I antiarrhythmics are further broken down by their potency. Class I-a are moderately potent sodium channel blockers which also increase action potential duration and the duration of the refractory period.

Class I-a antiarrhythmics include quinidine (Quinidex, Quinaglute), procainamide (Procan, Procanbid), and disopyramide (Norpace).

Class I-b antiarrhythmics
These drugs are relatively weak sodium channel blockers which do not reduce action potential duration and actually shorten the refractory period.

The class I-b antiarrhythmic drugs include agents such as lidocaine (Xylocaine), mexilitine (Mexitil) and tocainide (Tonocard).

Class I-c antiarrhythmics
are strong sodium channel blockers which have a pronounced effect on slowing conduction velocity, but have little impact on action potential duration or the effective refractory period.

The class I-c antiarrhythmic drugs include flecainide (Tambocor), propafenone (Rythmol), and moricizine (currently not available).

**Class II antiarrhythmics**
are essentially beta receptor blockers. These block sympathetic activity and reduce conduction velocity.

The B1 selective beta blockers include acebutolol, atenolol, bisoprolol, esmolol, and metoprolol.

Nonselective beta blockers include nadolol and propranolol.

Non B1 selective beta blockers with additional alpha blocking properties include carvedolol and labetalol.

**Class III antiarrhythmics**
primarily block potassium channels thereby delaying repolarization (phase III of the action potential). These drugs increase action potential duration and effective refractory.

Class III antiarrhythmic drugs include sotalol (Betapace), dofetilide (Tikosyn), amiodarone (Cordarone, Pacerone), ibutilide (Corvert), and bretylium.

**Class IV antiarrhythmics**
are essentially the calcium channel blockers. These block L-type calcium channels and are further categorized into dihydropyridines, which are selective smooth muscle dilators and include amlopidine, isradipine, felodipine, nicardipine, and nifedipine. These have very little effect on either AV or SA node conduction. Benzothiazepine calcium channel blockers, such as Diltiazem, and phenylalkylamines such as Verapamil, are most effective at slowing AV node conduction and to a lesser extent slow SA node conduction as well.
The class I-a antiarrhythmics, while amongst the oldest of the available antiarrhythmic drugs, have in many ways fallen out of favor. While they actually are quite effective in suppressing both atrial and ventricular ectopy, their toxicity is quite significant. All three agents in this class, quinidine, procainamide, and disopyramide are still clinically available but infrequently used. Quinidine is derived from the cinchona tree bark. It has a multitude of properties including being an active antimalarial, antipyretic and of course an antiarrhythmic. It has potent and common GI side effects including nausea, abdominal pain and diarrhea, and can also cause hemolytic anemia, thrombocytopenia and hepatitis. There is a known syndrome of acute CNS toxicity. However its most dreaded side effect is polymorphic ventricular tachycardia (Torsade De Pointe). “Quinidine syncope” is generally attributed to paroxysms of Torsade De Pointe and is often a marker of potentially disastrous complications. While quinidine had for many years been used to suppress symptomatic PVCs, the evidence mounted that doing so was largely unnecessary and potentially dangerous. It has fallen out of favor. It is also potent in suppressing atrial arrhythmias, but due to its toxicity and side effect profile, it is rarely used for that purpose.

Procainamide is excreted exclusively by the kidneys (unlike quinidine which is excreted via hepatic and renal roots), and has a very potent principal metabolite, N-acetyl procainamide, NAPA. This active metabolite is non-dialyzable and its accumulation in the setting of even modest renal insufficiency led procainamide to be a fairly dangerous drug, particularly in the acute care setting. One can measure quinidine levels in the blood and similarly, both procainamide and NAPA can be measured in patients being treated with this drug. Procainamide is available in intravenous and oral forms and is on rare occasion still used in certain settings. The most serious noncardiac side effect is agranulocytosis. A common and potentially dangerous side effect also includes a lupus-like syndrome with arthralgias, myalgias, pleuritis, pericarditis (polyserositis) and rash. The ANA commonly turns positive in this setting. For those readers old enough to recall, procainamide had been the mainstay of managing acute atrial and even ventricular arrhythmias for quite some time. Its intravenous administration during wide complex tachycardia also led to rapid termination if it was supraventricular in origin. Due to its toxicity and the fairly high risk of being proarrhythmic, procainamide is rarely used today.

Disopyramide is another class I-a antiarrhythmic which is still occasionally used, largely due to its side effects rather than its antiarrhythmic properties. Much like quinidine and procainamide, it is potent in suppressing ventricular ectopy, as well as atrial dysrythmias, specifically atrial fibrillation. Since there are better drugs with fewer side effects for these purposes, disopyramide is rarely used as the primary agent to manage dysrythmias. It is however, occasionally prescribed in order to take advantage of its other side effects which include it being a potent negative inotrope. It has been helpful in managing patients with hypertropic obstructive cardiomyopathy, as well as neurogenic (vasovagal) syncope. Since disopyramide is a potent vagolytic it can cause prominent symptoms of urinary retention, constipation and dry mouth. It also has the potential to be proarrhythmic and like procainamide and quinidine can cause widening of the QRS and the QT interval and increases the risk of Torsade De Pointe.

The class I-b antiarrhythmics, lidocaine, tocainide and mexilitine are used exclusively in the management of ventricular arrhythmias. Lidocaine is available only as an intravenous drug, while mexilitine is available orally. These drugs are hepatically cleared and have significant potential CNS toxicity including paresthesias, confusion, seizure and tremors. Blurred vision, nausea and vomiting are also common potential side effects. Lidocaine is still commonly used in the management of acute ventricular arrhythmias and mexilitine, is on rare occasion, still prescribed for long term management of symptomatic ventricular ectopy. It is occasionally used as adjunctive therapy in combination with other more potent antiarrhythmics in those refractory dysrythmias. Tocainide is another orally available class I-b agent which is occasionally used for suppression of ventricular arrhythmias. It carries the risk of blood dyscrasias, pulmonary fibrosis, as well as significant GI and neurologic symptoms and is uncommonly used today.

The class I-c antiarrhythmics have become a major part of the modern management of atrial arrhythmias. This class of drugs includes flecainide and propafenone. Moricizine has been taken off of the market due to the potential for proarrhythmia and increased risk of sudden cardiac death particularly in patients with prior myocardial injury (scar from ischemic heart disease). The class I-c antiarrhythmics are also indicated for use in the management of ventricular ectopy. However more malignant dysrythmias are often treated more aggressively with drugs described below. The class I-c antiarrhythmics are generally well tolerated, but they are at least modest myocardial suppressants. Propafenone in particular has mild beta blocking properties as well, and both propafenone and flecainide can impair sinus node and AV node conduction, as well as more distal conduction system disease (infrahisian conduction). These drugs should not be prescribed in patients with significant structural heart disease or in those with significant baseline conduction abnormalities. Both flecainide and propafenone are hepatically cleared, and both can cause hepatitis, nausea, emesis and commonly altered taste.

The class III antiarrhythmic drugs, those with predominantly potassium channel blocking properties, are also used in the management of both ventricular and supraventricular arrhythmias. Sotalol also has prominent nonspecific beta blocking properties and tends to
cause significant bradycardia, as well as lengthening of the QT and QRS intervals. It is renally excreted and potentially quite proarrhythmic. There is a distinct syndrome of bradycardia dependent QT prolongation which can exaggerate sotalol predisposition to cause Torsade De Pointe. Because of its nonspecific beta-blocking properties, sotalol can also exacerbate bronchospasm. It is, however, highly efficacious in maintaining normal sinus rhythm, although it is a poor choice for converting from atrial fibrillation to normal sinus rhythm. Ibutilide however is a short acting intravenous potassium channel blocker used for the acute termination of atrial fibrillation or flutter. It is most effective if used within seven days of the onset of the dysrhythmia. Dofetilide is available orally and is effective in both the termination of atrial arrhythmias, as well as the maintenance of sinus rhythm. Sotalol, ibutilide and dofetilide all carry potential risks of QT interval prolongation and proarrhythmia. All should be initiated in a hospital setting and monitored environment. Dofetilide use in particular, requires specific certification by the manufacturer for the FDA in order to prescribe it. Renal function and cardiac intervals need to be monitored regularly while using specifically sotalol or dofetilide. Ibutilide however is predominantly cleared by the liver and since it is used only for short term administration for the acute termination of dysrhythmias is not dependent on renal function. Generally speaking, creatinine clearance of 30 or less is considered a contraindication to the use of sotalol, dofetilide or ibutilide.

Bretylium is another intravenous class III antiarrhythmic cleared by the kidneys. It is rarely used today, but on occasion is required to terminate acute ventricular arrhythmias. It is potentially proarrhythmic and very commonly, when given in an urgent setting, provokes significant and often times refractory hypotension. Amiodarone is a complex drug, which although classified as a class III agent due to its potent potassium channel blocking properties, it also is a fairly potent sodium channel blocker. Its effect on sodium channels is considered “use dependent”, meaning that its effect on sodium channels becomes more prominent as heart rate increases. The faster the heart rate, the more potent the effect of amiodarone on slowing phase zero of the cardiac action potential. Since amiodarone also has potent potassium channel blocking properties, it can prolong the QRS and the QT interval consistent with delays of the action potential in all phases, slowing or stabilizing of conduction through the ventricular myocardium and slowing repolarization and increasing refractoriness to both enhanced automaticity as well as triggered activity. Thus amiodarone is highly effective in controlling all forms of cardiac dysrhythmia. In addition, it has potent nonspecific beta-blocking properties (class II effect), mild properties of calcium channel blockade (class IV properties), as well as nonspecific alpha blocking properties.

While amiodarone is highly effective and commonly used today for managing atrial and ventricular arrhythmias, its toxicity is broad and potentially quite limiting. It was originally developed as an antianginal agent due to its potent vasodilatory properties. It can be administered intravenously and orally and has an extremely long half life of between 40-50 days. One third of amiodarone is iodine by weight and the drug commonly can induce hyperthyroidism and on rare occasion hyperthyroidism. There are also two forms of pulmonary toxicity including an acute reaction, as well as long term chronic toxicity from pulmonary fibrosis. Either can be fatal in up to 10% of affected individuals. Amiodarone toxicity is influenced by total dose as well as duration of its use. Due to its long half life, and penetration into most tissues, it accumulates throughout the body and amiodarone levels are often measurable even in patients treated with low dose if they are treated for long durations. Amiodarone accumulates in the liver and can cause hepatotoxicity. LFTs as well as thyroid function tests should be monitored regularly. Amiodarone also accumulates in the skin and can cause a rare complication in which the skin turns slate blue, generally an irreversible but rare side effect. Amiodarone commonly causes photosensitivity in patients on the drug and they need to wear sun block and avoid direct sun exposure. Virtually all patients receiving amiodarone may ultimately develop corneal deposits that for the most part cause no more than nuisance symptoms which can be treated. On rare occasion, amiodarone can cause optic neuritis with blindness as well. As many of 25% of patients treated with amiodarone ultimately discontinue the drug due to complications or side effects.

The potential pulmonary toxicity of amiodarone remains the most ominous of side effects. This risk often precludes the use of amiodarone in patients with baseline abnormalities of lung function. While there is no generally accepted guideline for screening for amiodarone lung toxicity, most clinicians will do periodic chest x-rays (every 6-12 months) to assess for evidence of fibrosis, and some will obtain pulmonary function testing (annually). The only parameter which may be useful in screening for amiodarone lung toxicity, particularly in its early stages, is a decrease in diffusion capacity (DLCO). Thus, if screening patients on amiodarone, bedside Spirometry is inadequate. The key in assessing for lung toxicity is that there is no proof that any of these parameters help detect early toxicity, prevent worsening, or definitively allow for adjustment of the meds in a safe timeframe. One must carefully weigh the potential risks of amiodarone therapy with the benefits and assess each patient individually.

The class II (beta blockers) and class IV (calcium channel blockers) antiarrhythmics have many uses. They can be used both in the acute setting to gain control of heart rate during tachyarrhythmias and are extremely useful either alone or in combination with other antiarrhythmics in helping to maintain sinus rhythm. I will, for the sake of brevity, avoid additional discussion of these agents.

In summary, the arsenal of antiarrhythmic medications has grown considerably over the last few decades. With the advent of defibrillator therapy as a potentially less toxic and more efficacious strategy in treating infrequent ventricular arrhythmias, antiarrhythmic use has decreased. Conversely, atrial arrhythmias are extremely common, particularly in our aging population. The choice of medication regimen is often complex and fraught with potential risk, but many highly effective options do exist.

~ Maurice E. Varon, MD, FACC, UCVA Managing Partner