Current Management of Ventricular Arrhythmias

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INTRODUCTION.

Sudden unexpected cardiovascular death, defined as instantaneous death within one hour of the onset of an abrupt change in clinical status, accounts for approximately 300,000 deaths in the United States annually.[1] The great majority of these deaths are due to ventricular tachycardia or ventricular fibrillation (VT/VF). Although cardiovascular mortality has declined somewhat in recent years, approximately 50% of these deaths remain sudden (and presumably arrhythmic). When the 300,000 deaths per year are superimposed on the overall population, the incidence is 0.1% to 0.2% per year. In selected high-risk subgroups, that risk is multiplied. It remains a challenge to identify those at greatest risk, and to develop treatment strategies to reduce that risk. Today I will focus on current management of ventricular arrhythmias including diagnosis, risk stratification and therapy.

ETIOLOGY OF VENTRICULAR ARRHYTHMIAS.

The initiation of ventricular arrhythmia is dependent on the interaction of multiple factors.[1] Usually there is a structural abnormality that falls into one of four groups. First, myocardial infarction is the most common structural abnormality. This may take the form of an acute or healed infarction, and less commonly, a ventricular aneurysm. Second, there may be hypertrophy of the myocardial wall. Third, there may be a myopathic ventricle, with dilatation and fibrosis, infiltration or inflammation. Fourth, there may be structural electrical abnormalities. In addition to changes in the anatomic substrate, functional changes may influence the occurrence of ventricular arrhythmias. These include: 1)transient ischemia and reperfusion; 2)systemic factors, including hemodynamic dysfunction, hypoxia, acidosis and electrolyte imbalance; 3)neurophysiological interactions, including central influences; and 4)toxic

effects such as proarrhythmic medication. In the presence of the structural and functional factors enumerated above, normally benign ventricular ectopic beats and nonsustained ventricular tachycardia may initiate sustained, life-threatening ventricular arrhythmias.

The mechanism of ventricular tachycardia and location of the substrate for the arrhythmia depend on the underlying cardiac pathology. Most ventricular arrhythmias occur in the setting of structural heart disease, typically a healed myocardial infarction. When ventricular tachycardia occurs in a patient who has had a myocardial infarction, the tachycardia usually maps to the border zone of the infarction. Typically the rhythm is due to reentry occurring around functional anatomic barriers, often in a figure of 8.[2] Mapping studies in both animal models and humans have demonstrated that an area of slow conduction is critical to the perpetuation of the tachycardia.

Patients with the long QT syndrome make up another subgroup with ventricular arrhythmias. Jervell and Lange-Neilsen first described the relationship of a prolonged QT interval to syncope in sudden death associated with nerve deafness.[3] In 1963 and 1964, respectively, Romano et al and Ward described a similar syndrome (labeled "Romano-Ward Syndrome") which was unassociated with deafness and appeared to be transmitted as an autosomal dominant trait.[4,5] In 1991, Keating et al[6] demonstrated a tight linkage of the long QT syndrome to the Harvey Ras-1 gene locus on chromosome 11. Subsequent data show that approximately 65% of families have evidence of linkage to the Harvey Ras-1 Locus. The defect responsible for the long QT syndrome remains unclear, but it is thought to represent an intrinsic myocardial abnormality in repolarization, perhaps related to a disruption in the G protein that helps control the passage of potassium ions through membrane channels.[7]

A recently described syndrome is arrhythmogenic right ventricular dysplasia. The right ventricular myocardium is replaced in part by fatty and fibrous tissue. These

patients, who often present with exercise-related arrhythmias, may have several foci responsible for ventricular tachycardia originating from the right ventricle (causing a left bundle branch block tachycardia morphology).[8,9] There also appears to be a familial component of the disease, at least in some cases.[9]

Ventricular tachycardia may also occur in patients with otherwise structurally normal hearts. These arrhythmias fall into two types. First, left bundle branch block tachycardia typically originates from automatic activity (non-reentrant) in the right ventricular outflow tract. Unlike the reentrant tachycardias, this arrhythmia is frequently suppressed by adenosine, calcium channel blockers and beta adrenergic blocking drugs.[10] Second, ventricular tachycardia with a right bundle branch block, left axis morphology, is seen. This arrhythmia often responds to calcium channel blocking agents and is thought to originate from reentry in the Purkinje fiber network of the left ventricle.[11,12] Mapping studies have suggested that the site of reentry can be identified by a localized Purkinje fiber electrogram.[13]

DIAGNOSIS OF VENTRICULAR ARRHYTHMIAS.

In order to treat ventricular tachycardia correctly, it should be distinguished from other wide QRS complex tachycardias. A previous electrocardiogram may be valuable in demonstrating whether there was an underlying conduction defect (such as bundle branch block delay or pre-excitation) that could account for a supraventricular rhythm causing a wide complex tachycardia. The physical examination may demonstrate canon A-wave or a variable first heart sound, both consistent with an atrial rhythm that is unrelated to the ventricular rhythm, thereby suggesting a ventricular origin. If the physical examination and review of prior electrocardiograms do not allow diagnosis of the rhythm, further clues can be obtained from the electrocardiogram recorded during wide complex tachycardia. The only finding

that allows definitive diagnosis of ventricular tachycardia is the presence of atrioventricular dissociation. Since the ventricle is the source for the tachycardia, it is beating at a rate faster than the dissociated, sinus-driven atrial rhythm. The lack of association between the ventricle and atrium cause the clues on physical examination of variable S1 and canon A-waves. On the electrocardiogram, P waves "marching" through the electrocardiogram at a rate slower and unrelated to the wide complex tachycardia allow the diagnosis of VA dissociation with ventricular tachycardia. Furthermore, "fusion" and "capture" beats demonstrate VA dissociation. A fusion beat occurs during ventricular tachycardia when a sinus impulse is conducted through the atrium and through the AV node, to activate the ventricle simultaneously with the ventricular tachycardia QRS complex (yielding a QRS complex representing "fusion" between the native and ventricular tachycardia QRS morphologies). A capture beat has the same mechanism, only the ventricle is completely activated early by the sinus impulse and the QRS complex has the appearance of the native, sinus rhythm QRS.

The other electrocardiographic clues to the diagnosis of ventricular tachycardia in the setting of a wide complex tachycardia are suggestive only. These include a QRS duration of greater than 140 msec, left axis deviation, precordial concordance (all precordial leads are either upward or downward in their complex, and certain configurational characteristics of the QRS).[14,15] A further set of criteria for the diagnosis of ventricular tachycardia has included the absence of RS complexes in all precordial leads and, if RS is present, and RS interval is greater than 100 msec. These were found in one study to be highly specific for ventricular tachycardia.[16]

Table 1. Criteria for diagnosis of VT vs SVT.

1. Atrioventricular dissociation.
   a. P waves marching through VT, fusion and capture beats.
   b. The only criterion that is diagnostic.
2. QRS duration > 140 msec.
3. Left axis deviation.
4. Precordial concordance.
5. Certain configurational characteristics of QRS:
   a. Monophasic or biphasic QRS in V_1.
   b. Triphasic QRS, with left axis and R:S < 1 in V_6.
   c. LBBB with R in V_1 or V_2 > 30 msec.
   d. Any Q n V_6.
   e. Onset of QRS to nadir of S in V_1 or V_2 > 60 msec.
   f. Notching of the downstroke of the S in V_1 or V_2.

From references 14-16.

Finally, the diagnosis of ventricular tachycardia with ventriculo-atrial dissociation can be made using an esophageal electrode recording. This technique employs a small pacing catheter that is advanced via the nose to the esophagus. The electrode is adjusted to maximize the local atrial electrogram, allowing clear determination of the atrial activity. Alternately, a "pill" electrode can be swallowed orally, and yield the same atrial recording.

RISK STRATIFICATION FOR VENTRICULAR ARRHYTHMIAS.

Ventricular ectopic beats and even nonsustained ventricular tachycardia may occur in patients with no evidence of cardiovascular disease. In the absence of significant symptoms, the long-term prognosis is similar to a healthy population without ectopy.[17] In view of very low risk in this population, further evaluation and treatment is not warranted. It is in higher risk groups, such as those with structural heart disease, where further risk stratification is warranted.

Holter monitor.

The risk of sudden cardiac death after myocardial

infarction has been estimated to be approximately 5% per year for 3-5 years after infarction.[18] In the presence of nonsustained ventricular tachycardia, mortality is increased.[19] It has been suggested that ventricular arrhythmias may not be an independent predictor of subsequent mortality.[20] However, other studies suggest that there is an increased mortality (odds ratio of 2.35-4.7) in patients with ventricular arrhythmias that is independent of other cardiovascular risk factors. [21-23] Ventricular dysfunction also appears to be an independent risk factor.[24] (See Figure 1.)

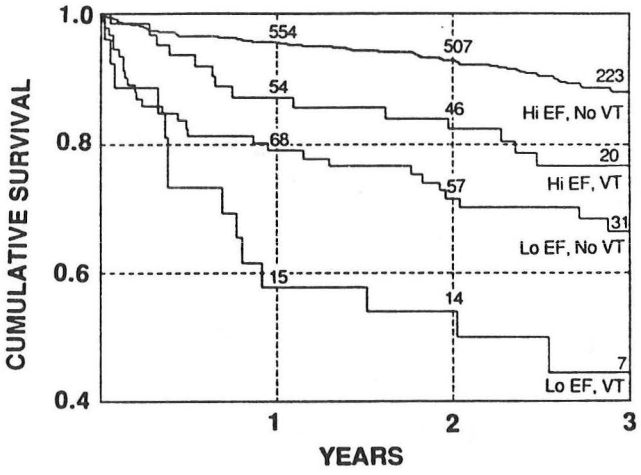

Figure 1. Kaplan-Meier survival curves for post-MI patients cross-classified by ejection fraction (EF, <30% or over) and presence or ventricular tachycardia (VT, ≥3 beats). From reference 24.

Because of the clear relationship between ventricular arrhythmias and post-infarction mortality, a large multi-centered study, the Cardiac Arrhythmia Suppression Trial (CAST) was undertaken. This study was designed to determine the degree of improvement of survival afforded by administering antiarrhythmic medication that successfully suppressed ventricular ectopy post myocardial infarction. Patients were eligible if screened between six days and two years after myocardial infarction and if they had an average of 6 or more ventricular premature beats per hour. In order to enroll potential high-risk patients, a left ventricular ejection fraction of ≤55% was required for inclusion in the study if the patient was enrolled within 90 days of

myocardial infarction; if enrolled between 90 days and 2 years following infarction, a left ventricular ejection fraction of ≤40% was required. Patients were excluded if they had severely symptomatic ventricular arrhythmias or had nonsustained ventricular tachycardia of greater than 15 beats in length. Of note, only 17% of the patients enrolled demonstrated nonsustained ventricular tachycardia. Each patient underwent an open-labeled titration phase of the antiarrhythmic medications encainide, flecainide, and moricizine. Patients who demonstrated adequate suppression of their ventricular ectopy, based on repeat Holter analysis, were enrolled in the study and then randomized to receive placebo versus medication. At first, this trial generated some concern that beneficial therapy was being denied to the placebo group. However, in April 1989, the trial was terminated prematurely because of an excess in deaths from arrhythmia and nonfatal cardiac arrest in the patients taking encainide and flecainide (relative risk 3.6).[25] There was a higher total mortality in the drug-treated group (56 of 730 [7.7%]) versus 22 of 725 (3.0%) in the placebo group.(See Figure 2.) The trial continued in a modified fashion as CAST II with the antiarrhythmic agent moricizine. This trial also was terminated because of a higher mortality during initial open-labeled titration and evidence that there was very little likelihood of survival benefit from chronic treatment.[26,27]

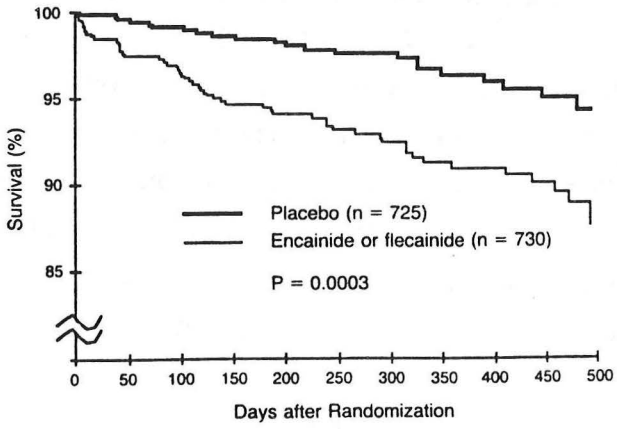

Figure 2. Survival among 1455 patients with prior MI and ventricular ectopy, randomly assigned to receive encainide or flecainide, or matching placebo. (From reference 25.)

The PVC suppression hypothesis is not entirely dead, however. The Basel Antiarrhythmic Study of Infarct Survival (BASIS)[28] looked at 312 patients with high grade ventricular ectopy and nonsustained ventricular tachycardia following myocardial infarction. They were randomized to no therapy, low dose amiodarone, or Holter-guided antiarrhythmic therapy. At one year, survival was significantly greater in the patients treated with amiodarone. (See Figure 3.) Of note, individualized therapy appeared to have a trend toward improved survival over control also. Subsequent analysis of this study has suggested that the survival benefit persisted for several years but the improvement was seen primarily in patients with preserved ejection fraction.[29,30]

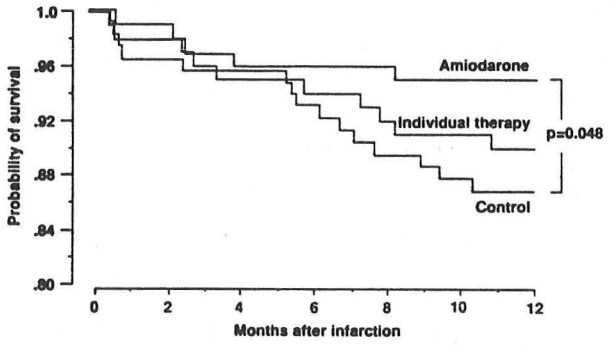

Figure 3. Probability of survival in patients with asymptomatic complex ventricular arrhythmias after MI, assigned to three groups (Holter-guided drug therapy, amiodarone, or no therapy). (From reference 28.)

Signal-averaged electrocardiography.

Most patients with ischemic ventricular tachycardia have small areas of diseased myocardium at the border zone of the previous infarction that exhibit slow conduction. These areas of slow conduction can participate in reentry that causes the ventricular arrhythmia. Very low amplitude signals originating from these pathologic regions of myocardium persist beyond the termination of the QRS complex recorded on a standard electrocardiogram. When the ECG is substantially amplified and computer-averaged so that

background noise is reduced, these very low amplitude "late potentials" at the termination of the QRS can be recorded.(See Figure 4.) Late potentials are characterized by a measurement of the overall QRS duration, the "root mean square" ("RMS", in microvolts) of the last 40 milliseconds of the QRS complex, and the duration of the terminal low amplitude signal ("LAS", in milliseconds). An abnormal signal average electrocardiogram has been associated with the presence of both clinical and laboratory-induced ventricular tachycardia. Although the negative predictive value of a signal average EKG following myocardial infarction is quite good (90%) the positive predictive value is only 16-31%, relating to a relative lack of specificity of the test.[31-37] For this reason, further evaluation is necessary,[38] and will be available following analysis of the MUSTT study (described later).

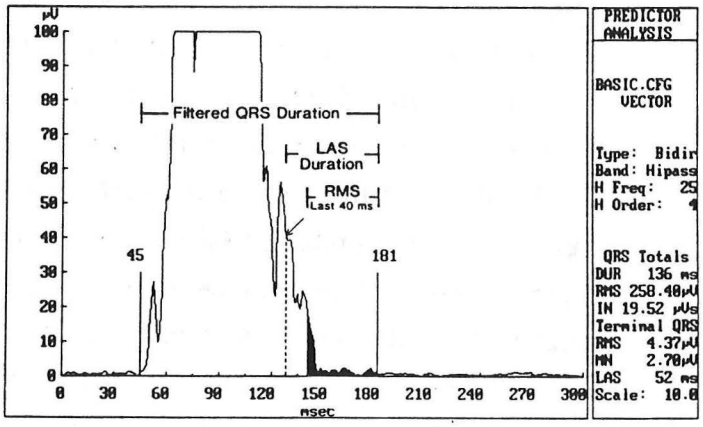

Figure 4. Signal averaged ECG. This is a "positive" study, as reflected in the long QRS, low RMS, and long LAS. See text for further discussion. From reference 38.

Heart Rate Variability.

In both experimental models and humans, enhanced vagal tone appears to exert a protective effect from ventricular arrhythmias. One method of assessing the vagal tone and sympatho-vagal interaction is to determine the variability in the heart rate (variability in the R-R interval). The "high" frequency oscillations are caused by the respiratory cycle, with greater variation relating to enhanced vagal tone. In certain populations (such as patients post-

infarction),[39] reduced heart rate variability in the high frequency domain has been associated with a worse prognosis. At present, there are no standardized criteria for the test and the sensitivity and specificity are not well defined. Further research is needed before heart rate variability should be used in routine clinical care.

Invasive electrophysiologic evaluation.

Programmed electrical stimulation has been employed for years to evaluate patients with ventricular arrhythmias. The technique is not entirely standardized, but here at Southwestern and at many other institutions, the protocol is as follows. The patient is brought to the Electrophysiology Laboratory in the fasting, non-sedated state. Several pacing catheters are advanced from the femoral veins using fluoroscopic guidance to positions in the atrium, ventricle and septum (to provide a His Bundle electrogram). The right ventricle is paced at a fixed cycle length, typically 400, 500, 600 msec for 8 beats, followed by the introduction of a premature ventricular beat. This pattern is repeated, with the premature beat being brought closer and closer to the last beat of the drive train, until the ventricular tissue is refractory (the stimulus fails to stimulate the myocardium). The premature beat is called an "S2" since it follows the drive train of eight "S1" beats. After introduction of premature beats at 3 pacing cycle lengths, the pattern is repeated with a second premature beat (S3). The S2 and S3 are brought closer and closer to the previous beat until refractoriness is observed. This pattern is continued typically at 3 pacing cycle lengths and two right ventricular sites (right ventricular apex and right ventricular outflow tract). A third extrastimulus (S4) is then introduced at each pacing cycle length and both right ventricular sites. (See Figure 5.) Occasionally, programmed stimulation from the left ventricle is performed.

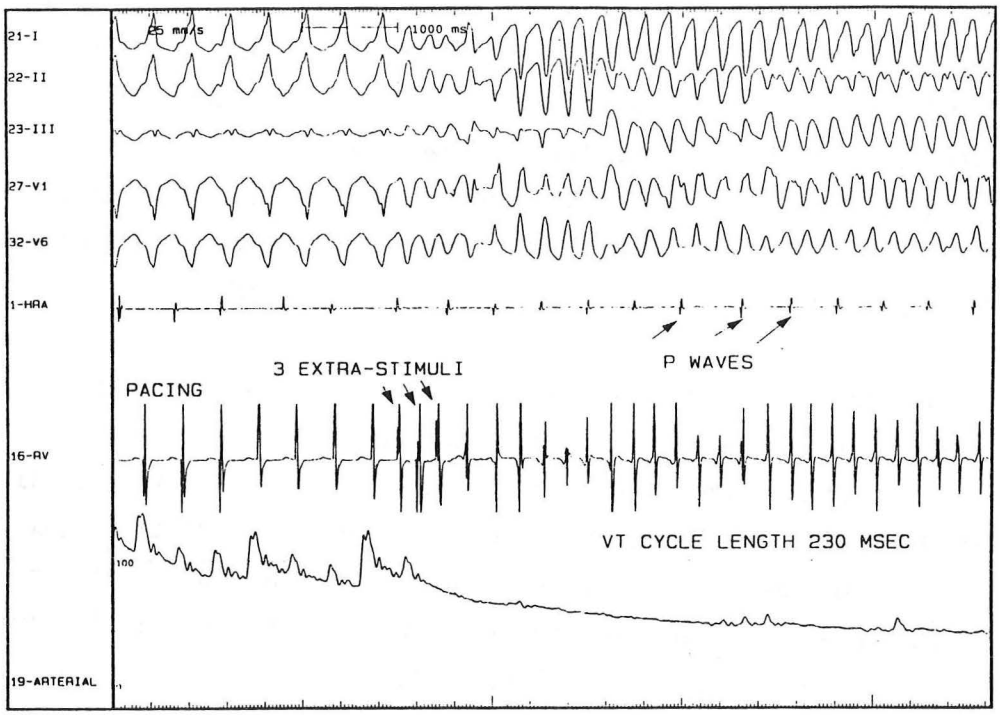

Figure 5. Induction of ventricular tachycardia with 3 PVC's (S4) in a patient who had CAD, depressed left ventricular function, and non-sustained ventricular tachycardia.

This stimulation protocol for programmed stimulation has been shown to be both sensitive and specific for ischemic ventricular tachycardias.[40] It has also been found to be of use (although with less sensitivity and specificity) in patients with non-ischemic cardiomyopathies.[41] In general, a ventricular tachycardia that is monomorphic represents an important finding independent of the induction protocol that produced it. On the other hand, ventricular fibrillation or polymorphic ventricular tachycardia, especially induced by triple extra-stimuli (S4) is of questionable significance.[38] Over the years, it has been demonstrated that repeat programmed stimulation during antiarrhythmic therapy has predicted future outcome. Specifically, when a patient is rendered

non-inducible with an antiarrhythmic drug, the survival is greater than in a patient who has persistent inducibility of the ventricular tachyarrhythmia.[42] In addition, when the ventricular tachycardia is made slower and well-tolerated, the survival is also favorable.[42] A further use of programmed stimulation is to evaluate whether antitachycardia pacing (as delivered by an implantable cardioverter-defibrillator) will be an effective therapeutic modality (See section below, Implantable Cardioverter-Defibrillator).

Programmed electrical stimulation has been used to risk-stratify patients with nonsustained ventricular tachycardia following myocardial infarction. Five studies have looked at the results of electrophysiology testing in patients with coronary disease and nonsustained ventricular tachycardia; sustained ventricular tachycardia was induced in 21-45% of patients.[43-47] When a full programmed electrical stimulation protocol was employed (using up to an S4), the inducibility ranged from 43-45%.(See Table 2.)

Table 2. Sustained VT in patients with clinical non-sustained VT.

Study	No. of Patients	Protocol	VT Induced
Gomes	37	S3	32%
Buxton	62	S4	45%
Klein	40	S4	43%
Manolis	52	S3	21%
Wilber	100	S4	43%

S3: two extrastimuli; S4: three extrastimuli.
From references 43-47.

Of the patients in these studies with no inducible ventricular arrhythmia, survival without subsequent arrhythmia event ranged from 88-96%, demonstrating excellent specificity of programmed electrical stimulation in this

population.[43-47] (See Figure 6.) In general, these patients were not treated with antiarrhythmic therapy.

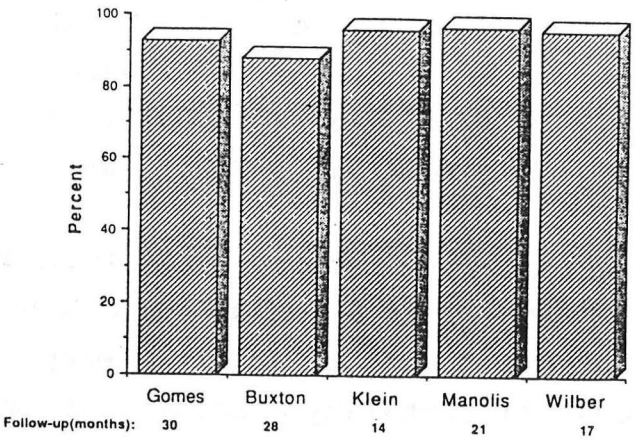

Figure 6. Survival without subsequent arrhythmia in patients with CAD and NSVT, who had negative electrophysiology studies. From references 43-47.

Patients with inducible arrhythmias had an higher arrhythmic event rate. Of the patients who were rendered non-inducible with antiarrhythmic therapy, arrhythmic event rates ranged from 11-31%.[44,45,47] (See Figure 7.) On the other hand, the arrhythmic event rate ranged from 35-88% in patients with inducible sustained ventricular tachycardia that could not be eradicated and were discharged on empiric antiarrhythmic therapy.[44,45,47] Nearly all the arrhythmia events occurred in patients with inducible arrhythmias and left ventricular ejection fraction below 40%.[48]

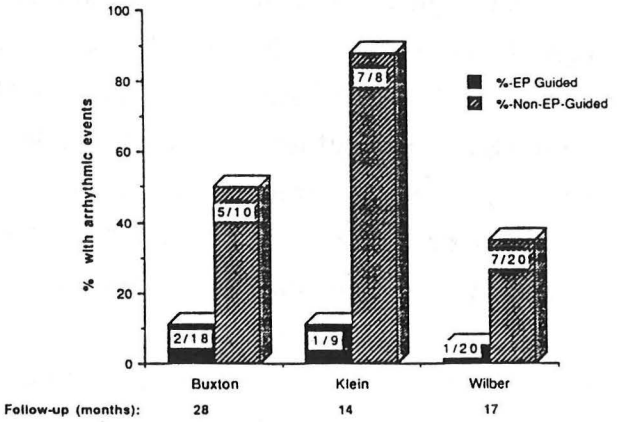

Figure 7. Arrhythmic events in patients with CAD and NSVT, who had positive EP studies. The patients with non-EP guided therapy often had persistently inducible VT after one or more drug trials. From references 44,45,47.

The results of these studies demonstrates that a negative electrophysiology study predicts a favorable outcome. On the other hand, it is unclear whether EP-guided antiarrhythmic therapy impacts on the survival of these patients or whether the suppression with drugs only identifies a relatively lower-risk population. Because of the importance of this question, the Multicenter UnSustained Tachycardia Trial (MUSTT) was undertaken.

Multicenter UnSustained Tachycardia Trial (MUSTT).

MUSTT is based on the following two hypotheses. First, EP-guided antiarrhythmic therapy can reduce sudden death and overall mortality. Second, the signal averaged ECG can identify the highest risk patients.[48] The objectives are: 1) to quantify the risk of sudden and sustained ventricular tachycardia in this patient population; 2) to determine if EP-guided antiarrhythmic therapy can reduce the incidence of sudden death and sustained VT; and 3) to determine the role of the signal averaged ECG in patients with nonsustained VT. The entry criteria require that patients have coronary artery disease and a left ventricular ejection fraction of 40% or less. They must experience nonsustained VT (defined as 3 beats to 30 seconds) that is asymptomatic or minimally symptomatic. They must not have experienced myocardial infarction or undergone coronary artery bypass grafting or angioplasty within 96 hours of the index arrhythmia.

All patients who are candidates for MUSTT undergo signal averaged ECG and baseline electrophysiology study, as consistent with our medical practice. Patients with no inducible arrhythmia are followed without antiarrhythmic therapy. Patients with inducible ventricular tachycardia are offered enrollment in the trial and, if they agree, are randomized to either serial EP study (and antiarrhythmic study or implantable cardioverter defibrillator) or follow-up off any antiarrhythmic therapy. Beta-adrenergic blocking agents and ACE inhibitors are administered as would be routine. Initially, the trial was designed to include up to

three drug tests prior to implantation of a defibrillator or initiation of amiodarone therapy. As practice standards have changed, the number of drug trials has been reduced from three to one trial prior to abandoning drug therapy and implanting an ICD. The first drug choice is randomized and assigned by the trial (class 1A [quinidine, procainamide or disopyramide], sotalol or propanol). A total of 411 out of a 900 patients have thus far been randomized in MUSTT. Preliminary data are not available, although review by the data and safety monitoring committee has allowed continuation of the trial, now in its fifth year.

VENTRICULAR ARRHYTHMIAS IN ACUTE MYOCARDIAL INFARCTION

The advent of closed chest direct current cardioversion in the early 1960's allowed the development of the modern coronary care unit. Since that time it has been recognized that the risk of ventricular arrhythmias is greatest in the early hours of a myocardial infarction and declines subsequently. The risk of ventricular fibrillation has been reported to be 15 times greater in the first 4 hours than in the subsequent 8 hours following onset of myocardial infarction.[49]

Routine administration of lidocaine to protect against ventricular fibrillation became standard in most coronary care units. Although lidocaine reduces the incidence of ventricular fibrillation, two independent meta-analyses demonstrate a trend toward increased mortality in patients treated with lidocaine (perhaps due to an excess of fatal bradycardia and asystolic arrest in the lidocaine group).[50,51] In addition, a further meta-analysis of the use of prophylactic lidocaine in acute myocardial infarction[52] has demonstrated that, from 1970-1990, the incidence of ventricular fibrillation in control patients has declined from 4.5% to .35%. In patients treated with lidocaine, the incidence has declined from 4.3% to 0.11%. It was estimated that 400 patients would have to receive lidocaine in order

to prevent a single episode of ventricular fibrillation. Finally, a recent study using prophylactic lidocaine on transfer of 204 patients with acute myocardial infarction revealed similar incidence of ventricular fibrillation (2.1% lidocaine group and 3.0% placebo group) but a trend toward an increase of cardiovascular collapse in the patients with lidocaine therapy (3.1% vs 0%--see Table 3).[53] Based on the data as described above, the routine use of lidocaine for prophylaxis against ventricular fibrillation in patients experiencing myocardial infarction is no longer recommended.(Singh)

Table 3. Effect of lidocaine in transfer of acute MI.

	Placebo	Lidocaine	P value
VF	3.0%	2.1%	0.95
CV Collapse	0.0%	3.1%	0.23

From reference 53.

When high grade ventricular ectopy is seen in the setting of myocardial infarction, treatment with lidocaine may still be justified. Furthermore, lidocaine is recommended if there are longer runs of ventricular arrhythmias or ventricular fibrillation.

Idioventricular rhythms, defined as ventricular rhythms with a rate of less than 100 BPM, are often seen in the setting of myocardial infarction. Despite anecdotal reports that these extrasystoles are due to recanalization of the infarct vessel, there is no evidence that these represent true "reperfusion arrhythmias". In general, idioventricular rhythms are well-tolerated and do not require therapy. Monomorphic ventricular tachycardia is rarely due to acute myocardial infarction and, unlike ventricular fibrillation, warrants further evaluation post-myocardial infarction.

ACUTE TREATMENT OF VENTRICULAR ARRHYTHMIAS.

When any arrhythmia causes hemodynamic collapse, refractory angina, or congestive failure, it should be treated with prompt electrical cardioversion. Conversely, if the patient is tolerating the arrhythmia, all reasonable efforts to generate a diagnosis should be made prior to cardioversion. The technique to determine the cause of a wide complex tachycardia has been described above.

When intravenous therapy for ventricular tachycardia is administered, continuous monitoring must be employed. The use of drug serum concentration measurement will aid in the safe administration of therapeutic drug dosing, as outlined in Table 4.

Table 4. Times to assess antiarrhythmic drug serum concentration.

-after acute loading (if patient is unstable)
-breakthrough arrhythmias
-steady state (5 elimination half-lives)

The first drug of choice is lidocaine. This is administered as an initial bolus and subsequent re-bolus doses (adjusted for the presence of heart failure) along with continuous infusion to maintain the therapeutic concentration (see table below). The target concentration is 3.5-5.0 mcg/ml. See table 5.

Table 5. Lidocaine administration.

	Bolus	Subsequent bolus	Maintenance
Usual	75 mg	50 mg q 5 min x 3	1 - 4 mg/min
CHF	75 mg	50 mg q 5 min x 2	1 - 1.5 mg/min

From reference 55.

The next choice of therapy, frequently added to

lidocaine infusion, is procainamide. Both the loading and maintenance dose of procainamide are adjusted in renal insufficiency. (See Table 6.) The drug can be safely administered at a rate of 50 ml per minute so that a full loading dose is administered in nearly all cases in less than 30 minutes. The therapeutic concentration is 6-10 mcg/ml of procainamide, with NAPA < 15 mcg/ml. The potential side effect of QT prolongation and secondary torsades de pointe needs to be considered.

Table 6. Procainamide administration.

	Bolus	Infusion
Usual	17 mg/kg	3 mg/min
Mild RI	15 mg/kg	2 mg/min
Severe RI	13 mg/kg	1 mg/min

RI: renal insufficiency. From reference 55.

Bretylium tosylate is also available for intravenous infusion in the setting of life-threatening ventricular arrhythmias. It is especially useful in the setting of refractory ventricular fibrillation. Therapy with bretylium is complicated by hypotension which can be substantial.

Further options for the treatment of ventricular tachycardia as well as prophylaxis against further arrhythmias is the placement of a ventricular pacing electrode. This can be used to pace-terminate ventricular tachycardia as well as overdrive-suppress ventricular arrhythmias with continuous pacing.

CHRONIC TREATMENT FOR PATIENTS WITH VENTRICULAR ARRHYTHMIAS.

Antiarrhythmic drugs.

Antiarrhythmic agents are classified according to their effects on the cellular action potential. A Purkinje fiber has a resting membrane potential of approximately -90 millivolts. When activated, the sodium channels open and there is rapid depolarization (phase 0) to a positive

potential. This quickly returns to a slightly more negative potential (Phase 1) and then maintains a relative plateau (phase 2) until the more rapid repolarization (phase 3) returns the cell to its resting potential. In some cells there is slow depolarization prior to upstroke (phase 4). In general, the QRS complex relates to the phase 0 depolarization and the QT interval relates to the time between depolarization and phase 3 repolarization. Slowing of phase 0 (sodium channel blockade) also slows conduction. Prolongation of the time to phase 3 repolarization prolongs the QT interval on the surface electrocardiogram.

The Vaughan Williams[56] classification system for antiarrhythmic drugs is summarized in Table 7. The class 1 agents are the sodium channel blocking drugs. The 1a drugs prolong the action potential (QT), while the 1b agents shorten it. Class 1c agents have a profound effect on conduction but little effect on repolarization. The class 2 agents are the beta-adrenergic blocking drugs. The class 3 agents have a selective effect of prolonging the repolarization phase (reflected in QT interval prolongation); these agents have generated substantial interest recently due to the promising results with sotalol in ESVEM (see below). The class 4 drugs are the calcium channel blockers, such as verapamil. In general, the class 1a, 1c and class 3 agents have been the most effective agents in suppression of both ventricular ectopy and inducible ventricular tachycardia. The 1b agent, lidocaine, is also very effective although the oral 1b agents are not nearly as effective.

Table 7. Vaughan Williams classification of antiarrhythmic drugs

Class	Action	ECG Changes PR	QRS	QT	Drugs
1.	Fast sodium channel blockers				
	a. Phase 0 depression-moderate	±	↑	↑	Quinidine
	Slow conduction-moderate				Procainamide
	Prolong repolarization				Disopyramide
	b. Phase 0 depression-minimal	±	±	± ↓	Lidocaine
	Slow conduction-minimal				Mexiletine
	Shorten repolarization				Tocainide
					Phenytoin
	c. Phase 0 depression-marked	↑	↑ ↑	±	Flecainide
	Slow conduction-marked				Propafenone
	Minimal repolarization changes				Moricizine
					Encainide
2.	Beta-adrenergic receptor blockers	↑	±	±	Propranolol
					(and others)
3.	Prolongation of refractoriness	±	±	↑ ↑	Amiodarone
					Bretylium
					Sotalol
4.	Calcium channel blockers	↑	±	±	Verapamil
					Diltiazem

Modified from reference 38.

Choice of antiarrhythmic therapy.

Antiarrhythmic therapy may be guided by the result of 24-hour ambulatory (Holter) monitors, exercise testing, and invasive electrophysiology testing (or any combination of the three techniques). Holter-guided therapy has the advantage of not requiring an invasive electrophysiology laboratory and assessing the ambient arrhythmias during the full spectra of daily experience (as opposed to the relatively artificial situation of an invasive electrophysiology test). Unfortunately, in many cases there is not adequate baseline ambient ventricular ectopic

activity to allow assessment of antiarrhythmic drug effects. Furthermore, the end-point of antiarrhythmic dosing is not well-established. Nevertheless, suppression of ventricular arrhythmia have been associated with improved survival.[57]

In contrast, invasive electrophysiology testing, as discussed above, offers an advantage of induction of a patient's clinical monomorphic ventricular tachycardia in most patients who present with that arrhythmia, and gives a reproducible test for evaluation of drug therapy.

For several years, there has been debate over the relative merit of Holter-guided versus EP-guided antiarrhythmic drug therapy. A study by Mitchell and colleagues[58] in 1987 demonstrated a statistical benefit using an invasive technique, although the numbers were relatively small (57 patients). The noninvasive approach required fewer drug trials and fewer hospital days, but the 2-year actuarial probability of reoccurrence was 0.50 ± 0.10 for the noninvasive technique versus only the 0.20 ± 0.08 for the invasive approach (P=0.02). (See Figure 8)

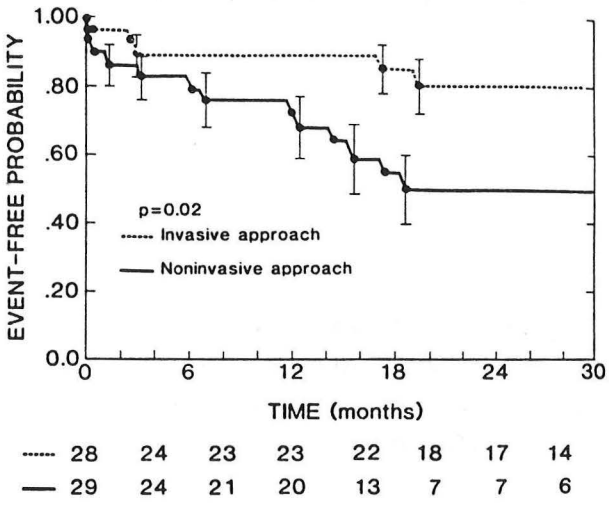

Figure 8. Probability of freedom from recurrence of symptomatic sustained VT among all patients randomized to either Holter- or EP-guided therapy.
From reference 58.

The relative advantage of invasive over noninvasive techniques became less clear following the recent publication of the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial.[59] ESVEM

examined 486 patients with documented tachyarrhythmias (documented sustained ventricular tachycardia or ventricular fibrillation [lasting 15 seconds or more], resuscitation from cardiac arrest, and syncope) who had both inducible tachyarrhythmia on electrophysiology study and had an average of 10 or more PVC's per hour on Holter monitor. These patients were randomized to EP-guided therapy or Holter-guided therapy. As shown in Figure 9, there was no significant difference in survival between the two groups over 6 years, although acceptable response to medications was seen more frequently in the patients treated with Holter-guided therapy. Of note, there was a 50% recurrence of both groups at 2-years. Of the 7 drugs used in ESVEM, (imipramine, mexiletine pirmenol, procainamide, propafenone, quinidine and sotalol) sotalol was more effective than the other antiarrhythmic drugs in preventing death in reoccurrence of arrhythmias, no matter which form of therapy guidance was used.[60] ESVEM has been interpreted as proving that the non-invasive approach to the treatment of patients with life-threatening ventricular arrhythmias is equivalent to the invasive strategy.

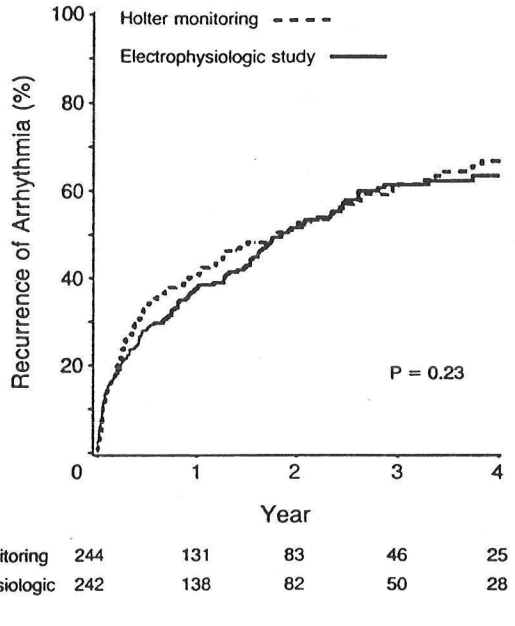

Figure 9. Probability of recurrence of arrhythmia in all randomized patients in ESVEM. From reference 59.

However, there are several problems with ESVEM. The trial required both inducible ventricular arrhythmias and high-grade ventricular ectopy, characteristics that are not in the majority of patients with symptomatic ventricular arrhythmias. The electrophysiology study protocol was less aggressive than is typically used today; this resulted in a higher apparent suppression rate but also resulted in a relatively higher recurrence rate. Only 22% of patients enrolled had a history of true cardiac arrest. Finally, both amiodarone and ICD therapy were not included in the trial. These two therapies are presently the principal treatments for patients with life-threatening ventricular arrhythmias.

The debate regarding EP-guided antiarrhythmic drug therapy has continued with the recent publication of the CASCADE study ("Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation"), which compared conventional versus amiodarone drug therapy.[61] This study randomized patients to either empiric amiodarone therapy or treatment with other antiarrhythmic drugs guided by electrophysiology testing, Holter recording, or both. The results of this trial are somewhat difficult to interpret in that placement of an ICD became standard in all groups in the middle of the trial. However, the patients treated with empiric amiodarone had a improved survival free of cardiac death, resuscitated cardiac arrest, or syncopal episode with ICD shock. (See figure 10).

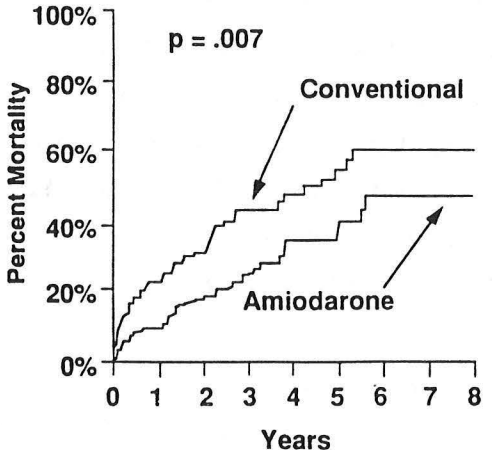

Figure 10. Mortality in CASCADE of patients randomized to EP-guided antiarrhythmic ("conventional") therapy or empiric amiodarone. From reference 61.

NON-MEDICAL THERAPY.

Surgery.

In the early 1980's, there was substantial development of a surgical treatment for ventricular tachycardia. This would consist of a sub-endocardial resection, typically along the border of a previous myocardial infarction. The ventricular arrhythmia usually mapped to the borders at a pre-surgical electrophysiology study and was subsequently mapped in the operating room in order to guide the surgical procedure. In well-selected cases, this therapy represented a potential for cure of the ventricular tachycardia. On the other hand, there was substantial associated mortality (20%).[62,63] For this reason, surgical resection for ventricular tachycardia has been substantially replaced by ICD therapy (see below). Resection remains an option at selected centers and in patients in whom surgical resection of a left ventricular aneurysm is indicated based on hemodynamic compromise.

Catheter Ablation.

Direct current (DC) was the first energy source used for catheter ablation. This technique was associated with complications of ventricular wall rupture and stroke, related to the explosive effect of directing up to 200 joules of direct current through an endocardial catheter tip. On the other hand, it was successful in selected cases.[64] With the development of radiofrequency ablation techniques, the risk has been substantially reduced in comparison to direct current ablation. In carefully selected cases of sustained, monomorphic ventricular tachycardia occurring in the setting of coronary artery disease, up to 73% success has been reported.[65] Patients with "normal heart" idiopathic sustained ventricular tachycardias have enjoyed even greater success in ablation, with up to 90% cured.[12,66]

Implantable Cardioverter-Defibrillator.

The implantable cardioverter defibrillator (ICD) is a

self-contained automatic system designed to identify and prevent sudden arrhythmic death in high-risk patients. Since the first implantation in 1980, well over 30,000 devices have been placed for the treatment of ventricular fibrillation and tachycardia. The device consist of a pulse generator that includes the battery, capacitors and circuitry, connected to one or more leads. In the past, these electrode leads had to be placed via thoracotomy in the epicardium. In recent years, the defibrillator leads have been placed endocardially in the manner similar to the placement of an endocardial pacemaker lead.

The newer systems are designed to treat cardiac arrhythmias according to the rate of the arrhythmia. The very fastest heart rhythms are treated with a full output shock, usually in the 30-36 joule range. Slower ventricular tachycardias may be treated with ventricular pacing at escalating levels of aggressiveness, followed by one or more lower output shocks, prior to delivery if a full output shock. Also, the newer devices can be programmed to pace for the treatment of bradycardia. Unlike earlier devices, the newer ICD are not "committed" to deliver therapy, so that shocks are withheld if the precipitating tachycardia resolves spontaneously (thus improving patient comfort and prolonging battery life). In addition, the ECG recorded at the time of antitachycardia therapy is retained in memory for analysis at a later time, so that therapy can be assessed.(See Figure 11)

A further advance in therapy has been the delivery of a biphasic shock. This is characterized by a reversal of the polarity between the shocking electrodes at a point approximately 2/3 of the duration of the overall discharge. Biphasic shocks have been found to reduce the energy required to defibrillate (defibrillation threshold, or DFT).[67] Using biphasic waveform, endocardial defibrillation is successful in 99% of attempted implantations.

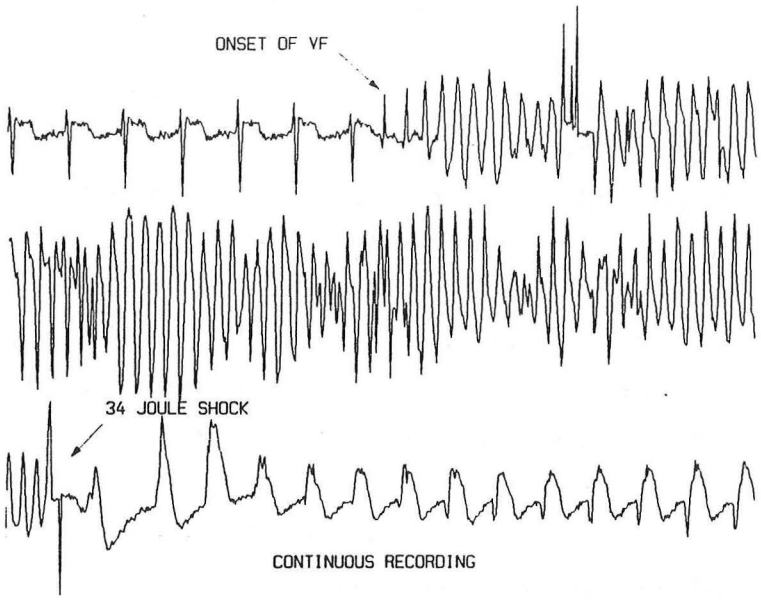

Figure 11. Episode of aborted sudden death in a 42 year old woman who was defibrillated by her ICD at 4:30 AM, during uninterrupted sleep. She recalled no shock, but this electrogram was retrieved from the ICD.

The DFT can be raised by most antiarrhythmic drugs, so when these are added, the shock efficacy needs to be assessed. One of the advantages of the newer devices is that assessment (such as a electrophysiology study) can be performed non-invasively.

The ICD is expected to last 2-5 years with in excess of 200-300 full-output shocks. The mortality of ICD placement with an epicardial system is more than 3%[68] while the mortality for implantation of a non-thoracotomy device is in the range of 0.5%.[69] Complications can include device failure, precipitation of arrhythmias, perforation, pneumothorax, and especially infection. Infection, which occurs in 1-5% of cases, usually requires removal of the device.

Although it seems intuitive that the ICD improves survival, this has not been proven in a prospective manner.

Data from case-controlled and historical-controlled have shown clear evidence of reduction in sudden cardiac death, although overall mortality changes are hard to identify. There is suggestion that certain high-risk groups (such as patients with low ejection fraction) benefit more than other patients. One study identified one- and five-year probability of survival free of cardiac mortality in patients with impaired left ventricular function as 94.3% and 69.3% with a defibrillator, compared with 82.1% and 45.3% without a defibrillator, respectively.[70] Another study estimated that the ICD improved survival from 72% to 89% at 1 year and from 49% to 65% at 3 years.[71] In spite of these suggestions of improved survival, concern has been raised that overall mortality (as opposed to sudden cardiac death mortality) is not substantially changed by ICD therapy.[72,73] In view of these doubts, and the substantial cost of ICD therapy, the NIH has sponsored the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial.

ANTIARRHYTHMICS VERSUS IMPLANTABLE DEFIBRILLATORS (AVID).

AVID is a NIH-sponsored trial that is designed to determine whether a strategy based on initial placement of an ICD or one based on antiarrhythmic drug therapy results in longer survival in patients with life-threatening ventricular arrhythmias. Secondary objectives of the trial include determination of: 1)quality of life; 2)cost; 3)mode of death; 4)surgical morbidity and mortality; and 5)ICD and lead performance.

The entry criteria for randomization in AVID, as well as the criteria for enrollment of the longitudinal study of non-qualifying patients (registry) are as shown in Table 8.

Table 8. Entry criteria for AVID trial and registry.

Trial and registry:

(A) VF

(B) VT with syncope

(C) VT, SBP <80 mmHg or CP/near-syncope and EF ≤0.40

Registry only:

(D) VT, SBP <80 mmHg or CP/near-syncope and EF >0.40

(E) VT, stable

(F) Out of hospital VT or VF with transient OR correctable cause

(G) Out of hospital unexplained syncope with structural heart disease and EP inducible VT with symptoms

(For categories A-E, the patient must be free of transient, correctable or intervention-based causes such as electrolyte imbalance, drug reaction or with new MI (especially for in-hospital arrhythmia.)

After patients have been identified, they will be offered enrollment in the trial. 50% will be randomized to placement of an ICD. The other 50% will be further randomized to either sotalol (with EP or Holter guided evaluation) or empiric amiodarone therapy. At present, the pilot study has successfully recruited 200 patients and recruitment for the full study has begun. The goal is to recruit a total of 1200 patients by February, 1997.

AVID has generated substantial controversy among electrophysiologists. The argument that placement of an ICD in a relatively "unselected" population will dilute any evidence of efficacy in the patients who are assessed to be at highest risk has raised some concern.[74] On the other hand, in view of the substantial cost, increasing frequency of placement, and lack of randomized data to support ICD therapy, many of us feel that such an attempt to rigorously prove a survival benefit is critical.[75]

CONCLUSIONS.

The treatment of ventricular arrhythmias remains a challenge. We are fortunate to have new tools for evaluation and therapy. Randomized trials have shed substantial light on the proper treatment, and will continue to shape the way we care for patients at high risk for ventricular tachycardia and fibrillation.

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