Sudden cardiac death (SCD) is an enormous public health problem with at least 300,000 deaths per year in the USA alone. The current state-of-the-art for treatment of SCD has several significant limitations. Because ventricular fibrillation (VF) quickly becomes irreversible, successful treatment requires immediate care. Even in metropolitan areas with excellent emergency medical services, survival of out-of-hospital cardiac arrest is extremely low. Attempts to prevent SCD with antiarrhythmic agents have had little success (and in some cases increased mortality). The development of implantable cardioverter-defibrillators (ICDs), which detect and treat VF almost instantly, has revolutionised the treatment of SCD. However, to be effective these devices must be implanted before cardiac arrest. This is the source of one of the major dilemmas in current SCD management: How to identify SCD victims before their first episode.

SCD is defined as unexpected, non-traumatic death within minutes of the onset of symptoms. Recordings obtained during spontaneous episodes of SCD (Holter, telemetry, etc) reveal that SCD results from ventricular arrhythmias in approximately 85% of cases (either primary VF or brief ventricular tachycardia (VT) degenerating to VF).1 Table 1 lists the main causes of SCD.

Rational strategies for prediction, prevention, and treatment of SCD require an understanding of the mechanisms responsible for the initiation and maintenance of ventricular fibrillation. Many risk stratification tests and medical treatment regimens, however, have been predicated on the physiology of ventricular tachycardia. While there is clear overlap between VT and VF physiology, their mechanisms are not identical. The lack of specificity in testing and lack of efficacy in treatment stem in part from their predication on VT rather than VF physiology. There are ample articles detailing clinical studies of prediction, prevention, and treatment of SCD. Rather than recreate an exhaustive review of such literature here, we will explore current concepts of VF mechanisms and examine current management as it relates to this physiology.

VF is a re-entrant arrhythmia; there is continuous electrical activity with each wave “recirculating” to produce the next wave. For activation waves to propagate continuously there must be at least two “paths” for conduction separated by unexcitable tissue. Activation must spread around one side of the unexcitable tissue allowing the other side time to recover from inactivation so it can be re-excited when the wavefront returns. Tissue refractory periods limit re-entry; the conduction time around the circuit must be greater than the refractory period of each component of the circuit. Therefore decreased conduction velocity or decreased refractory period facilitates re-entry by decreasing the likelihood that the activation wavefront will encounter its own refractory “tail” terminating tachycardia.

Re-entrant circuits can be divided into two types. In fixed re-entry a site of anatomic conduction block (for example, scar tissue post-infarction) provides an obstacle around which electricity must travel. Re-entry can also occur in the absence of anatomic obstacles. In this event the circuit path is determined by tissue refractoriness. A group of transiently unexcitable cells (secondary to refractoriness) create an obstacle to conduction around which a circuit can form. This latter type is referred to as functional re-entry.

A common example of ventricular re-entry is VT in the setting of ischaemic cardiomyopathy. Scar tissue from myocardial infarction forms a barrier to conduction; strands of living myocardium create channels for conduction through the scar. This forms an anatomically defined re-entrant circuit. The result, frequently, is stable monomorphic VT. SCD, however, rarely results from stable monomorphic VT but rather results from rapid polymorphic VT or primary VF.

MULTI-WAVELET RE-ENTRY
To understand VF we must examine the properties that create instability in VT leading to degeneration of VT into VF. Mapping studies of induced VF in animals reveal co-existence of multiple simultaneous wavefronts. In such multi-wavelet re-entry a “mother” wave divides
producing multiple “daughter” waves. The “restitution hypothesis” suggests a mechanism for development of instability in re-entry that may explain the predisposition for degeneration to fibrillation.

According to the restitution hypothesis the relation between heart rate and action potential duration is critical to the stability of re-entry. As heart rate increases action potential duration decreases. At fast heart rates oscillations of action potential duration can occur. If the refractory period and conduction velocity vary sharply with heart rate, oscillations tend to amplify causing wave break and degeneration to fibrillation. When the action potential duration varies more slowly with heart rate, oscillation tends to increase (dampen) resulting in stable single wave re-entry. According to the restitution hypothesis the slope of the restitution curve determines the risk of VF. Animal and computer modelling studies have demonstrated that interventions which flatten the restitution curve reduce the inducibility of fibrillation.

SPECIAL CASE: ISCHAEMIA AND INFARCTION
Ischaemia and infarction notably alter tissue refractory and conduction properties, promoting arrhythmia. When cells become ischaemic they develop resting membrane depolarisation. This causes sodium channel inactivation. With modest depolarisation only a small percentage of sodium channels are inactivated; cells remain excitable but with reduced conduction velocity. In the setting of infarction, cells die and potassium leaks into the extracellular space. Local extracellular potassium concentration can be as high as 15 mEq during infarction. This potassium diffuses through the extracellular matrix increasing potassium concentration in the surrounding tissue. The raised extracellular potassium concentration alters Nernst forces leading to resting membrane depolarisation. Depending on the degree of depolarisation (and hence sodium channel inactivation) cells either fail to conduct or conduct with reduced velocity. Because infarction is regional and diffusion of potassium is non-uniform, there is an increase in heterogeneity of conduction velocity and conduction block. The combination of these factors increases the likelihood of VT and degeneration to VF. Under certain circumstances ischaemia can cause automatic and/or triggered firing. Thus ischaemia can provide both fertile substrate for, and the trigger to initiate, re-entry.\(^5\)

Late after infarction there are several arrhythmogenic alterations in myocardial substrate which predispose the post-myocardial infarction (MI) patient to VF. One of these is the persistence of strands of surviving myocardium through areas of infarct scar. Following activation of ventricular tissue outside the scar, conduction spreads slowly through these channels, exiting the scar after healthy tissue has recovered from inactivation. This provides the substrate for re-entry. The electrical perturbations of acute ischaemia and infarction are particularly proarrhythmic when superimposed on the substrate of chronic ischaemic cardiomyopathy.

SPECIAL CASE: ELECTRICAL REMODELLING IN CARDIOMYOPATHY
It is well known that decreased LV function (from any cause) results in an increased incidence of SCD. The electrophysiological effects of cardiomyopathy have been studied in several different animal models as well as in human tissue from biopsies and explanted hearts. These studies reveal that electrical remodelling occurs in myopathic hearts. Globally there is cell necrosis and replacement of myocytes with scar tissue. Remaining cells develop hypertrophy and altered ion channel and gap junction expression. V, current density is decreased, sodium calcium exchanger expression is increased, and expression of SERCA, the sarcoplasmic reticulum (SR) calcium pump, is decreased. These changes effect ventricular mechanical function (decreased SR calcium content reduces contractile force) as well as promoting arrhythmia. In the myopathic heart catecholamine responsiveness is preserved (until late in heart failure). In the presence of increased adrenergic tone the balance of forces on intracellular calcium result in transient SR calcium overload. With SR overload calcium can be spontaneously released (that is, not in response to an action potential). Calcium release alters the balance of electrochemical forces on the sodium calcium exchanger reversing current flow to produce an inward (depolarising) current, I, The amount of membrane depolarisation from I, is greater in the myopathic heart because of reduced I,. Thus in the setting of heart failure catecholamine surges can produce spontaneous SR calcium release, I, and sufficient depolarisation to reach the sodium channel activation threshold. An action potential is produced which can provide the trigger for ventricular arrhythmias.

CURRENT PRACTICE
Current management of SCD is shaped by two overriding problems:

- We have very limited ability to prevent SCD and must therefore depend upon risk prediction and prophylactic implantation of an ICD.
- We are unable to predict SCD risk in patients with preserved left ventricular function despite the fact that these patients account for approximately 50% of SCD victims.

RISK ASSESSMENT
Appropriate ICD utilisation is predicated upon accurate assessment of SCD risk. The most obvious indication of increased SCD susceptibility is a history of resuscitation from cardiac arrest. Unfortunately few are lucky enough to survive

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**Table 1 Causes of sudden cardiac death**

- Coronary artery disease
- Ischaemic cardiomyopathy
- Non-ischaemic cardiomyopathy
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Sarcoidosis
- Amyloidosis
- Myocarditis
- Valvar heart disease
- Congenital heart disease
- Cardiac tumours
- Long QT syndrome
- Brugada syndrome
- Wolff-Parkinson-White syndrome
- Electrolyte abnormalities
- Thyrotoxicosis
- Proarrhythmia from antiarrhythmic agents
- Cocaine
such episodes, but of those that do up to 20% will have recurrent episodes by one year and 50% by three years. The goal of risk assessment is primary prevention. Certain groups have been identified as being at particularly high risk for development of VF. There is a clear relation between cardiomyopathy and VF susceptibility. Thus, perhaps the most potent determinant of risk is left ventricular dysfunction. In patients with ischaemic cardiomyopathy the presence of high grade ventricular ectopy and non-fatal ventricular arrhythmias such as non-sustained (or sustained) VT correlate with an increased likelihood of developing VF. In certain groups (for example, hypertrophic and non-ischaemic cardiomyopathy) ectopy is so common that it does not indicate an increased risk of SCD.

Attempts have been made to stratify patients in these groups. There are many studies that indicate autonomic abnormalities predispose to ventricular arrhythmias. Increased adrenergic tone and/or decreased vagal tone are abnormalities predispose to ventricular arrhythmias. Increased adrenergic tone and/or decreased vagal tone are associated with increased incidence of SCD. β Blockers have consistently been demonstrated to reduce mortality and arrhythmic death. Measurements of heart rate variability and baroreceptor sensitivity have been used to assess the balance of autonomic forces. However, these tests have only mediocre positive and negative predictive value.

Other studies seek to identify an underlying electrical substrate that predisposes to VF. In ischaemic cardiomyopathy scar tissue is sometimes traversed by channels of surviving myocardium as described above. In sinus rhythm spread of activation into these channels follows depolarisation of tissue outside of the scar. The magnitude of signal produced by depolarisation of these cells is so small that it is indistinguishable from background noise on the surface ECG. However, when averaging several hundred QRS complexes, noise (which is random) cancels out while the late potentials which are constant remain. Therefore signal averaging enhances the signal to noise ratio and late potentials (activation of channels) become apparent. These channels, however, provide the substrate for re-entrant single wave VT, not necessarily VF. This may explain the limited specificity of signal averaged ECGs.

In an electrophysiologic study, programmed ventricular stimulation is carried out to assess the inducibility of sustained monomorphic VT. A conditioning drive train (eight beats) is delivered to stabilise the action potential duration. Progressively earlier premature beats are then delivered in an attempt to cause unidirectional block and re-entry. Interestingly, despite the fact that electrophysiologic studies are performed to assess the risk of developing SCD, induction of VF is a non-specific finding while VT induction correlates with increased risk of cardiac arrest. The limited predictive value of these tests may reflect their predication on the substrate of VT rather than VF.

A novel approach to assessing SCD risk based more upon measurement of electrical instability than the substrate for VT is microvolt T wave alternans. Alternating action potential durations in a large population of cells can produce changes in T wave morphology. T wave variation (even in the microvolt range) can be discerned by computerised signal processing and has been correlated with risk of SCD. In animal models discordant alternans has been demonstrated to produce unidirectional block, re-entry, and fibrillation. Clinical absence of T wave alternans has been shown to have an excellent negative predictive value in both ischaemic and non-ischaemic cardiomyopathies. The improved negative predictive value (compared with other tests) may result from a closer relation between T wave alternans physiology and vulnerability to fibrillation (not VT).

**PREVENTION**

Several studies have examined the possibility of reducing sudden death with antiarrhythmic agents. Early strategies for prevention of SCD were based on the hypothesis that if inducible VT was correlated with increased risk of SCD then medical treatment that rendered patients non-inducible at electrophysiologic study would reduce SCD. The CASCADE (cardiac arrest in Seattle: conventional versus amiodarone drug evaluation study) trial randomly compared electrophysiologic (EP) guided therapy to empiric (non-EP guided) amiodarone in survivors of out-of-hospital cardiac arrest. There was a significant improvement in survival in the amiodarone group. The study had no placebo arm which was felt to be unethical in such a high risk population. There were subsequently several placebo controlled primary prevention trials of amiodarone in patients with (mostly ischaemic) cardiomyopathy with or without asymptomatic ectopy. The results of these trials were mixed although none showed a significant increase in mortality (table 2).9–11

Many attempts have been made to prevent episodes of VF with the prophylactic use of other antiarrhythmic agents. Unfortunately to date virtually all trials have demonstrated either no mortality benefit or increased mortality. It is useful to review two of the most blatant examples of antiarrhythmic failures; the CAST (cardiac arrhythmia suppression trial) and SWORD (survival with oral d-sotalol) trials.

**CAST**

In CAST, the class Ic agents flecainide, encainide, and morizicine were used to suppress ambient ventricular ectopy in patients with ischaemic cardiomyopathy.12 The trial was stopped prematurely secondary to increased mortality with antiarrhythmics as compared with placebo. Class Ic agents bind sodium channels, reducing the number of channels available for depolarisation. Decreased rate of depolarisation (dV/dt) and hence reduced conduction velocity are the result. Such an electrophysiologic effect in isolation would tend to stabilise re-entry (decreasing the likelihood that a wavefront will encounter refractory tissue and extinguish). Drug binding is increased when the channel is inactivated. Thus under resting conditions there is little drug effect. When the cell is excited sodium channels open and rapidly inactivate, drug then binds to the channel—after an action potential has been initiated. Only following repolarisation does drug begin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Improved survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polish trial</td>
<td>Post-myocardial infarction, ineligible for β blockers</td>
<td>Yes</td>
</tr>
<tr>
<td>CHF-</td>
<td>Congestive heart failure, asymptomatic ectopy</td>
<td>No</td>
</tr>
<tr>
<td>STAT</td>
<td>Asymptomatic ectopy</td>
<td>No</td>
</tr>
<tr>
<td>EMIAT</td>
<td>Post-myocardial infarction, low ejection fraction</td>
<td>No</td>
</tr>
<tr>
<td>CAMIAT</td>
<td>Post-myocardial infarction, asymptomatic ectopy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CAMIAT, Canadian amiodarone myocardial infarction arrhythmia trial; CHF-STAT, congestive heart failure survival trial of antiarrhythmic therapy; EMIAT, European myocardial infarct amiodarone trial.
to unbind from the sodium channel. Until the antiarrhythmic
drug dissociates the channel cannot be reactivated. Class 1c
agents therefore prolong refractoriness providing a less
favourable substrate for re-entry. As long as the refractory
period prolonging effects predominate over the conduction
velocity slowing effects the net result is antiarrhythmic.

The exact mechanism of proarrhythmia in CAST remains a
matter of speculation, but certain observations about the
clinical characteristics of the events combined with relevant
animal studies suggests a plausible hypothesis. Review of the
CAST data demonstrated that SCD events occurred with a
diurnal variation consistent with ischaemic events. Ischaemic
events (increased angina and non-fatal MI) were similar in
the drug and placebo groups. However, in the antiarrhythmic
group an ischaemic event was more likely to be fatal. Animal
data demonstrate increased flecainide binding during ischae-
mia. In ischaemic animals treated with flecainide there was
an increased incidence of QRS prolongation (indicating
reduced conduction velocity) and rapid sustained fatal VT.

**SWORD TRIAL**

Class III drugs are designed to prolong the action potential
duration and thereby the refractory period. Moderate action
potential duration prolongation has an antiarrhythmic effect
but pronounced prolongation can result in torsade de pointes
and SCD. Combined with the action potential prolongation of
class III agents, the normal increase of action potential
duration at slow heart rates increases the potential of
proarrhythmia. The ideal antiarrhythmic drug prolongs
refractory period at rapid heart rates (antiarrhythmic effect)
but has no effect at slow heart rates (reduced proarrhythmia).

In the ventricle two potassium channels are largely
responsible for repolarisation: \( I_{Kr} \) and \( I_{Ks} \). The subscripts r
and s (rapid and slow, respectively) refer to the kinetics of
activation and deactivation. The slow kinetics of \( I_{Ks} \)
deactivation contribute to the heart rate dependence of
action potential duration (APD). With short diastolic inter-
vals (rapid rates) \( I_{Ks} \) channels have not completely deacti-
ivated before they are activated again. Because there is
substantial channel reserve (that is, not all \( I_{Ks} \) channels are
activated under baseline conditions) \( I_{Ks} \) activation before
complete deactivation results in “stacking” or accumulation
of \( I_{Ks} \) current at fast heart rates. Thus outward current is
increased at rapid rates (reducing APD). In addition, because
\( I_{Ks} \) increases with increasing heart rate but \( I_{Kr} \) does not, \( I_{Ks} \)
accounts for a greater proportion of the total repolarising
current at faster heart rates.

In the SWORD trial the class III agent d-sotalol was used
prophylactically against SCD in patients with ischaemic
cardiomyopathy.\(^{11}\) d-Sotalol is a relatively specific \( I_{Ks} \)
blocker. Although d-sotalol binds \( I_{Kr} \) more avidly as heart rate
increases, \( I_{Kr} \) accounts for less of the repolarising current at
rapid rates. The result is a decreased significance (less effect
on APD) of \( I_{Ks} \) block as heart rate increases. Thus the
antiarrhythmic effect of d-sotalol is diminished at fast rates
while its APD prolonging effects are maximised at slow rates
increasing its proarrhythmic effects.

Increased heterogeneity facilitates torsade de pointes as
well as re-entry. Under normal circumstances there is
transmural heterogeneity of APD (with the longest action
potentials in the mid myocardium). This dispersion of
refractoriness results from a transmural heterogeneity of \( I_{Ks} \)
expression (reduced in the mid myocardium). Because there
is regional variation in \( I_{Ks} \) expression the APD prolonging
effect of \( I_{Ks} \) blockade is heterogeneous. d-Sotalol therefore
not only increases APD but also increases the dispersion of
refractoriness. This facilitates re-entry by creating voltage
gradients between adjacent cells (epicardial cells with
relatively short APD and mid myocardial cells with long
APD). Interestingly amiodarone, which prolongs the APD, has
not been associated with increased mortality. Amiodarone blocks \( I_{Kr} \) and \( I_{Ks} \) and reduces dispersion of
refractoriness.

**TREATMENT**

There have been many studies of medical treatment for the
prevention of SCD. As discussed above most traditional
antiarrhythmic agents have either been ineffective or have
increased sudden death. Several agents not typically con-
sidered to be antiarrhythmic have none-the-less been
demonstrated to reduce arrhythmic death. \( \beta \) Adrenergic
blocking drugs have been repeatedly demonstrated to
improve both total mortality and arrhythmic death (CIBIS
II, MERIT HF, CAPRICORN). Angiotensin converting enzyme
(ACE) inhibitors have had more mixed results, but the
TRACE and AIRE trials (trandolapril and ramipril, respec-
tively) revealed decreased SCD. In the RALES trial (aldoster-
one versus placebo; New York Heart Association (NYHA)
functional class II–IV patients, ejection fraction \( \leq 40\% \), on
ACE inhibitor, loop diuretic, \( \pm \) digoxin) the aldosterone
group experienced a 29% reduction in sudden death. Finally
in both the Scandinavian simvastatin survival study and the
long term intervention with pravastatin in ischemic heart
disease study sudden deaths were lower in the treatment
groups than in control (although statistical analyses of this
end point were not performed). There are several potential
“antiarrhythmic” effects of each of these drugs: beneficial
alteration of autonomic balance, decreased deleterious
remodelling following myocardial insult, and mild elevation
of serum potassium (aldosterone). Perhaps most importantly,
reduced ischaemic burden has profound antiarrhythmic
benefits. Revascularisation is in fact the first line of
intervention for reduction of sudden death risk in ischaemic
patients.

In light of the limited efficacy of SCD prevention and the
abyssal success of resuscitation from out-of-hospital cardiac
arrest, ICD implantation has become the foundation of SCD
management.

**IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS**

The advent of the ICD has made successful treatment of SCD
possible. With the availability of this potent tool comes the
question who should receive one? Initial ICD trials were
secondary prevention trials: they required survival of SCD
before ICD implantation. AVID, CIDS, and CASH all
demonstrated the efficacy of ICD in secondary prevention
of SCD.\(^{14,16}\) Subsequent primary prevention trials have had
progressively more inclusive entry criteria. The initial primary
prevention trials (table 3) required inducibility at EP study in
ischaemic cardiomyopathy patients (MADIT\(^*\) and MUSTT).
MUSTT suggested that even non-inducible ischaemic cardi-
omyopathy patients were at high risk for SCD.\(^{15}\) MADIT II
subsequently demonstrated mortality benefit from prophyl-
lactic ICD placement in post-MI patients with left ventricular
ejection fraction \( \leq 35\% \) without requiring EP study or other
positive risk markers.\(^{15}\) The most recently completed trial,
SCD-HeFT, which included patients with reduced left

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\*MADIT = Multicenter Automatic Defibrillator Implantation Trial

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ventricular function regardless of aetiology (and with no additional risk requirements), demonstrated mortality benefit from ICD implantation in the broadest group yet. The notable exception to this positive trend was the CABG patch trial in which ICDs provided no added benefit to surgical revascularisation (in ischaemic cardiomyopathy patients with positive signal averaged ECGs). Among other things, this trial underscored the powerful “antiarrhythmic” effect of revascularisation.

There is a significant “false positive” rate using current implantation criteria. Some patients receive ICDs but never develop SCD, exposing them to unnecessary morbidity and producing a substantial financial burden on the health care system. Conversely almost half of SCD victims have normal left ventricular function with VF as the first manifestation of heart disease. We are currently unable to predict SCD in patients with normal left ventricular function (with the exception of small groups with primary electrical abnormalities—for example, Brugada, long QT syndrome, etc.). Finally, even with prophylactic ICD implantation and best medical treatment, there is a 25% four year mortality.

FUTURE DIRECTIONS

There are several deficiencies in our current management of SCD. Risk assessment tools lack adequate sensitivity and accuracy, and while ICDs are an effective treatment they have not eliminated sudden death and to date SCD prevention has essentially been elusive. Future research should be directed toward elucidating the mechanisms specifically responsible for initiation and maintenance of VF. Diagnostic tests can then be developed to identify the electrical characteristics which predispose to development of VF. Finally we require a mechanism based strategy for prevention of SCD. Future paradigms for antiarrhythmic medication must have a higher specificity for the electrical properties that facilitate VF initiation or maintenance. Ultimately a better understanding of the factors responsible for adverse electrical remodelling may improve our chances of intervening to prevent the arrhythmogenic milieu that develops in the cardiomyopathic heart.

REFERENCES


Table 3 ICD trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>Population</th>
<th>Improved survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG Patch</td>
<td>ICD versus no ICD with CABG</td>
<td>EF &lt;36%, planned CABG (positive SAECG)</td>
<td>No</td>
</tr>
<tr>
<td>MADIIT</td>
<td>ICD versus “conventional therapy”</td>
<td>CHF, post-MI, EF &lt;35%, asymptomatic NSVT, inducible, non-suppressible</td>
<td>Yes</td>
</tr>
<tr>
<td>AVID</td>
<td>ICD versus class III</td>
<td>Resuscitated VF, CV of sustained VT, EF &lt;40%</td>
<td>Yes</td>
</tr>
<tr>
<td>MUSTT</td>
<td>EP guided treatment versus ICD</td>
<td>CAD, EF &lt;40%, asymptomatic NSVT, EF inducible</td>
<td>Yes</td>
</tr>
<tr>
<td>CIDS</td>
<td>ICD versus amiodarone</td>
<td>Cardiac arrest, symptomatic sustained VT, syncope, and inducible VT</td>
<td>No</td>
</tr>
<tr>
<td>CASH</td>
<td>ICD versus amiodarone versus β blockade</td>
<td>Cardiac arrest</td>
<td>Yes</td>
</tr>
<tr>
<td>MADIT II</td>
<td>ICD versus “conventional treatment”</td>
<td>EF &lt;30%, prior MI</td>
<td>Yes</td>
</tr>
<tr>
<td>SCD HeFT</td>
<td>ICD versus amiodarone versus placebo</td>
<td>EF &lt;35%, NYHA II and III</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AVID, antiarrhythmics versus implantable defibrillators study; CABG, coronary artery bypass graft; CAD, coronary heart disease; CASH, cardiac arrest study Hamburg; CHF, congestive heart failure; CIDS, Canadian implantable defibrillator study; CV, cardioversion; EF, ejection fraction; EF, electrophysiological; ICD, implantable cardioverter-defibrillator; MADIIT, multicenter automatic defibrillator implantation trial; MI, myocardial infarction; MUSTT, multicenter unsustained tachycardia trial; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD HeFT, sudden cardiac death heart failure trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

► An easy to understand summary of the restitution hypothesis.
► A compelling set of experiments demonstrating the dynamic nature of action potential characteristics and VF vulnerability.
► A well designed and provocative investigation of the antifibrillatory effects of flattening the slope of the restitution curve.
► An excellent review of the electrophysiological effects of ischaemia and infarction.
► A concise and coherent overview of the role of intracellular calcium handling in the electrophysiology of ventricular arrhythmias in heart failure.
► An elegant examination of electrical remodelling in the rabbit model of heart failure.
► A beautiful demonstration of the interaction between functional and anatomical substrate in re-entrant arrhythmias.
► An extremely important paper demonstrating that, despite reducing premature ventricular contractions, flecainide and encainide increased mortality in post-MI patients with ventricular ectopy.

A comparison of ICD and “conventional treatment” for prevention of SCD. This trial resulted in a dramatic shift in ICD usage as primary prevention of SCD.


An examination of ICDs for primary prevention of SCD in patients with ischaemic cardiomyopathy and no other risk factors. Like the MADIT I trial, MADIT II dramatically increased the indications for ICD implantation.


Additional references appear on the Heart website—http://www.heartjnl.com/supplemental