Cardiac arrhythmias—trials and tribulations

Patients with cardiac arrhythmias can be asymptomatic, suffer from serious symptoms and a degraded quality of life, or present with sudden cardiac death. Although rhythm disturbances of the heart have been recognised and treated for centuries, the basic, translational, and clinical aspects of the science of cardiac electrophysiology are relatively recent.\(^1\) The therapeutic aspects of cardiac stimulation (pacemakers), defibrillation using external and implantable devices, and ablation have propelled arrhythmology into an effective modern therapeutic arena. In The Lancet, three Series papers summarise current thinking and practice in arrhythmia care.\(^2\)\(^4\)
Cardiac pacemakers were initially used to prevent syncope and sudden death in patients who were having Adams-Stokes attacks. These simple devices were effective and no trial was thought possible to support their introduction into clinical practice. Trials of single versus dual chamber pacemakers showed better results with dual chamber pacing, and biventricular pacing, or cardiac resynchronisation therapy, has proven effective for symptomatic heart failure with ventricular dyssynchrony. Other trials showed little if any benefit from pacing to prevent atrial tachyarrhythmia, or eliminate syncope unless clearly related to bradycardia.

Electrical defibrillation was used for termination of atrial and ventricular fibrillation without the need for clinical trials, but there were many reports of therapeutic success. When the implantable defibrillator was developed in 1980 it was extensively used before the need for clinical trials was mooted. Eventually small trials of secondary prevention were conducted—the therapy was life-saving, although expensive.

It proved more difficult to provide convincing evidence that primary prevention (device implantation in a patient at risk of, but free from, life-threatening ventricular arrhythmia) was clinically valuable. However, one small trial in post-infarction patients with impaired systolic function and inducible arrhythmia yielded a positive result. This stimulated further trials in at-risk populations, with variable results. Clinical experience with implantable defibrillators has highlighted the inadequacy (low positive predictive value) of traditional and some novel risk-markers but, despite good ideas for refining the population at potential risk, no new trial of implantable defibrillator therapy, which would be needed to validate the potential risk-marker, has been established in recent years.

Patients with atrial fibrillation can be managed by restoration and maintenance of sinus rhythm (rhythm control) or more simply by controlling the ventricular rate in response to ongoing atrial fibrillation (rate control). Large trials consistently demonstrated no advantage to rhythm control, and that this approach was associated with more hospitalisations than rate control. Despite the evidence against rhythm control, the implications struggled for acceptance. Patients who remained in sinus rhythm did better than those in atrial fibrillation, but conventional antiarrhythmic drug therapy was associated with a poor outcome. This argument devolved into the need for better antiarrhythmic drugs or new methods to achieve rhythm control.

After the Clinical Arrhythmia Suppression Trial (CAST), which had shown that antiarrhythmic drugs could also be pro-arrhythmic, the pharmaceutical industry became wary of antiarrhythmic drug development. Successful management of sustained ventricular arrhythmias using implantable defibrillators relieved pressure to develop such drugs. However, there was an unmet need for safe antiarrhythmic agents for treatment of atrial fibrillation.

At first, agents intended primarily for prevention of sudden death, such as dofetilide, were also investigated for treatment of atrial fibrillation and then drugs, such as dronedarone, were developed only for prevention of atrial fibrillation. A high-risk atrial fibrillation population was enrolled to test the hypothesis that dronedarone would lead to a reduction in time to all cause mortality or unexpected cardiovascular hospitalisation; compared with placebo, dronedarone was effective. Its efficacy was thought not to be entirely related to its atrial antiarrhythmic effect and this concept was tested in a trial of dronedarone versus placebo in a population of patients with permanent atrial fibrillation. However, the trial was halted early because of hazard associated with dronedarone. The need for outcome trials was established during development of dronedarone and no antiarrhythmic is now likely to be approved for long-term treatment of atrial fibrillation without satisfactory trials of this type.

Ablation of accessory pathways has almost eradicated Wolff-Parkinson-White syndrome from adults...
in developed countries. Similarly, ablation of the re-entrant circuits that support paroxysmal supra-ventricular tachycardias (AV-nodal re-entry and atrio-ventricular re-entry) has proven highly effective. In 1998, it was reported that atrial fibrillation was usually triggered by atrial tachycardias arising from sleeves of atrial tissue extending from the left atrium and wrapping around the pulmonary veins.\(^{27}\) It was reasoned that electrical isolation of the pulmonary veins from the left atrium would prevent the initiation of atrial fibrillation. Results from patients with predominantly paroxysmal atrial fibrillation and little or no underlying heart disease have confirmed that 75% or more are effectively treated with this therapy, at least in the short-term.\(^{18}\) Longer term results (5–10 years) are now emerging, and it is clear that there is a steady attrition of patients remaining completely arrhythmia-free, but the episodes are often short and asymptomatic, and about a third of patients remain free of arrhythmia, and more after multiple procedures.\(^{29,30}\)

There have been many comparisons of the efficacy and complications associated with antiarrhythmic drug treatment and left atrial ablation/pulmonary vein isolation. In every study, ablation has proved more effective.\(^{28,31}\) Adverse procedure-related complications dominate in early follow-up, but the complications of antiarrhythmic drugs accumulate during longer follow-up. These trials have been criticised because patients have generally failed previous treatment with one or more antiarrhythmic drugs. However, one trial of patients naïve to previous antiarrhythmic drug therapy reported a clear advantage to left atrial ablation.\(^{32}\)

Follow-up in these trials has been relatively short (one year or less), and the endpoint was recurrence of atrial fibrillation rather than more meaningful cardiovascular outcomes. The atrial fibrillation endpoint was variously defined but there is now uniform agreement that 30 seconds of arrhythmia is sufficient to count as a recurrence. This identifies the potential for the arrhythmia to develop, but its relationship to other important clinical outcomes is unknown. At present several trials, eg, CABANA (Catheter ABLation versus ANtiarrhythmic drug therapy for Atrial fibrillation; NCT00911508) and EAST (Early Atrial fibrillation Stroke prevention Trial; NCT01288352) are exploring the effect of ablation on endpoints such as all-cause mortality and cardiovascular hospitalisations.

In the future, advances are expected in the genetics of sudden cardiac death and atrial fibrillation. Pharmacogenomics related to anticoagulation and risk of ventricular arrhythmia is likely to develop quickly. Better risk stratification of patients at risk of life-threatening arrhythmia is now beginning to make gains. Ablation for arrhythmias not dependent on simple macro re-entrant circuits—ventricular tachycardia, ventricular fibrillation, and atrial fibrillation—is being investigated now that better mapping techniques have been developed and multiple ablation energies are available. The search continues for antiarrhythmic drugs for the treatment of atrial fibrillation and there is new appetite to find drugs suitable for suppressing ventricular arrhythmias. Implantable diagnostics began in combination with pacemaker therapy several decades ago, but stand-alone monitors are implanted that will shortly be able to sense heart rate, arrhythmias, motion, respiration, blood pressure, temperature, glucose, electrolytes, oxygen saturation, and more, all capable of wireless transmission.

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