Defibrillation testing may not be necessary

Despite the fact that defibrillation threshold testing at the time of device implantation is generally safe, it does not improve implantable cardioverter defibrillator (ICD) shock efficacy or reduce mortality compared to a no-testing strategy, according to results from the SIMPLE (Shockless implant evaluation) study, which is the largest randomised clinical trial of ICD recipients to date.

Primary data were presented at a Late-breaking trial session at the 35th Heart Rhythm Society (HRS) Annual Scientific Sessions (7–10 May, San Francisco, USA) by Jeff S Healey (Population Health Research Institute, McMaster University, Hamilton, Canada).

Healey told delegates: “Traditionally ICDs have been implanted with the conduct of defibrillation threshold testing, and this procedure has been part of all major randomised ICD clinical trials. However, over the last 10–20 years potentially serious complications with defibrillation testing have been observed.” He also said that there have been significant improvements in ICD efficacy over the last 10 years and as a result many clinicians have begun to question the need for routine defibrillation testing at the time of ICD insertion. Therefore, he noted, the SIMPLE trial was designed to answer the question of whether routine defibrillation testing is safe and whether it is required.

“Our findings from the SIMPLE study demonstrate that those patients who received ICDs without defibrillation testing did as well as those who underwent the standard defibrillation testing at the time of implant,” Healey said. “Defibrillation testing is generally low-risk, but complications can occur.” He told Cardiac Rhythm News: “In our study, we occasion-ally did see serious complications, which were likely due to the testing; however, the rate was uncommon enough that our safety composites were not significantly different between arms.”

Specifically, he said, the trial showed non-inferiority for the primary endpoint of ineffective clinical shock or arrhythmic death (7.2% in the no-defibrillation testing group vs. 8.3% in the routine defibrillation testing group; hazard ratio 0.86; 95% confidence interval 0.65–1.14; non-inferiority p=0.0001). The rate of survival from arrhythmic death was 94.8% in the no-defibrillation group vs. 94.4% in the routine defibrillation testing group (p=0.50). The primary safety endpoint, comprised of complications within 30 days of the implant, was also similar between the two patient groups (5.4% in the no-defibrillation group vs. 6.5% in the routine defibrillation testing group, p=0.25).

Between January 2009 to April 2011, the SIMPLE trial randomised 2,500 patients in 18 countries at 85 centres to two groups receiving (n=1,253) or not receiving (n=1,247) defibrillation testing. Patients undergoing their initial ICD implant for standard primary or secondary prevention were included. ICDs and other ICDs with cardiac resynchronisation therapy (CRT-D) from Boston Scientific were studied. Average follow-up was over 3.1 years and was completed in February 2014. Only 1.4% of patients in the no-defibrillation arm and 2.1% in the defibrillation arm were lost to follow up.

The testing protocol, Healey said, required at least one successful termination of ventricular fibrillation at 173 or two successful terminations at 21J; the first shock energy in all zones was programmed to 31J in the defibrillation arm were lost to follow up. The primary end-point of the study was non-inferiority in the defibrillation testing arm and 2.1% in the no-defibrillation testing arm; hazard ratio 0.86; 95% confidence interval: 0.65-1.14; non-inferiority p=0.0001).

He also said that there have been serious complications with defibrillation testing at the time of implant, was also similar between the two patient groups (5.4% in the no-defibrillation group vs. 6.5% in the routine defibrillation testing group, p=0.25).

Between January 2009 to April 2011, the SIMPLE trial randomised 2,500 patients in 18 countries at 85 centres to two groups receiving (n=1,253) or not receiving (n=1,247) defibrillation testing. Patients undergoing their initial ICD implant for standard primary or secondary prevention were included. ICDs and other ICDs with cardiac resynchronisation therapy (CRT-D) from Boston Scientific were studied. Average follow-up was over 3.1 years and was completed in February 2014. Only 1.4% of patients in the no-defibrillation arm and 2.1% in the defibrillation arm were lost to follow up.

The testing protocol, Healey said, required at least one successful termination of ventricular fibrillation at 173 or two successful terminations at 21J; the first shock energy in all zones was programmed to 31J in both treatment arms. Baseline characteristics of patients were balanced, he noted, mean age for the defibrillation testing arm was 63 years and for the no-defibrillation arm was 62.6 years. Most of the patients were males (no-defibrillation testing arm: 81.4%, defibrillation testing arm: 80.5%).

“This is the first time the relation-
Defibrillation testing: End of an era, or pause for thought?

JEANNE E POOLE

The need to perform defibrillation testing at the time of implantable cardioverter defibrillator (ICD) surgery has been the focus of significant discussion and debate over the past years. Recognition that contemporary devices are distinctly different from those implanted during the developmental era of device, lead and electrical waveform has led many implanting physicians to abandon the practice altogether. A number of retrospective studies, prospective series, and recently, the results of the long-awaited randomised SIMPLE trial have further suggested that this may be an unnecessary procedure, Jeanne E Poole writes for Cardiac Rhythm News.

One of the earliest studies to suggest that defibrillation testing did not predict shock efficacy or mortality came from a retrospective review of the SCD-HeFT (Sudden cardiac death in heart failure trial) study, which examined outcomes in 811 patients implanted with a single-lead ICD (Blatt J A et al, J Am Coll Cardiol 2008; 52(7):551-6). Patients underwent a limited 10J safety margin protocol, but regardless of successful shock strength, all patients were implanted with the Medtronic 30J maximum output device used in the trial. Over 45.5 months of follow-up, no difference in first shock efficacy or mortality was observed when patients were stratified by lowest successful implant shock of 10J or less vs. greater than 10J.

Several other studies have found similar findings including the SAFE ICD study, which was a large prospective observational study of 2,120 patients (Brignole M J et al, J Am Coll Cardiol 2012; 60(11):981-987). Significant differences were not noted between defibrillation testing and no-defibrillation testing patients for the outcomes of major complications, first shock efficacy or mortality at two years. The results of the recently completed SIMPLE study were presented at a late-breaking trial session during the 35th Heart Rhythm Society Annual Scientific Sessions. The authors reported no difference in first shock efficacy, all-cause mortality or the primary safety composite endpoint between the no-defibrillation testing group and defibrillation testing randomised patients. Therefore, the authors concluded that performing defibrillation testing has no relationship to shock efficacy or long-term mortality and recommended abandoning this practice.

Is there still a role for defibrillation testing?

In light of these data and earlier studies, should we still consider that there is a role for defibrillation testing? To answer this, we need to clarify the reasons why we might want to test the patient and/or the system.

The first potential reason is the belief that we must observe the patient effectively terminated from ventricular fibrillation to assure ourselves that at the time of a spontaneous event, the ICD will in fact work. There are a number of problems with this assumption, beyond the results of SIMPLE. First, the rhythm that is tested in the electrophysiology laboratory is ventricular fibrillation whereas the majority of patients with ICDs experience ventricular tachycardia. Second, the probabilistic nature of defibrillation testing suggests that a failed defibrillation testing may not fail with repeat testing using the exact same configuration, or perhaps on another day. Third, true step-down or step-up defibrillation threshold testing has long been abandoned in lieu of the concept of 10J safety margin testing and finally, the patient clinical milieu in the electrophysiology lab is unlikely to be the same situation when a patient has a spontaneous arrhythmia. Triggers such as acute ischaemia, worsened heart failure or metabolic abnormalities may be arrhythmogenic triggers not present at the time of defibrillation testing. Thus, the efficacy of a “first” shock for a spontaneous arrhythmia may not be predicted by defibrillation testing.

The second potential reason to perform defibrillation testing is to assess the functionality of the ICD generator-lead system. Consider just some of the different components that are involved in this activity: 1) Reliable sensing of a highly variable (in terms of frequency and amplitude) signal source; 2) filtering and processing of the sensed signal; 3) classification of the detection as sustained vs. non-sustained, supraventricular vs. non-supraventricular tachycardia, noise vs. non-noise; 4) acquisition, processing and storage of the electrogram and event information; 5) assuming a sustained ventricular tachycardia, charging of the capacitors in preparation for delivery of defibrillation therapy, which involves transformation of the energy source to a stored high voltage on the capacitors in a matter of less than 10 seconds; 6) monitoring during charging to ensure the ventricular tachyarrhythmia is ongoing (confirmation); 7) upon completion of charging, identification of appropriate delivery window (synchronisation) if appropriate; 8) discharge of the capacitors through the output circuit, device feed-throughs, lead connections, lead conductors, and electrode/tissue interface, all accommodating peak currents as high as 40 amperes; 9) immediate resumption of signal acquisition from highly-polarised tissue to determine termination/non-termination of a treated episode and 10) re-detection and classification (if necessary) or detection and classification of termination.

The engineering feat required to accomplish these actions with a high level of success has been nothing short of remarkable. But, do we need to place the patient into a life-threatening tachyarrhythmia at the time of implantation in order to feel confident that the device will perform as expected in the event of a spontaneous arrhythmia? That answer appears to be “no”—at least for most patients. The failure rate for pulse generators is low, and when problems have been identified, device replacement at the time of implantation is unlikely to have uncovered the malfunction.

ICD system failure has primarily been confined to the high voltage leads. Patients with apparently functioning advisory/recall leads for whom the physician has decided to retain the lead at the time of pulse generator replacement should undergo system testing. This does not however require the patient to be placed into ventricular fibrillation. A synchronised full output shock could be delivered in normal rhythm and achieve the intended purpose of testing the device-lead-system, minimising the risk to the patient. Some might argue that any patient at the time of pulse generator replacement should have such testing performed as the lead, by that point, will be anywhere from on average four to 10 or more years old.

There are other patient factors that might favour defibrillation testing: patients in whom the shock vector is anticipated to be poor (eg. left ventricular mass dominantly posterior to the chest), other patients anticipated to have a high defibrillation threshold; also treatment of the patient with amiodarone, right sided implants (not included in the SIMPLE study) and secondary prevention patients.

While the results of the SIMPLE study are reassuring and can be used to support the increasing practice of implanting physicians to abandon defibrillation testing at the time of de novo ICD implantation, physicians should, nevertheless, consider carefully each patient and device-lead system. As encouraging as the SIMPLE results are that performing defibrillation testing did not appear to harm the patient, the counter of performing defibrillation testing also appeared overall to be a safe procedure.

Jeanne E Poole is with the University of Washington, Seattle, USA

Defibrillation testing may not be necessary

Nick Linker (The James Cook University Hospital, Middlesbrough, UK) told Cardiac Rhythm News that the results of the SIMPLE trial do not address the opposite question of which patients should have defibrillation tests. “This is an important area that will need to be evaluated,” he said. “This is a difficult group to tease out and there will clearly be individual clinical decisions to be made. However, I would think that patients having a right-sided ICD implant and those with abandoned leads should be tested. Patients with advisory leads may also require defibrillation threshold testing.”

John Day (Intermountain Healthcare, Murray, USA), president-elect of the Heart Rhythm Society, said: “Defibrillation testing at the time of ICD implantation is something that we have been doing, at least in this country [USA], since the first ICD was approved in 1985. The SIMPLE trial results are important in that they challenge this practice.”
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What is the best strategy for managing atrial fibrillation?

John D Day

COMMENT & ANALYSIS

After personally performing more than 3,000 atrial fibrillation ablation procedures I have to ask myself: am I even making a dent in this disease? I cannot remember seeing so many new patients, even young patients, with atrial fibrillation when I began my cardiology fellowship nearly 20 years ago. John D Day writes for Cardiac Rhythm News.

Indeed, based on the work of Sunmeet Chugh from the Cedars Sinai Heart Institute in Los Angeles, USA, and colleagues (Circulation 2014;129:837-847), the incidence of atrial fibrillation, in countries like the USA, has increased 71% in the last 20 years.

We have always thought that this was due to our ageing population, but the incidence is rising at a greater magnitude than our ageing population. Therefore, something—that cannot be explained by genetics or an older population—is happening.

We are in the middle of an atrial fibrillation epidemic. Did this epidemic have to happen? Chugh and colleagues have shown that the epicentre of this atrial fibrillation epidemic is right squarely in North America. The USA is a land of immigrants. We come from Europe, Africa, South America, Asia, and other regions, yet the prevalence of this epidemic is so much greater in the USA than in our ancestral countries.

It is true that genetic factors do play a role in atrial fibrillation. For example Caucasians and men are more prone to the condition. However, genetic factors cannot even begin to explain the 10-fold difference in the incidence of atrial fibrillation between Asia and North America as reported by Chugh et al. What is even more interesting is that once these Asians immigrate to the USA, the incidence of atrial fibrillation closely approximates that of other Americans.

Indeed, Greg Marcus from the University of California, San Francisco, USA, and colleagues also looked at this issue (Circulation 2013;128:2470-2477). Marcus et al showed that of 375,318 incident atrial fibrillation episodes over 3.2 years in California, there was no difference in the incidence of atrial fibrillation in Asians compared to Hispanics or Blacks. Caucasians, known to be genetically predisposed to atrial fibrillation, had just a 37% greater incidence of atrial fibrillation. It appears that whatever protective effect Asians enjoyed in their native countries was lost once they emigrated to the USA.

However, the problem is not just with the USA. Chugh’s article also shows that this atrial fibrillation epidemic is occurring in most developed countries around the world.

What could explain this phenomenon? Prash Sanders from the Royal Adelaide Hospital in Australia, published an article in JAMA last year (2013;310(19):2050-2060) which caught the world by surprise. In this study, Sanders and colleagues randomised 150 overweight and obese atrial fibrillation patients to a weight loss/lifestyle modification programme versus general healthy lifestyle advice. Remarkably, both groups of patients saw a reversal in their atrial fibrillation.

However, the group that was less randomised to a weight loss/lifestyle modification programme not only lost an average of 14.3kg but also experienced a nearly three-fold reduction in their atrial fibrillation burden over 15 months of follow-up as assessed by outpatient telemetry monitoring.

For the first time, in a well designed partially blinded, randomised controlled study, Sanders and co-workers showed that lifestyle modification, including weight loss, could reverse atrial fibrillation. Could the lifestyle of modern civilisation and our obesity epidemic explain the marked spike in new atrial fibrillation cases we are now seeing?

In the recently concluded 35th Heart Rhythm Society Annual Scientific Sessions, there were studies showing similar findings. Some of these studies are covered in this issue of Cardiac Rhythm News [see page 1 and page 16]. Specifically, the Mayo Clinic group [page 16] showed that bariatric weight loss surgery resulted in nearly a three-fold reduction in atrial fibrillation over seven years of follow-up in comparison to a control group that did not undergo weight loss surgery. In addition, the Adelaide group [page 1] showed that aggressive lifestyle modification following atrial fibrillation ablation procedures could double the success rate of this procedure.

Clearly there is a growing interest in non-pharmacological and procedural driven management of atrial fibrillation to combat this epidemic.

Aggressive DARE lifestyle modification programme for atrial fibrillation

Frustrated that we just could not seem to improve success rate of AF after ablation

Aggressive lifestyle management helps improve success rate of AF after ablation

Continued from page 1

antiarrhythmic drug use when compared with conventional care. These beneficial effects, they wrote, “may be attributable to decrease in left atrial area and ventricular wall thickness, thereby reducing the left atrial hypertension that is a common finding in obese patients.”

In ARREST AF, 149 patients (41% with non-paroxysmal atrial fibrillation) were included in the study after their first ablation. The inclusion criteria required patients with a body-mass index (BMI) of ≥27.5kg/m2 and one cardiovascular risk factor such as hypertension, diabetes, sleep apnoea, or abdominal lipids.

Pathak explained that all patients enrolled were offered aggressive risk factor management—which addressed weight, hypertension, diabetes, sleep apnoea, cholesterol, alcohol use and smoking—in a physician-led clinic directed at risk factor management in any attempt to reverse atrial fibrillation. Patients had clinic review and seven-day Holter monitoring at three-six monthly intervals. The absence of any arrhythmia ≥30 seconds and change in atrial fibrillation symptom score (frequency, duration, severity and symptom severity) were determined.

Results Pathak said that patients treated with the aggressive risk factor management strategy experienced greater reduction in weight (-12.1±1 vs. -1.5±0.8), systolic blood pressure (-34.8 vs. -20.5±3mmHg), better glycaemic control (HbA1c; p=0.001) and lipid profile (LDL/TG; p=0.01). At follow-up, atrial fibrillation frequency, duration, severity and symptom severity decreased more in the aggressive risk factor management group compared to controls. Pathak highlighted that single procedure drug-unassisted arrhythmia free survival was greater in the risk factor management arm compared to controls (32.9% vs. 9.7%) and multiple procedure arrhythmia free survival was “markedly better” in the risk factor management group compared to controls (87% vs. 17.8%) with 16% of risk factor management patients and 42.4% of controls using antiarrhythmic drugs.

On multivariate analysis, both the type of atrial fibrillation and risk factor management were independent predictors of outcome, he highlighted.

In conclusion, Pathak said that aggressive risk factor management significantly improves the long-term success of atrial fibrillation ablation.

“This study underscores the importance of therapy directed at the primary promoters of the atrial fibrillation substrate to facilitate rhythm control strategies.” Sanders told Cardiac Rhythm News that in light of these results current guidelines need to be changed including risk factor management in any attempt of rhythm control.

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Innovating for life.
Cryoballoon is more effective than conventional radiofrequency ablation

A randomised controlled trial comparing three methods of pulmonary vein isolation for paroxysmal atrial fibrillation has revealed that procedures were faster with Medtronic’s Arctic Front cryoballoon than with wide encirclement using conventional point-by-point radiofrequency ablation. Procedures using the cryoballoon also resulted in a higher single procedure success rate.

Ross Hunter, St Bartholomew’s Hospital, Bart Street, London, UK, presented the results of the trial at a Late-breaking trial session at the 35th Heart Rhythm Society (HRS) Annual Scientific Sessions (7-10 May, San Francisco, USA).

“Radiofrequency ablation for pulmonary vein isolation is technically challenging, time consuming and the first time success rate is variable. The cryoballoon is arguably easier to use, but there is a lack of head-to-head data [comparing cryoballoon with radiofrequency ablation] both in terms of procedural parameters but also in terms of efficacy. Pilot data from our institution suggested a higher success rate with a combined approach than with either modality alone. We compared the success rates obtained with these three strategies in a randomised controlled trial with the hypothesis being that the combined approach is superior to either treatment alone for paroxysmal atrial fibrillation,” Hunter said.

The investigators randomised patients undergoing first ablation for paroxysmal atrial fibrillation using radiofrequency energy, the cryoballoon, or a combined treatment. They defined pulmonary vein electrical isolation (as confirmed by using a circular mapping catheter) as the procedural endpoint for all cases.

In the study, the radiofrequency group underwent wide encirclement of the pulmonary vein using an irrigated radiofrequency ablation catheter guided by a 3D mapping system. Contact force sensing catheters were not used, Hunter clarified. The cryoenergy group underwent ostial pulmonary vein ablation using the Arctic Front cryoballoon. Hunter noted that if pulmonary vein isolation could not be achieved using the cryoballoon alone, then further focal lesions were added. The combined group underwent wide encirclement of the pulmonary veins to achieve isolation, followed by two empirical applications of the cryoballoon to each pulmonary vein ostia. Patients were followed up at three, six and 12 months with a clinic review and seven days of ambulatory ECG monitoring. The primary endpoint was the one year success rate, defined as freedom from arrhythmia following the three-month blanking period off antiarrhythmic drugs after a single procedure.

A total of 237 paroxysmal atrial fibrillation patients were randomised in a 1:1:1 fashion so that there were 79 patients in each group. In the radiofrequency ablation group, 77 were ablated with two patients being withdrawn. In the cryo group, 78 patients were ablated and one was withdrawn after being rendered asymptomatic following a change of antiarrhythmic drugs. All 79 patients randomised to the combined group were ablated. Patients were followed up to one year. Baseline demographics were similar in all groups. Approximately two thirds of the patients in each group were male. Patients were around 60 years of age and had atrial fibrillation for around five years. Patients in all groups had a left atrial diameter of around 4.3cm and had failed drug therapy with more than two antiarrhythmics.

Success at one year was achieved in 47% in the radiofrequency group, 67% in the cryo group, and 76% in the combined group (p=0.015 for radiofrequency vs. cryo, p<0.001 for radiofrequency vs. combined, and p=0.166 for cryo vs. combined). Procedure time was 211 minutes for radiofrequency compared to 167 minutes for cryo and 278 minutes for combined (p=0.001 for radiofrequency vs. combined, radiofrequency vs. cryo, and cryo vs combined groups). In the cryo group, 69% of patients had all pulmonary veins isolated with the cryoballoon alone and the rest needed additional point-by-point ablation to achieve pulmonary vein isolation.

Complications

Hunt explained that when four complications with radiofrequency ablation occurred there were three complications: one pseudoaneurysm and two phrenic nerve palsies.

Conclusion

“The cryoballoon was faster than radiofrequency ablation and had a higher success rate. The combined group also had a higher success rate than radiofrequency, but was not superior to cryoenergy alone. However, there is a learning curve with cryoenergy. Point-by-point ablation is still needed to achieve pulmonary vein isolation for some patients,” Hunter explained.

He stated that the implications of the trial results are that the cryoballoon is an appealing option for paroxysmal atrial fibrillation ablation. “The combined approach is less attractive. The impact of Arctic Front Advance and contact force sensing is still to be assessed, and prospective trials need to confirm the superiority of cryoenergy,” Hunter noted.

Substrate based ablation superior to conventional ablation of stable clinical ventricular tachycardia

For stable clinical ventricular tachycardias, a substrate based ablation approach is more effective than conventional ablation preventing recurrences from any ventricular tachycardias in patients with ischaemic cardiomyopathy, according to results of the VISTA study, which is the first randomised trial performed in this area.

Data from the VISTA (Ablation of clinical stable ventricular tachycardia versus substrate base ablation on long-term freedom from any ventricular tachycardia) open-label, randomised, multicentre study were presented by Luigi Di Biase (Texas Cardio Arrhythmia Institute at St David’s Medical Center, Austin, USA; and Albert Einstein College of Medicine, at Montefiore Hospital, New York, USA) at a Late-breaking trial session at HRS 2014.

Di Biase highlighted that non-randomised studies have previously suggested that substrate ablation is superior to conventional ablation of clinical stable ventricular tachycardia achieving freedom from any ventricular tachycardia at follow-up; however, randomised data were lacking.

Di Biase told Cardiac Rhythm News: “In the VISTA study, we found that the substrate based ablation approach allows performing ventricular tachycardia ablation while in sinus rhythm; therefore, the procedure might be a bit easier for the physician and for the patient with and better success rates.” He said that 84.5% patients treated with the substrate based ablation approach were free from any clinical ventricular tachycardia at 12 months follow-up compared to 51.7% patients treated with the conventional approach.

Between April 2009 and July 2013, 118 patients with symptomatic, drug refractory, haemodynamically stable clinical ventricular tachycardias were enrolled at seven centres in the USA and Europe. They were randomly assigned (1:1 ratio) to conventional ventricular tachycardia ablation (n=60, mean age 65±12 years) and to substrate ablation (n=58, mean age 67±9 years). Baseline characteristics were not different between both groups and all patients were followed up for at least 12 months, with interrogations and office visits every three months, noted Di Biase. He explained that the ablation strategy for the conventional approach included short linear ablation lesions placed across the ventricular tachycardia isthmus to terminate clinical ventricular tachycardia. It also included activation mapping, entrainment manoeuvres and pace mapping. For the substrate ablation approach, he said, lesions targeted the entire scar area as defined by 3D mapping to target abnormal electrograms. In both approaches, epicardial mapping and ablation were considered in case of inducible clinical ventricular tachycardias after endocardial ablation. Radiofrequency ablation with open irrigated catheter was used. Procedural and fluoroscopy times were not statistically different between groups, although a trend towards longer procedures was noted in the conventional ablation arm.

Results

Overall, “a substrate ablation approach may improve the success rate and might reduce mortality in patients with ventricular tachycardias,” said Di Biase. He told delegates that no patients were lost to follow-up. More patients were on antiarrhythmic drugs after conventional ablation (58%) than those treated with the substrate based ablation approach (12%).

Di Biase noted that combined incidence of rehospitalisation and mortality was “significantly higher” in the conventional group approach than in the substrate ablation approach (46.7% vs. 20.7%, p=0.003, respectively).

Conventional ventricular tachycardia ablation, after Cox multivariate analysis, was associated with three times more recurrence compared to substrate ablation (hazard ratio 3.1, p=0.01), said Di Biase. Regarding complications, he commented, one arteriovenous fistula and two pericardial effusions occurred in the conventional group and three pericardial effusions were reported in the substrate ablation group. All effusions were treated conservatively.

Di Biase suggested the need for further randomised studies to confirm these results.
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Increased adherence to remote monitoring associated with improved survival in patients

Data presented during a Late-breaking clinical trial at the 35th Heart Rhythm Society (HRS) Annual Scientific Sessions (7–10 May, San Francisco, USA) has revealed that increased adherence to remote monitoring leads to reduced mortality for pacemaker and defibrillator patients.

Suneet Mittal, director of Electrophysiology at the Valley Hospital Health System of New York and New Jersey, USA, presented the results of a prospective, national, observational study of 262,564 US patients, which found that the greater the adherence to remote monitoring, the better the patient fared. They restricted analysis to wireless devices capable of remote monitoring via the Merlin.net Patient Care Network (St Jude Medical). A press release from St Jude Medical stated that this was the largest study to-date of remote monitoring devices capable of remote monitoring.

The study demonstrated that patients with high adherence to remote monitoring had more than twice the probability of survival than that of patients without remote monitoring.

“In this very large cohort, we demonstrate that remote monitoring use is associated with improved survival, irrespective of device type. For the first time, we show that there is a relationship between remote monitoring adherence and survival. Patients with high remote monitoring use had 53% greater survival than patients with low remote monitoring. They also had 140% greater survival than patients not using remote monitoring,” Mittal said.

Research previously published (Saxon L et al, Circulation. 2010) has shown that patients with an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) who are enrolled into a remote monitoring programme have improved survival. However, it was unknown whether this association applied to pacemaker patients, Mittal explained.

Mittal and colleagues sought to determine the following: the relationship between extent of adherence to remote monitoring and survival; and the association between remote monitoring and survival in pacemaker patients and the potential explanations for improved survival in device patients undergoing remote monitoring.

The investigators included patients if they were implanted with a St Jude Medical pacemaker, CRT pacemaker, ICD, or CRT-D device (2008–2011; >90 days). Age, gender, device type, and surveillance duration were ascertained using device tracking data. The investigators prospectively compared all-cause survival for each device type among patients with high (≥75%), low (between 0% and 75%), or no (0%) remote monitoring service utilisation.

The researchers evaluated 262,564 patients (71±14 years, 65% male) with a pacemaker (n=112,692, 43%), ICD (n=82,621, 32%), CRT-D (n=59,547, 23%) or CRT pacemaker (n=7,704, 3%). Patients with remote monitoring sessions had significantly greater survival than patients without (p<0.001). This relationship was preserved for all device types, including pacemakers. Patients with high remote monitoring service utilisation had significantly greater survival than patients with low utilisation (p<0.001) or no utilisation (p<0.001).

Mittal and colleagues showed, for the first time, that improved survival is observed in pacemaker patients and patients with the highest adherence to remote monitoring. More than 50% did not enrol in remote monitoring. However, of those who did enrol, there was a significant decline in the likelihood of dying,” Mittal said.

The researchers also found that: “There was wide geographic variability in the degree of remote monitoring use nationally. Patients living in the highest population density zones of the USA such as Chicago, New York, California and Florida were the least likely to be enrolled and using remote monitoring, as opposed to those living in the Midwest and Pacific Northwest. “This is a readily available technology and all patients should enrol in remote monitoring and be encouraged to engage with remote monitoring at a high level because the mortality reductions associated with remote monitoring are of a very significant and sizeable proportion. In the more populous areas, there is a notion that it is easy to get to the doctor, but our study has shown that there is something beyond that. The mechanisms of these associations require further investigation,” Mittal said.

Mechanical transvenous extraction of ICD leads with a multiple venous entry-site approach is safe and effective

Physicians reporting 15 years of experience in extracting implantable cardioverter defibrillator (ICD) leads with a mechanical single-sheath technique and a multiple venous entry-site approach say they have found it is a complex but safe procedure, with a 99% success rate and no major complications.

The retrospective study recently published in Europace by Maria Grazia Bongiorni and colleagues (University Hospital of Pisa, Pisa, Italy) evaluates procedures and outcomes for 545 consecutive patients referred at their institution for extraction of 582 ICD leads between 1997 and 2012.

The authors describe that in the technique—developed in 1997—they performed an initial attempt at manual traction. If this resulted unsuccessful, they used a single-sheath approach with progressive dilatation inserting and advancing dilators (from Cook Vascular) through the venous entry-site. Finally, they considered an internal transjugular approach when dilatation was ineffective or judged too risky. Bongiorni et al report that in this study simple manual traction was effective in 35 leads (6%). Mechanical dilatation through the venous entry was effective in 484 cases (83%) and successful extraction through the internal jugular vein was achieved in 58 cases (10%). “Thus, the success rate increased from 6% with manual traction to 89% through the venous entry-site mechanical dilatation approach, and reached an overall value of 99% (577 out of 582) when mechanical dilatation was attempted via the internal jugular vein,” the authors note.

They also report that dwell-time, a passive fixation mechanism and dual-coil lead design were independently associated with the need for mechanical dilatation and for crossover to the internal jugular approach. This should be considered when planning the removal procedure. Moreover, passive fixation and dual-coil lead design predict a more challenging extraction procedure. Thus, an implantable cardioverter defibrillator lead with these characteristics should be considered for implantation only after careful evaluation of the expected benefits and possible risks.”

A total of five leads could not be removed over the period evaluated. Three leads fractured and two proved to be firmly encapsulated in fibrotic tissue at the level of the distal coil. In four cases, the leads were left in situ with no complications reported, and in the fifth the patient was referred to a cardiac surgeon for open-chest extraction.

The mean extraction time was eight minutes, ranging from one minute to 210 minutes. There were no major complications associated with lead extraction. Some minor complications did occur, including pericardial effusion in two patients, sustained ventricular tachycardia in five patients, sustained atrial fibrillation in five patients and haematoma at the pocket requiring drainage in five patients. Four patients required blood transfusion, while pneumothorax occurred in one patient and lead dislodgement in one patient.

The authors highlight that this is the largest published single-centre experience in ICD lead extraction and encompasses a wide range of ICD models that are still in use. “Although complex, the mechanical transvenous extraction of ICD leads is a safe and effective procedure,” they conclude.
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Leadless pacing: An exciting new technology

The concept of a totally self-contained intracardiac pacemaker, first explored over 40 years ago by J W Spickler et al, has finally become a reality with the implantations of the Nanostim leadless pacemaker (St Jude Medical) and the Micra transcatheter pacing system (Medtronic) in humans. Cardiac Rhythm News speaks to physicians who are currently implanting these devices and industry representatives about the features of this new exciting technology in cardiac pacing.

Chronic performance of the Nanostim, after one-year follow-up of the LEADLESS trial, has shown that the device continues functioning “as expected” with pacing threshold of 0.43 volts and 10.32mV sensing, which are “comparable to traditional pacemakers”, according to data presented by Vivek Reddy (Mount Sinai School of Medicine, New York, USA) at a Late-breaking trial session at the 35th Heart Rhythm Society (HRS) Annual Scientific Sessions (7–10 May, San Francisco, USA). Reddy also said that no safety events were reported at 12 months: “There was no device migration or no device dislodgments, no infections, no mechanical failures or early battery depletion and no pro-arrhythmia,” he noted.

At HRS Scientific Sessions 2013, Reddy presented data—recently published online in Circulation—which demonstrated the safety and feasibility of Nanostim and supported its CE mark approval in October 2013. Last year, the results showed a 97% implant success rate (32 out of 33 patients enrolled), a median procedure duration of 28 minutes and an average hospital discharge of less than two days. In terms of adverse events, one minor groin haematoma, which required no treatment, and one cardiac perforation and tamponade which led to stroke and death were reported—the overall complication-free rate was 94%.

The device, commercially available in Europe, following its CE mark approval, is also being evaluated in an investigational device exemption study for FDA approval (LEADLESS II pivotal trial) and in a European post-marketing approval study (LEADLESS Pacemaker Observational study).

The Micra system is an investigational device and is being assessed in a global pivotal clinical trial. The first successful in-human Micra implantation occurred in December 2013 in Linz, Austria.

Rationale for development of leadless pacing technology

Issues regarding pocket infection or haematomas caused by traditional pacemakers, risks associated with lead failure and the need for improvement in patients’ quality of life have driven the development of this new technology. Werner Jung (head of the Department of Cardiology, Schwarzwald-Baar Klinikum Villingen-Schwenningen, Germany) says that according to published data the in-hospital mortality rate for a traditional pacemaker infection is 8.4% and the 15-month post-implant mortality rate for pacemaker patients with infection is 36.3%, more than double the 15.4% mortality rate of uninfected pacemaker patients.

Regarding hospital length of stay for a pacemaker patient with an infection, he says that the average is 14.4 days compared to 4.8 days for pacemaker patients without infections. Agreeing with the common view that the lead is the “weakest link” in traditional pacing technology, Jung says that most common lead problems relate to chronic lead failure such as lead dislodgement or lead fracture, insulation defects, infections that require difficult lead extraction techniques, and to the incompatibility of some leads with magnetic resonance imaging.

Why is leadless pacing possible now?

Drew Hoffman (senior vice president and general manager of Nanostim at St Jude Medical) says that 40 years ago “the technology was not available to allow for miniaturisation sufficient to place a pacemaker directly into the heart without the loss of important functionality, such as battery life.”

The battery of the Nanostim, he notes, “despite the miniaturisation [Nanostim is less than 10% the size of a traditional pacemaker] is expected to have an average lifespan of more than nine years at 100% pacing, or more than 13 years at 50% pacing.”

In the case of Medtronic, Mike Hess (vice president of Research and Development for the Bradycardia business at Medtronic), comments, the Micra project took seven years to become a reality. He says: “A lot of the time was spent on designing how the Micra device attaches to the heart and how to deliver it into the heart. At the same time, we were working on new, more efficient circuits and designing a battery that was small enough to power the device for about 10 years.” Regarding dimensions, the Micra device is “the smallest pacemaker in the world being 30% smaller than Nanostim,” he says. This miniaturisation is part of a broader initiative at Medtronic called “deep miniaturisation” which has developed other devices such as the recently launched Reveal Linq, which is the smallest insertable cardiac monitor available for patients, Hess notes.

More similarities, differences and limitations

Both the Nanostim and Micra devices are single-chamber pacemakers placed directly into the heart with a steerable catheter through the femoral vein. It is a procedure that, according to Larry Chinitz (director of the Heart Rhythm Centre at New York University Langone Medical Centre, New York City, USA), is very familiar among electrophysiologists. “It is a relatively straightforward, easy-to-learn procedure, very adaptable to our usual techniques,” he says.

Chinitz, who implanted the first Micra device in the USA in February 2014, and Jung, who has implanted the Nanostim device in seven patients as part of the LEADLESS Observational European post-approval trial, both comment that procedure times with the Micra and Nanostim devices are shorter—lasting from 30 to 45 minutes—than those with traditional pacemakers (about one hour). Vivek Reddy noted at HRS 2014 that the experience implanting Nanostim in the two major studies for the device (LEADLESS II and LEADLESS Observational study) has shown an “overall trend in decreasing procedure time, so ultimately some of the procedures could last for 20 minutes”.

Retrieval of the Nanostim device at the time of implantation and later is possible. Drew Hoffman, from St Jude Medical, says, “The Nanostim device is designed to be fully retrievable so that it can be readily repositioned during the implantation and later retrieved if necessary.” The results of the LEADLESS trial revealed two
cases that needed device retrieval, one due to inadvertent placement in the left ventricle and another due to revealed ventricular tachycardia two days after implantation. Reddy et al reported successful retrieval and implantation of a new device placed in the right ventricle in the first case and successful Nanostim removal in the second patient, who was thereafter implanted with an implantable cardioverter defibrillator.

The Micra device has also been designed to be retrieved at the time of implantation if needed, Mike Hess, from Medtronic, comments, “there is a way that allows physicians to snare the device and pull it back into the delivery system, and then it will extract the tines or remove the tines from the heart and let them position the device somewhere else.” The Micra device is in its early stages of clinical investigation and, so far, no retrieval cases with the Micra device have been reported yet, he notes.

After Reddy’s one-year follow-up of the LEADLESS trial presentation at HRS 2014, strategies for device replacement and retrieval in the long run were addressed. Reddy mentioned that there is preclinical data showing that the Nanostim device can be retrieved at approximately six months after implantation in animal models. Regarding possibilities in the long term, he said: “Will the device endothelialise so thoroughly that the retrieval catheter would not be able to grab back? The real answer is: we will know 10 years from now when we start removing these devices. Having said that, there are plans in a few animal that have been implanted [in some studies] to allow for a chronic assessment of device retrieval and we should know later this year the feasibility of these removals.” Reddy also said that “it is not impractical to think about putting one or two or three of these devices, ultimately, in the patient.”

Among the differences between the two devices, Werner Jung highlights the introducer sheath and the fixation approach. He says that the Nanostim uses a smaller sheath in diameter (18F) than what it is required for the Micra device (23F). “This is an important difference in that it may impact access to stop bleeding after the procedure,” he notes. Chinitz also comments that Micra’s larger sheath “may lead to some transient vascular problems, but in our experience [four implantations reported on 14 April 2014] we have not seen any issues yet.”

The fixation approach used with the Nanostim device is “very similar to what is used today with conventional pacemaker leads,” explains Jung. “The device is fixed to the heart via a helix. This is key because it is part of the overall system that enables the device to be potentially retrievable over its entire lifetime.”

The Micra device includes active fixation tines (tines that actively attach into the tissue) that keep the device in place in the heart. However, “this fixation technique might be a potential problem for chronic retrievability,” Jung speculates. In contrast, Hess says that the fixation approach of Micra “is quite appropriate for this technology. We chose not to use the fixation that pacing leads use because this was a very different kind of device. We do not think that the pacing lead helix approach necessarily makes sense if you do not have a pacing lead attached to the device.”

Medtronic also believes the size of Micra gives it an advantage over Nanostim. Hess comments: “Our design goal was to have more flexibility in where you place the device, and so by having it much shorter it can be placed in more locations in the apex or the septum, if necessary, in the ventricle.”

The most relevant limitation, according to both the industry representatives and the physicians Cardiac Rhythm News spoke to, is that the current Nanostim and Micra devices are indicated for patients requiring a single-chamber pacemaker only, limiting their use to a “relatively small part of the overall pacemaker market,” says Hess. Jung comments that in Europe, the indication for a single-chamber or dual-chamber pacemaker varies between 22% to 32% and 64% to 75%, respectively. Current indications for Nanostim, as Jung reports, are for patients with chronic atrial fibrillation and second or third atrioventricular degree block, patients with sinus rhythm with second or third atrioventricular block and a low level of physical activity or short expected lifespan and patients with sinus bradyarrhythmia with infrequent pauses or unexplained syncope. Larry Chinitz says that the Micra device is indicated for patients with bradycardia, patients with syncope or patients with sick sinus syndrome.

Drew Hoffman comments that St Jude Medical is now researching options for dual-chamber leadless pacing technologies. “We have received feedback that as time goes on, and the technology is proven, implanters will use leadless technology exclusively.”

While initial official results with the Micra global pivotal trial, according to Medtronic, are expected in the second half of 2014, Chinitz comments that so far the reaction from patients receiving this technology has been “extremely positive.” With no complications reported from Chinitz personal experience with Micra to date, he says that leadless technology “is a very disruptive technology, it changes the way we think about implantable devices, and the future development of devices. I think it will be revolutionary in the field of pacing and eventually defibrillation.”

Jung, who has not reported complications with his Nanostim implantations, considers that leadless pacing is a “revolutionary breakthrough” that could potentially impact not only the quality of life of patients but also provide a reduction of costs compared to traditional pacing management systems.

Ongoing studies for Nanostim and Micra

- LEADLESS Pacemaker Observational study: European post-approval trial for Nanostim. It is a prospective, multicentre, post-market clinical study designed to build additional evidence to support the safety profile of Nanostim in patients with indication for ventricular single-chamber pacing. It is expected to enrol approximately 1,000 patients in approximately 100 centres in Europe.

- LEADLESS II pivotal trial for US FDA approval: the first implant took place in February 2014 by Vivek Reddy, chairman of the Steering Committee of the study. It will enrol approximately 670 patients at up to 60 centres worldwide with up to 50 sites in the USA. It is being conducted under an investigational device exemption from the FDA.

- Medtronic Global pivotal clinical trial: single-arm, multicentre global clinical trial planned to enrol up to 780 patients at approximately 50 centres. Initial results from the first 60 patients, followed up for three months, are expected in the second half of 2014.
Why did you choose a career in medicine and, in particular, why did you choose to specialise in electrophysiology?

From my schoolboy days, I remember always wanting a career in medicine. I was interested in cardiology and neurology but I felt that cardiology offered a greater opportunity to benefit patients since—at the time when I was making career choices—there was little, if any, treatments that could be offered for neurological conditions.

I developed an interest in electrophysiology by chance when I obtained my first registrar post working for Dr David Shaw in Exeter, UK. He had an interest in bradycardia and pacing which rubbed off on me. Then, Dr Shaw introduced me to Professor John Camm—who was just moving from St Bartholomew’s Hospital (London, UK) to St George’s Hospital (London, UK). Prof Camm, then [in 1986], offered me a research post at St George’s and my career developed from there.

Who were your career mentors and what advice did they impart to you?

My initial mentor was Dr David Shaw who awoke my interest in arrhythmias. Prof Camm and Dr David Ward had a major part in my career development. They fostered my interest in electrophysiology but Prof Camm cautioned me against being a “jack of all trades” advising me to focus on one area, i.e. arrhythmias. Having said that, my work environment at St George’s with colleagues such as Mark de Belder, Mike Griffith, Cliff Garratt, Chau Pak Lau, Ravindra Mehta and others, was a major influence in my career development.

How has electrophysiology evolved since you began your career?

There have been many developments in electrophysiology since I started at St George’s. Perhaps, the greatest is the evolution of ablation of cardiac arrhythmias. At that time [1986], electrophysiology was very interesting intellectually but there was little one could do in terms of treatment, apart from a few antiarrhythmic drugs. Radiofrequency ablation had not been invented, implantable cardioverter defibrillators (ICDs) were in their infancy and required major surgery for implantation. The first successful treatment for arrhythmias I was involved in was surgical; working with Mr John Parker on surgical treatment of Wolff Parkinson White syndrome and atrioventricular (AV) nodal tachycardia was a breakthrough. Now we have effective and less invasive therapies for these patients.

What area in the field do you feel most passionate about and why?

In the last couple of years, I have moved more into device therapy rather than electrophysiology. I think the revolution in the management of heart failure with the advent of cardiac resynchronisation therapy (CRT) is very exciting. I can still remember the first patient I implanted with a CRT device, he could not walk from his bed to the nurses’ station on the ward before the procedure. The next day, he was not in the ward when I went to see him, he had walked with his father to the entrance of the hospital.

Of the research you have been involved in, what do you consider to be your greatest achievement and why?

I have been involved in many research projects over the years; however, on a personal basis my most satisfying project has been the Protect-Pace trial. This was a study that tried to answer a question that has interested cardiologists for many years, which is: where is the best place to pace the right ventricle in order to minimise deleterious effects on cardiac function? There has been concern over the years that traditional apical pacing might not be optimal. This trial, which was recently presented at Heart Rhythm 2014 showed that there is no difference between apical and septal pacing in terms of left ventricular function over two years. Although in one sense a negative trial, it nevertheless does, to a large extent, answer this question.

Can you describe a memorable case you treated?

It is difficult to think of one single case that stands out over the years. One recent case that sticks in my memory regards to the extraction of an infected pacing system. The patient was unwell with endocarditis and lung abscesses. He had his original system implanted in 1994 via a left sided superior vena cava and then had a second system implanted via the right side a few years later. This was incredibly difficult to extract as the left sided electrodes were heavily calcified and there was an acute bend into the left superior vena cava. With the help of my surgical colleagues we ended up opening his chest to remove the electrodes, a procedure which took 11 hours to do. He had a stormy course but eventually got better and is now well and back at work. It was a very long case but ultimately satisfying as we managed to get everything out.

As a reviewer of various renowned journals, which research paper in the last year did you think was the most interesting?

In the last year, I have reviewed an interesting paper [the paper is still under review with the European Heart Journal] on the re-interpretation of tilt testing that, rather than being used as a diagnostic test, can show a susceptibility to reflex hypotension which may exist in coincidence with any cause of syncope. This may be one explanation as to why some patients will become syncopal in certain situations eg. with the onset of an arrhythmia whereas other patients appear to tolerate the situation.

What are your current research interests?

Currently, I am involved in a number of research projects both commercial and academic. The commercial projects include the evaluation of new products such as the insertable cardiac monitor (Reveal Linq from Medtronic) and the leadless pacemaker (Nanostim from St Jude Medical). Academic projects include a variety of audits looking at device complications and ablation outcome data.

Which are the main research priorities in electrophysiology?

Important trials recently presented include SIMPLE,
which shows that routine defibrillation testing is not necessary; however, it does not address the opposite question of which patients should have defibrillation tests. This is an important area that will need to be evaluated. We are still awaiting the outcome of CABANA, looking at the long-term efficacy of atrial fibrillation ablation versus antiarrhythmic drugs. We still need good evidence for efficacy of ablation in persistent atrial fibrillation. This is a controversial area where cost-effectiveness needs to be looked at and linked to outcome measures such as patient reported outcome measures (PROMS).

**You have a low infection and complication rate with implantation of cardiac devices. What advice can you give to physicians starting in this field?**

Your question almost answers itself! The problem is that we tend to look at device implantation as physici-ans rather than as surgeons. Without doubt, the main factor in reducing device related infection is a sound knowledge of surgical technique and treating device implantation as a surgical procedure rather than just another cath lab procedure. Emphasising the importance of ensuring good sterile technique both for the implanters and other people in the lab/theatre is paramount. Being obsessive in this area I am sure is the most important factor in reducing device infection.

**You have dedicated good part of your career to teaching and training. Could you describe your greatest achievement in this area?**

This is very difficult to answer. I think two areas stand out. The first is the development and re-formatting of the BHRS certification process. When I took this over, there was a single examination, the BPEG certificate of competency. I re-designed the process, developing examinations on devices, electrophysiology and clinical practice. I have also introduced a more robust question setting and validation system with electronic marking. Because of this, I was asked by the European Heart Rhythm Association (EHRA) to develop a similar system for allied professionals.

I am also very proud to have developed an MSc in Cardiac Care at Teesside University in Middlesbrough, UK. I was initially part of a programme developing an MSc in implantable cardiac devices at the University and with the emergence of the arrhythmia nurse role I was involved in setting up an arrhythmia module at Masters’ level. Developing this into an MSc programme took a lot of work and negotiating with the University plus working with colleagues in both the arrhythmia field and in other areas of cardiology to get this off the ground.

**You were appointed to lead and develop the electrophysiology unit at The James Cook University Hospital in Middlesbrough, UK. Could you tell us what the key aspects of running a successful electrophysiology unit are?**

Without doubt the key to setting up a successful department is appointing the right people who can work together as a team. Running an electrophysiology department requires working with specialist nurses and physiologists as well as physicians and developing a strong team ethic is essential to running a cohesive and successful unit. It is not good enough to appoint individuals, no matter how good they may be academically or practically, if they cannot function as part of the team.

**What are the highlights of this year’s Heart Rhythm Congress (HRC)?**

This year will be another exciting year at HRC. There will be a high quality faculty with a number of international speakers. The programme has yet to be finalised but will include more interactive sessions and lunchtime teaching.

**What are your goals as president-elect of BHRS during your tenure?**

The most important goal I have is to cement and develop the relationship between BHRS and Arrhythmia Alliance. Arrhythmia Alliance is the patients’ advocate and we, as physicians and allied professionals, will be stronger as a team working together with Arrhythmia Alliance and I believe this will benefit both organisations.

Over the next few years, financial constraints will determine how arrhythmia services develop within the UK and I believe BHRS needs to engage with the UK’s National Health Service (NHS) to ensure that patients’ needs are addressed and met in this area, particularly with the development of new technology and new indications for device and ablation therapy. This will be a challenging area!

**Outside of medicine, what are your interests and hobbies?**

I try to keep fit running and walking our giant schnauzers (Archie and Margot) and I look forward to my skiing holiday. I also enjoy reading—mainly fiction—for relaxation. I follow sport and whilst not an avid football supporter in my youth, as my wife is a very keen Liverpool supporter, I have learned the wisdom of following the same team! As with most men and also, I think, in common with many electrophysiologists, I am a keen gadget geek/nerd and have to have the latest Mac, iPad, etc, plus as many accessories as possible in my car.
**Genetics in cardiac arrhythmias awarded best oral abstracts at ECAS**

Researchers studying the genetic aspects of cardiac arrhythmias have won second and third prizes for the best oral abstracts at the 10th Annual Congress of the European Cardiac Arrhythmia Society meeting (ECAS; 23–25 March, Munich, Germany).

Ortiz Sinner (Ludwig Maximilian University Munich, Munich, Germany) and colleagues (from Denmark, Canada, Iceland, Japan, The Netherlands, Sweden, UK and USA) won second prize for their presentation explaining their discovery of five novel genetic loci for atrial fibrillation, while Anneline te Riele (University Medical Center Utrecht, Utrecht, The Netherlands and John Hopkins Hospital, Baltimore, USA) and colleagues won third prize for their study shedding light on successful screening for relatives of family members with arrhythmogenic right ventricular dysplasia/cardiomyopathy.

Given that atrial fibrillation has a heritable component, Sinner et al aimed to identify additional susceptibility loci on top of nine already identified in recent genome-wide association studies. Their analysis of 6,691 atrial fibrillation cases and 17,144 controls of European descent found four novel susceptibility loci exceeding genome-wide significance in the atrial fibrillation cases (NEURL, TBX5, CAND2, and GJA1). A further analysis of 8,373 atrial fibrillation cases and 17,190 controls of Japanese descent found two novel loci exceeding genome-wide significance (NEURL and CUX2).

Sinner told delegates that TBX5 was a transcription factor heavily involved in the cardiac conduction system, while GJA1 was a gap junction protein encoding connexin 43 which was abundant in the heart. However, he said the involvement of the other loci in atrial fibrillation pathophysiology was as yet unknown.

Sinner commented: “Atrial fibrillation is common and confers high morbidity. It is a heterogeneous disease, where several genetic loci have been described before by gene association studies. Here we were able to identify five novel association signals by systematic large-scale, multi-ethnic genetic replication analyses, and hopefully functional analyses will elucidate the possible role of these candidate genes in atrial fibrillation pathophysiology in the future.”

He said further investigation of the findings would include looking at gene expression in close to 300 human left atrial tissue samples, along with functional analysis of animal models.

**Screening for familial relatives with arrhythmogenic right ventricular dysplasia/ cardiomyopathy**

The study by Te Riele and colleagues, which won third prize, indicated that longer screening intervals and focus on ECG and Holter monitoring may be appropriate for family members of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Te Riele et al recognised that although family screening is now part of clinical practice, incomplete penetrance and variable expressivity of arrhythmogenic right ventricular dysplasia/cardiomyopathy relatives without a diagnosis at first evaluation have a good short-term prognosis, their disease progression during four years of follow-up is minimal and longer screening intervals may be justified. They should focus on ECG monitoring and Holter screening during follow-up when evaluating these patients.”

Award judge Massimo Santini told Cardiac Rhythm News that the genetic research abstracts were of particular interest at this meeting. “Genetics is very important for us, there are at least three or four illnesses which are congenital and can kill children. For example when they are sleeping in cases of Brugada syndrome. Long QT syndrome and arrhythmogenic right ventricular dysplasia are also genetic. We look very carefully at genetics, because the more we understand the more we will be able to treat them.”

The jury, blinded to researchers and teams, comprised Gunter Breithardt, John Camm, David Cannom, Kenzo Hirai, Neil Kay, Giles Lascaut, Massimo Santini and Gerhardt Steinbeck. Abstracts on pharmacological and non-pharmacological management of atrial fibrillation, sudden cardiac death, ICD therapy, diagnosis and management of ventricular tachycardia/ventricular fibrillation and antiarrhythmic drug therapy among others were also presented.

**Angiotensinogen gene polymorphisms could be “additional genetic predictor” of stroke in AF patients**

A study from Taiwan with long-term follow-up, published ahead-of-print in HeartRhythm, has revealed that in addition to the CHADS2 score, angiotensinogen gene polymorphisms may be considered an additional genetic predictor of stroke in patients with atrial fibrillation.

The authors, Chia-Ti Tsai, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, and colleagues, write that genotyping of the angiotensinogen gene is helpful to determine which atrial fibrillation patients may benefit from treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker.

The prospective study with 10-year follow-up analysed the ability of renin-angiotensin system genes polymorphisms to predict the risk of stroke in patients with atrial fibrillation. “Little evidence is available regarding the impact of genetic polymorphisms on the risk of stroke in patients with atrial fibrillation. Angiotensin II plays a pathophysiological role in prothrombotic atrial endocardial remodelling,” the authors write. In the study, their objective was to investigate the effect of polymorphisms of renin-angiotensin system genes on the incidence of stroke in a prospective cohort of patients with atrial fibrillation.

The researchers followed up 712 atrial fibrillation patients for 10.3±2.7 years and eight polymorphisms of renin-angiotensin system genes were genotyped. They found that patients carrying the G-6 allele in the promoter region of the angiotensinogen gene, which was associated with higher promoter activity, were more likely to develop stroke than were non-carriers (hazard ratio 2.54, 95% confidence interval 1.26–5.12, p=0.009, after adjustment for CHADS2 score).

The investigators noted that the G-6A polymorphism provides information additional to CHADS2, on stroke risk prediction (p=0.039). In haplotype analysis, angiotensinogen gene promoter haplotypes containing −217G−6G, which was associated with the highest promoter activity, were associated with an increased risk of stroke (p=0.004). G-217G−6G haplotype carriers were even more likely to develop stroke than were non-carriers (hazard ratio 2.78, 95% confidence interval 1.37–5.64, p=0.003 after multivariable adjustment). In pharmacogenetic analysis, the increased risk of stroke in subjects carrying G-6 was eliminated by concomitant treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (p=0.012 for interaction). “Although clinical factors that predict the risk of stroke in patients with atrial fibrillation such as the CHADS2 or CHADS2-Vasc score have been identified, these clinical factors do not explain the entire susceptibility to stroke for patients with atrial fibrillation. Furthermore, there are limited data regarding the impact of genetic polymorphisms on the risk of stroke in atrial fibrillation patients. Most of these studies focused on the genes related to thromboembolism and were cross-sectional studies, and the results were still controversial,” the authors write.

Tsai and colleagues further explain: “We have previously shown that polymorphisms of the renin angiotensin system genes are associated with an increased risk of atrial fibrillation. It has been demonstrated that atrial fibrillation or rapid atrial pacing increases endocardial VCAm expression, which may be related to a gradual thrombus formation and can be attenuated by angiotensin II receptor blockade. This provides evidence that angiotensin II plays a pathophysiological role in prothrombotic endocardial remodelling and mural thrombus formation. Therefore, we hypothesised that polymorphisms of the renin angiotensin system genes may also influence the risk of stroke in patients with atrial fibrillation and provide additional information other than the CHADS2 or CHADS2-Vasc score to predict the risk of stroke for atrial fibrillation patients and conducted this first long-term longitudinal observational study to prove this hypothesis,” they write.
Towards resolving the role of M-cells in electrophysiology

FU SIONG NG

At the 10th Annual Congress of the European Cardiac Arrhythmia Society (ECAS; 23–25 March, Munich, Germany), Fu Siong Ng (London, UK) and colleagues won the first prize for best oral abstract with their research on the role of M-cells in electrophysiology. Ng writes for Cardiac Rhythm News an overview of the subject and the results of their own research.

Over two decades since M-cells were first discovered, there remains a great deal of controversy and debate surrounding their role in humans. These cells were discovered in the Antzeliovitch laboratory in experiments designed to assess the transmural dispersion of action potential duration.1 They found a strong late sodium and sodium-calcium exchanger currents. These cells have been postulated to have significant physiological and pathophysiological roles, including underlying the T-wave and J-wave of the electrocardiogram, as well as accounting for the arrhythmogenic effects of transmural dispersion of repolarisation in conditions such as long QT syndrome.

However, over 20 years on, researchers disagree as to their potential functional significance in humans. This disagreement between esteemed and experienced researchers stems not from any reservations about the validity or reproducibility of the data, but rather a difference in interpretation of the data that have been generated on this subject. This has arisen because many of the experiments demonstrating a functional role for M-cells have been in isolated cells or wedge preparation. However, when researchers subsequently tried to look for evidence of M-cells in vivo in humans, in intraoperative studies of patients undergoing cardiac surgery, they have not been able to demonstrate the presence of M-cells.2 This has led to the view in one group of researchers that M-cells can only be clearly demonstrated in artificial experimental preparations such as isolated cardiomyocytes and in the explanted wedge preparation, but do not have any functional significance in the intact heart in humans.3

The effective intercellular coupling that exists in intact myocardium is thought to mask the effects of M-cells, thus rendering them functionally insignificant in intact hearts. However, a second group of researchers that have consistently supported a functional role for these cells have pointed to a number of potential deficiencies in the intraoperative studies, citing the effects of general anaesthesia and the complex distribution of M-cells as the potential reasons why they were not detected in those human studies.4 We recently performed some studies to address these disagreements, which we presented at the European Cardiac Arrhythmia Society Congress in Munich, Germany.5 We reported data from optical mapping experiments on ventricular wedge preparations from explanted human hearts. In these studies, we subjected human myocardium to a gap junction uncoupler, carbenoxolone, and investigated the effects of gap junction uncoupling on the transmural dispersion of action potential duration. We found no evidence of midmyocardial islands or layers with prolonged action potential durations representing M-cells at baseline. However, in response to the gap junction uncoupler carbenoxolone, we were able to detect M-cell regions not seen at baseline. We concluded from these results that M-cells clearly exist in human myocardium. However, they do not exert any significant functional effects under physiological conditions as effective cell-to-cell coupling masks their effects, and they can be unmasked in the context of gap junction uncoupling.

Although these results from our current studies are unlikely to settle the ongoing debates about the functional significance of M-cells in humans, they have added to the wealth of data on the subject, and go some way towards reconciling the difference between the two sides of the M-cell debate by explaining why these cells have been detected under certain experimental conditions but not in the intact heart.

References

Fu Siong Ng is a National Institute for Health Research (NIHR) clinical lecturer in Cardiology, Imperial College London, UK, and a specialist registrar in Cardiology, Imperial College Healthcare NHS Trust.
Is antiarrhythmic gene therapy the future of atrial fibrillation management?

DIERK THOMAS

Dierk Thomas (Heidelberg, Germany) writes on the results of preclinical research on antiarrhythmic gene therapy.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and accounts for significant morbidity and mortality. The arrhythmia has a prevalence of ~1% in the general population and is age-dependent with 24% (men) and 16% (women) of patients >85 years being affected. The epidemiological significance of AF is further illustrated by a predicted two-fold increase of AF prevalence in the European Union by the year 2060. Despite its high epidemiological and clinical relevance, effective and safe management of AF still constitutes a major clinical challenge. Medical therapy represents the initial standard treatment for most AF patients. However, pharmacotherapy is limited by reduced efficacy, side effects, and safety risks in a significant number of patients. Non-pharmacological therapy is improving rapidly, but only a fraction of AF patients are currently treated by catheter ablation.

Basic research has revealed insights into fundamental mechanisms contributing to the arrhythmia: AF results from a variety of pathophysiological processes, leading to electrical and structural remodeling. The generation of substrates that support slow conduction, shortening of atrial refractory periods, and electrical reentry is particularly relevant as it provides the basis for maintenance of AF. Atrial alterations are observed as early as 24–48 hours after the onset of AF. Multifactorial aetiology and pathogenesis of the condition requires multimodal treatment, tailored to patient-specific mechanisms. The efficacy of an antiarrhythmic intervention to prevent AF largely depends on its capacity to suppress the underlying mechanisms.

In search for mechanism-based treatment modalities, gene therapy offers greater selectivity than small molecule-based or interventional approaches. The gene of interest is packaged into viral carriers and delivered to the target area via direct injection or using catheter-based interventional techniques, providing the advantage of site-restricted action in contrast to systemic application of drugs. Antiarrhythmic gene therapy for rate and rhythm control was evaluated in a porcine model of burst pacing-induced atrial fibrillation (Bikou et al, 2011; Lugenbiel et al, 2012; Soucek et al, 2012; Trappe et al, 2013).

During AF, normal atrioventricular node conduction leads to rapid ventricular rate response, resulting in impairment of left ventricular function and of exercise capacity. To achieve genetic rate control, an activating component of the β-stimulatory pathway, Gαs, was suppressed with an adenosine encoding for a respective silencing RNA administered via percutaneous access and cardiac catheterisation. This approach reduced atrioventricular nodal conduction, decelerated ventricular heart rates by 20%, and improved cardiac function compared to control animals exhibiting tachyarrhythmia (Lugenbiel et al, 2012). Potentially limiting side effects such as increased adenylyl cyclase expression and heart rate acceleration upon catecholamine application were not detected. Thus, targeted biological modification of atrioventricular conduction may represent a viable strategy for heart rate control in atrial fibrillation.

To further explore this emerging field, we sought to suppress atrial fibrillation by specifically preventing AF-associated remodeling via targeted atrial gene therapy. A hybrid method of atrial gene transfer was employed in rhythm control approaches, combining direct virus injection and epicardial in vivo-electroporation to yield high efficiency. Shortening of atrial refractory periods and action potentials is critical to AF perpetuation and may be prevented by suppression of repolarising outward potassium currents in atrial myocytes. Biologic rhythm control was achieved in a pre-clinical study by direct atrial gene transfer of a dominant-negative ether-a-go-go-related gene (ERG) K+ channel mutant. Inactivation of ERG channels resulted in reduced repolarising IKr current, induced action potential prolongation and successfully suppressed pacing-induced AF (Soucek et al, 2012). Furthermore, impairment of left ventricular ejection fraction during AF was prevented by anti-ERG gene therapy. In addition to delayed repolarisation, electrical reentry and AF are facilitated by deceleration of electrical atrial conduction. Gap junctions serve as regulators of conduction velocity in the heart and are formed by connexin proteins. AF is associated with reduced connexin 43 expression. We found that genetic correction of AF-associated connexin remodeling by targeted atrial connexin 43 gene transfer prevented persistent AF and preserved left ventricular ejection fraction in pigs (Bikou et al, 2011). Finally, AF is linked to atrial cardiomyocyte apoptosis, leading to structural remodeling and reduction of electrical conduction velocity. We evaluated a genetic approach to rhythm control using siRNA-mediated inactivation of a key apoptotic enzyme, caspase 3 (Trappe et al, 2013). Apoptosis was successfully suppressed by targeted gene therapy. As a result, deceleration of atrial conduction was prevented and the development of persistent AF was inhibited or delayed. Taken together, these preclinical studies revealed that gene therapeutic targeting of structural and electrical remodeling represent novel avenues to optimise and personalise AF management.

It is important to recognise that follow-up work is required to further improve local gene distribution, potential tumorigenicity, and prevention of local and systemic inflammatory responses. Adenoviral vectors were previously used owing to their ability to induce peak expression within a short time and to their high efficacy in infecting cardiac myocytes. For long-term applications and to study stability, efficacy, and safety of gene therapy, the use of adeno-associated virus or lentivirus as vector is required. The application technique combining local virus injection and electroporation for anti-remodeling treatment could be readily performed during open-chest cardiac surgery in humans. To further refine the gene transfer method, thoracotomy should be replaced by intervention under local anesthesia via specific catheters in future studies.

In summary, proof-of-concept gene therapy studies confirmed fundamental mechanistic hypotheses of AF pathophysiology. Suppression of AF (rhythm control) or reduction of ventricular heart rates during the arrhythmia (rate control) was achieved by targeted biological modification of specific substrates in the atria or in the atrioventricular node. After successful establishment of minimally-invasive techniques and following safety assessment, antiarrhythmic gene therapy could expand the current polymerid treatment strategy to eliminate the most debilitating of arrhythmias.

Dierk Thomas is head of Electrophysiology at the Department of Cardiology, University of Heidelberg, Heidelberg, Germany.

Bariatric surgery prevents AF in obese patients

A first of its kind study has found that bariatric surgery helps to prevent incidence of atrial fibrillation in patients with morbid obesity. The study was presented at the 35th Heart Rhythm Society Annual Scientific Sessions (7–10 May, San Francisco, USA).

The retrospective study was conducted in 438 patients with a body-mass index (BMI) of 40 or higher and identified as good candidates for bariatric surgery. Of these patients, 326 were elected to undergo surgery for weight reduction and 112 patients (controls) were only managed medically. The diagnosis of atrial fibrillation was documented by ECG or ambulatory monitors and metabolic profiles were collected at baseline and follow-up. The baseline BMI was different in the patients that underwent surgery vs. those who did not have surgery (46.9 vs. 43.2 kg/m2). The prevalence of atrial fibrillation at baseline was not significantly different between the two groups (surgical 3.7% vs. control 4.5% p=0.63). However, after a mean follow-up period of 7.2±3.7 years, new onset of atrial fibrillation occurred in 6.4% of the patients treated surgically, significantly lower than 16.1% (p=0.01) in the medically treated group.

“Obesity has become an epidemic in our culture and prevention efforts are more important now than ever,” says Yong-Mei Cha, professor of medicine at Mayo Clinic, Rochester, USA, and co-author of the study. “Bariatric surgery is a preventative measure that obese patients may choose to take and our study shows that the surgery helps them not only lose weight, but also reduces their risk of developing a serious cardiac condition, like atrial fibrillation. It is important to continue the conversation about how to help prevent this epidemic from becoming even more widespread.”
Antiarrhythmic drug therapy increases hospitalisation risk for older patients with AF

A single-centre analysis of antiarrhythmic drug therapy in older patients with atrial fibrillation (AF) and coronary artery disease has found it is associated with increased rehospitalisation at one year, and recommends safer and more effective therapies for symptom control in this group.

Researchers in the USA, led by Benjamin Steinberg (Duke Center for Atrial Fibrillation, Durham, USA), write: “Antiarrhythmic drug therapy in patients with coronary artery disease raises several safety concerns including toxic side effects and the potential for fatal proarrhythmia.” However, they point out that few data are available in older patients; therefore, they analysed antiarrhythmic drug therapy and outcomes in 1,738 patients aged over 65 with atrial fibrillation and coronary artery disease.

The study, published ahead-of-print in Europace, identified patients from the Duke Databank for Cardiovascular Disease who had undergone cardiac catheterisation with coronary angiography from 2000 to 2010 when they were 65 or older. All had obstructive or non-obstructive coronary artery disease and a diagnosis of atrial fibrillation. Of the 1,738 patients studied, 609 were treated with an antiarrhythmic drug. The most commonly-taken drug was amiodarone (taken by about 60% of the antiarrhythmic drug group) followed by sotalol (6.3% of all patients) and dofetilide (2.2% of all patients). After one year, only 35% of patients on antiarrhythmic drug therapy at baseline remained on the therapy.

The researchers found that mortality rates were highest in patients aged over 75, while rehospitalisation rates were highest in patients on antiarrhythmic therapy. The use of antiarrhythmic drug therapy was not significantly associated with increased mortality (adjusted hazard ratio 1.23) or cardiovascular mortality (adjusted hazard ratio 1.27) in the year following cardiac catheterisation. However, it was associated with increased all-cause rehospitalisation (adjusted hazard ratio 1.20) and cardiovascular rehospitalisation (adjusted hazard ratio 1.20).

In patients who were event-free at one year and had additional follow-up, antiarrhythmic drug use at baseline did not appear to affect adverse outcomes over the subsequent four years. However, the researchers note that these patients were at very high risk of death (55% of those over 75 and on antiarrhythmic drug therapy) and all-cause rehospitalisation (87% of those over 75 and on antiarrhythmic drug therapy).

Steinberg et al conclude: “Treatment with antiarrhythmic drug therapy was associated with increased risk of hospitalisation at one year. These data highlight the need for improved therapies for symptom control in this population.” They also write that “Older patients with atrial fibrillation and coronary artery disease are at high risk of death and rehospitalisation in the long term, irrespective of antiarrhythmic drug therapy.”

With regards to alternative therapies that can be implemented in this patient population, Steinberg told Cardiac Rhythm News: “There is some evidence that catheter ablation can be performed safely and effectively in older patients. While the proper role for an invasive strategy in this population deserves further study, it might be one option.”

The study was funded by the Duke Clinical Research Institute.
Sports for young patients with implantable cardioverter defibrillators: Refining the risk

Elizabeth Saarel (University of Utah, Salt Lake City, USA) arguments, based on prospective registry data, that young patients with implantable cardioverter defibrillators can participate safely in most competitive sports.

Despite a dearth of research, published guidelines in the United States and Europe—based on expert opinion—recommend against competitive sports participation in activities more strenuous than bowling or golf (Class IA) for patients with pacemakers or implantable cardioverter defibrillators (ICDs).1,2

In 2006, a prospective multicentre registry was launched to study the safety of sports participation for patients with ICDs. This international investigation includes patients with ages from 10 to 60 years who received ICDs for primary or secondary prevention of sudden cardiac death. Diagnoses include inherited arrhythmia syndromes, inherited or acquired cardiomyopathies, congenital heart disease, and valvular heart disease. The first published results from this registry indicate that athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia despite the occurrence of both inappropriate and appropriate shocks.3

Data from a prospective registry in our paediatric and adult congenital heart centre includes 21 young patients with ICDs who regularly participate in competitive or vigorous sports (greater than IA for dynamic and/or static component). Our data show no mortality and no increase in morbidity after four years.4 Patients’ choice of athletics include running, jogging, alpine hiking, swimming, skiing, snowboarding, rock climbing, basketball, football, baseball, gymnastics and other sports. One teen with congenital heart disease experienced two appropriate ICD shocks for treatment of ventricular tachyarrhythmias during basketball and then decided to withdraw from competitive athletics. No other patients have had an increased incidence of ICD therapies during athletics, either inappropriate or appropriate. We have seen no increased rate of damage to the ICD system during organised sports. Of note, most of our patients with ICDs are on beta blocker therapy to prevent inappropriate ICD shocks due to sinus or supraventricular tachycardias, and most underwent formal exercise testing to screen for arrhythmia prior to sports participation.

When questions arise about sports participation it is our practice to counsel patients and families about the risks, including potential for increased rate of ventricular tachyarrhythmias and damage to the pacemaker or ICD system. Counseling is patient specific; the underlying cardiac disease, type of device, indication for implant, position of leads and pulse generators, underlying heart rhythm, patient age, and type of athletic activity are considered when estimating risk.

The potential benefits of sports participation for young patients include decreased risk for obesity, metabolic syndrome, coronary and peripheral artery disease, stroke and diabetes. There are additional benefits of exercise including a positive effect on general mental health, decreasing risk for depression and overall improvement in wellbeing, all of which affect quality of life. Ultimately, the importance of sports participation to each patient’s quality of life must be estimated by the individual and their family.

In summary, the risk of sports participation for our patients with implanted cardiac devices may include an increased tachyarrhythmia burden, injury after loss of consciousness from cardiac device function or malfunction, and permanent damage to the implanted device system during sports. Sports that evoke a high potential for serious injury to self or others if a patient were experience syncope, including those using motor vehicles, should be discouraged. In the future, our estimates of risk should be guided by research rather than opinion. The risks of sports participation must be weighed against the benefits, including potential for improved quality of life, for all young patients with implanted cardiac devices.

References

Elizabeth Saarel is with the University of Utah, Salt Lake City, USA
10th International Symposium on Catheter Ablation Techniques

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The Fibrillating Heart

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Antidote for rapid reversal of dabigatran progresses into next stage of clinical research

Boehringer Ingelheim has announced the next step in the clinical development of idarucizumab, the investigational antidote for rapid reversal of dabigatran-induced anticoagulation.

According to a company release, idarucizumab has already demonstrated immediate, complete and sustained reversal of the anticoagulant effect of dabigatran in healthy volunteers. Now the potential antidote will be investigated in the clinical setting in patients taking dabigatran (Pradaxa). Boehringer Ingelheim states that this is the first time that an antidote under development for a novel oral anticoagulant is investigated in a study in patients.

A press release states that the pivotal patient study will provide knowledge on the potential of the specific antidote to support the treatment of patients taking dabigatran who may benefit from rapid reversal of dabigatran-induced anticoagulation.

Emergency rooms in more than 35 countries worldwide will participate in this study. Physicians will be equipped with the investigational antidote idarucizumab as a ready-to-use solution for infusion. The company says that the first study sites in Europe have been initiated, and more sites and countries will follow during the course of the year.

Prior clinical research of the antidote in a healthy volunteer study with 145 participants has already demonstrated the potential of the antidote for immediate, complete and sustained reversal of the anticoagulant effect of dabigatran. In the placebo-controlled study, the antidote was well tolerated and did not cause any clinically relevant side effects.

Importantly, no pro-thrombotic effect was observed after the administration of the antidote and also no return of anticoagulant activity of dabigatran over time at adequate doses.

“For those patients who do need reversal, the antidote would provide an additional option beyond the already existing measures in a physician’s toolbox. The antidote would remove the anticoagulant effect of dabigatran from the clinical scenario so that physicians can focus on the other aspects of patient management,” says Charles Pollack, professor of Emergency Medicine at the University of Pennsylvania School of Medicine and chairman of Emergency Medicine at Pennsylvania Hospital in Philadelphia, USA, and lead investigator of the patient study.

The antidote is still under investigation, has not been approved for clinical use, and further safety and efficacy testing will be required prior to market launch.

**IN-TIME subanalysis shows equal benefit of home monitoring in ICD and CRT-D patients**

Home monitoring is equally effective in ICD and CRT-D patients, a subanalysis of the IN-TIME IV trial has shown. The findings were presented at the Heart Failure Congress 2014, held 17–20 May in Athens, Greece.

The prospective IN-TIME multicentre trial, sponsored by Biotronik, included 664 patients with chronic heart failure, class II or III New York Heart Association (NYHA) symptoms and left ventricular ejection fraction <35% who were receiving optimal medical therapy. Nearly two-thirds of patients (60%) received a cardiac resynchronisation defibrillator (CRT-D) while 40% received an implantable cardioverter defibrillator (ICD). All of the implanted devices had a home monitoring capability. Patients were randomised in a 1:1 fashion to have the monitoring function switched on or off. For those patients who had the monitoring function switched on, data from their device was transmitted to a monitoring physician or clinic to enable early detection of arrhythmias or other complications. Patients with the monitoring function switched off were followed up during visits to the clinic.

The current subanalysis of the IN-TIME trial investigated whether home monitoring was equally effective in patients with a CRT-D and patients with an ICD. Gerhard Hindricks, principal investigator of the study, says: “We predefined this subanalysis because we wanted to know if our overall findings were the same in both device types. This would have an impact on the interpretation of the data and recommendations for treatment in these patient populations.” He continues, “The patient population receiving a CRT-D is quite different to the patient population receiving an ICD. Usually the patients with an indication for CRT implantation are at higher risk of iatrogenic heart failure during the natural course of the disease, and they profit more from defibrillator therapy with a cardiac resynchronisation function.”

The researchers found that the relative risk of the primary outcome in the monitoring versus control group was similar in the ICD (0.61, p=0.06) and CRT-D (0.75, p=0.10) patients. The relative risk of the secondary outcome was also similar in both device groups (ICD: 0.38, p=0.15; CRT-D: 0.35, p=0.014).

This subanalysis adds to the general finding of the IN-TIME IV trial. We now know that ICD patients and CRT-D patients benefit from an almost equivalent extent from home monitoring.”

**New data show defibrillators programmed to wait longer for deliver therapy are safe for secondary prevention ICD**

Medtronic has announced the results from the first prospective randomised clinical trial to show that Medtronic implantable cardioverter defibrillators (ICDs) can safely extend detection times before triggering therapy in secondary prevention patients. The results of the PainFree SST sub-study, unveiled as a Late-breaking presentation at the 35th Heart Rhythm Society (HRS) Annual Scientific Sessions (7–10 May, San Francisco, USA), demonstrate that physicians can choose to programme ICDs with delayed detection interval settings without compromising safety for high-risk patients.

“The results of this study are important for secondary prevention patients, who are often treated with more aggressive ICD programming to address arrhythmic events as quickly as possible,” says Laurence D Steinberg, M.D., medical director at Cleveland Clinic’s Lerner Research Institute and director of electrophysiology at The Cleveland Clinic Foundation in Ohio.

Clinical News

**TOCCASTAR trial meets primary safety and efficacy endpoints**

St Jude Medical announced, at HRS 2014, positive results of the TOCCASTAR clinical trial, which is examining the safety and efficacy of the TactiCath irrigated ablation catheter for the treatment of paroxysmal atrial fibrillation.

**TOCASTAR** is a prospective, double-blind, multicentre, non-inferiority study evaluating 300 patients in the USA and Europe. The investigational device exemption (IDE) clinical trial, which followed device performance and assessed patient outcomes through 12 months of follow-up, met its primary safety and effectiveness endpoints.

Results demonstrated that the TactiCath irrigated ablation catheter exceeded the safety and efficacy non-inferiority benchmarks set forth in the trial by 5.9% and 4.3%, respectively, based on a novel endpoint called ‘time to sudden cardiac death’.

In addition, approximately 75.9% of the patients who were treated optimally with contact-force ablation therapy via the TactiCath catheter were free from paroxysmal atrial fibrillation at the end of the 12-month follow-up period, compared to 58.1% of patients who did not receive 10 grams of force. This was consistent with previous studies, including TOCCATA, EFFICAS I and EFFICAS II, optimal contact-force parameters for the TactiCath catheter had been defined as 10 grams of force over the ablation procedures.

“These findings from the TOCCASTAR trial further demonstrate the strong safety and efficacy profile of the TactiCath irrigated ablation catheter for the treatment of atrial fibrillation,” says Vivek Reddy, director of electrophysiology at Mount Sinai Hospital in New York, USA.

Data that are produced by the TactiCath irrigated ablation catheter is displayed on the EnSite Velocity system, a cardiac mapping and navigation system via the EnSite contact force module. The study has been conducted to gather data in support of US FDA approval and is the basis for the company’s premarket approval submission that has been filed with the FDA. TactiCath has received CE mark approval and is commercially available in Europe.
Spectranetics receives CE mark for TightRail Rotating Dilator Sheath platform

Spectranetics has announced receiving CE mark approval for its TightRail Rotating Dilator Sheath platform for mechanical cardiac lead extraction procedures.

The announcement includes TightRail and a companion product: TightRail Mini Rotating Dilator Sheath. The Mini is designed to gain vascular access, dilating heavily fibrosed and calcified tissue. The new platform, the company announced, will be used to treat patients at facilities in Europe that are participating in Spectranetics’ initial limited launch.

SightRail Manual Dilator Sheath, a partner platform, was awarded the CE mark in April and features visual indicators that show bevel orientation and tip alignment, supplementing fluoroscopy as a means to determine position and orientation. A company release states that these new platforms represent Spectranetics’ entry into the mechanical extraction device market, complementing its laser-based technology for cardiac lead extraction.

Spectranetics also announced, in May, completion of the first in-patient case using the TightRail Rotating Dilator Sheath performed by Charles Love (NYU Langone Medical Center, New York, USA).

“I was very pleased with how TightRail handled and tracked through the vasculature,” says Love. “It easily passed through occlusions in the chronically occluded innominate vein and superior vena cava. These included areas that had some calcification. We easily and safely achieved the clinical goal. TightRail had no effect on the non-targeted leads in our experience.”

Spectranetics debuted TightRail at the 35th Heart Rhythm Society Annual Scientific Sessions in San Francisco, USA. The company announced that over 200 physicians participated in the “hands-on” solutions experience hosted by Spectranetics. TightRail will also be showcased at Cardiotstim/EHRA Europe (18–21 June, Nice, France).

Boston Scientific gets FDA approval for new defibrillators and heart failure devices

Boston Scientific has announced receiving FDA approval for its latest generation of defibrillators and heart failure devices. The newly approved devices include the Dynagen Mini and Inogen Mini ICDs, as well as the Dynagen X4 and Inogen X4 CRT-Ds.

According to a company release, the X4 line of quadripolar CRT-Ds offers 70% more pacing options to address high capture thresholds and phrenic nerve stimulation effectively, along with the largest battery capacity in the industry.

The Mini family of ICDs are up to 20% smaller by volume and up to 24% thinner than competitive devices from other manufacturers, the press release states.

“The tiny size of the Mini ICD provides a real benefit to some patients, in particular those with a smaller frame,” says Hans-Joachim Trappe, University Marien Hospital Herne, Hospital of Ruhr-University, Bochum, Germany.

Viva cardiac resynchronisation therapy-pacemaker now available in Europe

Medtronic has announced CE mark receipt and the European launch of its newest cardiac resynchronisation therapy-pacemaker, Viva CRT-P.

The Viva CRT-P device includes Medtronic’s AdaptivCRT software, which is, according to a company release, the only algorithm demonstrated to improve heart failure patients’ response to the therapy and reduce the risk of atrial fibrillation (as compared to conventional biventricular therapy).

The AdaptivCRT algorithm works by preserving normal heart rhythms and automatically adjusting to the patient’s needs every minute, creating a customised therapy for each patient. Viva CRT-P also features advanced diagnostics tools, such as OptiVol fluid status monitoring and Cardiac Compass Report, which provide insight into patients’ physiological condition. These tools, according to a company release, are proven to identify patients at risk for rehospitalisation within 30 days of discharge.

The Viva CRT-P is not approved for sale in the United States.

Advanced Cardiac Therapeutics announces new financing for TempaSure cardiac ablation catheter

Advanced Cardiac Therapeutics, a medical device company that is developing a novel, temperature-
Product News

sensing, irrigated, radiofrequency ablation catheter for treatment of cardiac arrhythmias has announced the completion of a new round of equity financing for its technology.

TempSure comprises a temperature-sensing irrigated radiofrequency ablation catheter for treatment of cardiac arrhythmias. It features proprietary microwave radiometry technology that can accurately assess volumetric temperature in the heart in real time so that physicians can control and predict lesion formation for improved clinical outcomes.

The financing, which was led by New Enterprise Associates and supported by existing investor, NBGI Ventures, will enable the company to continue to advance its next generation TempSure ablation catheters and related clinical development programme.

FDA approves Biotronik Entovis pacemaker system with ProMRI technology

Biotronik has announced that the FDA has granted approval for its Entovis pacemaker system with ProMRI technology. The Entovis system allows patients to undergo magnetic resonance imaging (MRI) scans with a limited exclusion zone. FDA approval covers both single chamber (SR-T) and dual chamber (DR-T) Entovis pacemakers when implanted with Setrox pacing leads.

“With the Entovis longevity and the history of lead reliability, this is a system that will serve a wide variety of pacemaker patients for the foreseeable—and unforeseen—future needs,” says Carlton Nibley (John Muir Medical Center in Concord and Walnut Creek, USA), participant in the ProMRI study.

FDA approval comes 16 months after the initial clinical study was launched, and five months after the approval of that study’s expansion to include full-body MRI scans. These studies are required by FDA for product evaluation, and are designed to assess the safety and efficacy of Biotronik’s existing single- and dual-chamber Entovis pacemaker systems and Setrox 53 and 60cm leads during MRI scans. These devices are already commercially available in the USA, but lacked FDA approval for use in the MRI environment.

Biotronik’s defibrillators for 3.0 Tesla and full-body MRI get CE mark approval

Biotronik has announced receiving CE mark approval for its ProMRI technology for ultra high field 3.0 tesla (T) and full-body magnetic resonance imaging (MRI) with the standard 1.5 T scan strength.

The company states that it is the first one gaining CE mark approval for patients with cardiac devices to undergo 3.0 T MRI scans. Single-chamber and DX implantable defibrillators (ICDs) with atrial diagnostics—including: Illesto, Iloira, and Ilousa single-chamber and DX ICDs with Linox and Progeo ProMRI leads—are now approved with backwards compatibility for ultra high field 3.0 T scans with an exclusion zone. Full-body 1.5 T scans are available with Illesto and Iloira single-chamber, dual-chamber and DX ICDs with Safio S and Linox ProMRI leads.

“Approval for full-body and higher resolution scans offers my ICD patients unparalleled access to potentially life-saving imaging. I often treat cardiac patients with comorbidities who would benefit from MRI diagnostic capabilities,” says Antonio Curmis, Spedali Civili Hospital, Brescia, Italy. “Now I can be confident in the safety of MRI scans for these patients.”

Until recently, patients with a pacemaker or ICD were denied MRI scans due to the strong magnetic fields and radio waves that could negatively influence the devices. While 1.5 T machines remain the clinical standard, 3.0 T MRI scanners improve image quality and reduce scan time.

Calendar of events

18–21 June
CARDIOSTIM/EHRA Europace 2014
Nice, France
T +33 (0) 1 475 62483
E cdmregistration@reedexpo.fr
W www.cardioeurope.com

27–28 June
2nd International
Europa-Park Symposium on Cardiac Arrhythmias
Chicago, USA
T +1 646-434-4136
E kpurdy@cfr.org
W www.cfr.org/baa

30 August–03 September
ESC—European Society of Cardiology Congress
Barcelona, Spain
E congress@escardio.org
W www.escardio.org/congress-esco/2014

5–8 October
Heart Rhythm Congress
Birmingham, UK
E info@heartrhythmcongress.org
W www.heartrhythmcongress.org

15–17 October
10th International Symposium on Catheter Ablation Techniques (ISCAT)
Paris, France
T +33 (0) 1 4092 0120
F +33 (0) 1 4641 0521
E iscat@curved.fr
W www.iscat.net

2–5 December
XVI International Symposium on Progress in Clinical Pacing
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Markets of Care

Cardiac Rhythm News

June 2014
### Ablate What You See,

**Studies Demonstrate High Rates of Acute and Durable PV Isolation with Short Learning Curve**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Acute Procedural Results (n=56 Patients)</th>
<th>Acute Procedural Results (n=60 Patients)</th>
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<tr>
<td></td>
<td>Acute Pulmonary Vein (PV) isolation (202 of 206 PVs)</td>
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<td>PVs isolated on first attempt</td>
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<td>Fluoroscopy time, min (mean)</td>
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<td>Procedure time, min (mean)</td>
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**PV Lesion Durability (105 +/- 44 days) (n=52 Patients)**

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<th>Metric</th>
<th>Durability</th>
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</table>

**Durable Isolation (162 of 189 PVs)**

### Long-term Results

<table>
<thead>
<tr>
<th>Metric</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up time (days)</td>
<td>311</td>
</tr>
<tr>
<td>Free of Tachycardia recurrence off antiarrhythmic drugs (HD)</td>
<td>83%</td>
</tr>
</tbody>
</table>

*HD/LD refers to High-dose / Low-dose group*

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**Bibliography**


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This information is intended for European and Australian Audiences. The HeartLight System is not approved in the USA.

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Effective pacing for years.

Combining proximal pacing options with industry-leading longevity.

The ACUITY™ X4 family of leads redefines quadripolar pacing by positioning multiple electrodes along a proximally located 3D spiral. When combined with meaningful design elements – industry’s smallest lead tip, inner catheter delivery and proven battery technology – the X4 CRT-D system provides the tools needed to efficiently pace at the target location with Boston Scientific’s device longevity.*

*On Time® File

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