

HRS 2011: What's Hot, What's Not, in AF Ablation

by Mary Thompson

US electrophysiologists (EPs) are expected to perform over 100,000 catheter-based ablation procedures this year to treat atrial fibrillation (AF), an abnormal heart rhythm associated with an increased risk of embolic stroke. AF affects more than three million Americans and is expected to expand rapidly over the next few decades as the population ages. (See Exhibit 1.) Patients with AF are increasingly turning to catheter-based ablation procedures, and most notably, a procedure known as pulmonary vein isolation (PVI), which is now firmly established as the new standard-of-care for the treatment of drug-resistant paroxysmal (intermittent) AF (PAF).

A number of studies now clearly demonstrate the benefit of ablation therapy for PAF over antiarrhythmic drugs (AADs). (See Exhibit 2.) However, although EPs are now routinely reporting PVI success rates (defined as freedom from AF) of 70% or higher at one year (albeit often with repeat procedures and concomitant use of AADs), long-term follow-up data that has begun to emerge paints a more sober picture of the PVI procedure. According to Hugh Calkins, MD, of Johns Hopkins University's Johns Hopkins Hospital, Baltimore, MD, one of the pioneers in this field, electrical reconnections in previously isolated PVs are not uncommon following AF ablation, and AF recurrence rates continue to climb even years after the procedure. There is still much we don't know about AF ablation, he said, including longer-term efficacy and the safety and efficacy of the procedure in higher-risk patients, such as the elderly and those with heart failure. (See Exhibit 3.)

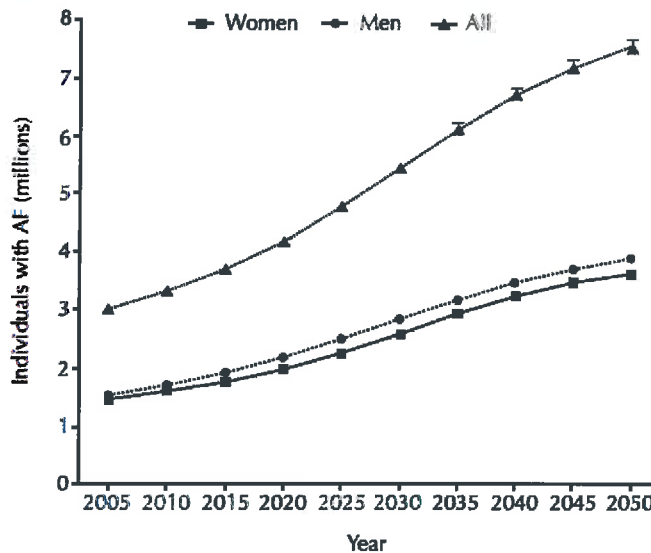
Calkins spoke during a day-long AF Symposium held just prior to this year's Heart Rhythm Society (HRS) meeting, which took place in San Francisco in early May. During the HRS meeting, attendees heard the same story from a number of presenters who lamented the disappointing long-term results with AF ablation and spoke about upcoming technological advances in catheters and adjunctive tools that may improve the procedure's efficacy and durability.

During a session on new balloon-based technologies, Vivek Reddy, MD, of Mount

Sinai Medical Center (NY)'s Mount Sinai School of Medicine, pointed to a study by Bertaglia et al, published last year, that nicely illustrates the durability issue. The study followed 229 consecutive patients treated with a single AF ablation procedure at three Italian centers. One year after the procedure, 78% of the patients were free from atrial arrhythmia recurrence; however, delayed recurrences were observed in 41%

Exhibit 1

Projected Prevalence of Atrial Fibrillation in the US, 2005-2050E



SOURCE: Gerald Naccarelli et al, Am J Cardiol 2009;104:1534-1539

Exhibit 2

Ablation vs AADs: 1 Year Success

| Study | AADs Success Rate | Ablation Success Rate | 2 nd Ablations | Still on AADs |
|----------------|-------------------|-----------------------|---------------------------|---------------|
| A4 | 23% | 89% | 80% | 0% |
| Thermocool IDE | 17% | 63% | 13% | 7% |
| STOP-AF | 7% | 70% | 19% | 12% |
| CABANA Pilot | 38% | 61% | 21% | 28% |

SOURCE: Vivek Reddy, MD from a presentation given at the 2011 HRS conference

of those patients up to six years following the procedure. Longer-term recurrence rates for these patients were 13% at two years, 22% at three years, 35% at four years, 47% at 5 years, and 55% at six years. (See Exhibit 4.) The recurrence rates were similar regardless of whether or not the patients were on AADs and whether they had paroxysmal or persistent AF. The authors conclude that “even patients in whom catheter ablation prevents recurrence at one year should not be considered ‘cured’ since over 40% will

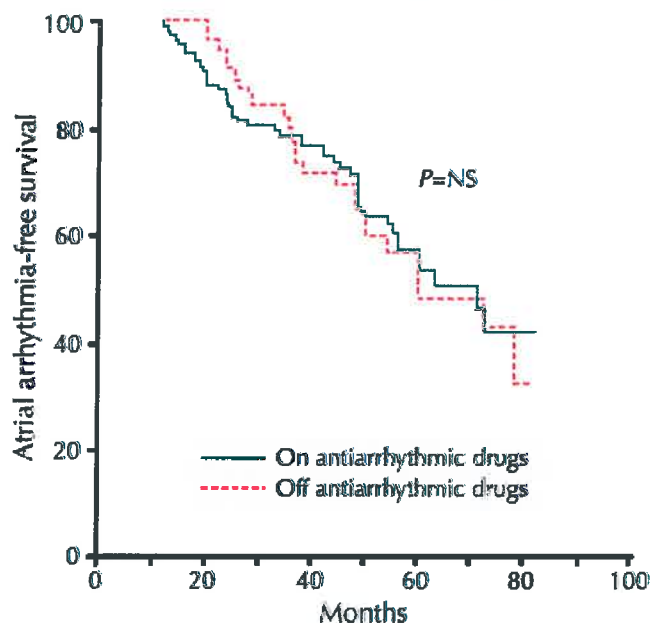
Exhibit 3

| What We Still Don't Know About AF Ablation | |
|--|--|
| • | Efficacy > 12 months |
| • | Safety and efficacy in certain groups <ul style="list-style-type: none"> - The elderly - Patients with heart failure - Persistent AF - As a first-line therapy |
| • | Impact on stroke risk, survival |
| • | Optimal ablation strategy for long-standing AF |
| • | Cryoballoon vs RF |

SOURCE: Hugh Calkins, MD; from a presentation at the 2011 HRS AF Summit

Exhibit 4

Kaplan-Meier Estimation of the Time to AF Occurrence After Ablation in Patients On or Off Antiarrhythmic Drugs
Single-procedure Outcome of Six-year Multicenter Experience



SOURCE: E. Bertaglia et al, *Europace* (2010); 12:181-187

suffer an AF recurrence over longer-term clinical follow-up.”

The HRS meeting gave physicians a chance to discuss several new technologies that could help address the durability issue and make AF ablation simpler, more reproducible, and safer in the process. Promising emerging technologies include balloon-based ablation catheters, devices that enable direct visualization during the ablation procedure, and contact force (CF)-sensing technologies, all of which are either already on the market or are in the relatively near-term pipeline. In addition, there was a good deal of interest in novel image-guidance and mapping technologies under development, some of which have the potential to usher in a future paradigm shift in the way AF ablation procedures are performed.

Growing Emphasis on CF Measurement

CF measurement received a good deal of attention at this year’s meeting, with several presenters stressing the growing body of data linking CF during radiofrequency (RF) ablation with clinical outcomes. Studies have shown that there is high variability in the degree of force applied during RF ablation and that both lesion size and depth are dependent on the amount of CF applied. Areas of gaps in the ablation line following RF ablation have also been linked to low CF.

Endosense Leads the Way

Pioneered by privately held Swiss company Endosense SA, real-time CF sensing is designed to help physicians deliver optimum catheter tip contact and force during an RF ablation procedure. Too little CF may result in an ablation that fails to fully isolate the PVs, while too much can injure the surrounding tissues and result in serious procedure-related complications. Speaking during the AF Summit, Karl-Heinz Kuck, MD, of Asklepios Klinik St. Georg, Hamburg, Germany, who has been involved in the clinical trials with this technology, called CF sensing the next “revolution” in RF ablation and predicted that five years from now, some type of contact-sensing technology will be used in all RF ablation catheters. And Kuck was not alone in his sentiment. In fact, a number of speakers at the summit voiced positive opinions about CF monitoring as

a means to improve both the efficacy and safety of RF ablation.

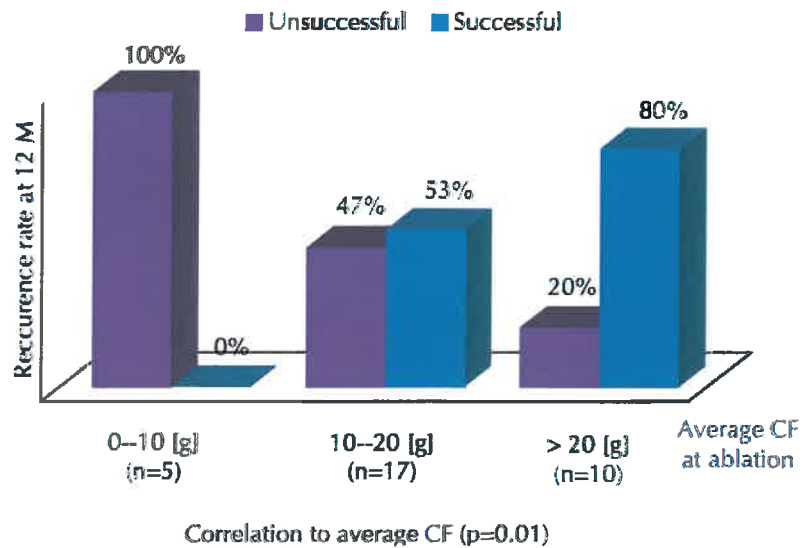
Much of what is known about the variability in CF during AF ablation and the link between CF and outcomes/adverse events has been obtained through clinical studies conducted by Endosense, which developed the *TactiCath* System, the first commercially available CF-sensing RF ablation catheter. *TactiCath* is a 7-French (F), open-irrigated RF ablation catheter with a fiber optic force sensor embedded in its tip. The sensor detects deflections in force at the catheter tip, both axially and laterally, and the system provides a display of real-time full-force vector measurements during the ablation procedure via the accompanying *TactiSys* Support System.

Endosense's initial clinical trial, TOCCATA, was designed to evaluate the safety and performance of the *TactiCath* System, but the study garnered much more information than the company originally anticipated, according to Endosense VP of sales and marketing Laurent Grandidier, who spoke with *Medtech Insight* at the HRS meeting. Thanks to the TOCCATA trial, researchers now know that there is a high degree of inter- and intra-operator variability in the forces applied during a RF ablation, a finding that Grandidier says surprised everyone. Moreover, ablation success in the study (defined as the absence of AF recurrence at 12 months) was directly correlated with the degree of CF applied. Lower CF was associated with the presence of gaps in PVI lines, suggesting that AF recurrence following ablation is strongly associated with suboptimal tip-to-tissue CF. Further data from this study, presented in poster form at the 2011 HRS meeting, showed that all patients in the study who were treated with a CF less than 10 g had AF recurrence at 12 months, while 80% of those treated with a CF greater than 20 g had no recurrence. (See Exhibit 5.)

According to Endosense, insufficient CF is associated with the need for redo procedures, a lengthier ablation procedure, and wide variability in success, while excessive CF increases the risk of cardiac tamponade, esophageal injury, and other adverse events. In fact, the data to date suggests that the creation of even one poor ablation lesion due to insufficient CF can determine the overall success of a PVI procedure, and poor initial lesions can be very difficult to correct, a find-

Exhibit 5

Toccata Patient Outcomes at 12 Months Stratified by Contact Force (grams)



SOURCE: Endosense

ing that researchers speculate may be due to edema formation in the tissues.

Following completion of the TOCCATA trial, Endosense began a series of additional studies called EFFICAS to further investigate the relationship between CF and AF ablation outcomes. At the 2011 HRS meeting, researchers presented results from the first of these studies, EFFICAS I, a single-arm, prospective, nonrandomized trial performed in Europe, which completed enrollment in February 2011. EFFICAS I enrolled 45 PAF patients who underwent PVI using the *TactiCath* System, and ablation operators in EFFICAS I were blinded to the CF-sensing information obtained during the procedure.

After three-months, all patients in the study received an invasive mapping procedure to gain detailed information on each ablation point and identify areas of electrical re-conduction. Of the 38 patients with three-month follow-up at the time of the HRS presentation, 24 (63%) showed at least one gap in their PVI lines via invasive mapping, and 47% of the PV lines created in those patients had reconnected (ie, they failed to remain electrically isolated). Both minimum CF and minimum force-time integral (FTI; a measure of force applied per second) were determinants of gap/reconduction.

Dr. Reddy, who presented the EFFICAS I data at HRS during an abstract session, comment-

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ed that there was a direct association between the gap locations observed in the study and areas of low FTI. Each ablation with an FTI of less than 200 g/second decreased the probability of procedure success by 20%, he said. According to Reddy, studies suggest that only 15%-25% of AF ablation patients treated today achieve complete isolation of their PVs, and arrhythmia recurrence increases over time following ablation, with reconnections common. Thus, he said, there is a "pressing need" to improve the rate of durable isolation.

In December 2010, Endosense began enrolling patients in the next study in this series—the nonrandomized, 45-patient EFFICAS II trial—which allows operators to monitor the force they apply during the procedure and once again includes invasive mapping for all patients during three-month follow-up. This study will track isolation gaps as well as procedural improvements as compared to EFFICAS I. According to Grandidier, operators involved in the trial are already reporting substantial improvements in procedure efficiency and effectiveness. At HRS, Reddy said early data from the trial show that real-time monitoring of CF can significantly reduce the time needed to achieve PVI, suggesting that CF information enables operators to more effectively position the ablation catheter within the heart. Following completion of EFFICAS II, anticipated by the end of 2011, Endosense plans to launch the EFFICAS III trial, which will randomly compare CF-directed versus non-CF-directed AF ablation.

Meanwhile, the company continues to mark important commercialization milestones. *TactiCath* was CE marked in May 2009 and commercialization in Europe began in January 2010 via a partnership with Biotronik SE & Co. KG, the exclusive distributor for *TactiCath* in Europe, Latin America, Canada, Africa, and the Middle East. A second-generation version of the device was fully launched in Europe in September 2010, offering a more flexible catheter along with upgrades to the *TactiSys* Support System, including the addition of real-time FTI data displays and automatically generated summary reports. Over the last year, more than 1,000 AF and supraventricular tachycardia patients have been treated across Europe with the second-generation system, which the company says is a testament to the growing acceptance of the value of CF sensing in the EP community.

TactiCath is also undergoing investigation in a US Food & Drug Administration (FDA) investigational device exemption (IDE)-approved, randomized, noninferiority clinical trial (TOCCASTAR), which began enrolling patients in January of this year and is "enrolling well," according to Grandidier. The study will involve about 20-25 sites in the US and Europe with an enrollment goal of about 300 patients, who will be treated with a single PVI procedure only. Patients will be randomized to treatment with either *TactiCath* or Biosense Webster Inc.'s (a unit of Johnson & Johnson [J&J]) *ThermoCool* irrigated AF ablation catheter (*ThermoCool* is the only RF catheter with specific FDA-approved indications for use in AF). Follow-up for the trial will continue for 12 months and Endosense hopes to obtain FDA approval for the *TactiCath* by the end of 2013 or early 2014. Grandidier says the company hasn't decided yet how it will market the device in the US (whether directly or through another company), but at this point, "all options are on the table."

Collaborative Approach

So far, Endosense has adopted a collaborative approach to this market, as evidenced not only by the company's partnership with Biotronik, but also by three recently announced product development agreements aimed at integrating the firm's open-platform force-sensing technology into advanced imaging/mapping systems. The first is a joint development agreement announced in January with Siemens Healthcare (a division of Siemens AG) that will integrate *TactiCath* CF data with Siemens' 3-D fluoroscopy imaging system. The intention, according to Grandidier, is to enable EPs to view real-time catheter tip-to-tissue CF within a fluoroscopically enabled 3-D anatomic heart model during the ablation procedure and to provide an alternative to the complex EP navigation systems (such as the *Carto* System from Biosense Webster), currently in use for AF ablation procedures. The Siemens system will also enable all information collected during the procedure to be recorded directly into the patient's hospital record. At the HRS meeting this year, the companies announced completion of prototype software for the new application.

The second agreement, revealed during HRS, is a joint project to integrate the *TactiCath* Catheter into a next-generation advanced 3-D cardiac mapping, visualization, and navigation system under development by start-up Rhythmia Medical Inc. This system is designed to be faster and simpler than existing devices and to provide higher resolution images. It will integrate 3-D mapping of electrical activity, tip-to-tissue CF data, and views of the catheter moving inside the heart, Grandidier said. Current EP mapping technology requires up to three hours to fully map arrhythmia locations prior to ablation, but Rhythmia believes it can provide a 3-D map in only minutes using an 8-F deflectable catheter with a multiple (64) electrode basket array and improved algorithms to speed data processing.

As *Medtech Insight* went to press, Endosense announced that it had entered into a joint development agreement with General Electric Co.'s GE Healthcare to integrate the contact-force data provided by Endosense into GE's *CardioLab* electrophysiology recording and *Innova* imaging platforms. The companies aim to develop an all-in-one system for performing catheter ablation procedures for treating cardiac arrhythmias.

CF Competition Heats Up

Endosense is likely to announce additional collaborations in the near future, as the company is in discussions with several other potential partners. Explains Grandidier: "We're trying to partner with as many companies as possible that are big players in the cath lab." And for good reason. Although Endosense pioneered CF sensing technology and has contributed significantly to this field with its impressive and still growing compilation of clinical data supporting the clinical utility of CF monitoring, the company faces some stiff competition going forward as the big players in AF ablation jump on the bandwagon. In fact, two of the leaders in the AF field—Biosense Webster and St. Jude Medical Inc.—already are in advanced development with force/contact-sensing systems of their own, which they are integrating into their market-leading mapping and guidance systems.

Biosense Webster received CE mark approval for its *ThermoCool SmartTouch Contact Force Sensing Catheter* in November 2010 and is preparing to launch the device

in Europe. In January, the company reported completion of the first clinical cases with the device in the European Union. A US IDE trial is expected to begin within a few months, according to company reps. The device was on display in the international section of Biosense Webster's booth at this year's HRS meeting. It contains a precision spring below the tip of the catheter and three sensors that measure lateral and axial movement as well as tip pressure. CF data is transferred into the company's *Carto 3 Navigation System* and enables physicians to build a force map with a real-time force display.

One unique aspect of the system is a clearly displayed arrow-shaped force vector that appears on the screen during the procedure at the location of the catheter tip, indicating the direction of the catheter tip force in 3-D geometry. The vector is green if the operator is achieving good contact within predefined minimum and maximum force thresholds, but it turns red if CF exceeds the threshold, and it flashes red with excessive force. Measurements are taken 20 times per second, resulting in what is essentially a continuous, real-time CF display. Unlike the current *TactiCath System*, the entire display is integrated into the *Carto 3 Imaging Screen* so the physician does not need to look at a second screen to monitor the force data during the procedure (Endosense is addressing this drawback to its system via the recent collaborations with Siemens and Rhythmia Medical).

J&J reported strong, 18% growth for its Biosense Webster division in Q1 2011, which the firm attributed to the continued success of its *Carto 3 Mapping System* and gains in market share. The positive news was juxtaposed against a backdrop of substantial weakness in several of its other businesses. Overall, sales in the company's Medical Device and Diagnostics business increased by 1.3% in the quarter, to \$6.4 billion; however, US sales declined by 0.5%. The Cordis Corp. franchise was particularly hard hit, with US sales down 7.5% in the quarter and sales outside the US down 9.9%. According to company officials, the results were impacted by a continuing decline in sales of the *Cypher* drug-eluting coronary stent, which fell by a whopping 41% compared to the prior year. The firm estimates *Cypher's* worldwide market share declined 12% in the first

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quarter, which is a two-point drop sequentially and a six-point drop year/year.

The company's inability to keep up in the drug-eluting stent market, a space that it pioneered, prompted J&J to announce recently its intention to exit the space altogether and focus on its higher-growth Cordis divisions, including Biosense Webster, peripheral vascular, and endovascular products. (See "And Then There Were Three: J&J/Cordis Exits Drug-Eluting Stent Market," "The Gray Sheet," June 20, 2011.)

St. Jude is also attempting to address the rising interest in CF measurement, but the company has taken a slightly different tack with its *EnSite Contact* Catheter. This device is designed to work with St. Jude's next-generation *Cool Flex Flexible Tip Ablation Catheter* (as well as the firm's other ablation catheters), and conventional ways to measure force would not be compatible with the flexible tip. For that reason, St. Jude's technology does not actually measure CF at the catheter tip. Instead, the company has developed an electrical coupling indicator capable of measuring resistance and reactance values (essentially impedance between the tissue and the tip of the catheter) following delivery of RF energy to the tissues.

The device delivers a small, nontherapeutic amount of RF current to the tissues and uses the impedance value obtained to determine electrical coupling—a measure of the level of electrical contact the catheter's tip has with the endocardial tissue. A real-time measurement of tip-to-tissue electrical contact is displayed on the company's *EnSite Mapping and Navigation Screen*. The drawback is that this system, unlike the CF products from Endosense and Biosense-Webster, doesn't actually quantify catheter tip force, which, based on recent clinical data, appears to be an important parameter for determining optimal lesion creation. St. Jude received European CE mark approval for the *EnSite Contact System* in June 2010 and plans to launch the device this year. A US IDE trial is slated to begin in the second half of 2011.

Other companies are likely working on force-sensing technology as well, including Medtronic Inc., which according to a presentation at HRS, has done some clinical work on a multielectrode, temperature-controlled contact detection system.

Impact of CF on AF Market Dynamics

There are plenty of incentives for companies to invest money in the CF arena, including growing physician interest and demand for the technology as well as the prospect of offering a premium-priced ablation catheter. According to Endosense's Grandidier, *TactiCath* is positioned as a premium-priced product, but the company believes it will reduce overall costs by lowering procedure time and AF recurrence rates.

Grandidier also points out that CF data improves physician training and reduces the learning curve for EPs seeking to enter the AF ablation arena. And while new balloon-based ablation technologies designed specifically for PVI, such as Medtronic's *Arctic Front Cryoballoon* device—FDA-approved in December—also promise to simplify the process for new users, Grandidier says there's little chance balloon-based systems will ever completely replace point-by-point RF ablation.

RF will remain an important part of the AF ablation toolbox, he says, because it is more versatile in comparison with balloon catheters like the *Arctic Front*, which can only isolate the PVs and is best suited for patients with PAF. Still, the *Arctic Front* could prove to be a significant boon for Medtronic by potentially providing an easier entryway into AF ablation for many of the company's existing cardiac rhythm management (CRM) customers seeking to branch out from ICD and pacemaker implantation. Introducing balloon ablation systems like the *Arctic Front* to these physicians is a good way to get them started, since balloon catheters, which can potentially achieve electrical isolation with a single application of energy covering the entire PV orifice at once, offer a simpler, potentially easier-to-learn alternative to the more technically challenging RF technique. Eventually, the availability of balloon cryoablation could expand the total number of EPs performing ablation, which Grandidier asserts is "positive" for the entire AF ablation industry.

Cryoablation vs RF

It may be a while, however, before the cryoballoon fully hits its stride. Physicians are still learning the nuances of cryoballoon ablation and have yet to determine exactly where this technology will fit into the treat-

ment armamentarium. The *Arctic Front* is an over-the-wire, double-balloon system that is compatible with 0.035" guidewires. Although some concerns remain with this first-generation technology, particularly in terms of balloon noncompliance and correct balloon positioning across varied anatomies, phrenic nerve injury, the need for multiple freezes to achieve vein isolation, and the frequent need for RF touchups to achieve complete PVI, reports on the *Arctic Front* at HRS were largely positive. In the pivotal STOP-AF trial, first presented at the 2010 American College of Cardiology meeting, the device showed significantly better primary treatment success versus AADs (69.9% vs 7.3%). However, adverse events, particularly transient phrenic nerve injury (phrenic nerve palsy, or PNP), were fairly high in this study, as noted during the AF Summit by Dr. Kuck.

The *Arctic Front* is available in two balloon sizes—23 and 28 mm—but Kuck and others experienced with the device now advocate using only the larger, 28-mm cryoballoon whenever possible in order to improve safety and efficacy. The smaller balloon tends to result in a more distal ablation that is closer to the phrenic nerve, Kuck explained during the meeting.

As mentioned, the device's balloon is non-compliant and physicians have reported some difficulties with correct positioning of the balloon in the PV orifice, which can lead to inadequate tissue contact, failure to fully isolate the PVs, and collateral tissue damage. Poor tissue contact with the cryoballoon is not uncommon, particularly in harder-to-reach areas and in oddly shaped veins, but it can often be improved with an aggressive "pull down" maneuver, which if appropriately performed enables the device to achieve lower temperatures and better outcomes, according to Vivek Reddy. Although comparative data is lacking, efficacy outcomes with RF and cryoablation appear similar, he said. However, large, randomized trials comparing cryoablation and RF are still needed to fully assess the potential benefits of one technology over the other; and it is likely to be at least two years before such data is available, Reddy said.

At HRS, researchers from Barts and The London NHS Trust presented preliminary results from an ongoing 246-patient randomized study comparing cryoballoon ablation, RF ablation, and a combination of the two in

patients with PAF. In 133 patients with six-month follow-up, they observed a trend toward improved outcomes (freedom from AF) in patients treated with cryoablation alone versus RF alone (65% vs 41%), with little benefit to the combined approach. Interestingly, although 61% of veins treated with cryoablation were isolated with two freezes, only 11% of the cryo patients achieved total PVI with two freezes. The rate of PNP following cryoablation was 4.7% but all cases resolved by six months. There also was a relatively high rate (20%) of crossover to RF ablation in the cryo group. In addition to AF recurrence and complication rates, the final study will compare costs, radiation exposure, and long-term success out to 12 months.

Other randomized studies comparing cryoablation and RF are underway or in the planning stages. Ongoing studies include the 244-patient, randomized, controlled, prospective FREEZE AF noninferiority trial in Germany and the CE-AF Trial in The Netherlands. The latter is investigating the incidence of cerebral embolism following ablation performed using the *Arctic Front*, the PVAC (Medtronic Ablation Frontiers LLC's RF Catheter), or the *Navistar ThermoCool* RF catheter.

The fact that cryoablation patients often require RF touchups to achieve complete PVI remains a point of contention among some current ablation providers, who question why they need to add another expensive technique to their practice if it cannot stand on its own. In a review article published in December in the *Journal of Atrial Fibrillation*, Gian Battista Chierchia, MD, and colleagues from the Heart Rhythm Management Centre in Brussels, Belgium, highlighted this issue, pointing out that although cryoballoon ablation is a "very promising technology," the cryoballoons available today "do not always adapt themselves well to the anatomical variants and do not systematically isolate the PVs in one application, sometimes requiring "touch up" lesions with a traditional [RF] ablation catheter."

Successful PVI with the cryoballoon is "highly dependent" on perfect contact with the atrial wall, which allows the balloon to achieve lower temperatures, they assert. However, anatomical constraints, such as oval-shaped ostia, often prevent ideal contact. The authors suggest that using imaging guidance during the procedure may help, as will further technological improvements in

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balloon systems. Ideally, a “softer and more compliant balloon” that fits snugly into most PVs “might lead to a more effective procedure.” They also point, once again, to the need for studies directly comparing cryoballoon ablation with RF ablation “in order to assess the real efficacy of this technology.”

Medtronic Reports Strong Growth in AF Business

While researchers work to more fully understand the benefits and drawbacks of cryoballoon ablation, Medtronic says physician adoption of the *Arctic Front* is accelerating. The company posted 40%+ growth in its AF Solutions business in Q4 2011 (ended April), driven by the US launch of the *Arctic Front* as well as continued adoption of the device in Europe, company officials said during the firm’s May earnings call. The company anticipates additional share gains in its AF business in fiscal 2012, with growth in the 30% to 40% range.

During the quarter, Medtronic also launched its *Achieve* Mapping Catheter in Europe, a device designed to address positioning/efficacy issues by helping EPs verify vein isolation during the cryoballoon procedure. *Achieve* was FDA cleared in May and made its US debut at HRS. The device combines PV diagnostic and ablation capabilities in a single system, enabling EPs to assess PV potentials before, during, and after cryoablation, the firm says. Moreover, because *Achieve* is deployed through the *Arctic Front* guidewire lumen, the entire procedure can be performed with a single transseptal puncture and minimal catheter exchanges.

Challenges Ahead?

The recent growth in Medtronic’s AF business is in stark contrast to the company’s overall performance in the quarter. Total revenue for fiscal Q4 came in nearly \$1 billion below original expectations, the firm said, due in part to dismal sales of CRM devices (ICDs and pacemakers), which declined 4% worldwide and 14% in the US, on an adjusted basis. Total revenue for the firm’s Cardiac and Vascular group was \$2.322 billion, a decrease of 1% year/year, with declines in the CRM business partially offset by strong growth in AF, coronary and peripheral, structural heart, and endovascular products.

Although the *Arctic Front* appears to be performing well, Medtronic could face some challenges ahead with its Ablation Frontiers

AF technology, which it acquired in early 2009 for \$225 million. A 108-patient study published online in March in the *Journal of Cardiovascular Electrophysiology* found that PAF patients treated with Ablation Frontiers’ *Pulmonary Vein Ablation Catheter (PVAC)* Multielectrode RF Catheter had a 1.48 times greater risk of experiencing a silent cerebral ischemic event compared to those treated with an irrigated RF catheter or with cryoballoon ablation. The study utilized magnetic resonance imaging (MRI) before and after the procedure to identify patients with new silent ischemic cerebral lesions postprocedure. New lesions were uncovered in 38.9% of the PVAC patients, 8.3% of the irrigated RF catheter patients, and 5.6% of the patients treated with the cryoballoon.

Although the study is relatively small, the findings could raise safety concerns at the FDA, where the PVAC is currently under review. The device has been on the market in Europe since 2007. Interestingly, Medtronic is positioning the Ablation Frontiers line of multielectrode, anatomically designed catheters as potential options for patients with permanent AF, which was not the population studied in the trial noted above.

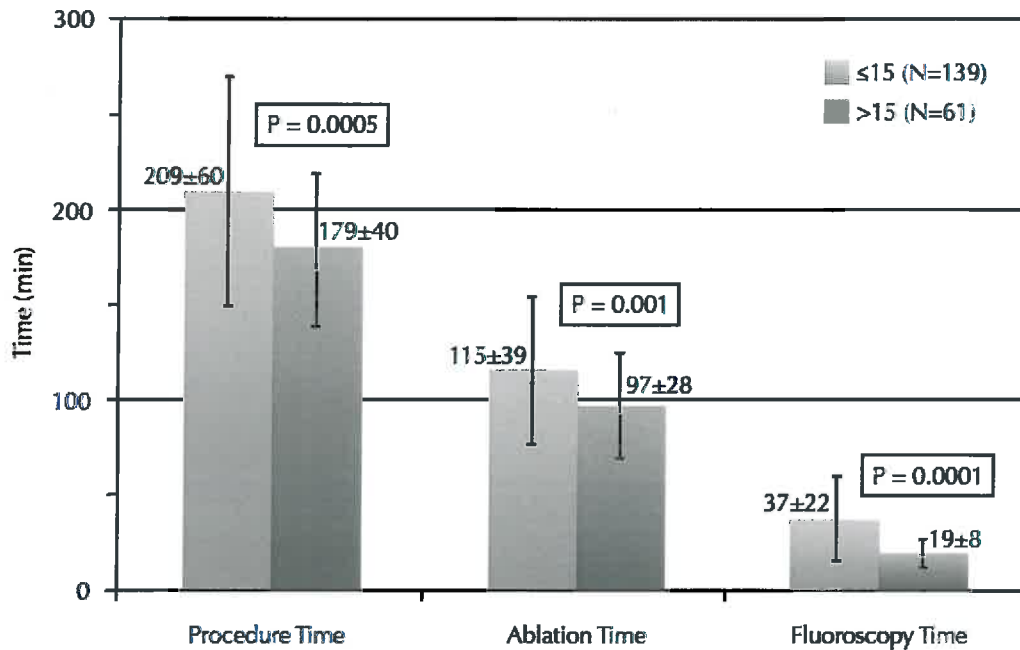
The Next Wave of AF Ablation Technology

Despite the challenges and risks, competition in the AF ablation arena continues to heat up as several competitors work to bring the next generation of ablation technology to the market. Several promising new ablation tools were discussed during the HRS sessions, including laser-guided balloon ablation, heated saline balloon ablation, and a variety of other technologies and devices in development.

CardioFocus Hits the Big Time

One emerging company that attracted a great deal of positive attention at this year’s HRS was CardioFocus Inc., which is developing a unique, visually-guided laser balloon ablation technology it now calls the *HeartLight* Endoscopic Ablation System. The *HeartLight* enables physicians for the first time to directly visualize the inside of the heart as they are performing the ablation procedure. The device consists of a multilumen catheter with a compliant, inflatable balloon at its distal end, which is introduced into the left atrium via a 12-F steerable transseptal sheath. The fluid-inflated balloon is highly conformable and can expand

Exhibit 6

First 200 Patients Treated with HeartLight Endoscopic Ablation System
 Procedure Times Stratified by Physician Experience (≤ 15 procedures vs. >15 procedures)


SOURCE: Vivek Reddy, MD, from a presentation given at the 2011 HRS conference

to over 30 mm, enabling it to treat PVs from 9 mm to about 32 mm in diameter.

The central catheter lumen contains a 2-F fiberoptic endoscope with a wide field of view, which enables direct visualization of the surrounding tissue. A second laser delivery fiber, which can be moved and rotated, is used to deliver a 30-degree arc of light as an aiming beam to identify the exact location for ablation. Once the location is selected, 980-nm diode laser energy is delivered to create the ablation lesions, each covering the 30-degree arc, with multiple lesions placed in an overlapping manner to achieve a continuous lesion set.

Two important studies were presented on this technology at HRS and both showed extremely promising results. Dr. Reddy presented a compilation of four trials that represented results for the first 200 patients treated with the device worldwide. The procedures were performed at 15 sites in four countries and involved 33 physician operators, so the data offered a fairly wide experience.

The results compare very favorably with current ablation technologies. Of the 770 PVs targeted in these patients, a total of 761

(98.8%) were isolated and 604 (78.8%) were isolated on the first attempt. In 107 patients who reached six-month follow-up, the drug-free, single-procedure rate of freedom from AF was 65%. Procedure time averaged 200 minutes, but procedure, ablation, and fluoroscopy times all declined significantly as operators gained more experience with the technology. (See Exhibit 6.)

Complications were relatively rare and included five phrenic nerve injuries (2.5%) and four cardiac tamponades (2%). There were no strokes, transient ischemic attacks, esophageal fistulas, or PV stenoses. However, the 2% rate of tamponade did prompt the company to redesign the catheter tip to make it softer, according to CardioFocus president and CEO Stephen Sagon, who spoke with *Medtech Insight* at the HRS meeting. The company believes the softer tip will sufficiently address the tamponade issue, according to Sagon, who says the new softer-tip catheter has been in clinical use since February of this year and will be the device used in the upcoming US IDE clinical trial.

In his HRS presentation, Dr. Reddy concluded that the aggregate experience to date with the CardioFocus device shows that the

Kuck noted during the AF Summit that if the recently reported durability outcomes with the HeartLight persist over the longer term, the device could be "significantly better" than any other technology developed so far.

system can achieve a high rate of PVI with a single balloon catheter and a low rate of complications. This "sets the stage" for studies comparing the long-term efficacy and safety of the *HeartLight* with RF ablation, he said.

The other important news on this technology at HRS came from a remapping study presented by Srinivas Dukkipati, MD, of Mount Sinai School of Medicine in New York. This three-center, 10-operator study enrolled 56 PAF patients who were treated with the *HeartLight* device. Uniquely, all the patients were asked to return for PV remapping at three months, regardless of symptoms, in order to identify PV reconnections and assess procedure durability.

A total of 202 out of 206 PVs treated in the study (98.1%) were successfully isolated during treatment, with an average of 1.3 attempts per vein and 1.05 catheters used per patient. Complications were rare and included one cardiac tamponade and one phrenic nerve injury.

Fifty-two of the patients returned for remapping at three months. Durable electrical isolation was observed in 85.7% (162/189) of the PVs treated in these patients and 61.5% of the patients (32/52) still had all of their PVs isolated. Once, again, operator experience impacted outcomes. Those operators with at least 10 procedures under their belt achieved significantly better procedure durability, with 89.4% of PVs persistently isolated at three months, compared to 73.1% for operators who had performed fewer than 10 procedures. However, the percentage of patients with all of their PVs persistently isolated was not significantly different between the two groups (57.1% for less experienced operators vs 65.8% for more experienced operators), suggesting that even inexperienced operators can achieve good results with the system.

Long-term outcomes were also positive, with 25 of 35 patients followed out to 12 months (71.4%) free of AF off drug therapy. The authors concluded that the visually guided laser balloon system can safely achieve high rates of acute and durable PVI, even with limited operator experience. The durability of the procedure compares very favorably with published RF remapping studies, Dukkipati said. Very few RF remapping studies have been performed to date, but Dukkipati pointed to two small studies, one published in 2008 that showed a durable PVI rate of only 37.5% three

months after RF ablation and another, published last year, showing a rate of 57%. However, in the latter study, only 23% of patients had all of their PVs isolated at three-months.

But the larger clinical experience suggests that RF ablation may achieve even lower rates of durable PVI, in the range of about 24% of PVs treated, with even fewer patients (about 4%) achieving isolation of all PVs, according to Dukkipati who compiled "redo" data from several studies published over the past four years. And that is one big reason the *HeartLight* spawned so much enthusiasm at the HRS meeting this year.

Although there are some apparent drawbacks to the current system's design (Andreas Metzger, MD, and colleagues from Asklepios Klinik St. George, Hamburg, Germany, noted in a recently published study that because the device is not designed as an over-the-wire system, it is sometimes challenging to direct and stabilize in the heart), physician reaction to the technology at HRS appeared to be extremely positive. Kuck noted during the AF Summit that if the recently reported durability outcomes with the *HeartLight* persist over the longer term, the device could be "significantly better" than any other technology developed so far.

According to Sagon, the remapping study results, in particular, attracted a steady stream of physicians to the CardioFocus booth during the meeting. But physicians were also drawn by the fact that the system allows them to see what they're doing, which reduces the learning curve compared with RF or even cryoballoon ablation, he said. "The efficacy we're getting, even with physicians who have done only 15 cases, is better than what has been achieved with RF by doctors who have done 300 cases, and that's what this field really needs [to move ablation forward]. If only one out of four EPs is doing AF ablation today, there must be something preventing them from attempting this in their hospital. And where is someone who is five years out of their fellowship going to get training to do 50 or more cases?"

Unlike the *Arctic Front* Cryoballoon System, the *HeartLight* can treat almost all anatomies with a single balloon, Sagon asserts. "We had some predefined anatomical exclusions in the trials involving our first 200 patients, but in all the patients we've enrolled so far, we've never excluded a patient from treatment due to anat-

omy. So when we say we successfully isolated 98.8% of veins; that was in all-comers."

The *HeartLight* was CE marked in June 2009 and a limited European launch began in late 2010. To date, ten European centers have used the system and six have been upgraded to the latest version, Sagon said. Worldwide, 298 *HeartLight* procedures have been performed as of early May. According to Sagon, physician reaction to the system in Europe has been very positive so far, but the company still has a lot of work to do. "This year will be about establishing more centers in Europe," he said.

The company is also moving forward rapidly with its US commercial plans. A 10-site US feasibility trial completed enrollment last October and that data will be used to gain IDE approval for a pivotal US trial, which is expected to begin late this summer. The pivotal trial will enroll about 350 patients at 20-25 sites and will follow patients for one year. It will be designed as a randomized, noninferiority study pitting the *HeartLight* against Biosense Webster's *ThermoCool* RF catheter. "We thought about randomizing versus the *Arctic Front*, but the device wasn't prevalent enough to be assured the operators we wanted would have the necessary

level of knowledge," Sagon told *Medtech Insight*. "Plus, AF is an RF field and we didn't want to marginalize the results."

The company is also doing well financially. CardioFocus completed its latest round of private financing in February of this year, raising \$30.6 million. The funds are enough to take the company "deep into the FDA process," Sagon says "Then we'll see at what level our sales are ramping and whether or not it makes sense to do additional fundraising or be open to some partnership proposals that have been on the table."

Other Emerging Technologies

There are a number of other interesting technologies in development for AF ablation, including the *Tempasure* Ablation Catheter from Advanced Cardiac Therapeutics Inc., which was CE marked in early June. The *Tempasure* System is an RF catheter that for the first time provides both saline irrigation and real-time temperature-sensing technology. The aim is to reduce procedure time and increase effectiveness while preventing adverse events. The system employs passive sensing microwave radiometry to provide real-time temperature measurements, enabling automatic power titration during the

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NewCor GMBH is developing a noncontact laser ablation catheter with an esophageal probe that senses photons and automatically switches off the laser energy before it reaches energy levels that could cause tissue damage.

ablation procedure. The company expects to launch the device in Europe later this year.

Another investigational technology mentioned at the AF Summit was Toray Industries Inc.'s Toray Medical Co. Ltd.'s (Japan) *Toray-Satake* Hot Balloon Ablation Catheter, which uses an RF coil to heat fluid inside the balloon. Following early technological problems, the device was redesigned and now has a compliant balloon and over-the-wire, steerable delivery system. Unlike traditional RF ablation catheters, the system provides very predictable heating and may reduce side effects such as esophageal injuries, according to David Haines, MD, of William Beaumont Hospital, Royal Oak, MI, who presented an update on the technology at the AF Summit. The company is currently working to reduce the catheter size to 11 F and expects to begin a pivotal Japanese trial in Q3 2011, with US trials getting underway in Q4 2011 or Q1 2012, Haines said.

Meanwhile, another AF hopeful, German-based NewCor GMBH is developing a noncontact laser ablation catheter with an esophageal probe that senses photons and automatically switches off the laser energy before it reaches energy levels that could cause tissue damage. The technology should provide a better way to monitor energy output than temperature measurement, and it will enable physicians to create transmural lesions in the shortest time without unwanted effects, company reps told *Medtech Insight*. NewCor expects to receive CE mark approval for the device, along with a transseptal puncture device (the *LaserTranseptor*), by the end of 2011 and will begin a multicenter clinical trial at around the same time. The trial may be extended to include US sites in late 2011 or early 2012.

Monitoring and Guidance Are King

What is clear from the new and notable AF ablation technologies discussed at this year's HRS meeting is the strong desire among clinicians for more sophisticated ablation tools that provide additional, specific information about the procedure as it is taking place. Combining real-time visualization or imaging guidance with information on CF, temperature, or other energy-dependent measurements could help physicians optimize ablation lesions and improve long-term outcomes while avoiding complications.

Although CardioFocus is leading the effort to develop a system that provides direct imaging

capabilities during the ablation procedure, it is not alone. Voyage Medical Inc. is continuing development of its *IRIS* Catheter System, a multilumen, steerable, fiberoptic catheter with integrated RF ablation capabilities that uses saline to clear blood from the field of view and enables direct, high-resolution imaging via a tiny camera and light source connected to the fiberoptic. The system includes bipolar, electrogram feedback and a 3-D mapping and navigation interface, according to information presented recently. An abstract on the technology presented at HRS detailed the results of a preclinical study performed in dogs. The authors concluded that the system was safe and effective in creating transmural lesions at the PV ostia. Moreover, energy titration based on direct visual feedback was able to minimize tissue superheating, limit injury to collateral tissues, and improve lesion consistency, the authors said.

Other researchers are working on ways to combine existing in vivo imaging technologies, such as ultrasound and MRI, with ablation tools to provide real-time, high-resolution image guidance during the procedure. MRI is one imaging modality that is emerging as a powerful tool in cardiology, not only for ablation procedures, but also to help guide ICD lead placements and for many other cardiac applications.

One emerging company with a focus on MRI-guided ablation is Irvine, CA-based MRI Interventions Inc. (the company changed its name from SurgiVision Inc. in May), which is in preclinical development with an MRI-compatible 7-F steerable RF ablation catheter that enables real-time MRI guidance during the ablation procedure. The device, which features temperature monitoring at its tip and four tracking microcoils, is designed to enable real-time visualization of myocardial destruction during the procedure so that lesion formation can be assessed and, if necessary, corrected during ablation.

The company is working together with Siemens, which is providing its 3-Tesla *Verio* MRI Scanner for use during the procedure. In a preclinical study published in *Heart Rhythm* in February, researchers described a protocol that involved an EP-MRI suite located adjacent to the conventional EP suite. Treated animals were transferred between the two rooms via a system of rails, also from Siemens (*Angio-MR Miyabi*).

Four projectors attached to the MRI host, real-time MRI computers, ablation unit, and telemetry system projected MRI images through waveguides onto MRI-compatible projection panels inside the suite, providing the operator in the MRI suite the same real-time information that the MRI technologist received outside the room.

The researchers treated six pigs under MRI guidance using a gradient-recalled echo MRI sequence to image the catheter in real-time during navigation. During ablation, the catheter tip was located using another specialized MRI sequence, which enabled the team to localize specific points within the atrium and deliver RF lesions while simultaneously visualizing and assessing the tissue for injury and lesion formation. An abstract presented at HRS also detailed use of the system to identify and accurately target gaps in lesion sets, something the authors said could potentially lead to significant improvements in AF ablation outcomes.

Ultrasound imaging is also under investigation as a tool to enable real-time procedure visualization. One company that appears to be leading this effort is Philips Research Laboratories (a division of Royal Philips Electronics NV), which has published preclinical work in conjunction with Matthew Wright, PhD, of Kings College London, on a system that combines an RF ablation catheter with integrated ultrasound real-time lesion assessment to visualize tissue necrosis during the ablation procedure.

Start-Ups Pursue Mapping Advances

Advanced mapping and navigation tools also were highlighted at HRS, and there are a number of companies—both large and small—working to innovate in this area. The aim here is to improve the quality of the ablation while at the same time reducing procedure times and x-ray exposure.

Established companies active in this area include St. Jude, with its MediGuide technology, which the company acquired in 2008 for \$300 million. St. Jude is developing MediGuide's gMPS Real-Time Medical Positioning System for use with diagnostic and ablation catheters, guidewires, and other interventional devices, but plans to integrate the technology initially into its *EnSite* 3-D EP mapping system. The MediGuide System offers nonfluoroscopic, sensor-guided

navigation via a miniature sensor that can be attached to a catheter. The sensor tags anatomic structures and creates landmarks for procedures. According to an abstract presented at HRS, clinical work to date suggests the system enables precise catheter tracking, provides realistic compensation for the beating heart, and has the potential to reduce fluoroscopy time.

There are several start-ups with interesting advances in this area as well, including Rhythmia Medical; CardiInsight Technologies Inc., a company founded in 2006 that is developing a noninvasive mapping technology capable of providing dynamic mapping in one heartbeat; and Topera Inc.

As mentioned earlier, Rhythmia Medical is developing a 3-D mapping, visualization, and navigation system that uses an 8-F deflectable catheter with a basket array containing 64 electrodes. The system automatically generates heart chamber geometry and a high-resolution activation map using all electrograms recorded within 5 mm of the chamber surface, according to an abstract presentation at HRS. Initial results from 10 patients in that study showed that the system produced high-resolution maps in only 11.5 minutes, on average. Compared to conventional point-by-point maps, which can take hours to generate, the system included more electrogram sites, had higher resolution, and required less time, the authors said. Founded in 2004 and based in Burlington, MA, Rhythmia Medical began clinical trials of its mapping system last fall. The company has raised \$19 million in venture financing to date.

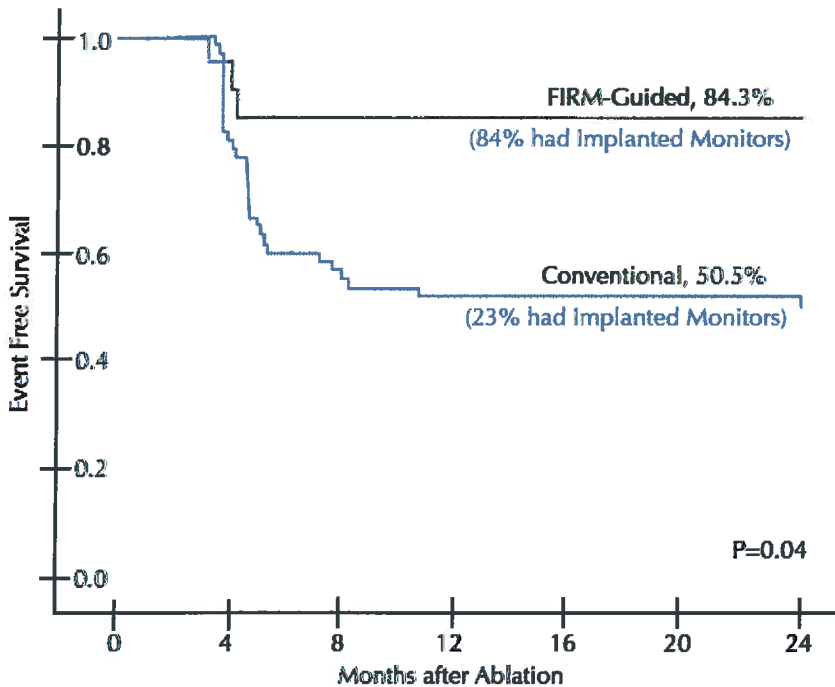
Another promising new technology that received a lot of attention at HRS is a unique computational mapping software algorithm developed by Topera, a start-up founded in 2008, and based in Lexington, MA. Topera's CSO, Sanjiv Narayan, MD, PhD, presented results of the firm's 103-patient CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial during a late-breaking clinical trial session at HRS and spoke with media at a press conference prior to the presentation.

Narayan, who also is an associate professor of medicine at the University of California, San Diego, has spearheaded most of the development work on the system, which first entered clinical trials in 2005.

MRI Interventions Inc. is in preclinical development with an MRI-compatible 7-F steerable RF ablation catheter that enables real-time MRI guidance during the ablation procedure.

Exhibit 7

Confirm Trial: Long-Term Single Procedure Efficacy



SOURCE: Sanjiv Narayan, MD; from a presentation at the 2011 HRS meeting

He said the technology offers a novel, patient-tailored physiological mapping system that for the first time enables physicians to identify actual causal factors for AF during the ablation procedure by imaging electrical rotors, or focal drivers, in the heart that are believed to perpetuate abnormal atrial rhythms. These rotors can be found anywhere on the atria, he said, and represent localized areas of electrical activity.

CONFIRM researchers recorded AF in the study patients using conventional 64-pole mapping catheter baskets guided by intracardiac echocardiography as well as fluoroscopy to ensure optimal basket coverage. They then applied the company's novel computational system to image AF rotor sources. Patients were randomized to receive either FIRM-guided ablation followed by conventional wide area circular RF ablation (WACA) for PVI ($n = 32$) or WACA alone ($n = 71$). In the FIRM group, ablation was applied to each identified rotor/focus for 10 minutes or less. Patients were monitored postprocedure using either implanted loop recorders or continuous ambulatory electrocardiograms and were followed for up to two years.

Rotors or focal drivers were identified in 98% of the study participants. In the FIRM group, ablation of the rotors/foci for 10 minutes or less successfully terminated or slowed AF prior to WACA, with 88% of the FIRM group achieving acute termination or slowing of their AF with less than 30 minutes of ablation. FIRM-guided ablation also improved procedure durability, increasing freedom from AF at two years by 70% compared with the WACA-only group. Single-procedure freedom from AF in the FIRM group was 84.3%, compared with 50.5% in the WACA-only group, which was statistically significant. (See Exhibit 7.) These results are substantially better than single-procedure outcomes demonstrated with existing technologies and are all the more impressive since two-thirds of the patients in the study had persistent AF, a notoriously difficult condition to treat with catheter ablation techniques. In addition, the outcomes were well-documented, with 84% of patients in the FIRM group receiving implanted monitors during follow-up.

During the press conference, Doug Packer, MD, of the Mayo Clinic, Rochester, MN, and outgoing HRS president, commented on the trial, noting that the technology enables physicians to map arrhythmias based on real physiology, unlike the anatomical methods currently in use, and it has the potential to shorten procedure times. Anything that can achieve the latter goal would offer an "enormous benefit," he said. Topera may soon see just how successful the technology is in the marketplace. The company filed a 510(k) application for FDA clearance in March of this year and hopes to begin rolling out the system, which it has named *RhythmView*, in the US in the first half of 2012.

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