Trends-in-Medicine

June 2004

By Lynne Peterson

SUMMARY

HRS (NASPE) has been lobbying CMS very hard to grant broad coverage for ICDs for MADIT-2 patients, but it appears CMS will keep QRS as a criteria and introduce tiered DRGs in an effort to encourage use of lower-cost devices. ♦ SCD-HeFT has not increased the volume of MADIT-2 patients for ICDs, and there is no bolus of MADIT-2 patients to be implanted if CMS does broaden coverage, but doctors are hopeful that referrals will pick up when primary care doctors are better educated about sudden cardiac death and the indications for an ICD. The HRS Foundation is planning a direct-to-consumer advertising campaign to help with educating doctors and patients. ♦ Doctors are getting more comfortable with the idea of a low-cost device, and they estimate that it could be used in about a third of their patients. ♦ AF ablation is a hot topic, and interest has increased in cryoablation, mapping, and navigation systems.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

HEART RHYTHM SOCIETY

San Francisco
May 19-22, 2004

Heart Rhythm Society is the new name for NASPE (North American Society for Pacing and Electrophysiology).

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDS)

The current U.S. indications for ICD in long-QT are for:

- Survivors of cardiac arrest
- Recurrent syncope despite beta blockers
- Family history of sudden cardiac events, though this is starting to be questioned
- Symptoms with QTc>520 ms
- Symptoms patients with LQT3
- The use in asymptomatic Brugada Syndrome patients and to patients with "provokable" Brugada Syndrome is still debatable.

THE ICD MARKET

Is the untreated MADIT-2 market as large as some people have suggested? Maybe not. A speaker said, "Industry believes that 80% of (potential) prophylactic ICDs are not being implanted…Our society is caught in a conflict of what is right and ideal and what is practical in the community."

Other doctors said that there are patients who would benefit from an ICD but that primary care and internal medicine doctors are not referring them. An Oregon doctor said, "There are more patients out there, but primary care physicians never screen for (the indications). I tell the primary care doctors that the patients exist, and they should refer, but for every three patients who qualify, only one is interested in a device because it is surgery…If CMS issued a broad coverage decision for MADIT-2 indications, the number of patients we see would go up, but it wouldn't double." Another source said, "We still need a lot of work on primary care referrals." A third doctor commented, "I'm not turning any patients away. We need to educate primary care doctors on referrals."

After the results of SCD-HeFT, sources said their ICD volume generally did not increase, but most doctors expect their volume to increase as patients and referring doctors get educated more about sudden cardiac death and ICDs. A South Carolina doctor said, "There was no increase after SCD-HeFT. The trial showed the value of ICDs, but we need reimbursement, and there is always a lag period while people digest the information." A Florida doctor said, "The pent-up demand

will be there from primary care doctors as they get educated …The SCD-HeFT data has not been published yet, and we don't have a CMS reimbursement ruling." A Texas doctor said, "There is no waiting list. Patients are getting devices anyway."

The Heart Rhythm Society, which is funded by donations from industry and from grateful patients, is planning to help educate people with a direct-to-consumer advertising campaign. An HRS official said the campaign is "to promote public awareness of sudden cardiac death," but the official would not say whether this campaign would start before or after the CMS decision on ICD reimbursement. Reportedly, various ICD companies have tried local direct-to-consumer advertising in the past with little success, but the hope is that a national campaign by HRS would be more effective.

Yet, some doctors are beginning to question whether: (1) There really are this many eligible patients who are being missed, or (2) Some patients simply do not want surgery or a device.

Doctors questioned about what devices they are putting in MADIT-2 patients insisted they are putting in whatever devices they believe the patient needs – which most often is a dual chamber device. However, most also said they are primarily using single chamber devices in SCD-HeFT-type patients. A Florida doctor said, "They often get a three-lead CRT…An awful lot of patients have AF, so there is a valid indication for a dual chamber device or CRT…Only about 5% of my patients are getting a 'stripped down' device…If patients have an indication for pacing or AF, then they get a dual chamber device. Otherwise, they get a single chamber device – and that's about a third of my patients." A California electrophysiologist said, "I would use a low-cost device in about 30% of patients – in patients with a history of SCD and normal EF."

On average, sources estimated that 23% of their ICD patients are getting a CRT-D.

WHO IS – AND WHO SHOULD – IMPLANT ICDS?

Survey of Physician Attitudes on Capacity Constraints

Issue	% of responders
Constrained by own capacity	22.2%
Constrained by other factors	62.4%
Not constrained	15.4%

Type of EP procedure	% of time spent
Pacemaker implants	28%
ICD implants	19%
Ablation	18%
ICD replacement	4%
Other	31%

Dr. Douglas Zikes of Indiana University, a past president of NASPE and of the American College of Cardiology, offered some insight on this issue:

- **Does the volume of ICD implants exceed the capacity of electrophysiologists at the present time? No.** Dr. Zikes said total implants are relatively constant for surgeons and cardiologists but up significantly for electrophysiologists (EPs).

- **Is there a need for heart failure specialists to understand CRT/ICDs? Yes.**

- **Is there a need for non-EP implanters? No.** He said, "If we did consider non-EP implanters, this could be done in the future with those who meet credentialing criteria for implantation, regardless of whether the doctor is a surgeon, a cardiologist, or an EP. This would require HRS, along with the American College of Cardiology (ACC) or the American Heart Association (AHA) to establish those criteria." Asked what will happen at his hospital, Dr. Zikes replied, "We will talk to our hospital credentialing committee...and say these are the criteria which doctors who seek privileges will be required to satisfy...and I think we can accomplish that. Hospitals are thirsty for (these) kind of guidelines…I advise you to take these guidelines to your hospital and make sure the credentialing committee understands them and includes them." However, about half the audience at this session thought non-EPs should be able to implant ICDs.

- **Should we have a combined fellowship? Yes.** He said, "One year of heart failure training could be accepted after EP training …but there is no heart failure specialty right now, and I think that would have to be established. And who would pay for the extra year of training?"

- **Should we consider shortening training? Yes.** He said, "I think we should reduce internal medicine to two years from three, and this is being considered by the American Board of Internal Medicine."

- **Should we extend the training of EPs? Yes.** He said, "The field has become increasingly complex. I do think a year of EP training is insufficient."

Medtronic's Implanter Capacity Analysis

Specialty	Share of all electrophysiology implants	Share of pacemaker implants	Share of biventricular pacemakers	Share of ICD implants	Share of CRT-D implants
EPs	58%	45%	68%	88%	90%
Cardiologists	22%	30%	20%	3%	4%
Surgeons	20%	25%	13%	9%	6%

THE CMS ICD REIMBURSEMENT DEBATE

In June 2003 CMS made a controversial decision that it would pay for ICDs for MADIT-2 Medicare patients only if they had a QRS>120, but the agency also said it would revisit this decision after the SCD-HeFT data was available. In March 2004, Medtronic submitted a request for a new national coverage decision based on the SCD-HeFT data, and CMS has until September 30, 2004, to issue its draft proposal, which will then be open for public comment for 30 days. Then, by December 30, 2004, CMS will issue a final rule, to go into effect in April 2005.

The Impact of the Decision

Doctors at the Indiana Heart Institute did a study of the impact of the ICDs vs. current CMS reimbursement. They screened 16,001 patients, found 2,750 with LVEF ≤40 and a previous MI, and of these, 1,156 met the MADIT-2 criteria. For this analysis, they used the following pricing assumptions:

- Inpatient ICD implant without EP study ……. $28,981
- Inpatient ICD implant +EP study……. $34,514
- Outpatient EP study…….. $ 1,290

They concluded: CMS MADIT-2 criteria exclude 74% of all patients and 8% of those ≥65. Depending, on the use of an EP study and the age group evaluated, CMS criteria reduced ICD costs $7.6 - $24.9 million.

Another ICD study looked at the impact of CMS reimbursement on ICD use in the Marshfield, Wisconsin, Epidemiology Study Area (MESA) on patients with cardiomyopathy, and found that, using the CMS criteria, there are far fewer MADIT-2 patients eligible for an ICD under Medicare than previously thought. MESA reportedly captures nearly all the healthcare provided to the approximately 60,000 residents in the region, so it was a good way to find a population that could be extrapolated nationally. Researchers looked at all MESA patients who survived an MI from January 1979 to February 2002, and identified 1,221 who had survived an MI, a point prevalence of 2.5 per 1,000 adults. Of these:

- 112 met the CMS criteria (LVEF ≤30 +QRS>120)
- 10% had LVEF≤30
- 53% were Medicare age, and 35% of these had QRS>120
- The point prevalence was 2.5

Researchers concluded from this that only 67,000 of the entire U.S. population would qualify under CMS 2003 guidelines for an ICD. A speaker said, "This is an 85% reduction from our previous estimate of 460,000 patients satisfying MADIT-2 criteria."

The CMS View

At the American College of Cardiology meeting in March 2004, CMS Chief Medical Officer Dr. Sean Tunis said his agency would consider the SCD-HeFT results "with great interest over the coming weeks and months...(placing) a tremendous amount of weight and emphasis on SCD-HeFT."

However, he noted that CMS may not get the full SCD-HeFT data until it is published, which is about the time the draft decision is due. He said, "The hang-up is when we can see the SCD-HeFT data. Sometimes things change in the peer review process. The publication date is about the time of our decision."

He also suggested CMS could decide to:

- Restrict ICD reimbursement to NYHA Class II patients either in addition to or in lieu of QRS>120.
- Introduce incentives for doctors to use less expensive, stripped-down devices.
- Do a meta-analysis of all ICD trials to help them make a decision.

At this meeting, Dr. Tunis:

➢ **NYHA Class.** Did not discuss using NYHA Class as a determinant.

➢ **QRS**. Seemed committed to retaining a QRS cutoff. He spent some time explaining the agency's rationale for using QRS. Dr. Tunis said, "Four separate trials have shown trends on QRS, and that doesn't challenge the CMS decision very well."

➢ **Meta-analysis.** Again, suggested the agency may do a meta-analysis of all ICD trials – including MADIT, COMPANION, and DEFINITE – to help them make a decision.

➢ **DRGs.** Discussed CMS's proposal for different levels of DRGs for ICDs. He said there was precedent in doing this, citing the case of LVADs. He said, "(A tiered DRG) is not common, but we did it with LVADs and with PET scanners."

➢ **Medicare Coverage Advisory Committee (MCAC).** Announced that CMS would not seek an MCAC meeting or recommendation on this issue. Asked why CMS wouldn't seek an MCAC opinion in order to avoid a decision coming out a month before the presidential election, Dr. Tunis responded, "I honestly think industry has no idea what it is talking about…To say you can never get information from subgroup analysis is wrong."

➢ **Subgroup analysis.** Defended the use of subgroup analysis in the decision making process. He said, "I want to highly emphasize how little weight I put on subgroup analyses…but to say you can never get information from subgroup analysis is wrong…All of us should be very interested in identifying patients at risk of sudden cardiac death (SCD) due to coronary heart disease (CHD). All the studies we've done so far address only a very small percentage of the patients who die of SCD. The vast majority are patients we have no way to identify…Figuring out who is at risk is a critical issue…Interpreting subgroup analyses can't be done in

a straightforward way…It is politically and practically more difficult to imagine…but that QRS width is plausible is already known…so that is not completely an out-of-the-blue idea…You might look at QRS with a different level of attention than male/female, where there is no biological basis (for a difference)…Most people have no understanding of the complexity of thinking of subgroup analysis…or how much CMS thought about this before making its decision. There is a lot of data on the value of QRS width as a predictor…What someone really needs to do rather than slicing by QRS…is to do a meta-analysis of individual patient data looking at QRS width across all the trials and do a linear regression against ICD benefit…That is do-able if you get all the data…That is better than salami slicing different data."

Dr. Tunis also put the ICD coverage decision in a broader **political** context. Among his comments were:

- "It is my impression that there has been silent agreement over the years that no one connected with Medicare or in Congress can talk about the economic pressures translating into making difficult decisions."
- "I decided that the Clinton (healthcare) plan was going to fail early on when I heard everyone was going to have as good or better health care at a lower cost – that didn't fit with the laws of physics."
- "The notion is that patients will become more informed, more responsible for their own costs and decisions, that is a little bit of code for, 'It is their money, and they can use it however they want'…but there is not a lot of evidence that people make very rational decisions...We need to do a lot to increase health literacy to make that a reality. There is no one in Medicare that endorses this idea."
- "The model I see of tiered formularies where the economic impact on individuals, based on some information on the cost effectiveness of drugs, with a higher tier where they pay more for a drug with a brand name…I think that model can be extrapolated to other situations – where the percent copay is linked to the cost-effectiveness of the intervention…Things that are so incredibly cost effective like ACE inhibitors would have no co-pay…but things with an uncertain benefit or experimental or incredibly cost-ineffective, then the co-pay might be in a different category. That way you merge the notion of patients having to be responsible for their own decisions and relative value. No one is talking about that, but it makes sense."
- "We at least ought to have a public dialogue about economic factors in coverage decisions."
- "In the past, if it worked, we paid for it. Now, spending trends in healthcare are leading to where a lot of things we don't like are happening – and maybe a discussion is appropriate."

Dr. Tunis appears to have the support of the new CMS Director, Dr. Mark McClellan (former FDA Commissioner). Dr. Tunis said, "The past administrator never had the confidence to raise economic and affordability issues. Dr. (Mark) McClellan talks about economics of healthcare a lot…I can't say Dr. McClellan endorses what I say, but he hasn't told me to shut up."

Asked if CMS could grant a broad indication and then, later, restrict it further when better data was available, Dr. Tunis said there are two challenges with that:

1. "Putting the genie back in the bottle is very difficult. For payers to restrict or narrow what is currently paid for is not unprecedented...but even with extraordinarily good evidence – like with arthroscopic knee surgery where we found no benefit to surgery vs. placebo – it was a major war…and we ended up with a policy that technically narrowed indications but probably matched practice."
2. "Who is going to invest in the studies? They could be done, but there is a question of whether it would be systematically done. And it raises a question of whether we should think carefully about whether trials that are so impressive will still raise questions…Do these trials need to be even larger to answer subgroup questions up front?"

The American College of Cardiology reportedly is considering making MADIT-2 criteria for ICD implantation a Class I guideline. CMS has always reimbursed for Class I indications. Asked about this, Dr. Tunis said, "I hope they don't do that. We will talk to them a lot before they do it. We'll make it clear that there are economic issues that need to be on the table…It would be unprecedented for us not to cover a Class I device. That ACC decision would be a mistake…And we could set new precedent."

Other interesting comments Dr. Tunis made include:

- "If HRS continues to insist on broad coverage, the physicians are going to be in a bind."
- "It is interesting that the trial (SCD-HeFT) was done with a device that was never sold."
- "This is an indirect stimulus to industry. If they are creative, there are ways to creatively lower cost."
- "We are trying to send a signal to industry, hospitals, and doctors to make decisions."
- "If the medical profession wants to duck these issues, then those decisions will be made by the payers. Everyone can't duck."

The HRS (NASPE) Perspective

HRS officials have been lobbying CMS (and Dr. Tunis specifically) hard on this issue, and they continued that effort at the meeting. The society is urging CMS to provide full coverage of the SCD-HeFT patient population. An HRS official said, "The appropriate cardiovascular device for heart rhythm and heart failure patients needs to be at the medical

discretion of the treating physician who is in the best position to select the most appropriate device for the specific patient…CMS has been incredibly open and willing to meet with stakeholders…CMS has three options: (1) Keep the status quo, but the concern is overpaying or underpaying for ICD technology relative to costs, (2) A single/dual/triple chamber DRG, and (3) An indication DRG, but the concern is that this departs from the averaging principle that the whole DRG system is based on…This is an election year, and anything is possible. I encourage you to get involved in the process." HRS does not yet have a position on multiple DRGs.

The Physician View

Some doctors are ready to accept both a wide QRS restriction and multiple DRGs if industry – which they said specifically means Guidant, Medtronic, and/or St. Jude – provides them with lower cost single chamber devices.

Among the comments doctors made about this reimbursement debate were:

- *Pennsylvania:* "CMS is suggesting reimbursement favoring a minimalist approach…The house of medicine has done a poor job educating CMS, private payers, and patients related to the cost efficacy of ICDs…Most physicians still implant ICDs when appropriate…That is what happens in the majority of situations."
- *Indiana:* "Doctors are caught between a rock and a hard place."
- "If you implant a device now (<120 QRS), there is no reimbursement, but you can still be sued for complications. If you delay implantation, there is the possibility of a bad patient outcome plus potential medicolegal issues."
- "I have to implant 55 ICDs to save one life in low risk patients, but then I subject 54 patients to the risks of an ICD, including changing them out. I have a problem with subjecting those 54 patients to that risk."
- "Current policy may create an accidental disincentive to perform the procedure as an outpatient procedure, even if it could be done safely outpatient."
- "Does QRS width identify patients at greatest risk? Yes…(but) a coverage policy based on QRS would exclude about 60% of patients."
- "I am well aware we can't pay everyone what they want for what they do…We now need to have a serious conversation with the medical community, payers, and probably the public about how to deal with this in the least stressful way."

Physician comments about the idea of tiered DRGs to spur use of lower-cost ICDs include:

- "It has been proposed that there could be 3 DRGs for ICDs – single lead, dual lead, and CRT. Speaking for me and the majority of heart rhythm physicians, we would not be very supportive of all SCD-HeFT devices having to be a single chamber device…but it could be that secondary indications would be part of this process – that the SCD-HeFT patient who has other indications might get that."
- *Indiana:* "A two-level DRG is okay if the choice is left to the physician…and the reimbursement is reasonable for the hospital…I also could accept continuing the current QRS cutoff (>120)…68% of patients would then be eligible for a single chamber device, and then I would have to prove why they needed a dual device…70%-75% of patients could get away with a single chamber device….but I don't mean a 'shock box.' I wouldn't give up backup pacing, electrograms, and anti-tachycardia pacing." He estimated that a $15,000 price-tag for a single chamber device might be reasonable.
- *Washington, D.C.:* "I would use a low-cost device from Medtronic or Guidant…If the cost were about $15,000, about 30% of my patients would get a low-cost device…General cardiologists putting in ICDs are mostly using single chamber devices."
- *Oregon:* "I would only use a low-cost device if CMS ordered it and private payers followed, but I think that is coming."
- *Texas:* "Any new idea to contain costs is good. (Tiered DRGs) are better than limiting patients, as they do now. QRS>120 is stupid. Now, whoever has the money or private insurance, gets a device…I would use a single chamber, single lead device if it cost $7,000-$8,000 and had high energy and intracardiac tracing."

What features would doctors be reluctant to give up in a low-cost device? Some doctors said they would refuse to give up dual chamber devices except in AF patients, but most sources were willing to accept a single chamber device for a good proportion (about one-third) of their patients. Most doctors want even a low-cost device to include:

- Bradycardia pacing
- Support for the heart rate
- Shocking
- Anti-tachycardia pacing
- Programmable

The Industry Perspective

Physicians appear caught in the middle of a battle between industry and CMS. CMS wants cheaper ICDs available and implanted, and industry – at least Medtronic, Guidant, and St. Jude – have not answered the call. Biotronik's "no frills," low-cost ICD, the Cardiac Airbag, was approved by the FDA during NASPE 2003. It caught the attention of many electrophysiologists, who predicted that it would take significant market share over the next year. However, the device did not catch on, and sources said it is because Biotronik does not have the service and support that Guidant, Medtronic and St. Jude offer

If CMS institutes a tiered DRGs for ICDs, electrophysiologists are counting on the Big Three to introduce lower-cost devices. Medtronic and Guidant have admitted to having "economy" devices in development, and St. Jude most likely does, too. An industry source said, "We can offer a cheaper device, but it will have to be without the level of service and support we now provide. There will be a number to call, but we won't be able to give the personal service doctors have been used to."

New Analysis of SCD-HeFT Data

A new subgroup analysis of the SCD-HeFT data was presented that an HRS official said may call into question CMS's decision to limit ICD reimbursement to MADIT-2 patients with a QRS>120. The analysis found:

- Wide QRS was worse than narrow QRS as a predictor of response when a QRS of 120 was included with patients having a QRS<120 rather than with patients having a QRS>120.
- Wide QRS was comparable to narrow QRS when a QRS of exactly 120 was removed from both groups.
- The one group with a significant benefit based on QRS measurement was patients with a QRS of exactly 120. The audience chuckled at hearing this.

Mortality by QRS Width in SCD-HeFT

QRS measurement	Number of patients	Hazard ratio	97.5% confidence interval
SCD-HeFT Analysis			
<120	977	.84	.62, 1.14
≥120	699	.67	.49, .93
Traditional Analysis			
≤120	1,064	.74	.56, .99
>120	612	.80	.57, 1.13
New SCD-HeFT Subgroup Analysis			
<120	977	.84	.62, 1.14
=120	87	.21	.08, .59
>120	612	.80	.57, 1.13

In addition, another analysis of the SCD-HeFT data was presented based on a MADIT-2 definition, and that also found no advantage to ICDs based on QRS width.

A speaker concluded: "No ECG measure is specific enough to provide subgroup risk categorization for either exclusion or selection of patients for ICD therapy…ICDs are beneficial in narrow as well as wide QRS patients…Investigators all agree that to exclude patients based on a subgroup analysis is hazardous…Even the most conservatively-powered trial will have some outliers, and why would QRS be a risk stratifier? To pick that out seems a little random compared to other things we might want to look at."

OTHER ICD NEWS

CAMERON HEALTH

This company is working on a lead-less ICD, and most electrophysiologists are very excited about the idea. An Oregon doctor said, "It needs to be proven, but I would use it if it works." A California doctor said, "I heard about it, but I haven't looked at it. I'm very excited about it. I think it would be amazing. Fluoroscopy time would go down, and operating time would go down. It would be fantastic." A Texas doctor said, "It's a fantastic idea. I'm happy someone is developing one. That is the way to go in the future – five or 10 years from now." Another source said, "The device can't do anti-tachycardia pacing, and it is far away."

However, some doctors are skeptical. A speaker offered this criticism: "It is aimed at cardiologists. It's untested and unproven. It is based on cynical assumptions regarding physician behavior. I'd like to see debate on this device on its merits rather than the $900 implanting fee." A Florida doctor said, "Cameron is not as far along as the company said. It needs to prove the efficacy, and I'm dubious about their ability to prove it in the right patients. It has to be 99% effective, not 95%. Another problem is discrimination and detection of arrhythmias – when to and when not to deliver shocks…An implantable monitor does not give as good data as a lead. Cameron has a long way to go. It is not ready for prime time."

The POST Trial: Metoprolol (ASTRAZENECA'S Toprol, NOVARTIS'S Lopressor)

This 204-patient prevention of vasovagal syncope trial found:

- No significant benefit from metoprolol in the population at large.
- A baseline tilt test does not predict clinical benefit with metoprolol.
- Patients ≥42 years old taking metoprolol had a 59% relative risk reduction in syncope.

Researchers concluded:

- Metoprolol can be considered first-line therapy for vasovagal syncope in patients ≥age 42.
- Metoprolol is not a suitable first-line treatment for syncope in younger patients (<age 42).
- It is unclear whether the findings are a class effect.

SANOFI-SYNTHELABO'S dronedarone and ICDs

A researcher reported on a pilot study of dronedarone, a de-iodinated congener of amiodarone. This was a 73-patient, randomized, double-blind, parallel dose, placebo-controlled trial in which 47 patients completed the study.

Pilot Study of Dronedarone

Measurement	Placebo	600 mg BID	800 mg BID	1000 mg BID
#SS DSM	19	19	16	4
DM<10 joules	0	0	2 (13%)	0
Inappropriate ICD shocks *	67%	53%	22%	25%
Adverse events	68%	68%	90%	93%
Serious adverse events	11%	26%	35%	33%
Deaths	0	0	0	1 (7%)
ALT>2ULN	0	11%	5%	14%
Creatinine ≥150 µmol/l	6%	32%	37%	14%
QT>500 ms	13%	25%	17%	40%
LVEF change (Day 5 to 31) **	+1.3	+3.8	+3.7	+5.5

* Patients on drug had fewer shocks than patients on placebo (p=.0331).

**Nss change between placebo and drug arms

Researchers concluded:

- The drug was well tolerated with no evidence of cardiac toxicity and has a well-characterized PK/PD profile.
- Dronedarone has a reasonably safety profile at doses <2000 mg/day. The 1000 mg BID dose is not tenable.

Mortality at 2-years	Placebo	ICD	p-value
Primary endpoint: Total mortality	14.1%	7.9%	p=.08
Secondary endpoint: Arrhythmic mortality	35%	115	p=.006
Other cardiac mortality	30%	36%	Nss
Non-cardiac mortality	30%	50%	N/A

- The most frequent side effects were GI, but some transaminase elevation was seen.
- The drug prolongs QT.
- Dronedarone did not cause deterioration in ICD function or reduce the incidence of ICD therapy.
- The half-life is 16-24 hours, which means QD dosing may be possible.

New Data from the DEFINITE Trial

This study, sponsored by St. Jude, looked at 458 patients with LV dysfunction and non-ischemic dilated cardiomyopathy.

Researchers reported that:

- Annual mortality was lower than expected in patients treated with ACE-inhibitors and beta blockers.
- Among patients on drug therapy, arrhythmia accounts for only 1/3 of deaths, which was also lower than expected.
- There was a 20% relative reduction in mortality with ICD implantation.
- ICD implantation tended to reduce all-cause mortality, but the reduction was not statistically significant.

New Data from the DINAMIT Trial

This open-label, multicenter, randomized, prospective study compared ICD implantation on top of optimal medical therapy vs. optimal medical therapy alone. The primary endpoint was all-cause mortality in high-risk patients within 40 days after MI.

Doctors in the audience didn't quite know what to make of the findings, which identified a population that will **not** benefit from prophylactic ICD therapy. Researchers reported that at four years ICD therapy significantly reduced arrhythmic death by more than 50%, but there was an off-setting increase in non-arrhythmic death:

- ICD therapy did not reduce overall mortality in high risk patients early after an acute MI. There was no difference between ICD and control in the cumulative risk of death from any cause (p=.066).
- The cumulative risk of arrhythmic death was statistically significantly reduced with ICDs (p=.009): 10% with control vs. 4% with ICD at the end of four years.
- The cumulative risk of non-arrhythmic death was higher in the ICD group: 20% with ICD vs. 8% in control (p=.016).
- Following ICD therapy, mortality from non-arrhythmic causes is very high.
- ICDs as primary prophylaxis are not uniformly beneficial.
- Among ICD patients who got a first shock, mortality was extremely high – over 10% within days and 50% by two years. At four years, 17% of ICD patients who never got a shock died, but 45% of ICD patients who had a shock died.

V/V Timing

Some of the comments on V/V include:

➢ An expert said, "The great benefit of CRT is the LV lead. The timing of when RV or LV is stimulated is of less importance than having LV. With V/V you can tune things up, but that is less important."

➢ "We don't have the technology to reliably optimize V/V timing. There is no good algorithm yet. V/V is only good for ameliorating a bad LV lead placement."

ST. JUDE Leads

The new St. Jude leads – for which the company expects to get FDA approval in about a month – were getting positive comments from doctors at the meeting. An Illinois doctor said, "They are heavier than (some others), but they make it easier to push through torturous vessels…The new leads will really help St. Jude. Without that, they are totally out of the game, and the sales reps are frustrated." Another expert said, "In Europe where the St. Jude leads already are approved, the company is selling more of the new leads than generators."

ATRIAL FIBRILLATION (AF)

About 2.5 million Americans have AF, and the number of people with the problem is growing at a rapid rate because of the aging of the population. AF is the only arrhythmia increasing in prevalence. Some other interesting facts about AF:

- 15% of all strokes result from AF.
- Among people in their 80s, as much as 30%-40% of strokes may be the result of AF.
- The number of people with AF is expected to double over the next 25 years.
- AF uses more hospital beds and costs considerably more than all other arrhythmias combined.

Reimbursement for AF device therapy was described as "neutral." However, AF ablation is paid at the same rate as SVT ablation, but it is "infinitely more complex." An expert said there will need to be a new code reflecting the greater resource utilization, time, and skill required with AF ablation.

Three treatments are currently available for AF:

➢ **Antiarrhythmic drugs**. At one session, doctors debated whether antiarrhythmic drugs are superior to ICD therapy in patients with SVT and preserved EF. The protagonist argued in favor of antiarrhythmic drugs, saying, "I'm not sure we are erring on the safe side to put in an ICD in these cases." He pointed out that ICDs are associated with:

- **Inappropriate shocks:** 15%-30% of shocks in the general ICD population, and 35% of shocks in SVT patients over a two year period.
- **Re-operations:** 8% of ICD patients undergo re-operations, and 13% of SVT patients undergo re-operations for complications within two years.
- **Lead failures:** Up to 50% of leads fail over 10 years.
- **Reduced quality of life:** Mainly in shocked patients.
- **Sexual dysfunction:** Up to 50% experience sexual dysfunction due to anxiety, fear, shocks, or recurrent events.

The antagonist argued in favor of ICDs, saying, "No trial shows antiarrhythmic drugs superior to ICDs…If I decide to get an ICD, and I guessed wrong, I have an ICD. If I decide not to have an ICD, and I guess wrong, I'm dead."

➢ **Surgery**. This is used primary in patients already undergoing cardiac surgery (e.g., valve replacement).

➢ **Catheter ablation**. AF Ablation was described as "very challenging." An expert said, "AF ablation is the most challenging ablation procedure that has come along…It will get more applications and become easier as new technologies work their way through the regulatory process."

Are outcomes better with ablation? Dr. Jeremy Ruskin, director of Massachusetts General Hospital's cardiac arrhythmia service, said, "We don't know yet…but we know that when ablation works, which is 75% of the time, it has a dramatic effect on the quality of life. These are patients with often highly symptomatic and sometimes disabling AF that is unresponsive to drug therapy or who have side effects to drug therapy…These are among the most grateful patients I've encountered in 34 years of clinical practice."

Comparison of Ablation for SVT and AF

SVT	AF
Mechanism well understood	Mechanism not understood
Single target	No single target
Anatomically localized	Diffuse and complex
Focal or re-entrant	Both

AF procedure drivers are:

- Success rate
- Procedure time
- Reproducibility
- Safety

How to design AF ablation trials has been a problem. The randomized, double-blind, multi-center, placebo-controlled trials the FDA generally prefers are not usually practical in AF. Non-randomized, open label trials with the patients as their own controls have been proposed, but these lack scientific rigor and are subject to bias. AF trials generally can be six months in duration, but 12-month data will be required in at least a significant subset of patients. A speaker commented, "My own feeling is that sham is unethical in this environment. Antiarrhythmic drugs are probably the best option, but this also is problematic because many of the patients who arrive in the electrophysiologist's office are resistant to antiarrhythmic drugs – which biases the control

AF Trial Design Options

Randomized	Non-Randomized
Scientifically rigorous	Less rigorous
Avoids biases	Subject to bias
Patient discomfort with design	All patients receive ablation
Randomized	Patients as own control
Drug control arm impractical	More practical
Referring doctors uneasy	Referring doctors comfortable

group – or the patients don't want to take them…Using patients as their own control is not an entirely unreasonable option…If we are going to do non-randomized design, we need to be very rigorous."

Differences Between Clinical Practice and Clinical Trials in AF*

ISSUE	Clinical Practice	Clinical Trials
Trial size	Small studies typical	Large number desirable
Mixed populations	Typical	Problematic
Randomization	Difficult	Desirable
Dichotomy	Outcomes often not dichotomous	Need dichotomous endpoints
Partial response	Meaningful	Not informative
Symptomatic improvement	Often used as outcome measure	Difficult to objectify
Time constraints	Less important	Significant
Late responders	Not rare	May be missed
Asymptomatic AF or clinical sequelae (stroke, CHF)	Cannot measure	Both needed for claim of cure

* Courtesy of Dr. Jeremy Ruskin

A panel of experts said it is not yet feasible to use pulmonary vein isolation as an endpoint in AF trials. An FDA official said, "The agency is required to show clinically relevant outcomes…and pulmonary vein isolation is a surrogate…The use of that as a surrogate endpoint would simplify approval, but our concern is that it is not a relevant endpoint." An electrophysiologist said, "I agree…I'm not sure we know that PVI with any technology is equivalent to a cure for AF…So, it is reasonable to ask for clinical outcomes in this disease with these devices…Safety is as big a part as efficacy in these trials, and you don't have that with PVI." Another FDA official said, "This is not a mature technology by any means. There are lots of scientific questions to answer."

Suggestions for eligibility criteria for catheter ablation of AF:

- Recurrent symptomatic paroxysmal or persistent AF (≥2 episodes of AF in preceding two months and ≥6 in previous 6-12 months) and ECG documentation of AF during symptoms.
- Unresponsive to – or intolerant of – ≥2 drugs. This requirement may be outdated, but at least one anti-arrhythmic drug should be tried first because of the small but finite risk of ablation.
- Absence of severe heart disease/CHF.
- LVEF>40.
- LA≤50.

Circumferential Pulmonary Vein Ablation vs. Electrical Pulmonary Vein Isolation (PVI)

Results from an investigator-sponsored trial comparing these two strategies for AF treatment was presented. The study did not show any superiority of circumferential pulmonary vein ablation to electrical (segmental) PVI for the treatment of paroxysmal atrial fibrillation in highly symptomatic patients (at least two AF episodes/week). Researchers concluded:

- The estimation of the effect of ablation on symptomatic episodes considerably over-estimates the ablation efficacy for both techniques.
- PV stenosis occurred more frequently after segmental ablation.
- Symptom-free survival was much higher with segmental PVI.
- Patients with circumferential pulmonary vein ablation are more symptomatic, most probably due to left atrial flutter.
- There was a trend (p=.052) to more side effects (neurologic events, PV stenosis, etc.) with segmental PVI.

What's New in AF Therapy

There are exciting new devices on the horizon for treating AF, but they are not from the "Big Three" – Guidant, Medtronic, and St. Jude. Boston Scientific has a big lab presence now and a division that is very much engaged in the area. Medtronic reportedly backed out of ablation, though it still has a small division that makes ablation catheters. Guidant recently bought some technologies; it doesn't have a big presence, but it has "thrown its hat into the ring."

Interesting new AF devices include:

New catheter ablation systems, including one developed at Mass General for accessing the pulmonary veins, which are believed to be the source of many of the triggers of AF. These are designed to allow the operator to electrically isolate the PV from the rest of the left atrium. A speaker said, "In 2001, PV-guided was hot. We all tried PV isolation with a 30%-70% success rate. Today, more and more the trend is to anatomical-based ablation and to a more hybrid approach between anatomic and electronic approaches. We have a circumferential approach with a 70%-85% success rate."

➢ **CARDIOFOCUS,** which has a CO_2 laser balloon system. The hope is that this will make the procedure more efficient…There is a balloon with a light ring that is projected in a 360 degree arc on the area you want to ablate, and then you just lase into the arc…So, instead of the procedure taking four to six hours, hopefully it will take two hours."

➢ **CRYOCATH.** This is approved for SVT, not AF. An expert said, "We are very excited about CryoCath because cold has some potential advantages. They are unproven, but the hope is it will be less thrombogenic, so it may reduce the stroke risk of the procedure. The preclinical evidence suggests it may not cause pulmonary vein stenosis, which all the other heat-based treatments seem capable of causing. That gives it two potential safety advantages, and maybe some others. CryoCath is planning an AF trial…They are also developing a balloon purely for AF."

➢ **CRYOCOR.** The company's Cardiac Cryoablation System consists of three components: a cryoablation console, a cryoablation catheter, and a vascular sheath introducer system.

New imaging systems for the left atrium. A speaker said, "Over the last 12 months, imaging has become very important. Everyone is talking about imaging integration and technology, 3-D display integration, and visualization of non-fluoroscopic shaft…EP companies are starting to put 3-D systems in the cath lab…and those images are being integrated…The benefits of integration and streamlining include:

- Centralization of data in the EP lab
- Accurate mapping and treatment delivery
- Pre-acquired imaging as a productive tool
- Data right at your fingertips"

➢ **STEREOTAXIS'S Niobe**, a magnetic navigation technology which has a robotics guidance system. An expert said this is "complicated, expensive, and probably not ready for prime time." However, there is a lot of interest in Niobe. A company official said 11 systems are currently in place, with others on order. Stereotaxis has strategic alliances with Siemens and Philips in fluoroscopy and with Johnson & Johnson/Biosense-Webster in electro-anatomic mapping."

Some of the advantages of this system over manual navigation include:

- Device controlled directly at the distal tip
- Highly flexible devices
- No device torque required
- Remote navigation
- Navigation is independent of manual dexterity
- Computerized control and integration (software)

A doctor in the audience commented that the technology is "cool," but he wondered if it is cost effective. An expert said, "AFib procedures cost a lot in the lab because of the length of procedures. At the Mayo Clinic, it is an all-day procedure… Some labs are holding back because the procedures are lengthy and not cost-effective. These technologies will allow us to do two procedures per day, and that will help. The cost may go up, but we could do two per day." A company official said, "Our goal is to bring procedure time way down – to make AF a very time-efficient system."

Asked about integration with other systems, a Stereotaxis official said, "We will not integrate fully with NavX…but it works today side by side with Stereotaxis…The systems are compatible – except for the (Boston Scientific) RPM system because you need special things on the catheter with that…In a few years we will be integrated with everyone."

➢ **3-D MRI/3-D CT.** Mass General has a homegrown system that has not yet been out-licensed that holds promise. It is basically a software approach to using MRI or CT.

New mapping systems for the left atrium. An expert said all three of these are worth looking at, "They are all useful, and all have significant advantages, but all have some limitations, too."

➢ **JOHNSON & JOHNSON/BIOSENSE-WEBSTER'S Carto XP EP Navigation and Ablation System.**

➢ **ENDOCARDIAL SOLUTIONS (ESI).** There was standing room only at an evening symposium sponsored by ESI. Speakers discussed the company's new mapping systems, and doctors appeared very interested.

- **EnSite Array.** A speaker said these catheters allow ablation of the focal sources of AF.

- **EnSite NavX.** This is a navigation system that uses six surface electrodes to direct either the EnSite Array Catheter or almost any other catheter. It is a flexible, open system that offers voltage mapping (DSM). The disadvantage is its sequential modality. It is managed with conduction block as the endpoint.

So far, Endocardial Solutions has ~375 systems installed worldwide. The disadvantage is the sensitivity distance from the array surface (high accuracy only within 4 cm), though a speaker said this could be managed with proper placement.

Dr. Carlo Pappone discussed his experience in Italy in an open label, non-randomized study with EnSite in 2,980 patients from 1998 to 2004. He reported an AF curative success rate overall of 88% and 91% in paroxysmal AF. He said, "Four years ago, people did EP-guided ablation…and now anatomic PV ablation is catching on…NavX merges the electrophysical and anatomical approaches."

Among the advantages speakers cited for NavX were:

- Can be used to isolate 100% of PV veins.
- Safe with no complications.
- Significant reduction in fluoroscopic exposure.
- Allows rapid creation of geometry.
- Offers real time visualization of catheters.
- Enables a combined strategy for PV isolation and linear ablation.

➢ **BOSTON SCIENTIFIC'S BLAZER RPM Navigation System.** This catheter system is based on ultrasound ranging, not imaging. The mapping/navigation functionality is integrated with EP recording functionality. In the future, a speaker said the company plans to improve the ease of use, enhance catheter navigation, and further integrate it.

Minimally invasive surgical technologies

➢ **AFX,** which has a series of minimally invasive microwave ablation probes with wide-experience world-wide. The advantage of microwave over RF (radiofrequency) ablation is deeper and more even penetration with less surface heating. Energy delivery times are short (25-60 seconds). The unidirectional probes help protect surrounding tissue. ♦