Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Medications: The evidence is substantial that erythropoietin can improve outcomes in heart failure (HF) patients with low hemoglobin. Amgen is beginning a trial aimed at getting an indication for Aranesp in heart failure. ♦ Inotropes ***may*** make HF patients feel better, but they worsen outcomes, so many doctors are skeptical about the outlook for Myogen's enoximone or Abbott's levosimendan. ♦ Doctors also are skeptical that NitroMed's BiDil (isosorbide dinitrate + hydralazine) could catch on, though this BID combination pill will have heavy competition from the separate generics. ♦ Other investigational therapies worth watching include: Titan's dipta, Vasogen's Celacade, and Yamanouchi's conivaptan.

Devices: Heart failure doctors have become believers in ICD/CRT-D therapy, and they are referring most eligible patients to electrophysiologists, but the message still needs to get to primary care doctors and internists. ♦ HF specialists are concerned about the high percentage of non-responders. ♦ RV pacing is decreasing, but use of tissue doppler is increasing.

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HEART FAILURE SOCIETY OF AMERICA (HFSA)

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An estimated five million Americans suffer from heart failure, 20% of these die within one year of diagnosis, and 50,000 people die from heart failure every year. Sudden cardiac death is the leading cause of death in heart failure patients, not progression of disease, accounting for 44% of all heart failure patient deaths.

Only about 30% of heart failure patients see a cardiologist, and only half of these consult a heart failure specialist. Experts agreed that the message needs to reach internal medicine and family practice doctors that these patients should be referred to heart failure specialists and electrophysiologists. All of these patients need careful management of their medications, and many can benefit from implantable devices (ICDs, CRT-Ds).

Common myths about acute exacerbations of heart failure, from Dr. Milton Packer of UT Southwestern:

Myth: It is due to severe but reversible decreases in LV function.

Truth: Major pathophysiology is intense peripheral vasoconstriction. Patients are usually cold and clammy, with low urine output. All established treatments for acute decompensated heart failure (ADHF) act to antagonize peripheral vasculature.

Myth: In the absence of myocardial infarction, cardiac injury does not occur during acute exacerbations.

Truth: Every time there is an exacerbation, the slope of the disease progression increases. The episodes of decompensation are mild and infrequent in the beginning and become progressively more frequent at the end. Troponins are increased in 15%-40% of patients with an acute exacerbation. The risk of a major adverse event (death or re-hospitalization for worsening heart failure) is 2-7 times greater in patients with troponin release vs. those without troponin release.

Myth: Treatments that can sustain patients during the period of decompensation are all appropriate.

Truth: "We have this unbelievable sense of urgency when a patient comes in with ADHF…We say anything that can get the patient through the episode is justified …Diuretics, nitroglycerine, nitroprusside, and nesiritide are all intense peripheral vasoconstrictors, but some of these may activate the neurohormonal systems, and if that is a cause of myocardial injury (troponin release), they may adversely affect the course of the disease…There is data that some vasodilators may have adverse effects in these ADHF patients…The inotropes dobutamine and milrinone may be directly cardiotoxic…Short-term infusions of 24-48 hours can adversely affect the natural history of heart failure…So, current therapies used for ADHF may produce hemodynamic benefit, but that doesn't mean they will favorably alter the natural history of the disease."

MEDICATIONS

Erythropoietin for Heart Failure

Heart failure appears to be a promising new market for erythropoietin. There was a wealth of data at this meeting from a variety of sources on the role of anemia in heart failure, and all found that controlling anemia impacts outcomes in heart failure patients.

Amgen is sponsoring a prospective trial, HIPPOCRATES, to test this hypothesis. The trial, which is due to start in early 2005, is a six-month, multicenter, double-blind, placebo-controlled study trial of 500-1,000 patients, comparing Aranesp (darbepoetin alpha) to placebo. It is an outcomes-based trial, looking at quality of life, length of life, etc. Amgen reportedly expects to use this trial for a label expansion (sNDA). There was no information indicating that Johnson & Johnson or Roche is doing anything in this area.

A speaker estimated that anemia affects up to 55% of chronic heart failure (CHF) patients, depending on their disease severity. Anemia in moderate-to-severe CHF is associated with worsened symptoms, impaired exercise capacity and reduced NYHA Class. The patients most likely to benefit from erythropoietin therapy are anemic heart failure patients with:

- Class IV symptoms.
- Severe renal insufficiency.
- No or inadequate response to standard medical therapy.

Dr. Reynolds Delgado III of the Texas Heart Institute reported on his single-center, non-randomized, retrospective study of 467 CHF patients, 81 of whom were treated with erythropoietin stimulating proteins (ESPs) – Amgen's Epogen (epoetin alpha) or Aranesp – between January 2000 and October 2003. The ESP had been given as a "last-ditch" effort in NYHA Class IV patients on maximal conventional therapy where all other efforts had failed and transplant was not an option. Treated patients had Hgb <11 g/dL. Epogen or Aranesp was given every 1-4 weeks until the patient reached Hgb >12. Iron was supplemented orally if the serum level was below the reference range. Mean follow-up was 438 days.

Dr. Delgado found ESP treatment associated with an improvement in hemoglobin, renal function, and hospitalizations. However, there was no statistically significant improvement in mortality, which he speculated was due to the small number of patients in the trial.

Texas Heart Retrospective Study of Erythropoietin Treatment in CHF

Measurement	ESP-treated patients n=81	Control Group A n=98	p-value
Entire Cohort			
Average baseline QTc	486	452	.002
BUN	51 before treatment 38 after treatment 39 end of follow-up	30	Baseline <.0001
Creatinine	2.1 before treatment 1.7 after treatment 1.9 end of follow-up	1.4	Baseline .004
Hgb level	9.9 before treatment 12.3 during treatment 11.7 after treatment 11.6 end of follow-up	N/A	<.0001
Hospital admissions	1.8 in 6-months prior to treatment 1.0 at end of follow-up	N/A	---
Survival	83%	73%	.173
Measurement	**ESP-treated patients n=60**	**Control Group B n=60**	**p-value**
NYHA-Matched Groups			
Average baseline QTc	491	463	.044
Baseline BUN	54	35	<.0001
Baseline Creatinine	2.1	1.5	.76
Number of hospital admissions at 6-month follow-up	1.0	1.7	.019
Mortality	20%	32%	.144

Other studies looking at anemia in heart failure included:

- Columbia University researchers reported on their study of 286 consecutive acute heart failure patients with anemia (defined as <12 in women and <13 in men).
- Researchers at the University of Ottawa Heart Institute also reported on their study of anemia in 437 heart failure clinic patients (defined as <13 for men and women).
- A retrospective Northwestern University chart review of 80 patients that found anemia more common in diastolic dysfunction than systolic dysfunction, but 65% of the patients were anemic.
- A State University of New York (SUNY) study of 293 consecutive patients from April 2003 to February 2004 found that higher hemoglobin (>11) was associated with:
  - Lower EF (p=.002).
  - A shorter length of stay in the hospital (5.1 days vs. 6.4 days).
  - More use of diuretics (84% vs. 64% with Hgb ≤11).
- A survey conducted at the HFSA 2003 meeting, which found:
  - 65% felt anemia is important and treatable.
  - Heart failure doctors are knowledgeable about the association between anemia and outcomes in heart failure patients, and they are generally comfortable with the use of ESPs.
  - >30% do not routinely check Hgb.
  - 51% said anemia occurred in 11%-20% of their patients.

- A Duke University retrospective study examined 4,951 angiography patients, with anemia (defined as <12 for women and <13 for men), and divided them by LVEF ≤40 or >40. They concluded:
  - There is no interaction between anemia and systolic function with regard to survival.
  - Anemia is a powerful independent predictor of mortality regardless of systolic function.
  - Anemia was independently associated with increased mortality (p<.001), and patients with impaired systolic function (LVEF ≤40) had a worse prognosis (p<.0001) than patients with preserved systolic function (LVEF >40).
  - The hazard ratio for anemia was 1.58 for LVEF >40 and 1.74 for LVEF ≤40.

Columbia University Study

Measurement	Without Anemia		With Anemia	
	Low EF	Normal EF	Low EF	Normal EF
Number of patients	66	42	105	73
CAD	62	24	60	46 *
Dialysis	3	7	7	6
Mean hospitalizations in last 6 months	1.4	0.89	1.4	0.7
Heart failure risk score at 30 days	94	95	95	104 *
Heart failure risk score at 1 year	106	105	110	119 *
CRI	65	71	77	89 *
EF	27	60	27	62

*p<.05 anemia vs. no anemia

University of Ottawa Heart Institute Study

Measurement	Anemic	Non-anemic	p-value
Total ER visits	17.3%	9%	.0196
ER visits for CHF	68.2%	74.1%	---
ER visits for other cardiac reasons	13.6%	7.1%	---
ER visits for non-cardiac reasons	18.2%	35.7%	.3938
Total hospital admissions	42.5%	19.4%	<.001
Hospital admissions for CHF	55.6%	61.4%	---
Hospital admissions for other cardiac reasons	18.5%	15.8%	---
Hospital admissions for non-cardiac reasons	25.9%	22.8%	.8362
Total mortality	22.8%	8.7%	<.0001
Mortality from pump failures	54.6%	61.5%	---
Mortality from SCD	27.3%	30.8%	---
Mortality from other cardiac causes	0	30.8%	---
Mortality from non-cardiac causes	18.2%	0	.2596

Is There a Role for Inotropes in Heart Failure?

A debate over the value of inotropic therapy in heart failure was a very popular session. The President of HFSA called it a draw, but it really appeared that the anti-inotrope side had the advantage. The debate suggested that any new inotrope – e.g., Abbott's levosimendan or Myogen's enoximone – that gets approved may face a skeptical market, no pent-up demand, and a slow launch.

The pro arguments included:

- Inotropic drug therapy should be considered, but in a new form, such as:
  1. Gene therapy.
  2. In combination with conventional therapy: (a) ACE, ARB, or aldosterone, or (b) β-adrenergic blockade.
  3. To support titration of β-adrenergic blockade.
- CRT-D is an electrophysiologic inotrope.
- The guidelines for advance heart failure include the use of a continuous inotrope as palliative therapy.
- A speaker said, "We agree the inotropes used in the past are unbelievably bad drugs…but we need newer and better therapies. We ought to revisit the inotropic therapy, maybe dress them up a bit…There may be a kernel of good in those mechanisms, and we haven't uncovered them yet."

The con arguments included:

- Several trials – including ADHERE, FIRST, CASINO, OPTIME-CHF – have shown that mortality is worse with inotropes (e.g., milrinone, dobutamine, vesnarinone) than placebo, that chronic inotropic therapy worsens pump failure, hospitalizations, and death.
- The only valid indication for an IV inotrope is cardiogenic shock – when patients have their back against the door, and there is nothing else left.
- There is no benefit on symptoms or functional class.

ABBOTT'S Simdax (levosimendan)

The outlook for this inotrope – an oral calcium sensitizer – got murkier with the release of less-than-impressive data on Myogen's inotrope (enoximone) at HFSA. However, some references to levosimendan at the inotrope debate (see above), make it appear as if this drug might find a slightly more receptive audience than enoximone will. One speaker said, "Levosimendan is less risky than dobutamine, but the risk is still greater than no inotrope." Another expert said, "If the randomized trial shows a levosimendan benefit, that might change the rules that all inotropes are dangerous." A third expert said, "There will be an appetite for levosimendan. There shouldn't be any regulatory (FDA) problems if the trial is good."

Several posters at the HFSA meeting looked at levosimendan. Among the findings were:

➢ A meta-analysis of three levosimendan trials concluded that levosimendan is equally effective whether the heart failure is ischemic or non-ischemic.

➢ The prospective, non-randomized PORTLAND study comparing the experience with levosimendan in 129 patients at 15 centers found it was efficacious and safe "in the vast majority" of decompensated heart failure patients. Hypotension and hypokalemia were observed, but the outcome was favorable in all cases. There was no increase in heart rate, no new episodes of angina, and no increase in QTc.

➢ The ability to combine levosimendan with beta blockers is one potential advantage of levosimendan over dobutamine, since the response to dobutamine is attenuated by concomitant use of beta blockers. Researchers reported on a subgroup analysis of the LIDO trial that supported the concomitant use of levosimendan and beta blockers.

Measurement	Beta Blocker Used		No Beta Blocker	
	Levosimendan n=28	Dobutamine n=23	Levosimendan n=48	Dobutamine n=52
Patients reporting improvement in dyspnea at 24 hours	~78% (p=.027)	~50%	~60%	~63%
Patients reporting improvement in global assessment at 24 hours	~86% (p=.031)	~60%	~85%	~82%
Change in cardiac output (L/min)	~1.2 (p=.01)	~0.5	~1.0	~0.75
Change in PCWP (mm Hg)	~ -7.5 (p=.03)	~ -2.0	~ -4.2	~ - 3.0

➢ A study on levosimendan done at the University of California, San Francisco (supported by Abbott) looked at a prospective cohort of outpatients referred to the cath lab, and found:

Measurement	Change	p-value
LVEF	Up 19%	.009
Myocardial oxygen uptake	Down 9%	.04
Myocardial oxygen consumption	Up 35%	.15

Two Phase III trials of levosimendan are ongoing in acute CHF:

REVIVE-II is the U.S. pivotal trial of levosimendan. It compares placebo to loading dose of 12 mcg/kg levosimendan followed by 0.1 mcg/kg for 50 minutes and then 0.2 mcg/kg. About 1,300 patients with dyspnea at rest after IV diuretics who have been hospitalized for worsening heart failure have been enrolled. The trial is based on 330 events. The primary endpoint is the number of patients improved (symptom improvement) at 6 hours, 24 hours, 5 days, or worsened anytime ≤5 days. Mortality is a secondary endpoint. The principal investigator is Dr. Milton Packer. Dr. John Teerlink of the University of California, San Francisco, is co-chair of the Steering Committee.

An Abbott official said the company may file levosimendan with the FDA on this data and not wait for the SURVIVE data (the other Phase III trial), but it hasn't decided for sure and is discussing this now. Reportedly only three patients still need to be enrolled, and that is expected to be completed this week (9/17/2004). An investigator said the REVIVE-II data may be presented at the European Society of Cardiology meeting in August 2005. He called it a good sign that the trial has not been stopped yet by the DSMB for safety.

SURVIVE is an international (Finland, France, Germany, Israel, Latvia, Poland, Russia, and the U.K.), multicenter, randomized, parallel group, double-blind, double-dummy trial in ~1,300 patients with acute heart failure requiring inotropic support. SURVIVE originally planned to enroll 700 patients, but the steering committee recommended changing it to an event-driven study (330 events). As in REVIVE-II, a loading dose of 12 mcg/kg levosimendan is followed by 0.1 mcg/kg levosimendan for 50 minutes and then 0.2 mcg/kg levosimendan, but the comparison is to dobutamine not placebo, which one expert suggested may prove to be a problem. The principal investigator is Dr. Alexandre Mebazaa of Hopital Lariboisiere in Paris. An interim analysis based on data on 450 patients was performed by the DSMB, and the study was allowed to continue. As of August 20, 2004, 1,037 patients had been enrolled, and 238 deaths had been observed. No information was available on when and where the data from this trial will be available.

The primary endpoint is all-cause mortality at 180 days. Secondary endpoints include:

- Days alive and out of hospital at 180 days
- All-cause mortality at 31 days
- Global assessment at 24 hours
- Change in patient evaluation of dyspnea at 24 hours

Abbott got this agent from Organon, and an Organon researcher offered some interesting comments, including:

- He expects both REVIVE-II and SURVIVE to be positive.
- Abbott has the U.S. and European rights to levosimendan.
- Development has been slow because Organon was discouraged by the early trial results.
- He expects levosimendan to launch slowly in the U.S. – saying it will initially be hard to sell to the American market.

ACTELION/GENENTECH'S Veletri (tezosentan)

This IV dual endothelin antagonist has had a rocky road in heart failure. Both the RITZ-1 and the RITZ-2 trials raised safety issues. Those trials found that Veletri improved cardiac hemodynamics in acute heart failure patients, but at both 50 mg/hour and 100 mg/hour, there was an excess of dose-related vasodilatory adverse events. In terms of efficacy, an investigator said RITZ-1 showed no significant difference in the symptom endpoint vs. placebo, but RITZ-2 showed a trend to improved outcome in worsening heart failure (p=.06) and an improvement in wedge pressure and cardiac output. A new analysis of the RITZ-1 study concluded that the renal dysfunction in that trial "appeared related to the high dose used (50 mg/hour)."

Investigators believe that a lower dose will avoid these problems, and two new Phase III trials (totaling 1,760 patients) of Veletri vs. placebo – **VERITAS-1** and **VERITAS-2** – were initiated with a loading dose of 5 mg/hour, followed by a 1 mg/hour dose, which is far below RITZ dosing. VERITAS-1 and -2 are identical trials, and each is being conduct both in the U.S. and in Europe; the only difference is that VERITAS-1 started earlier. Patients also had to get a diuretic before entering the trial and still had to be sick after treatment with diuretics to be enrolled. The only limitation on concomitant medication use that patients who were on an IV vasoreactive therapy (e.g., nitroglycerine or nesiritide) before randomization had to have a higher blood pressure (>110).

The VERITAS trials are event-rate-driven, so the sample size is adjusted for the event rate. The two primary endpoints are: (1) worsening heart failure or death at 7 days and (2) dyspnea reduction (AUC), but there will be six-month follow-up for safety. The trial also has passed its first futility endpoint and wasn't stopped. The co-chair of the steering committee said he is "very hopeful and encouraged" by this. An Actelion source said data from the interim analysis will be presented at the American Heart Association meeting in November 2004 as a Late Breaker. He called the VERITAS trials the "make it or break it" for tezosentan.

In early June 2004 (before enrollment was completed), the DSMB conducted the first interim analysis of the two trials (of 75% of the patients) and determined they could continue. Final results are expected in early 2005.

Asked if short-term symptoms like a 3-hour dyspnea score is sufficient for approval, an investigator said, "That is why VERITAS is designed the way it is…In previous trials, they picked one time point. We tried to design this trial with AUC improvement or change in dyspnea during the first 4 hours, to say a patient has to be consistently feeling well in the first 24 hours – and being better than standard therapy – to be a positive trial."

JOHNSON & JOHNSON/SCIOS' Natrecor (nesiritide)

A meta-analysis by Dr. Jonathan Sackner-Bernstein of St. Luke's-Roosevelt Hospital Center in New York raised questions about excess mortality with Natrecor. He found that in patients treated within nine hours of an AMI, mortality was 7.2% with Natrecor vs. 3.6% with placebo (p=.057). He commented, "I don't think doctors should use Natrecor until the company does a mortality trial."

Experts at HFSA generally were not concerned about this issue, and none indicated it has affected their use of Natrecor since the findings have not been repeated. Thus, the noise about this issue appears to have died down somewhat, but it has not been eliminated entirely. At a Scios-sponsored symposium a doctor said, "That analysis was not a proper data set, so it has not borne out. Essentially, it has been debunked." Another expert said, "With the data now, I don't have a concern. But it is a contentious issue that needs to be looked at."

When the Sackner-Bernstein analysis is published, that should generate more discussion. The FDA is extremely unlikely to take Natrecor off the market based on this analysis, and the FDA cannot require the company conduct a study to resolve this issue, but a label revision (black box warning, etc.) is possible if the company doesn't disprove this concern. An FDA official commented, "The six-month mortality looks like it is trending in the wrong direction, but it becomes a benefit:risk decision, and there was demonstrated clinical benefit, at least in the opinion of some in the Agency."

Meanwhile, use of Natrecor is growing, sources said. An expert said, "Natrecor use is up post-CABG, in acute coronary syndromes, and the outpatient potential is growing." A retrospective analysis of six patients suggested that Natrecor will be useful in transplant candidates, noting, "Prolonged infusion may result in a sustained decrease in pulmonary arterial pressure, a decreased need for RV support, and a decrease in RV failure following therapy." A Midwest nurse practitioner said, "Natrecor use is up because of the renal aspect."

A poster from the Mayo Clinic suggested that BNP could be delivered for chronic use with transdermal patch. The researchers concluded that this approach "could be an effective treatment for hypertension and decompensated heart failure."

An observational study by researchers at Virginia Commonwealth University School of Pharmacy compared dobutamine, milrinone, and nesiritide. They concluded the nesiritide was associated with a significantly lower in-hospital mortality rate and length of stay vs. the other drugs. The total cost of care and the 30-day readmission rate also were lower in the nesiritide patients.

Measurement	Dobutamine	Milrinone	Nesiritide
In-hospital mortality	10.2%	7.9%	2.9%
Length of stay	10.4 days	12.2 days	7.0 days
Total cost of care	$23,116	$29,507	$18,517
Readmission	5.0%	9.5%	3.9%

The FUSION-II, a 900-patient, randomized efficacy trial in NYHA Class III and IV heart failure patients, has started enrollment. This $90 million trial will compare Natrecor administered once-weekly outpatient to Natrecor administered twice-weekly outpatient as maintenance therapy for 12 weeks, followed by another 12 weeks of follow-up. The first patients will be followed until the last patient has been followed for six months, so an official said it is likely to be two years before the full data are available. However, a 450-patient interim analysis is planned. The primary endpoint is the composite of all-cause mortality and re-hospitalization. An expert said, "Most doctors are waiting for the results of FUSION-II before using Natrecor for chronic use."

MYOGEN'S Perfan (enoximone)

Enoximone is both a positive inotrope and a vasodilator. It is currently marketed by Myogen in Europe as an IV formulation (Perfan) for the treatment of acute decompensated heart failure. The company has an oral formulation in development to treat chronic heart failure. The IV formulation was never submitted to the FDA for U.S. approval. Dr. Michael Bristow, Myogen's Chief Scientific Officer, explained, "The previous sponsor was developing an oral enoximone, but if the IV got on the market, then the patent life would start ticking. They were waiting for the oral, which was then picked up by Myogen…So, the IV sits there. The rules for IV therapy approval have changed, and we would need to do another trial showing symptom improvement, not just hemodynamic improvement." However, he said Myogen is considering submitting the IV version if the oral formulation gets approved by the FDA.

How the results of the Phase III EMOTE trial of oral enoximone, a selective PDE-3 inhibitor, should be interpreted depend on whom you asked. Enoximone researchers claimed the data were positive, but other experts found the data less than reassuring. Experts generally agreed that heart failure specialists are likely to be skeptical of enoximone, unless the data from both EMOTE and ESSENTIAL are very, very good – and even then additional trials may be necessary to convince them. Among the comments:

- "Enoximone may require careful thought. I really need to see the data."
- "Six-month data are not sufficient to make us comfortable on safety, but it would be a good start."
- "That's a failed trial (EMOTE); it has the same problems as other inotropes."
- (NIH) "The trend toward higher mortality (with enoximone vs. placebo) is concerning, but the data are strong enough to justify doing another trial."
- "It won't be hard to market because people want something better. They are not happy with milrinone or dobutamine."

Dr. Bristow defended the results.

- **On efficacy**, he said, "This (EMOTE) is not a failed trial. I think this is very positive. The objective was to demonstrate you could remove patients from IV therapy to oral therapy …We knew there would be a short-term effect, that the effect was not likely to last the full six months because these are end-stage, dying patients…We set the trial up for a 30-day effect because that is what we had in Phase III, but it turns out the effect lasts to 90 days. Placebo worked pretty well for 30 days, but after that, placebo worked less well, and we detected a signal…But efficacy (with enoximone) was indicated out to 90 days. So the efficacy part of this is almost better than expected…We hit (the wean endpoint) at 60 days and not 30 days…Patients were less inotrope-dependent than the Phase II patients studied…There was a trend toward a reduction in hospitalizations, but we have not finished that analysis."

- **On safety**, he said, "There was no statistically significant difference in safety between enoximone and placebo…There was no evidence of any safety issue. The safety aspect of enoximone will be determined by the ESSENTIAL trial (the ongoing, pivotal Phase III trial). EMOTE was not powered to evaluate mortality…but the safety data in EMOTE will be pooled with the ESSENTIAL trial…The total number of deaths here (in EMOTE) is 69, and in ESSENTIAL there will be >350, so the real mortality study will be ESSENTIAL …The FDA has a statistical test for this (safety), and you need neutrality at least on mortality. There can't even be a trend to higher mortality, and there are very conservative stopping rules (for the EMOTE and ESSENTIAL trials), and we were not stopped."

EMOTE enrolled 201 patients with NYHA Class III or IV heart failure who were either on continuous inotropic therapy (dobutamine or milrinone) or an intermittent inotrope. Inclusion criteria included LVEF ≤25%, LVEdD ≥5.4 cm, and conventional background therapy (with an ACEI or ARB required). Enoximone patients on intermittent therapy got 20 mg or 50 mg TID, and continuous therapy patients got 50 mg or 75 mg for one week, followed by 25 or 50 mg TID. Based on Phase II studies, the EMOTE sample size assumed a wean rate (primary endpoint) of 25% placebo and 50% with enoximone, with 90% power to show a p-value of 0.44 by ITT analysis.

The two EMOTE arms were well-matched demographically except there were more women in the placebo group. An investigator said that, so far, there does not appear to be a difference in outcome based on gender. Beta blocker use was comparable in both arms, ~50%.

Among the issues with enoximone and the EMOTE data are:

- **Quantity of data.** Several sources said that two trials with six-month data is not sufficient, though it is a beginning. However, experts agreed that no placebo-controlled trial is likely to be possible in the future.
- **Safety.** An expert said, "Enoximone has baggage! The EMOTE and ESSENTIAL trials both have to show zero safety problems to get approval or usage." In particular, the mortality risk is a concern; in this trial as in previous trials it has trended to be higher – but not by a statistically significant amount – with enoximone than placebo. However, an EMOTE investigator said, "Most of the deaths actually were in patients not on the study medication at the time of death."
- **Mechanism of action.** This is not known. One theory is that the pathology has to do with the underlying contractility, but the president of the HFSA said he disagreed with that.
- **Problems with other inotropes.** An expert said he is dubious about ***any*** inotrope, including enoximone, "I suspect any inotrope because of the history of inotropes…(But) there may be clinical situations where they are appropriate. I use inotropes, but I realize the risk they carry…Only if there is a high event rate, would six-month survival data be sufficient." Another expert said, "Regardless of how you compartmentalize, it (enoximone) is still an inotrope."
- **Re-hospitalization rate.** In the earlier UK-29 study of 100 mg enoximone TID, the hospitalization data suggested that patients on enoximone had more re-hospitalizations than placebo (p=.044). Dr. Bristow explained, "That was a much less sick population and a much higher dose."

26-Week EMOTE Trial Results

Measurement	Placebo n=100		Enoximone n=101		p-value
	Intermittent	Continuous	Intermittent	Continuous	
Females	80% male		65% male		<.05
SBP	104		101		
Average LVEF	19		19		
Discontinuations	40		40		
Discontinuations	27% during treatment period; 46% at Week 26				
Primary endpoint: Alive and free of IV inotropes at 30-days post scheduled weaning	51%		61%		.138
Alive and free of IV inotropes at 30-days post scheduled weaning	N/A	N/A	71%	43%	---
Secondary endpoint: Alive and free of IV inotropes at 60-days post scheduled weaning	30%		30% reduction vs. placebo		.098
Alive and free of IV inotropes at 60-days post scheduled weaning	N/A	N/A	50% reduction	22% reduction	N/A
All-cause mortality at 30 days	N/A	N/A	30% relative risk reduction vs. placebo		.098
All-cause mortality at 60 days	N/A	N/A	38% relative risk reduction vs. placebo		.009
All-cause mortality at 90 days	N/A	N/A	39% relative risk reduction vs. placebo		.031
Mean time to death or re-initiation of inotropic therapy	N/A	N/A	32% relative risk reduction vs. placebo		.042
Total days on IV inotropic therapy	N/A	N/A	43% relative risk reduction		.049
Deaths	31 patients		38 patients		Nss
CV death	26.0		33.6		.28
Sudden death	42.3		17.6		N/A
Non-sudden death	57.7%		82.4%		N/A
Adverse events at 26 weeks	More anemia More sepsis More brachycardia (p=Nss)		More vomiting More diarrhea		<.05

- **Efficacy.** In an early trial, enoximone improved VO_2 but not dyspnea. Sources said they will be looking at ESSENTIAL to see what effect there is on symptoms (especially dyspnea), exercise duration, and VO_2. Dr. Bristow said, "If we had had the number of patients in EMOTE that we have in ESSENTIAL, we would be very happy with the signal. The effect size (in EMOTE) is on order of what we hoped for."
- **Dropouts.** As in previous trials, there was a high dropout rate in EMOTE.
- **Adverse events.**
- **Additive effect with beta blockers.** Earlier studies suggested that combining a PDE-3 with a beta blocker would have additive efficacy and decreased safety concerns.

ESSENTIAL, the Phase III pivotal trial of an oral enoximone formulation, in ~2,000 patients is fully enrolled and will complete in November 2004. A Myogen official said it will take three to four months to lock the database and then several months to analyze the data, so it is likely to

be presented at the European Society of Cardiology meeting in August 2005.

If oral enoximone gets FDA approval, Dr. Bristow said that it is likely to be used in very advanced heart failure patients – NYHA Class III and IV – to replace IV inotropes in patients who are progressing despite maximum medical management. He said QT studies have been done, and no QT problem or signal was seen.

A new trial, IMPOWER, has just started enrolling patients. This trial is looking at patients unable to take a beta blocker because of intolerance. The thinking is that enoximone will enhance the administration of beta blockers in that population.

NITROMED'S BiDil (a fixed-dose combination of isosorbide dinitrate 20 mg plus hydralazine 37.5 mg)

This is a combination of two generic drugs, with the planned schedule two pills three times each day, for a total of six pills a day. Doctors questioned about this therapy were skeptical, but if the data holds up they predicted that adoption of this therapy – either as separate pills or a combination pill – will be quicker than usual in heart failure patients. One source commented, "This is an unmet need, like arthritis before the Cox-2 inhibitors came along. Patients as well as doctors will drive demand for this. Most of the time I hate direct-to-consumer advertising, but this is one time I think it would be good."

The question is whether doctors will opt for two generics or NitroMed's combination product. Most sources admitted that reducing the pill burden would be helpful, but many pointed out that the cost of a brand-name product would be more important. An Illinois doctor said, "Drug costs are not necessarily the issue in heart failure…(BiDil) makes sense in some cases, such as renal insufficiency or intolerance to ACE/ARB." A Midwest nurse practitioner said, "When the data is out, we need to study it. I want to see the data before I use this. I would use generics over the combination pill – and convincing people to dose the hydralazine that high will be a problem." An Illinois doctor said, "This is only an option for patients who can't take an ACE or an ARB. But I don't like generics because they can vary in appearance, and that can be confusing for elderly patients. I would use BiDil if the trial data are good." A Minnesota nurse practitioner said, "Initially, I like to start two drugs separately, and when the patient is stabilized, then I don't mind switching to a combination pill."

The outlook for the BiDil pivotal trial looks promising. In July 2004, at the recommendation of the DSMB, NitroMed halted the six-month, 1,050-patient, Phase III A-HeFT trial of oral BiDil in African-Americans, citing a significant survival benefit to the drug from a preliminary review of the data. A-HeFT patients were given BiDil in addition to the best current therapy (which variably included beta blockers, ARBs, aldosterone inhibitors, digoxin, and diuretics), and patients were titrated up to a target daily dose of 120 mg isosorbide dinitrate (ISDN) and 225 mg hydralazine (HDL).

The primary endpoint A-HeFT is the composite of mortality, first hospitalization for heart failure, and quality of life. The preliminary data also indicated that serious adverse events and cardiovascular events were less frequently observed in the BiDil arm of the trial. The data from this trial are currently being collected, and the data lock is October 12, 2004. The outcomes data from the trial – the combined endpoint as well as each of its individual components – will be presented as a Late Breaker at the American Heart Association meeting in November 2004. One of the things to look for in that data is the average dose. Patients were started on different doses, and titrated up to a target of 225 mg HDL+120 mg ISDN daily (six pills per day), but it is not known how many got to that level.

Secondary endpoint data, beyond the individual components of the primary endpoint, are not likely to be available at AHA. Those endpoints include:

- Death for any cause
- Total number of CHF hospitalizations
- Total number of all hospitalizations
- Total days in hospital
- Change in BNP
- Newly recognized need for cardiac transplant
- Change in LVEF, LVIDD, and LV wall thickness
- Number of unscheduled ER and office/clinic visits
- Overall quality of life

Members of the A-HeFT Steering Committee declined to recommend that doctors should start treating patients with a combination of the two generic agents before the A-HeFT data are formally presented or published. One said, "I won't prescribe generic ISDN plus generic HDL, separately, until the final data are available…but if the data holds up, it would be reasonable for patients to add this, and they could do it with either generics or the combination pill…I won't say that you should never use the two individually as generics. The cost may make that reasonable for some patients, but convenience and compliance will be better with the combination pill." Another source said, "I will not prescribe this regimen before I see the data. I want the details first."

These investigators insisted that there will be real advantages to using the NitroMed fixed-dose formulation instead of prescribing each generic separately, including:

- A fixed and determine dose that will avoid over- or under-dosing, which is common in heart failure.
- No generics are available in the particular doses tested, which would require more daily pills for patients.
- One co-pay instead of two co-pays.
- The A-HeFT dosing matches the V-HeFT dosing.

- Convenience.
- Compliance.
- Subtle differences in the interaction of the drugs when given together vs. given separately (e.g., AUC). An investigator said, "A single pill is what was studied, not two pills."

A NitroMed official said the company is working on a 40 mg ISDN + 75 mg HDL combination that would reduce the pill burden to one pill three times a day (a total of three pills a day). However, he said this would not replaced the lower dose combination which probably will be needed for dose titration. He claimed NitroMed has patent protection on ***any combination*** of these two drugs in African-Americans.

PFIZER'S Inspra (eplerenone)

Pfizer is actively marketing Inspra, but sources were not very enthusiastic about it. A New York doctor was typical, saying, "I'm not using much Inspra for chronic heart failure. Aldosterone (spironolactone) works fine and is less expensive." Another doctor said, "I understand about half of patients have to discontinue Inspra for hyperkalemia, which is not being monitored enough."

TITAN'S Ditpa (3,5-diiodothyropropionic acid)

Titan got this thyroid hormone analog for the treatment of CHF in its acquisition of Developmental Therapeutics. A randomized, Phase II trial of Ditpa in NYHA Class II-IV heart failure patients with low thyroid hormone (T3) levels is due to start soon. The principal investigator is Dr. Milton Packer of UT Southwestern in Dallas. Dr. Packer said the results should be available in about a year and a half.

Thyroid hormone plays an important role in maintaining cardiovascular function, and many patients with advanced CHF have decreased thyroid hormone levels. Currently available thyroid hormone preparations generally are not well-suited for continuous administration to CHF patients for a number of reasons, including the potential for increasing heart rate. In previous trials, Ditpa was shown to improve cardiac function without increasing heart rate.

VASOGEN'S Celacade

This is an immune modulation therapy (IMT) that involves the ex vivo exposure of a sample of autologous blood to three oxidative stress factors – heat, an oxidative environment, and ultraviolet light – followed by intramuscular re-injection. Celacade is administered once a month as an outpatient procedure.

Celacade is in a 2,000-patient, event-driven, Phase III trial (ACCLAIM) for the treatment of chronic heart failure and peripheral arterial disease (PAD) in the U.S., Canada, Europe, and Israel. The primary endpoint is all-cause mortality. The trial is about one-quarter enrolled, with enrollment expected to be completed by March 2005, with follow-up continuing for 12 months.

IMT has been called "voodoo" medicine, but doctors are starting to believe it just might have a chance of working. The principal investigator, Dr. James Young of the Cleveland Clinic, said he was skeptical at first about IMT, but he participated in a pilot study which he said "showed a signal – a reduction in hospitalizations and mortality." As a result, he agreed to run the Phase III trial. He commented, "IMT is starting to make sense. There is a rational hypothesis." However, he is reserving judgment until the final results are in, and he isn't speculating about what the trial will show. He predicted that when and if Celacade gets approved, doctors are most likely to use it in NYHA Class III and IV patients on good medical therapy as an add-on treatment. He expects that patients would get two or three injections every six months, and he thinks that is a viable dosing schedule for patients.

A murine study of Celacade concluded: "Celacade lowers cellular infiltrates as well as myocardial TNF-α content in a murine model of myosin-induced myocarditis. These findings characterize for the first time the anti-inflammatory action of Celacade within myocardium and provides mechanistic support for the benefit of Celacade in heart failure patients."

YAMANOUCHI'S conivaptan

Yamanouchi submitted this dual V_{1a}/V_2 vasopressin receptor antagonist to the FDA in early February 2004 for the treatment of hyponatremia, a potentially life-threatening condition that occurs when the body's blood sodium level falls below normal. Three double-blind, placebo-controlled, randomized, multicenter studies were conducted in the U.S. and abroad. Conivaptan, which is targeted at restoring sodium levels, would be the first drug to be approved to treat hyponatremia. Currently, hyponatremia patients are treated with fluid restriction, diuretics, and hypertonic saline, which are often associated with inconsistent results and significant side effects. Conivaptan also is being investigated to treat chronic heart failure.

Two, small, pilot studies showed that short-term IV administration improved the sense of well-being and was well-tolerated in patients hospitalized for worsening heart failure. A 142-patient, placebo-controlled, short-term study found favorable changes in urine output and hemodynamics (reduced pulmonary capillary wedge pressure and right atrial pressure) without affecting blood pressure or heart rate.

A multicenter, randomized, double-blind, placebo controlled, dose-finding Phase II pilot study is underway in patients with decompensated chronic heart failure. There are four arms:

- Placebo (40 patients).

- Conivaptan 20 mg loading dose followed by 40 mg/day infusion for two days (40 patients).
- Conivaptan 20 mg loading dose followed by 80 mg/day infusion for two days (40 patients).
- Conivaptan 20 mg loading dose followed by 120 mg/day infusion for two days (42 patients).

Patients in this trial will be followed for 90 days. Efficacy measurements include patient and physician global assessment, patient VAS scores for global and respiratory status, patient and clinician dyspnea assessments, respirator rate, fluid balance, clinical signs of heart failure, body weight, duration of index hospitalization, post-hospital survival, need for IV therapy for heart failure, visits to the emergency room for (or associated with) worsening heart failure, and admission to the hospital for worsening heart failure ≥24 hours in duration and the necessity for IV medication for heart failure within 24 hours of admission. Safety parameters include adverse events, serious adverse events, clinical laboratory evaluations, vital signs, and ECGs.

DEVICES

About two million American heart failure patients fall in NYHA Class II-IV, but only about 380,000 of these see an electrophysiologist, a speaker estimated. Heart failure specialists have become more enthusiastic about ICDs and CRT/CRT-Ds. While they still believe in maximizing medical therapy, they also are much more positive about the value of device therapy than they were just a couple of years ago. A Canadian doctor said, "Our comfort level is increasing. The challenge is reimbursement. The number of qualified patients is large, and we have to be the gatekeepers. We realize devices are part and parcel of the universe of treating these patients." An Oklahoma doctor said, "(In the past) I wrote an article that device approval was premature because there was no outcome data, but now there is, and I refer more patients." An electrophysiologist said, "Heart failure doctors are becoming much stronger believers in devices, but we need more primary care physician education."

Heart failure specialists estimated that they are referring more than 80% of their current CHF patients who meet the indications for an ICD/CRT-D to an electrophysiologist. They don't see much change in the percentage of their patients who will be referred for ICDs/CRT-Ds over the next three years, but they expect the actual numbers to go up as the number of patients with heart failure increases, the number of patients who are referred to heart specialists increases, and the indications for ICD/CRT/CRT-D therapy increases.

Doctors cited several reasons for not referring all qualifying patients:

- Some patients (<5%) reject the idea of a device.
- Concern over cost.
- Some patients are too ill, too late stage, or can't lie flat long enough for the procedure. A Midwest source said, "Quality of life and cognitive function are also criteria for us. We have especially elderly patients, and a lot of them are from nursing homes. Arrhythmic death is a kind death."
- Reimbursement issues. A Midwest doctor in a large, non-academic heart failure group said, "What if we put a device in a patient and spend that resource, and Medicare doesn't pay? We are in fear of non-payment because that could bankrupt us. That is the biggest restriction on our use of CRT-D."
- In some patients, a lead can't be placed in the coronary sinus either because of occlusion or anatomy.
- Patient closeness to a hospital that implants devices. An Indiana doctor explained, "EPs are a scarce resource, so there is a long delay for evaluation, and some patients live too far away."
- Non-responders. Some doctors are worried about subjecting patients to a device and procedure when the non-response rate is 20%-50%.
- Concern that electrophysiologists may be too aggressive in implanting devices. A Maryland doctor said, "There is a trend to use devices too early, to look for a device solution when the patient has not been medically managed optimally. We get calls all the time asking, 'Does this patient need biventricular pacing?' But we need to examine the patient. Many of these patients don't need a device, they need a doctor." An Alaska nurse practitioner said, "I think electrophysiologists are a little gung-ho and will find a reason to put a device in."
- Co-morbidities. A survey at HFSA 2003 found that the presence of cancer has a profound effect on their treatment choices and use of ICDs. For instance, only 31% of doctors would implant an ICD in a Stage 2 breast cancer patient with a life expectancy of >8 years. There was a suggestion in the survey which indicated that providers may be reluctant to intervene on cardiac issues when cancer is a co-morbidity, even if the projected mortality is acceptable.

The patients that heart failure doctors refer for device therapy generally are coming from patients they see in their clinic. They are not limiting referrals primarily to hospitalized patients, but they also are not mining their patient databases and are not proactively calling patients who appear to be device candidates and suggesting they come in for a referral. A New Jersey doctor said, "I'm not looking (through my database) for patients. It is as they show up. But I am referring more patients now, since SCD-HeFT. I didn't expect SCD-HeFT to be that dramatic with convincing numbers." A Maryland doctor said, "More and more of the referrals are patients who visit our clinic either on a routine visit or with symptoms. It is incorrect not to refer now." A Canadian doctor said, "The majority of patients are still patients in the

outpatient clinic who need better tailoring of treatment or the risk of deterioration or sudden cardiac death is increased." An Illinois doctor said, "SCD-HeFT will increase referral when it is published."

The CHART Registry of symptomatic heart failure patients with LVEF <40 at tertiary care centers with a combination heart failure/electrophysiology program looked at 248 patients since April 2003. Researchers concluded:

- About half of patients referred (for device) have an implantable device. The majority are placed for primary prevention, and half have CRT capability.
- A significant number of patients with a CRT indication have an RV-ICD that hasn't been upgraded.
- The largest number of patients without devices fall under emerging indication of LVEF <35 and NYHA Class II or III.

CHART Registry

Measurement	Patients
Average age	55.3
Male	73%
Ischemic etiology	37%
Average LVEF	22
Implantable device	45.6%
2 devices (pacemaker+ICD)	4%
Device Patients (n=88)	
History of VT or cardiac arrest	24%
Primary prevention indication	76%
CRT-D	28%
Average QRS	131 (vs. 117 in patients with no device)
Patients who qualify for CRT-D with ICD only	46%
Patients without a device who qualify for ICD under FDA-approved indications	36%
Patients who qualify for ICD under emerging conditions	64%

Some other key issues in ICD/CRT/CRT-D use include:

➢ **Non-responders.** About a third of CRT/CRT-D patients are "non-responders," and doctors wish they could identify who those patients are. In some cases, it is believed due to lead placement. A 300-patient, Medtronic-funded trial is underway that is attempting to predict responders using tissue echo, but it is not outcome-powered. An Indiana doctor added, "Technically, echo may be a better indicator, but the two manufacturers use different scales, which makes comparisons difficult."

Some of the reasons for unsuccessful implants were estimated as:

- 10% implant failure.
- 33% clinical failure.

➢ **Tissue doppler.** The use of tissue doppler to help identify patients who are candidates for CRT/CRT-D is growing. At a how-to session on selecting and managing patients for CRT/CRT-D, two speakers said they do tissue doppler on all the patients referred for CRT to confirm dyssynchrony. However, a California doctor in the audience noted, "There are patients without measurable dyssynchrony who benefit from CRT." An expert said, "I get echoes on all my patients …In patients with narrow QRS, I think it would be irresponsible not to have something to say the patient is in dyssynchrony, so I do echo...That is the only time echo makes the decision. I don't really run into people with wide QRS in whom all dyssynchrony parameters are normal…They sometimes are borderline, and I may go back and decide if it really was worth going ahead in borderline patients…The jury is still out on that." A speaker said, "Clinical failure, I believe, is related to where the LV lead is placed. Tissue doppler shows that…about one-third of paced sites are not ideal and about half of patients are paced discordantly …Ultimately, I think the solution is direct epicardial lead placement guided by tissue doppler. The pilot REVERT study using endovascular lead systems vs. epicardial lead systems will begin in October 2004."

➢ **RV pacing.** The evidence suggests that RV pacing may worsen heart failure, and many patients still have RV pacemakers that have not been upgraded to CRT. New data show that remodeling responses to upgrading RV paced patients causes more reverse modeling. A speaker said, "It is my strong belief that RV pacing or RV pacing-indicated patients with low LVEF are an obvious group to expand use of CRT, especially shifting from pacemaker to a CRT-D subset." Another expert said, "The utilization of RV pacing in post-infarct patients with severe left ventricular dysfunction was associated with worsened heart failure…An analysis of the MOST, DAVID, and MADIT-2 trials suggest – but do not prove – that RV pacing may increase the risk of developing heart failure…I have changed my practice, as many people in the field have. I still generally implant dual devices, but I program them not to pace the RV…I think LV pacing is extremely enticing…One of the things we are looking forward to is getting more information on…the studies looking at RV to LV timing...There has been some suggestion that perhaps leading LV by 40 ms may be a benefit." A third source said, "If you need RV pacing for another reason, you have to look at optimizing the setup…We are not moving away from RV pacing, but it is a concern."

➢ **V/V timing.** An expert said, "Usually LV and RV are paced simultaneously, but pacing LV ahead or RV ahead may be better, and some devices allow that…Most doctors program simultaneously, with zero V/V. V/V is a niche idea."

➢ **Lead systems.** St. Jude may have the best lead technology for ICD/CRT-D, but leads are generally interchangeable, so great leads do not necessarily translate into higher ICD/CRT-D sales. One expert said, "Most leads today

are unipolar. I'm not aware of any advantage to bipolar leads. I'm not sure that is a trend."

In July 2004, the FDA's Circulatory System Devices advisory committee recommended the Agency add the COMPANION trial data to the label for Guidant's ICDs/CRT-Ds. Sources agreed this is likely to encourage more use of ICD/CRT-D devices – but only slightly.

Regulatory issues are a concern, but less to heart failure specialists than electrophysiologists. An Indiana doctor said, "I think CMS will limit access to devices. Their role is to lower the cost to the entire system, not increase the health of the country." The expectation of both heart failure specialists and electrophysiologists is that the new reimbursement levels CMS is expected to issue soon for ICDs:

- Will use an eligibility cutoff of LVEF ≤30. Doctors were unable to estimate the percentage of ICD/CRT-D patients who fall between LVEF 30-35, but they did not think it matters much because LVEF is an "eyeball" measurement. They predicted that doctors will simply call an LVEF of 30-35 a 30. A Maryland doctor said, "EF is an estimate. One doctor may say 30 and another 35." Another source said, "EF 30 or 35 doesn't matter because doctors eyeball it." A third source said, "One of the problems with EF is that people treat it like it is a firm number, but it really is an estimate." A nurse practitioner said, "EF is an estimate, so more patients will be under 30 if that is the criteria."
- May include a provision that allows reimbursement for devices in patients with an LVEF of 30-40 if certain other specified criteria are met. Sources did not specify what those criteria are likely to be. This idea was floated at a recent think tank meeting with CMS at Duke University, and sources were hopeful that CMS will buy this concept.
- Will ***not*** be based on QRS. Sources believe that CMS has been convinced that QRS is not a reliable risk stratifier. However, if a QRS>150 ms were used, the eligible population would be 18%-50% of what it would be at QRS ≥120. A Midwest nurse practitioner in a large heart failure practice said, "A lot of patients have a QRS between 130 and 140. A limit on QRS>150 would really cut back on our referrals (for devices)." A Maryland doctor said, "CMS does not have a leg to stand on with that (QRS >150), and it would be very arbitrary. We are seeing patients with normal QRS and relevant dyssynchrony."
- Will not be based on NYHA Class. The surprising finding in SCD-HeFT that NYHA Class III CHF patients had worse outcomes than NYHA Class II is viewed as an anomaly.

Very few heart failure specialists have any input into the choice of a particular device or lead; that decision is left to the electrophysiologist. This may change in the future, with the margin blurring between heart failure specialists and electrophysiologists. A few electrophysiologists (EPs) also attended this meeting, and those who were questioned indicated that:

- Devices from Guidant, Medtronic, and St. Jude are considered fairly comparable. The choice is made less on features or cost than relationships. A Maryland doctor said, "The devices are all about the same. It is a highly competitive environment, but people have long-standing liaisons with sales reps and companies."
- Epic, St. Jude's new CRT-D, is being well-received. Over the next year, St. Jude may be able to capture 20% market share with this device. The first customers are likely to be doctors using other St. Jude products, and then St. Jude is expected to take market share rather equally from both Medtronic and Guidant.
- Sources did not know whether there has been any increased pricing competition among the vendors since St. Jude's launch of Epic.
- Among electrophysiologists, Biotronik's Shock Box – a stripped down ICD – is unlikely to gain favor over full-featured devices even if CMS introduces changes to reimbursement policies to incentivize them. To them, service is just too important, and Biotronik offers virtually no on-site service. A Midwest source said, "You get so much other data/information from the devices that are needed for patient care, especially in NYHA Class II and III." However, some sources predicted that the Shock Box or something similar could catch on with non-EPs who want to get into implanting devices. A Canadian doctor said, "Tailoring therapy to individual patients is a trend, and for post-AMI patients who are clinically stable but with a sudden cardiac death cloud, a Shock Box would be perfect." Another doctor said, "In heart failure patients, Shock Boxes are not likely to be the device of choice; they need more programming. But in less sick patients, there may be a role for simpler devices." A fourth source said, "You can program a full-featured device as a basic shock box. I think prices could moderate for full-feature biventricular devices. Shock Boxes are most attractive to non-EP implanters… Biotronik will never have much share in the U.S.; it doesn't have service. But I will put single chamber devices in SCD-HeFT patients, but I hate not to have the (dual) capacity in the future."

Experts debated whether the results of ICD trials should be applied generally to the heart failure population.

PRO *(argued by Dr. Arthur Moss of the University of Rochester):*

- ICDs save lives by reducing mortality in high risk patients.
- The mortality hazard ratio in five of seven primary prevention ICD trials all favored ICDs, with $p<.01$.

- The patients who should not get an ICD are "very poor risk patients, those with major non-cardiac co-morbidity with an expected short lifespan."
- The efficacy of ICDs has been shown in various subgroups, with greater efficacy in patients at higher risk.
- An absolute mortality reduction of 5%-6% with a relative risk reduction of 25%-30% is "quite considerable and clinically meaningful, especially since patients in the trials were receiving optimal medical therapy."
- "When talking about cost per life year saved, you need to consider the time horizon. If you use a 12-year time horizon, ICDs become very cost effective, but if an ICD is in for one day, it is very expensive…And it raises the issue of what a life is worth. The overall cost of treating patients effectively with ICDs is equivalent to four days of the Iraqi war."

CON *(argued by Dr. N.A. Mark Estes III of Tufts University):*

- The ICD benefit is double in primary prevention trials compared to secondary prevention trials (e.g., 27% in AVID vs. 52% in MADIT-1 and MUSTT).
- Randomizing patients to devices and procedures is more difficult than randomizing them to drugs. "Double-blind trials are practically impossible, and the regulatory requirements for devices and procedures are not as rigorous as for drugs."
- CHF patient populations that have not been demonstrated to benefit from ICDs include diastolic dysfunction, congenital heart disease, valvular disease, etc.). Less than one-third of heart failure patients would benefit from ICDs.
- The key question about ICD use in heart failure patients is not whether ICDs work overall but how much the risk, benefits, and costs vary amongst the subgroups.
- The ICD benefit to total mortality is a function of the ratio of arrhythmic to non-arrhythmic deaths and absolute arrhythmic death rates.
- Up to one-third of patients have inappropriate shocks, lead problems, and infections. Indication creep and complications would go up with general use.
- DDD or VVI pacing from an RV lead has adverse hemodynamic effects, including dyssynchrony.
- Cost of the therapy is an issue, and ICD therapy is expensive. Broader use of ICDs in patients at low risk of sudden cardiac death increases the cost and makes the cost-effectiveness of ICDs less favorable. "We are in the range of cost-effectiveness with ICDs now, but if we use them more generally, the cost-effectiveness will not be there…Optimal selection of patients will maximize the cost-effectiveness of ICDs."
- Selective use of ICDs is the best approach. Almost all the sudden cardiac death (SCD) comes from low risk patients, so we don't have a major impact on SCD just by putting ICDs into primary prevention patients."

Experts also debated whether mortality should remain the major primary endpoint for heart failure trials.

PRO *(argued by Dr. Christopher O'Connor of Duke University):*

- An event rate of >350 is required to be adequate, and this means a trial of about 6,000 patients.
- Mortality trials are definitive, change practice, are the best estimate of safety, and are less expensive to run because they require fewer patients and less complexity.
- "You can imagine a therapy that improves the composite of quality of life, slightly reduces hospitalizations, and in which mortality is low…but vesnarinone (which actually increases mortality) could be positive using that composite endpoint."
- "Surrogate endpoints must be predictive of relevant clinical outcomes…and that hasn't been proven yet."

CON *(argued by Dr. Jay Cohn of the University of Minnesota):*

- Mortality is an insensitive and non-specific guide to treatment effect. It affects only a small minority of patients (<10%/year).
- Not all deaths are a consequence of heart failure or potentially responsive to heart failure therapy (e.g., MI, stroke, non-CV mortality).
- Mortality does not provide a guide to individual patient treatment or efficacy.
- Mortality cannot distinguish efficacy from safety. The effect on symptoms may be discordant from the effect on mortality.
- All-cause mortality does not provide any mechanistic therapeutic insight.
- Non-mortality observations are more sensitive and specific.
  - Adjudicated heart failure hospitalizations provide data in a larger fraction of patients.
  - Quality of life can be assessed objectively in all patients.
  - LV structural remodeling can be monitored in all patients as a guide to progression.
- A composite endpoint optimizes the power of the trial.

OTHER HEART FAILURE NEWS

Hawthorn extract. The HERB-CHF trial found that there is no benefit to the use of hawthorn extract in heart failure. This herbal product, which is available in health-food stores, was found not to improve six-minute walk, quality of life, or patient global assessment. However, a 2,600-patient mortality study is currently underway in Eastern and Central Europe. Enrollment in that trial is completed and follow-up is ongoing.

Antithrombotic therapy

A three-year update was presented on the 1,587-patient WATCH trial, a VA cooperative study which compared warfarin, aspirin, and Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel) to try to find the optimal antithrombotic therapy. Researchers reported:

- No statistically significant difference in the composite endpoint of all-cause mortality, non-fatal MI, and non-fatal stroke.
- No statistically significant difference in mortality or the secondary endpoint of the composite of all-cause mortality, non-fatal MI, non-fatal stroke, UAP, and embolism.
- A lower incidence of non-fatal stroke with warfarin than aspirin (0.7% vs. 2.1%, p=.016).
- A lower incidence of heart failure hospitalization with warfarin than aspirin (16.1% vs. 22.2%, p=.01).
- Less stroke with warfarin than either aspirin or Plavix.
- No statistically significant difference between aspirin and Plavix in any subgroup.
- The fewest hospitalizations with warfarin, Plavix, and aspirin, in that order. An investigator said, "This is intriguing, especially because it…is evidence that prostaglandin inhibition can have an adverse effect in heart failure."

Bone marrow cell transfer

The six-month, randomized, BOOST trial found intracoronary bone marrow stem cell transfer is safe, but does not improve LVEF, regional wall motion, or otherwise affect LV remodeling after an MI.

ARCA DISCOVERY'S bucindolol

A late breaking substudy of the BEST trial found that a β1-adrenergic receptor polymorphism – Arg-389 – can predict which heart failure patients will respond to beta blocker therapy. This substudy looked at 1,040 patients with moderate-to-severe heart failure for a median of 765 days and found that the β1-Arg-389 variant predicted a favorable response to the beta blocker bucindolol, but Gly-389 showed no survival response to bucindolol. Patients with Arg-389 also had lower hospitalization and death rates vs. placebo. An investigator said, "There was a 36% improvement in outcomes by bucindolol in Arg-389 homozygous patients…Genetic testing of β1-Arg-389 may be useful for guiding bucindolol treatment in chronic heart failure." Interestingly, the polymorphism is more common in whites than blacks (about 49% of whites have it, compared to only about 30% of African-Americans).

An investigator said that Arca Discovery plans to move ahead to get bucindolol approved in the U.S., and a discussion with the FDA will take place in the near future. However, he said another placebo-controlled study couldn't be done in the U.S., Europe, or Japan.

So far, the Arg-389 test is only available in a couple of research labs, but a company reportedly is being set up to commercialize a quick, high-throughput, automated test. This would not be a bedside test.

BAYER'S BAY-58-2667

A poster looked at the combination of this heme-independent activator of soluble guanylyl cyclase with BNP. Used alone, BAY-58-2667 lowered wedge pressure and increased cardiac output and renal insufficiency. Co-administration with BNP results in an increase in: naturesis, diuresis, and the glomerular filtration rate. Researchers concluded BAY-58-2667 has potent cardiac-unloading and renal-enhancing activity with co-administration.

THE REGULATORY SITUATION

The limitation of traditional therapy for acute decompensated heart failure (ADHF) include:

- Small number of studies which included a small number of patients.
- Late outcomes not evaluated.
- Safety issues, including hypotension, arrhythmias, renal insufficiency, and increased mortality. Two commonly used inotropes, milrinone and dobutamine, have a favorable hemodynamic effect but are associated with increased hospitalization and worsened long-term mortality.

Estimated Incidence of Negative Outcomes in ADHF

Measurement	In-hospital	60 days	6 months	12 months
Mortality	~4%	7%	20%	30%
Hospital readmission	---	22%-28%	---	50%

An Otsuka Pharmaceutical official said, "I believe ADHF trials are at a crossroad…The FDA seems to have moved away from relying on hemodynamics for approval. Nitroglycerin approval was based on hemodynamic endpoints …but nesiritide (Natrecor) approval was based on dyspnea with hemodynamics only supportive information…The Agency prefers as broad a population as possible…Generally, acute therapies have had less burden (of proof) than chronic therapies…but in heart failure we have found acute treatment may affect long-term outcomes, so we need 6-month or longer mortality estimates. The need to prove a lack of negative

long-term effect on outcomes will result in greater sample size, greater complexity, and higher trial cost…The major challenges are: selection of acute endpoints, validation of scales and instruments in the target patient population, and development of composite endpoints."

Another speaker noted that inclusion and exclusion criteria for ADHF trials are not very "real world." He said, "The majority of patients with ADHF do not qualify (for these trials)…Patients who meet the selection criteria do not represent the general patients with ADHF, which I think is a major problem."

Dr. Jeff Borer, the chairman of the FDA's Cardiovascular and Renal Drugs Advisory Committee, addressed several ADHF trial design issues:

- What is studied is what a company is likely to get in the label for that drug.
- Since the average ADHF hospitalization is for six days, controlling for that period is good, but at least 72 hours should be covered.
- The primary endpoint should demonstrate clinical benefit:
  - To use mortality as the endpoint, studies would have to be massive, making them economically unfeasible.
  - Symptom relief is a good endpoint but has great variability and is hard to measure.
  - Length of stay as an endpoint is a good integrator but "dischargeable time" would have to be defined.
  - A composite endpoint is possible but has to be very clear.
- Secondary endpoints are for a different purpose than a primary endpoint; they are to demonstrate the persistence of effect and plausibility, so there is a bridge to the next step in treatment. He said, "You need to know they don't feel better at three hours but die at 24 hours."
  - The primary outcome variable at 30 days to find out if all the therapeutic benefit is lost.
  - The primary endpoint variable at three and six months for safety.
  - Heart failure hospitalizations over ***at least*** 3-6 months.
  - Safety. He advised, "Look for everything you can. Approval is based on an understanding of the relationship of benefit: risk."
  - Pharmacologic effects:
    - Fluid balance (e.g., pre-breakfast weight), which is Dr. Borer's favorite measure.
    - LV endodiastolic (volume by echo)
    - PA/CW pressures
    - LVEF and cardiac output. These are not strong components of benefit, but if they go the wrong way, it would be a concern.

Dr. Shari Targum, a medical reviewer in the FDA's Division of Cardio-Renal Drug Products, CDER, offered some tips for approval of new drugs for ADHF from the FDA perspective. She said the information needed for approval is:

- **Efficacy.** What is the benefit to patients? Does the drug make people live longer, feel better, or perhaps ideally, both? She said, "Drugs may be approved on quality of life even if the mortality trend is in the wrong direction, but one needs a reasonable estimate of the effect on mortality."
- **Safety**. She said, "A drug may be approved if people feel better even if the drug makes people live shorter, but there must be a reasonable estimate of how bad the mortality risk is…The ideal drug is one that improves symptoms and makes you live longer. It is one thing to ask patients to choose between symptoms and mortality…but what we do acutely may affect this disease biologically long-term…It is easy to make patients feel good in two or three days…Six-month follow-up is a pain, but it is absolutely critical to get it."
- **Instructions for use.** Can the Agency write labeling? She said, "Efficacy and safety are not enough. We have to be able to write labeling for the drug."

Registries are more real world than randomized clinical trials, another speaker asserted. They provide detailed information on patients, are all-inclusive, can identify assessment of infrequent events or unusual patient subpopulations, and multiple analyses can be performed on the same cohort. The ADHERE registry of ADHF patients now has more than 144,000 patients enrolled at more than 280 hospitals (primarily community hospitals).

The lessons learned so far from this registry include: Choice of acute therapies may determine in-hospital mortality, and in-hospital mortality is doubled with the use of an inotrope. A speaker said, "There is at least a signal that there may be

Mortality in ADHERE Registry

Mortality	Nitroglycerin vs. milrinone	Nitroglycerin vs. dobutamine	Natrecor vs. milrinone	Natrecor vs. dobutamine	Natrecor vs. nitroglycerin	Dobutamine vs. milrinone
Unadjusted in-hospital mortality	.34	.24	.53	.37	1.64	1.39
Mortality adjusted for covariates	.69	.46	.59	.47	.95	1.27
Mortality adjusted for covariates and propensity core	.69	.46	.59	.47	.94	1.24

ADHERE Registry

Measurement	Randomized clinical trial patients	ADHERE patients
Average age	55-65	72.5%
Women	20%-25%	52%
CAD	~50%	60%
Preserve function	Excluded	50%
AF	<25%	31%
Diabetics	25%-30%	44%
Renal insufficiency	Usually excluded	30%
On ACE	40%	40%
On diuretics	---	70%
Any dyspnea	---	89%
Dyspnea at rest	---	34%

increased mortality with short-term administration of these agents."

Asked how the FDA deals with the differences between randomized clinical trial and registry populations, Dr. Targum said, "Personally, I'd like to see broad populations so we can look at different groups…I was stuck by (the comparison) of randomized clinical trials and the real world…I would like to see more real world in randomized clinical trials." Another expert said, "We need fewer inclusion/exclusion criteria in randomized clinical trials." An industry expert said, "Industry is between a rock and a hard place…The broader the population, the greater the noise and the larger sample size needed…How much can you afford?…An all-comer population requires a sample size that is not practical or doable." Dr. Borer said, "You want the broadest population possible, but you have to think of the goal of the trial…It is necessary to show a drug/treatment has a clinical benefit or doesn't…You have to have minimum background noise and that may result in a limited population…If a drug shows a benefit in a population, one can then approve for that population or write a label for instructions for use highlighting where the drug is effective and then do studies to broaden the label."

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