Trends-in-Medicine

October 2008

by Lynne Peterson

SUMMARY

ICD and CRT referrals by heart failure specialists are flat and expected to stay that way. ♦ There have been reports of header/lead problems with Boston Scientific's new ICD, Teligen. ♦ Abiomed's Impella Recover is catching on, perhaps slower than the company might like but steadily, perhaps more at the expense of CardiacAssist's Tandem Heart than IABP. ♦ Orqis Medical's Cancion aortic flow pump is intriguing, but it needs better data for FDA approval. ♦ CytoKinetics' CK-1827452 holds promise as both an IV and oral inotrope, and data at HFSA looked good, but experts believe it needs more study, and questions were raised about the ongoing pivotal trial in Russia/Georgia. ♦ Use of CPAP for sleep apnea in heart failure patients is expected to increase over the next year. ♦ Doctors are dubious about the outlook for Amgen's RED-HF trial of Aranesp in anemia of heart failure. ♦ ARCA biopharma may have more than just another beta blocker with bucindolol; doctors are willing to do genetic testing to determine responders.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

HEART FAILURE SOCIETY OF AMERICA (HFSA)

Toronto, Canada
September 21-24, 2008

There was no big news out of this relatively small, focused meeting this year. At the European Society of Cardiology meeting in early September, a series of drugs failed to show a benefit in heart failure, promoting some people to quip, "Nothing works in heart failure." It was much the same story at HFSA: Trials of new heart failure drugs – and devices – continued to fail. The Phase II trial of Titan Pharmaceuticals' DITPA missed its primary endpoint, as did the MOMENTUM trial of Orqis Medical's Cancion aortic flow pump, and Solvay's trial of its adenosine A_1 receptor antagonist SLV-320. Not every trial failed, but the positive news was rather marginal. For example, a study showed GlaxoSmithKline's Coreg CR (carvedilol extended release) is non-inferior to Coreg IR (immediate release).

- - DEVICES - -

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDS) AND CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Doctors unanimously described ICD and CRT referrals as flat, flat, flat for heart failure patients, and they have no expectation that this will change over the next year. Doctors said the recalls and lead problems have had an impact on public confidence in the devices, and they said this will not improve any time soon. Dr. John Boehmer of Penn State University said, "Device use in heart failure has plateaued. Only 40%-50% of patients who should get devices are getting them because about nine in ten patients don't benefit from an ICD, and that discourages referrals. If you can do active monitoring, there is a benefit beyond the shocks, but we have a long way to go with monitoring before that will increase the use of devices."

Heart failure doctors are not good indicators of any device share shifts or pricing trends; they said those questions really need to be asked of electrophysiologists. Sources did agree that the biventricular pacing market is growing somewhat, not so much as swap-outs as new implants.

The disappointing results of a Medtronic-sponsored CRT trial, REVERSE – which was published recently in the ***Journal of the American College of Cardiology*** – haven't helped. REVERSE was a randomized, double-blind, parallel-controlled, multinational, clinical trial of CRT use in asymptomatic and mildly symptomatic NYHA Class I-II heart failure patients. The key 12-month results of this trial failed to show any improvement with CRT in a clinical composite primary endpoint.

However, an interim 18-month analysis of the REVERSE trial was presented at HFSA, and with longer follow-up CRT appears to have more benefit, though conclusions based on a failed trial are only hypothesis generating. Dr. William Abraham of Ohio State University emphasized that at 18 months there appeared to be a benefit to CRT, particularly among the European patients who were less ischemic, had better baseline 6-minute walk distances, and had fewer ICDs, longer QRS, higher LVEDD, and greater use of ACE inhibitors and ARBs. He called the 58% reduction in first heart failure hospitalization "remarkable," adding, "The results demonstrate the CRT significantly produces LV reverse remodeling, reduces the risk of heart failure hospitalization, lowers the combined risk of morbidity and mortality, and was not associated with an increase in mortality or non-heart failure hospitalization – so it was safe."

Interim 18-Month Results of REVERSE Trial

Measurement	CRT off n=191 US n=82 EU	CRT on n=419 US n=180 EU	p-value
Composite endpoint worsened	29%	15%	0.007
Composite endpoint unchanged	40%	31%	---
Composite endpoint improved	30%	54%	---
LVESVI	90 mm^2	68 mm^2	<0.0001
LVEF	29.8%	35.4%	<0.0001
Death from any cause	2.9%	2.8%	Nss, 0.81
First heart failure hospitalization	13.5%	5.5%	0.005
All-cause mortality heart failure hospitalization	5.7%	7.5%	0.01
Non-heart failure hospitalization	27.4%	27.3%	Nss, 0.96

There may be 24-month data from REVERSE at the American College of Cardiology meeting in 2009.

Experts are hoping that the ongoing MADIT-CRT and RAFT trials will confirm the value of CRT in heart failure patients. RAFT is expected to be fully enrolled by the end of December 2008 or January 2009. MADIT-CRT has completed enrollment, and the data are likely to be presented at either the Heart Rhythm Society or the American Heart Association in 2009, though HFSA 2009 is a possibility.

Commenting on the REVERSE results, Dr. William Stevenson of Brigham & Women's Hospital said, "The 18-month results are important because they show favorable remodeling that continues to 18 months – and a favorable impact on heart failure outcomes with no signal of an adverse effect on mortality." He speculated that the positive results at 18 months and not at 12 months could have been due to either the longer follow-up or the differences in the European and U.S. cohorts, "Many of us feel the longer the QRS, the more likely you are to respond."

But Dr. Stevenson also cautioned that the 18-month results are a subgroup analysis and 20% of patients had missing data in the main trial, which could have increased the responders in the later analysis. He concluded, "I would say, in summary, that REVERSE supports the beneficial effect of CRT on remodeling in mildly symptomatic patients…I think CRT will evolve into an important role in the prevention of heart failure in selected patients but further confirmatory trials are needed and will be welcome."

BOSTON SCIENTIFIC's Teligen ICD

Teligen was just launched this summer, but there have been reports of loose connections between the Teligen leads and the header – or the header itself being loose. The problem could not be confirmed at HFSA, but there definitely was a buzz about it at the meeting, and industry sources – other than Boston Scientific – suggested it is more than a minor problem. The thing to keep in mind: It is doubtful the FDA would lift Boston Scientific's warning letter at the same time or just after a new lead problem/recall if there were one.

One explanation that was offered is that operator technique and training could be the issue. However, that excuse was used by Boston Scientific with the Taxus stent before its recall. Generally, when operator error is blamed, there are also design flaws. Whether there are any design flaws that will require a recall or significant design change is the question.

LEFT VENTRICULAR ASSIST DEVICES

THORATEC's HeartMate-II

This was not a big topic at HFSA, but sources questioned said they have switched almost entirely from HeartMate to HeartMate-II. Dr. Eric Weiss of Johns Hopkins said, "Our outcomes are much better with HeartMate-II. There are fewer infections, and we see a trend to better mortality."

PERCUTANEOUS CARDIAC SUPPORT DEVICES (internal and external)

Dr. Joseph Rogers of Duke University said there is potential utility for several new devices to be used in lieu of intra-aortic balloon pump (IABP). He said, "You can imagine using these devices to support high risk PCI (percutaneous coronary intervention), to support patients during percutaneous valve repair, and to hemodynamically support patients during high risk electrophysiology (EP) ablations in the EP lab… Percutaneous mechanical support devices are growing in compatibility and complexity. We are moving away from IABP to these more complex strategies. The most important issue we will grapple with is patient selection. Centers that get invested in these will require more than one device. It won't be one-pump-fits-all-types of patients…To move the field forward it will take us thinking about trial design and endpoint selection, so to do trials important for our patients."

ABIOMED's Impella Recover

Dr. Rogers said the data on this small, axial flow pump – which is available for either percutaneous (2.5 L/min) or

surgical (5.0 L/min) applications – "look very similar to Tandem Heart." He added, "There is proof-of-concept information that this may be a reasonable approach." Another expert said, "We only use Impella in high-risk PCI as part of a clinical trial, but I'm excited about it for the future…I'm an invasive cardiologist, and we all should be able to put it in. Community hospitals can use it to stabilize patients and then ship them. It provides more support than IABP. But it doesn't take an interventionalist to implant Impella. Impella is already taking the place of Tandem Heart in Europe. The real potential for Impella is in heart failure, and the company is considering a trial in heart failure." Another source said interventionalists at his hospital are using Impella to stent the left main.

CARDIACASSIST's Tandem Heart pVAD

Dr. Rogers said, "I learned when we bought this device that there is a new specialty: transseptalists. And there aren't many of them in any hospital…That is one of the limitations of this device. Someone able and willing to perform a trans-septal puncture to put this in. The cannulas are fairly large, but it has a fairly large flow (3.5-4 L/min)…It failed to show a mortality advantage with short-term use in a small trial."

Dr. Roberta Bogaev of the Baylor Heart Clinic said, "We use a lot of Tandem Heart for: high risk PCI, EP ablations, after a cardiac arrest, and as a bridge-to-decision."

CIRCULITE's Synergy Pocket Circulatory Assist device

German researchers presented a poster on the initial clinical experience with Synergy, a miniature blood pump designed to be placed superficially like a pacemaker for the long-term treatment of chronic heart failure. They reported on the first 12 of 20 patients from the C.E. Mark trial of this device. Eight of the patients were successfully bridged to transplant, 3 patients died prior to transplant (2 from sepsis and 1 from stroke during a replacement surgery), and 1 patient is doing well on support. The cumulative time of device support was 1,018 days, with the longest patient successfully supported for 213 days.

The researchers said:

- Synergy is easy to implant (a 90-minute off-pump, minimally-invasive procedure).
- Recovery is rapid (~2.4 days in the ICU and discharge in ~17 days).
- The most significant adverse event was the need for several device exchanges due to pump thrombosis, prompting the addition of modifications to the pump to reduce the risk of pump thrombosis. In the case of pump thrombosis, the device can be changed with a ~30-minute procedure. In one case, a thrombus was dislodged during the exchange that resulted in a fatal stroke. The other exchanges were relatively free of serious adverse events.
- Hemodynamics are significantly improved, and that improvement is sustained.
- Heart failure symptoms were significantly improved.
- Patients were able to manage the external components.

ORQIS MEDICAL's Cancion

Cancion, an external, percutaneously-inserted aortic flow device – an extracorporeal centrifugal pump that produces ~1.5 L/min in the aorta, was submitted to the FDA in 1Q08. An Orqis official said the FDA had questions, to which the company responded, and the company met with the FDA about a week before HFSA. Exeleras, an implantable version about the size of an automatic ICD that is put into the abdominal cavity and controlled with an external controller, has begun a first-in-man study.

In the MOMENTUM trial, which was stopped early for futility and excess bleeding in the treatment arm, Cancion failed to show an advantage on the primary endpoint of change in pulmonary capillary wedge pressure (PCWP) – 29% with Cancion vs. 29% with control. The multicenter, randomized, double-blind MOMENTUM trial compared Cancion to control in 168 CHF patients with acute decompensation not adequately responding to an IV inotrope and/or vasodilator and a diuretic. The results were published in ***Circulation*** recently. An expert said, "Cancion works, but the trial population was too sick. There is probably a sub-population that will benefit. It needs to be used before the patient gets that sick."

At HFSA, Dr. Mandeep Mehra of the University of Maryland Medical Center in Baltimore presented the results of a post hoc subgroup analysis of MOMENTUM. The subgroup analysis found that the predictors of clinical success were patients with: non-ischemia, higher sodium at baseline, lower LVEF, NcPROM >2200, and PCWP >29. He said, "Perhaps it is the patients with less advanced heart failure who may be the right population to benefit from this therapy…In the 21% of patients with BUN=32, NR proBPNP <5200, and non-ischemic etiology of heart failure, there is a 23% absolute improvement in discharge from the hospital and no read-mission for heart failure, mechanical support, or death within 35 days."

Commenting on the subgroup analysis, Dr. Clyde Yancy, medical director of the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas, raised a question about the safety of this device. He estimated the number needed to treat (NNT) for a benefit is 4 patients, and the number needed to harm (NNH) is 9, concluding, "There is a concern regarding risk."

Going forward, Dr. Yancy said there should be a requirement not only for prospective testing but also some thought given to the control population – and the risk of bleeding needs to be mitigated, "If the bleeding risk remains at 16% of patients

undergoing therapy, that would be (a problem)…This is intriguing work, but the findings could still be a play of chance…I would remind you that Dr. (Salim) Yussuf said, 'More than 90% of post hoc subgroup analyses are wrong when they demonstrate a signal of benefit.'"

PERCUTANEOUS VALVES

Dr. Peter Block of Emery University, a member of Evalve's Scientific Advisory Board, provided a brief, but interesting overview for heart failure doctors of the surgical and percutaneous devices in development for treating mitral regurgitation (MR). He was, perhaps surprisingly, muted in his predictions for the near-term outlook for these devices. Among the points he made were:

- "Is this really something that is useful or not? In the long run is the percutaneous approach even going to be a viable alterative? I don't know the answer to that."
- "MR is not a valvar problem; it is a ventricular problem."
- "Will the reverse remodeling seen early in the EVEREST trial be borne out in EVEREST-II? I hope so."

On specific devices, he offered these comments:

- **EVALVE's MitraClip.** This percutaneous mitral repair device already has a C.E. Mark. Dr. Block said, "This is the leader in the pack…It is useful in patients mostly with degenerative MR and in some patients with functional MR. The neat thing is that this works…The EVEREST-II trial will teach us a lot about the technique and about the surgical randomized trial…We will see. I think this is still out there. We don't know the answer. In one year we will know. Enrollment closed last week."

  Evalve announced, separately, that the first two European patients have been treated successfully in Germany with MitraClip. The company also has expanded the number of European training sites.

- **Coronary sinus devices – VIACOR's PTMA, EDWARD LIFESCIENCES' Monarc, and CARDIAC DIMENSION's Carillon**. Dr. Block said, "When you look at the data (for these), you say the data are disappointing, at best…About 80% of patients chosen can be implanted, and, of those, about half get a 1-1.5 reduction of MR. On balance, that is not a ton. Maybe this isn't going to change things very much…but if you have 3+ MR and your MR is a significant contributor to left ventricular dysfunction, will reducing that to 1.5 MR make a difference? No one on God's green earth knows that…and I don't think we can get that trial done because it would take two million patients…It is an interesting area for which I don't have an answer…Is 1-2 reduction of MR enough? I hope so."

- **Other "thorny" players:**
  - **AMPLE MEDICAL's PS3**, a mitral valve repair system for asymmetrical annuloplasty. Dr. Block said, "It may sound like it makes no sense, but it works."
  - **MITRALIGN's Mitralign Percutaneous Annuloplasty System.** He said Dr. Eberhard Grube in Germany will start doing this in 20 patients. He called it an "interesting concept" but said "whether it makes a difference is unclear."
  - **MYOCOR's iCoapsys**, a device to treat mitral valve insufficiency via two pads that are positioned on the outside of the heart and connected by a flexible cord that can be adjusted to reshape the geometry of the heart and to realign the leaflets of the mitral valve. The surgical TRACE feasibility study was described as "enrolling slowly" but as "having promise." The Phase I VIVID trial of a percutaneous version of this device recently enrolled its first two patients. Dr. Block said, "How long it will work and how much it will help patients is not clear to me. But we'll see… It is a conceptual step forward…Will ventricular support devices (iCoapsys) have a long-term benefit? I have no idea, but if it works, it will be dynamite."
  - **Mitral valve replacements.** Medtronic and Endovalve are working on this.

PRESSURE SENSORS AND HEMODYNAMIC MONITORING

Among the different types of pressure sensors in development are:

1. **Right ventricular pressure monitors.**
2. **Left atrial pressure (LAP) monitors.** Dr. Abraham described these as having good accuracy, showing a good relationship between LAP and PCWP, and being technically feasible, with an "encouraging" preliminary signal of efficacy. He said an observational study found, "There were significant improvements in LVEF that averaged ~8 points, improvements in cardiac index and stroke volume, improvements in patient global assessment, and no worsening of renal function – so we are not drying our patients out too much…A pivotal trial of a LAP monitoring system is warranted."
3. **Pulmonary arterial pressure monitoring** – e.g., CardioMEMS' wireless device. Dr. Philip Adamson of Oklahoma Heart Hospital said a proof-of-concept/feasibility study found no unanticipated device adverse events, and the accuracy was very good compared to a Swan Gann catheter. The CardioMEMS device has no battery or leads and is powered by radiofrequency (RF) interrogation. There is a very small sensor with nitinol wire-loop tines that hold it in place and a silicone outer coating. It is put in through a right heart cath. The randomized, single-blind, multicenter CHAMPIONS trial, a U.S. pivotal study, is underway in 550 NYHA Class III patients at 75 U.S. sites; so far 281 patients have been enrolled.

Asked how physicians will choose among these devices when and if they are all available, Dr. Abraham said, "I am very bullish on this arena of implantable hemodynamic monitors...I

think there is room for all of them. (The choice) may depend on whether you are handling a particular group of heart failure patients…I think a lot will depend on ***who*** is managing the patient as well. Some of these devices have an advantage in terms of ease of implantation and use, and others require more expertise for implantation and more intensity of follow-up… So, there will be physician preferences…And a lot depends on whether the device is stand-alone vs. combined (with another device)…I think each has a place...As this technology and the area evolve – and as we understand pressures more – I think we will see a clinical application that mirrors the development of a disease management system similar to diabetes…but we have to make sure the information is understandable, accurate, and has little risk of falsely changing medical therapy. Right now, we ask patients to change diuretics based on weight…I think this will represent a major improvement in the quality of the information the patient receives and allow a better outcome." Another expert said, "They all have value, but the left atrial pressure monitors have an inherent negativity to most cardiologists. Not everyone wants to do a transseptal placement…I think the easiest device to implant is the stand-alone CardioMEMS device…It is very easy to implant, but it does lose the ability for continuous recording…so you have to weigh ease of use and data."

The regulatory perspective on pressure sensors

Dr. Randall Brockman, a medical officer in the FDA's Center for Devices and Radiological Health (CDRH), offered the FDA perspective on hemodynamic monitoring. In a take-off on the old E.F. Hutton commercial: When the FDA speaks, people (should) listen.

Dr. Brockman emphasized that pressure sensors are complex, and the review is challenging for the FDA. He said, "The FDA review of implantable heart failure monitors focus on the risk and benefits of the entire treatment, not just the accuracy of the measurement…We have a little trouble putting devices in patients just so they get contacted more often."

Dr. Brockman said the FDA's critical questions about these devices are:

- **What kind of information is presented?** "Is it basic physiology parameters like heart rate, temperature, weight …or something less familiar, like intra-thoracic impedence?…The further we (the FDA) get away from our comfort zone, the more information we will want."
- **Is the monitoring parameter one that physicians are experienced in interpreting?** "If yes, is the measurement accuracy acceptable? If no, has clinical utility been demonstrated?"
- **To whom and under what conditions is the information presented – directly to the patient or directly to the physician?** "We have some concerns that the information from the monitor may be used as a principle part of the decision-making, and then we look for more information to justify that implication. Is there something about it – like even the name – that implies clinical utility? If that is implied, we will probably ask for a demonstration of clinical utility. And what is the patient supposed to do with the data?…One end of the spectrum is track and show it to the doctor. But what if they are supposed to make an intervention – change diet, go to the emergency room, etc.? In the latter scenarios, we would want to see clinical benefit to support that."
- **What triggers the presentation of data?** "If there is a pre-specified schedule (weekly, daily, etc.), we consider that fairly low concern. If there is physician-initiation of access, however, we have concerns about undue reliance on the data. Patient-initiated access, on-demand data, comes back to what the patient is supposed to do. The highest level of concern is when an alarm is built in. We want to know clinical data supporting the alarm. What intervention is needed and when? The only way to answer that is with clinical data."
- **For an alarm, are the sensitivity and false alarm rate acceptable?** "With low sensitivity, patients may have a misplaced sense of security or ignore important symptoms. With a high false alarm rate, our diagnostic statisticians have convinced us that it is challenging to calculate specificity, so we have to shift to looking at a high false positive or high false alarm rate. Scenarios that concern us: When an alarm goes off, phone contact is made. Rather than instructing the patient to come in, the patient is told to increase the diuretic for a few days. If the patient is volume overloaded, fine…but what if it is not volume overload, and the patient is over-diuresed? If there are a lot of false alarms, another possibility is patients and doctors get tired, and then ignore it or turn it off."
- **For an implant, is the monitoring feature coupled to a therapeutic or stand-alone?** "We are concerned about the risks involved. Does the addition of a monitoring feature to a therapeutic device present any additional risk? Does the clinical benefit outweigh the chronic risks of the implant? This is an issue we continue to deal with."
- **What are the other risks of the system**? "There is some concern with the risk of the implant, but also the long-term risk. Is there battery drain, so it has to be replaced often?" Other risks include: the implant, misinterpretation of the information, misuses, device error, clinical benefit.

OTHER DEVICES TO WATCH

BIOCONTROL MEDICAL'S Vagus Nerve Stimulation (VNS) for congestive heart failure

A poster was presented by Italian researchers who are conducting an open-label, multicenter, 6-month pilot study of VNS in 28 patients with moderate-to-severe CHF. They reported at HFSA on 3-month interim results on 25 patients.

There were 3 early deaths, all attributed to disease. Adverse events included cough (5 patients), jaw pain (3 patients), and voice alteration (4 patients).

Interim 3-Month VNS Results in CHF

Measurement	Baseline	3 months	p-value
Quality of life	49.1	63.1	<0.0001
6-minute walk test	390.1	455.9	<0.0001
LVEF	22.4%	27.6%	<0.05
NYHA Class	2.8	2.0	---

CVRx's Rheos

Experts divide into two camps on this baroreflex stimulator for lowering blood pressure: (1) Those who think it will have a role, and (2) Those who describe it as a "Frankenstein" device with little or no likelihood of gaining FDA approval.

Most of the heart failure experts questioned who believe that Rheos may have a role said it will have value in a ***limited*** number of refractory hypertensive patients and a ***limited*** number of heart failure patients as well. They estimated that 5%-10% of hypertensives and ~5% of heart failure patients might be eligible for the device, and perhaps half of those might agree to try it. Yet, given the size of the hypertensive and heart failure populations, this is probably not a small number. One expert said, "I'm doing Rheos. Several patients have normalized and gone off medications. Rheos will have a role in heart failure as well as hypertension. It is very interesting."

Some sources suggested Rheos will have value, but only as a research tool. One said, "In heart failure, it needs a lot of work to optimize the technology and titrate the treatment. It will have a fabulous role in the ***study*** of heart failure."

On the other hand, some experts are absolutely convinced that this device will never, ever gain FDA approval, but they hedged this by saying that, should it get approved, usage is likely to be limited. Perhaps the experience of Cyberonics VNS system in treatment-resistant depression is a parallel. A few of these said that nothing short of clear outcomes data will convince them – or their patients – of the value of this device.

Currently, the battery life is about 1.5 years, but a company official said they are working on improving this. He insisted that the company is not making any design changes during the ongoing trials.

The ongoing pivotal trial is about one-third enrolled (~100 of the planned 300 patients), and sources said it is having trouble enrolling – that enrollment is going slowly, which they described as a portent of likely eventual device acceptance. However, company officials insisted the trial is not having problems enrolling.

A new European trial in diastolic heart failure is being conducted in Germany and the Netherlands. This trial has not enrolled any patients yet, but the company is planning to expand this trial to include some U.S. sites, though those sites and those details have not been worked out yet. The primary endpoint is change in LV mass index, and the secondary endpoints are change in blood pressure, blood levels, and quality of life. The trial is expected to be completed in 2011.

New data were presented in a poster at HFSA from a post hoc analysis of the original patients in the proof-of-concept study, which showed that Rheos reduces blood pressure, induces substantial cardiac reverse remodeling, improves cardiac systolic function, and may also improve diastolic function.

Changes in Cardiac Structure and Function, Blood Pressure, and Medication with Rheos Use

Measurement	Baseline n=33	Change at 3 months n=33	Change at 12 months n=20
Systolic blood pressure (SBP)	178.9 mmHg	- 22.0 mmHg *	- 28.0 mmHg *
Diastolic blood pressure (DBP)	104.4 mmHg	- 11.0 mmHg **	- 13.8 mmHg †
Anti-hypertensive medications	5.2	- 0.2	- 0.6
Cardiac structure			
Left atrial dimension	44.9 mm	- 1.0 mm	- 2.3 mm †
Left atrial dimension index	20.9 mm/m^2	- 0.5 mm/m^2	- 1.1 mm/m^2 †
Septal wall thickness	14.5 mm	- 1.2 mm *	- 1.6 mm *
LV posterior wall thickness	14.0 mm	- 0.9 mm *	- 1.5 mm *
LV mass	302.7 g	- 39.4 g *	- 53.3 g *
LV mass index	138.8 g/m^2	- 17.8 g/m^2 *	- 25.0 g/m^2 *
Relative wall thickness	0.57	- 0.03 †	- 0.05 **
Cardiac function			
Heart rate	72.1 bpm	- 4.5 bpm †	- 3.1 bpm
LVEF	66.1%	+ 1.2%	+ 1.6%

* p<0.001 ** p<0.005 † p<0.01

Dr. Michael Zile of the Medical University of South Carolina (MUSC) discussed Rheos during one HFSA session. He described how it works, noting that it has been shown to lower systolic and diastolic blood pressure as well as LV mass index and left atrial dimension.

Efficacy of CVRx's Rheos *

Measurement	3 months	12 months	24 months
SBP	---	Down 33 mmHg	Down 35 mmHg
DBP	---	Down 24 mmHg	Down 22 mmHg
LV mass index	Down 16 points	Down 25 points	---
Left atrial dimension	Down 1	Down 2.4 (p<0.01)	---

* Source: Dr. Zile presentation

MEDTRONIC's EnRhythm MRI SureScan Pacing System

There were no new data or any discussion of this at HFSA, but doctors questioned about it agreed it has great promise. An Oklahoma doctor said, "It is a huge deal. Pacemaker patients tend to be older, with hip or knee problems, and need MRI. I would preferentially use it." Another said, "I would change from (another pacemaker manufacturer) to Medtronic for this."

PARACOR's HeartNet

This mesh device looks a bit like the failed Acorn device, but company officials and a researcher insisted it is very different. They cited several differences, including:

- It is deployed via a small thoracotomy, not a sternotomy.
- The material is silicone-coated nitinol, and the elastic property doesn't cause constriction.
- It is being studied in selected heart failure patients (NYHA Class II-III) who are not candidates for mitral valve replacement or CABG using hard endpoints. About 120 of 272 planned patients have been enrolled in this study.
- Re-operation is easier afterwards.

Sleep apnea

Obstructive sleep apnea (OSA) ***and*** central sleep apnea (which is a less recognized problem) – is getting more attention in heart failure, and doctors predicted that use of continuous positive airway pressure (CPAP) devices will increase over the next year. Doctors recognize that compliance with the devices for OSA is not good, but they said that heart failure patients may be more compliant because they are more symptomatic. Comments included:

- "I'm a big believer (in treating sleep apnea in heart failure patients). My own son has sleep apnea (but not heart failure), and he refuses to use a device."
- "There is a lot of data suggesting a benefit in central sleep apnea, but the question is whether treatment leads to a benefit (in heart failure). There is a suggestion of benefit, but it is not definitive…I think use will increase because the technology to deliver CPAP has improved. There are better fitting masks, more variety in masks, and auto titration."
- "It is well known that heart failure patients with sleep apnea do worse. CPAP use is increasing."
- "CPAP use is increasing, but compliance is very poor, and there is no good treatment for central sleep apnea."

The key beneficiary, initially, may be Respironics; doctors praised the small size and features of its newest generation device. Another company to watch may be Cardiac Concepts, which is working on a central sleep apnea device. An expert said, "This has really great potential."

Dr. Darshak Karia, director of heart failure services at Albert Einstein Medical Center in Philadelphia, presented several posters on the problem of sleep apnea in heart failure. He said, "The story that has been untold: Up to 70% of acute heart failure patients can have sleep disordered breathing." Dr. Karia studied 42 consecutive heart failure patients (40 were evaluable) and found: only 30% had no sleep disordered breathing, while sleep disordered breathing was mild in 24%, moderate in 21%, and severe in 24%. He said, "Sleep disordered breathing during acute heart failure does not resolve with standard heart failure medical therapy…Sleep disordered breathing is not even mentioned in the (heart failure treatment) guidelines."

He is conducting an in-hospital trial of CPAP therapy in heart failure patients with sleep disordered breathing, and he is planning an outpatient trial as well. He admitted that "patients and doctors hate CPAP," but he insisted that new devices are much easier to use and more patient-friendly.

Troponin testing

Asked about the utility of an ultra, ultra high sensitivity troponin test – such as the gold nanoparticle test Nanosphere is developing – for monitoring heart failure patients, doctors insisted that there has been no demonstration of the clinical utility of measuring troponin at those low levels, and until there are outcomes data, they won't be convinced. A California researcher said she is skeptical about these tests and concerned that the false positive rate will be high, so her institution is doing a study on their own of an ultra, ultra high sensitivity test in the emergency department and in the clinic.

REGULATORY ISSUES

Shawn Forrest, a lead reviewer and biomedical engineer at the FDA, and colleagues presented a poster at HFSA on statistical methods for cardiac output measurement. Forrest said, "This may morph into a guidance document, but we wanted to get our thinking out."

The take-away from the poster was: "Comparing two imperfect methods of cardiac output measurement is challenging, and conventional analyses can be misleading. We propose an error grid based on practical and clinical judgment, which can facilitate the comparison of devices used for cardiac output measurement."

The recommendation to use an error grid applies to devices that estimate cardiac output or cardiac index less invasively and more continuously. The poster noted, "FDA recognizes that the accuracy of any cardiac output estimation method is subject to substantial measurement error (~20%)…We recommend a reference measurement value over a pre-specified

number of measurements to reduce error…Comparison of cardiac index rather than cardiac output is problematic as a primary comparison (cardiac output is better)."

- - DRUGS - -

Dr. John Cleland, chair of the department of cardiovascular and respiratory studies at the University of Hull, U.K., pointed out, "No drugs have been shown to reduce morbidity or mortality in heart failure patients." He compared the progress so far with heart failure medications to "rearrange the chairs on the Titanic." However he predicted 30% of heart failure patients will be able to be cured by 2020, but, because there is no prevention for heart failure, prevalence will continue to rise.

About available drugs and treatments, speakers commented:

- **Aggressive management of diabetes** – actually can increase mortality.
- **Angioplasty.** "There is little evidence this reduces mortality."
- **Aspirin.** A substantial excess of heart failure hospitalizations may be due to aspirin. There is no evidence for long-term aspirin use in patients with ischemic heart disease.
- **Astellas' Vaprisol (conivaptan)**. This was approved to treat hyponatremia in December 2005. An expert suggested that conivaptan is not used more often in heart failure because it is expensive and people are not comfortable with it yet.
- **Calcium channel blockers (CCBs)** – should be used "with caution or not at all in heart failure patients."
- **Class I agents,** like felcainide. "Getting rid of these probably has saved lives!"
- **Interferon-β-1b.** A retrospective study presented by German researchers looked at 53 patients with dilated cardiomyopathy (32 treated with IFN-β-1b vs. 21 with control) over six months. They concluded that off-label use of IFN-β-1b in patients with chronic viral decompensated cardiomyopathy is feasible and safe, but promising results in Phase II studies were not confirmed here. Individual patients showed a tremendous increase in heart function with IFN-β-1b treatment. A multicenter, placebo-controlled, randomized trial is necessary with different dose rates."
- **Johnson & Johnson/Scios's Natrecor (nesiritide).** There is some concern about renal function and mortality from meta-analyses, but an ~7,000-patient trial is ongoing to answer that.
- **Milrinone.** "Because of adverse effects, it should not be used unless absolutely necessary."
- **PDE-3 inhibitors** – are generally contraindicated.
- **Statins** – "benefit patients at lowest heart failure risk but not higher-risk patients." A poster by Mayo Clinic researchers offered an explanation of why AstraZeneca's Crestor (rosuvastatin) did not alter cardiovascular outcomes in trials of elderly heart failure patients. They reported that chronic rosuvastatin in a model of severe cardiorenal syndrome did not effect changes in cardiorenal hemodynamics, sodium retention, neurohormonal activation, echo parameters, or LV fibrosis.
- **Ultrafiltration.** While some doctors are using it with good efficacy, experts called for more longer-term data on more patients, which may come from ongoing NIH trials.
- **Warfarin** – is "almost as good as nothing in heart failure hospitalization rates."

Novel drugs in development for heart failure include:

AMGEN's Aranesp (darbepoetin)

Dr. Cleland said there is a "strong rationale why anemia might be bad and correction good. A couple of studies have not been as positive as we had hoped, but…the RED-HF trial should answer this question. There is still considerable uncertainty about the effects." Other sources were dubious about the outlook for the RED-HF trial. Even if it is positive, they said that the number of applicable heart failure patients is likely to be far, far less than originally thought. One expert said, "The original assessments (of eligible patients) were way overblown. It is a difficult trial to do because the incidence (of anemia) in heart failure is probably less than anticipated." Another said, "The question is how many patients are anemic enough to warrant EPO."

ARCA BIOPHARMA's bucindolol

Is there a role in heart failure for another beta blocker? Maybe not unless there is something really unique about it. But ARCA just may have found that unique feature for bucindolol. Using genetic testing, researchers have identified a dual polymorphism that predicts responders.

1. Patients who respond extremely well to bucindolol (the 47% with the betal 389 Arg/Arg polymorphism + the α2c322-325 WT polymorphism). In a substudy of the 1,040-patient BEST trial which was presented at HFSA, patients with this dual polymorphism had a:
   - 38% reduction ($p<0.05$) in all-cause mortality.
   - 48% reduction in cardiovascular mortality ($p<0.05$).
   - 44% reduction ($p<0.01$) in heart failure hospitalizations.
   - 36% reduction ($p<0.01$) in cardiovascular hospitalizations.
2. Other patients in whom it is comparable to other beta blockers (the 40% with the betal 389 Arg/Gly and the α2c322-325 WT polymorphisms).

3. A group of patients (13%) who had an unfavorable response to it.

Doctors questioned about the outlook for the use of the genetic test with bucindolol were generally positive. One said, "Genetics in heart failure is coming. No one knows how to use it yet, but genetic tests are increasing. They are not for every patient, but there is a role at some point in some patients. But genetic testing is still five years down the road. To me, their place is in African Americans."

Bucindolol was submitted to the FDA on September 19, 2008. An investigator said, "Labeling discussions will be extensive," predicting that the drug won't be commercially available until early 2010. A PMA for a genetic test is expected to be submitted in "a couple of months." The test, which will be available through LabCorp, is expected to cost $150-$200. Dr. Michael Bristow, co-director of the University of Colorado Cardiovascular Institute, said he would use bucindolol for *de novo* patients on a beta blocker who are not doing particularly well.

CYTOKINETICS' CK-1827452, a myosin activator

Cytokinetics has an agreement with Amgen, and Amgen will decide how this drug goes forward. A pivotal trial is ongoing in Russia and Georgia (the country, not the state), which is being run by Evidence, a contract research organization (CRO). A Cytokinetics official said there were regulatory and IRB hurdles but that the trial has not been affected by the recent military actions in Georgia.

Dr. Cleland called CK-1827452 "interesting" because, unlike classic inotropic agents such as dobutamine, it doesn't increase the speed of contraction of the myocardium but does increase the duration. He called it "a radically different mechanism for improving stroke volume." The problem, according to Dr. Cleland, is that it is too well absorbed orally and a more controlled drug delivery system is needed for oral dosing. However, the company believes it has solved this problem.

At HFSA, the results were presented from the first clinical trial of CK-1827452 in heart failure patients, Study CY-1121. In this randomized, double-blind, dose-titration trial, CK-1827452 was administered IV in patients with stable heart failure (EF <40 and sinus rhythm). A speaker said, "There is no intention to develop this as an IV drug for NYHA Class II heart failure."

The results included:

- LV systolic ejection time improved ($p<0.0001$).
- Ejection fraction overall improved ($p<0.05$), but it was not statistically significant for each individual dose. The speaker said, "The relationship was weakest for this, and we think it is a methodological problem in measuring the volumes accurately."
- LV stroke volume improved ($p<0.0001$).
- Fractional shortening improved ($p<0.0001$).
- No significant effect on blood pressure. There was some suggestion of a reduction in heart rate, but this was mostly in the standing position.
- Adverse events were sinus bradycardia, orthostatic hypotension, and hypotension (each 17% at the highest dose tested).

The speaker's conclusion: "CK-1827452 has a strong relationship between plasma concentration and the pharmacologic effect of the drug…Patients with heart failure have a steeper dose response than healthy volunteers…There is some evidence that the sicker the patient, the greater the response to the drug…There was a statistically significant, and we believe clinically meaningful improvement in ejection time, stroke volume, fractional shortening, and cardiac output – and a decrease in heart rate."

The IV formulation is being developed for the acute setting, and an oral formulation is being developed for the chronic setting. Reportedly, the oral formulation has already been tested with one-week dosing, showing that it is well absorbed orally.

Dr. Mihai Gheorghiade, associate chief of the Division of Cardiology at Northwestern University Feinberg School of Medicine, said there is a need for a new agent, "Uniquely, its effects are not associated with an increase in intracellular calcium, which occurs with other 'inotropes.' That is an important distinction. The results in the animal model are extremely encouraging…We all know there are unmet needs in heart failure. Although congestion is the main reason for heart failure admission, a significant number of patients have a low cardiac output state. Except possibly for digoxin, there currently are no effective or safe agents (inotropes) to directly and immediately improve cardiac function…We need other agents…(But) we also need to pay particular attention to patients with coronary disease who may react differently to our agents from patients with primary cardiomyopathy…Data suggest that coronary disease patients in whom an inotrope is given may be associated with a post-discharge increase in mortality…Giving an inotrope even a short time may negatively affect long-term prognosis."

The ideal inotrope, according to Dr. Gheorghiade:

- Should improve only "abnormal" hemodynamics. If cardiac output is 6, you don't want to raise it to 12.
- Should not increase heart rate or MVo_2 (peak venous oxygen saturation).
- Should not decrease blood pressure/coronary perfusion.
- Should not affect ischemic or hibernating myocardium.
- Should be available in both IV and oral formulations and should have a rapid onset of action.
- Should not have a narrow therapeutic/toxic ratio.

- Should have an adjunctive if not additive effect when added to other agents.

Commenting on the CK-1827452 study, Dr. Gheorghiade said, "Patients who got a double dose – overdosed – had a significant increase in heart rate, a major decrease in blood pressure, and a troponin release…We have to note the drug is not only beneficial but also deleterious at too high a dose. In addition, this study was not specifically designed to assess hemodynamics, so it was not really tested, in patients who need it – patients with low cardiac output…There were promising results in an animal model, and CK-1827452 may fulfill an unmet need in 'low cardiac output' patients, but prior to embarking on a large clinical trial, we need to better understand the effects on: hemodynamics in patients with severe heart failure, MVo_2, and coronary perfusion, particularly in patients with coronary disease; ischemic/hibernating myocardium; and reduction in diastolic time should be well studied."

GLAXOSMITHKLINE's Coreg (carvedilol)

The 24-week COMPARE trial showed that once-daily 10 mg Coreg CR is non-inferior to twice-daily 25 mg Coreg IR in heart failure patients naïve to beta blockers, but the trial also didn't shown superiority, though it was not designed to look at superiority. Yet, there were questions about the conduct of this trial; the initial primary endpoint was changed and the sample size increased after a blinded interim analysis indicated higher than expected measurement variability and patient discontinuations.

Coreg CR vs. Coreg IR

Measurement	Coreg CR 10 mg QD n=153	Coreg IR 25 mg BID n=65	p-value
Discontinuations	17.6%	20.0%	---
Discontinuations for adverse events	3.3%	4.8%	---
Target dose achieved at end of study	79.2%	80.5%	---
Primary endpoint: LVESVI	- 20.8%	- 18.4%	Nss, 0.96
Secondary endpoint: LVEF	N/A	N/A	Nss
Heart rate	- 6	- 5	Nss
Heart failure hospitalizations	3.9%	3.7%	Nss
All hospitalizations	19.2%	19.6%	Nss
SBP at 3 months	Up 7 points	Up 1 point	0.0005

Dr. Gregg Fonarow of UCLA commented on the presentation, noting, "The FDA considers these two preparations to be bioequivalent and gave them the same mortality reduction indications…(But) there was an unexpected finding – the change in SBP (with Coreg CR)…The differences in SBP are unexpected and not fully explained…You could speculate that release kinetics could account for this…but perhaps this is just a statistical fluke…Both drugs produced ***impressive*** improvements in LVEF from baseline and other measures of LV structure and function and impressive reductions in BNP (brain natriuretic peptide) levels and were both well tolerated."

Doctors in the audience questioned the use of brand Coreg CR since a generic carvedilol is available. One said, "I'm concerned this is a way to move us from a generic to a more expensive brand drug." Another said, "I can send a patient to Wal-Mart for $4 (for the generic). Am I going to recommend a $100 drug (Coreg CR), especially when banks are going bust?" Dr. Steven Goldman of Tucson VA Medical Center said, "That is the $64 question, literally and figuratively…I think that is a good point. We didn't show any clinical efficacy of CR vs. IR…For some patients, particularly younger patients, taking fewer medications by switching to a QD dose improve compliance, and I believe that with better compliance, better outcomes could be expected. So, in at least some patients with heart failure, you might consider that. In other patients, you would not."

NILE THERAPEUTICS' CD-NP, a chimeric natriuretic peptide

Dr. John Burnett of the Mayo Clinic said this is the most advanced new cardiorenal peptide in development. It is a designer peptide combining elements of CNP and DNP that may improve natriuresis without excessive hypotension.

In animal (dog and rat) studies, CD-NP was shown to, dose-dependently, have natriuretic, diuretic, and glomerular filtration rate (GFR) effects with less increase in blood pressure than BNP. In an open-label, dose-escalation, 12-patient, first-in-man study, a 17.5 ng/kg/min dose activated cGMP, had a natriuretic effect, caused "very minimal change" in mean arterial blood pressure, and demonstrated a trend to a decrease in aldosterone.

Several other studies are underway or planned:

- Phase Ib to determine the maximum tolerated dose in heart failure – underway.
- Phase Ib (at the Mayo Clinic) on renal physiologic actions in CHF – underway.
- Phase IIa cardiac hemodynamic study in heart failure – underway.
- Randomized, double-blind, placebo-controlled, multicenter, safety/tolerability trial of IV CD-NP in STEMI patients undergoing primary PCI. The principal investigator will be Dr. Bertram Pitt of the University of Michigan School of Medicine.

The side effect to watch with this drug will be hypertension, but Dr. Burnett does not think that will be a major issue because CD-NP binds only weakly to the clearance receptor, causing less displacement of endogenous peptides.

Mayo Clinic researchers are also looking beyond CD-NP to other designer peptides, including:

- ASBNP – which may have unique renal actions.
- CU-NP – a follow-up to CD-NP.
- $A_{11\text{-}15}B_{27\text{-}32}C_{REA}$-NP.

NOVARTIS/SPEEDEL's Tekturna (aliskiren), sold in Europe as Rasilez

Tekturna is approved for hypertension but not heart failure. Dr. Cleland said Tekturna has not shown improvement in heart failure symptoms (yet), so more information is needed to know if this is a good intervention in heart failure.

PFIZER's sildenafil (sold as Revatio in pulmonary artery hypertension and as Viagra for erectile dysfunction)

Dr. Cleland called this "very effective in terms of pulmonary hypertension," noting that heart failure is one of the commonest causes of secondary hypertension.

SANOFI-AVENTIS's Multaq (dronedarone)

Dr. Cleland said, "It is like amiodarone but with no iodine and less toxicity. The problem is the ANDROMEDA study in advanced heart failure that showed a trend to ***excess*** mortality. When you take that with the SCD-HeFT trial, which showed excess mortality with amiodarone, it raises the question of what the final position of this drug will be. Perhaps it will be useful for the milder end of the spectrum – mild heart failure but not more severe heart failure." Dr. Gerald Nacarelli, chief of the Division of Cardiology at Penn State Hershey Heart and Vascular Institute, said, "It is a concerning trial at best. There is no way it will get approval in some heart failure patients – not NYHA Class IV or acute decompensated heart failure. The FDA knows doctors will use it widely if it is approved. There could be a ban on use in NYHA Class III-IV or it could be restricted by ejection fraction (EF). If I were the company, I wouldn't ask for NYHA Class III-IV or acute decompensated heart failure."

SOLVAY's SLV-320, an adenosine A_1 receptor antagonist

Dr. Veselin Mitrovic of Germany reported on a randomized, double-blind, parallel-group, Phase II study of SLV-320, but the data didn't look very promising in NYHA Class II-III patients with LVEF ≤35%. In fact, on almost every measure, SLV-320 (5 mg, 10 mg, or 15 mg IV over 60 minutes) performed significantly poorer than furosemide 40 mg IV bolus or placebo.

TITAN PHARMACEUTICALS' DITPA (3,5-diiodothyropropionic acid) – *and other thyroid hormone analogs*

DITPA also failed to show a benefit in heart failure. Dr. Goldman presented the results of a multicenter, randomized, placebo-controlled, double-blind, 6-month, VA-sponsored Phase II study in which DITPA, a drug for which he holds a patent that was assigned to the University of Arizona and then licensed to Titan, failed to show any benefit.

Results of Phase II Trial of DITPA

Measurement	DITPA n=57	Placebo n=29
Primary endpoint: Heart failure morbidity/mortality, change in NYHA Class, and change in patient global assessment		
Improved	19%	38%
Worsened	33%	21%
No change	48%	41%
Other results		
Heart failure mortality/morbidity/urgent care	10%	10%
Discontinuations	44%	N/A
Weight change	Down 11 pounds	No change
LDL cholesterol	Down 30%	N/A
Total cholesterol	Down 20%	N/A
Systemic vascular resistance	Down 11%	N/A

In animals and in a Phase I pilot study, DITPA showed positive results, prompting the VA to run a Phase III trial with no industry support. The study was started in 2004 but stopped early by a VA review board in October 2006 when they determined that the trial had little chance of reaching the primary endpoint. In the Phase II study researchers did determine the maximum tolerated dose is ~90 mg/day, and there was a favorable effect on lipids.

Dr. Goldman suggested three potential scenarios for DITPA and other thyroid hormone analogs:

- Find a lower dose that is better tolerated.
- Use them as weight loss agents.
- Develop DITPA as a lipid-lowering agent for patients unresponsive to other medications. Dr. Goldman said two pharmas are looking at this approach now.

Dr. Gary Francis of the Cleveland Clinic offered a commentary on the trial, giving it a C+ grade. He commented, "There is probably some gold in them thar hills, but it is not going to be easy to get it out…Finding the right dose is important…I don't know the proper dose of this (DITPA)...but because there were so many side effects, it may have hidden what may have been a positive clinical response…I don't think all is lost…I liked the idea…I still think there may be something there."

Vasopressin receptor antagonists (VRAs)

VRAs were discussed during several lectures, but there were no significant new data presented. One of the concerns with these drugs is their metabolism by CYP450-3A4 and some CYP450-2D6. There are differences among the various vasopressin receptor antagonists, including PK, half-life, rate

of absorption, and mode of administration (IV or oral). Dr. Dominic Sica, a nephrologist with Virginia Commonwealth University School of Medicine, said the field is advancing toward oral therapy. A major side effect of VRAs is thirst.

Comparison of Vasopressin Receptor Antagonists

Measurement	Otsuka	Biogen Idec/ CardioKine	Sanofi-Aventis	Astellas
	---	---	Aquilda	Vaprisol
	tolvaptan	lixivaptan	satavaptan	conivaptan
Receptor	V2	V2	V2	V1a/V2
Route of administration	Oral	Oral	Oral/IV	IV
Urine volume	Up	Up	Up	Up

VRAs in development include:

- **Astellas' Vaprisol (conivaptan)**, an IV agent and the only approved VRA. Conivaptan has drug interactions with ketoconozole, clarithromycin, and digoxin. Dr. Sica said, "This is not like grapefruit juice…so oral conivaptan was abandoned. Any drug involved with 3A4 can have its metabolism interfered with because of conivaptan… One of the reasons it is labeled for no more than four days is because of drug/drug interactions, especially in the hospital…Ketoconozole increases conivaptan AUC 11-fold. That is major league in anyone's terms. Oral 40 mg conivaptan q12h increased the AUC for simvastatin and amlodipine by 11-fold and 24-fold, respectively."
- **Biogen Idec/CardioKine's lixivaptan (VPA-985).** A poster reported on the results of a double-blind, placebo-controlled, dose-escalation Phase I trial in 42 chronic heart failure (NYHA Class II-IV) patients in the U.S. (35 evaluable). The study found significant changes in urine volume and serum sodium, weight loss (with all doses, though it was not dose-dependent), and no serious treatment-related adverse events.

Phase I Results with Lixivaptan in Chronic Heart Failure

Measurement	Placebo n=8	Lixivaptan 30 mg n=6	Lixivaptan 75 mg n=8	Lixivaptan 150 mg n=7	Lixivaptan 250 mg n=6
Body weight change	- 1.4 kg	- 3.2 kg	- 3.2 kg	- 1.8 kg	- 2.0 kg
Sodium concentration change from baseline on Day 6 at Hour 12	- 1.7	+ 1.53	+ 2.4	+ 2.1	+ 5.4
C_{max}	---	182	776	1509	2855
AUC	---	871	3,956	10,006	17,120
T_{max}	---	3.5	2.6	2.9	5.8
Urine volume					
Baseline	1963	2234	1870	2548	2479
Day 1	2396	3186	3777	3841	5450
Day 6	2555	2176	3838	3558	4862
Adverse events					
Dizziness	0	3 patients	1 patient	2 patients	2 patients
Headache	2 patients	1 patient	0	4 patients	0
Thirst	1 patient	0	4 patients	0	2 patients

- **Otsuka's tolvaptan.** A speaker said, "Maybe the problem has been its use in acute heart failure. Maybe this drug is better suited to chronic heart failure." A study is expected to be published in the ***Journal of the American College of Cardiology*** in the next few weeks.
- **Sanofi-Aventis's Aquilda (satavaptan, SR-121463B).** In May 2008, Sanofi-Aventis withdrew its application to the European Medicines Agency (EMEA) for Aquilda in hyponatremia. The application was filed in May 2007, and it was withdrawn after the agency's Committee for Medicinal Products for Human Use (CHMP) asked for additional information.

VRAs may have a therapeutic role in areas other than hyponatremia, including Raynaud's, dysmenorrhea, anxiety, depression, and potentially glaucoma, brain edema, etc. Dr. Sica said, "One of the exciting areas is polycystic kidney disease. This is now in a Phase III study with tolvaptan high dose given BID. This may be a more tangible benefit of these drugs."

Are the effects of VRAs class effects? Dr. Sica said, "I believe the drugs are quite similar. We don't have much on the orals that truly distinguish them yet...We have to appreciate there is a series of compounds coming forward. The sluice gate will open as soon as the first oral gets approved, making it easier for other orals to come forward."

Other agents to watch:

- **Abbott's levosimendan**, a calcium sensitizer. A speaker said the favorable efficacy data are offset by the adverse events, and he doubted that this will ever be approved.
- **Actelion's ACT-064992**, an orally active endothelin ETA and ETB receptor antagonist. The Phase III SERAPHIN trial recently enrolled its first patients.
- **Actelion/Genentech's tezosentan**, an intravenous short-acting endothelin receptor antagonist.
- **Biogen Idec's BG-9928**, an oral adenosine A_1 receptor antagonist. There were two Biogen posters on BG-9928:
  - ***Results in heart failure patients.*** A randomized, multicenter, dose-escalation, double-blind, placebo-controlled study conducted at eight U.S. sites, looked at the effects of single IV doses of BG-9928 in 40 patients with NYHA Class II-IV heart failure. The highest dose (3 mg/kg) was terminated, and the 0.3 mg/kg dose appears to be the dose going forward.

BG-9928 in Heart Failure Patients

Measurement	BG-9928				Placebo
	0.03 mg/kg n=8	0.3 mg/kg n=8	1.0 mg/kg n=8	3.0 mg/kg n=3	n=6
Sodium excretion (change from baseline, mEq)	+ 55.41	+ 114.81 *	+ 70.20	+ 64.60	+ 14.51
Creatinine clearance change from baseline (mL/min/173m^2)	+ 15.78	- 8.37	- 5.39	+ 1.10	+ 8.05
Change in body weight	- 0.80 kg **	- 1.10 kg **	- 1.50 kg	- 1.30 kg	+ 0.3 kg
C_{max} (ng/mL)	200	1,502	4,795	18,805	---
AUC (ng*hr/mL)	562	5,262	14,487	61,832	---
T_{max} (hour)	0.01	0.02	0.03	0.0	---
Treatment-related adverse events					
Status epilepticus	0	0	0	1	0

* p=0.023 ** p<0.05

No statistically significant differences between groups were reported at any time point for PCWP, PAP, MRAP, cardiac index, PVR, and SVR. The association between change in PCWP and change in body weight at 24 hours was statistically significant (p=0.0005).

- ***Safety and tolerability.*** The design of a 3-month study in patients with heart failure (NYHA Class III-IV) and renal insufficiency. This parallel-group, double-blind, placebo-controlled, ~300-patient study is expected to begin enrolling patients in 1H09. The primary endpoint is safety and tolerability; secondary endpoints are disease-related quality of life, exercise capacity, renal function, and use of concomitant medi-cations.
- ***Effect on body weight.*** This on-going study will assess the effect of BG-9928, dosed for up to 5 days, on body weight in patients with acute decompensated heart failure and renal insufficiency. This double-blind, ~900-patient, randomized, placebo-controlled, parallel-group trial began enrolling patients in July 2008. The primary endpoint is change in body weight at 24 hours; secondary endpoints are worsened renal function, number of days of hospital-free survival, and dyspnea.

➢ **Biological interventions**. Dr. Cleland wasn't very optimistic about these, saying, "This may be tomorrow's treatment – and may always stay that way. The main purpose may be to detect new drug targets."

➢ **Corthera's Relaxin** – This is a hormone that is increased during pregnancy, causing vasodilation and allowing cardiac output to rise. A speaker said, "This is now being developed for use in acute heart failure and seems quite successful…There will be data next year in acute heart failure."

➢ **Debiopharm's istaroxime (PST-2744)**, a novel Na/K-ATPase inhibitor – The HORIZON study showed a small but substantial increase in systolic blood pressure and a "quite striking" reduction in cardiac volumes and improvements in LVEF. It was described as "looking good so far."

➢ **Gensia's GP-531**, an adenosine regulating agent.

➢ **hBNP-054.** Mayo Clinic researchers reported that in a dog model of acute heart failure, this oral humanized BNP lowered blood pressure over a six-day period and showed natriuretic actions when administered chronically.

➢ **Myogen's darusentan.** There were no new data on this ARB at HFSA. Experts offered no predictions about the outlook for the DAR-311 trial in resistant hypertension. One expert commented, "Most ARBs are just ARBs. It is hard for them to differentiate themselves, but there are a number of patients we would like to put on an ARB."

➢ **Palatin Technologies' PL-3994.** This natriuretic receptor agonist, which binds to the same receptor as Natrecor, could be more than a competitor for Natrecor. A researcher also suggested it could be a competitor to CVRx's Rheos device therapy.

A poster on a Phase I study was presented at HFSA. The half-life of PL-3994 is 3 hours (vs. ~22 minutes for Natrecor), suggesting it could be either a QD or BID drug. The researcher said the formulation may need to be changed to a sustained release if the current formulation needs to be BID. The maximum tolerated dose (MTD) is 1 µg/kg, but this will be re-tested in other indications. The company is looking at use in acute decompensated heart failure, but the researcher said that if that doesn't work, the focus may be hypertensive heart failure admissions, which he said are about half of all heart failure admissions, "Chronic use is the key market, especially looking at the Natrecor market…It would be disappointing if it just competes with Natrecor…We hope it will be an add-on to standard of care."

Several PL-3994 trials are underway:

- A second Phase I in patients with hypertension. This trial is completed but has not yet been submitted for publication.

- Phase II in acute decompensated heart failure. This is in process of getting set up.
- Phase II pilot study in chronic therapy, but this will be preceded by a dose-finding study in chronic therapy first.

➢ **Protein Design Lab's ularatide**, synthetic form of a natriuretic peptide synthesized in the kidney.

➢ **Testosterone** for men with heart failure.

Anti-diabetic Drugs and Heart Failure

A speaker reviewed the safety of metformin and TZDs in heart failure patients. The conclusions:

➢ **Metformin** is not contraindicated in most NYHA Class II-III heart failure patients unless they have concomitant renal dysfunction.

➢ **TZDs.** Dr. Prakash Deedwania of the University of California in Fresno CA said, "Rosiglitazone (Glaxo-SmithKline's Avandia) fell out of favor because of concern with cardiovascular effects, but pioglitazone (Takeda's Actos) has several positive CV effects….The TZD edema is not heart failure…Metformin is probably safe and potentially effective in heart failure patients. TZDs (are) more complex. They appear to increase the heart failure diagnosis and hospitalization rates. If used, they should be used only in stable, compensated patients, at the lowest doses, probably never with insulin, and with very cautious monitoring of fluids."

➢ **GLP-1s.** These look promising in heart failure. Dr. Richard Shannon, chair of the Department of Medicine at the Hospital of the University of Pennsylvania in Philadelphia, said that animal data indicate that GLP-1s prolong survival rates, and the increased survival is associated with preservation of left ventricular systolic function and a modest increase in LV mass. Three proof-of-concept human trials are underway with GLP-1 infusions:

- **Post-MI.**
- **NYHA Class III-IV heart failure.** In a pilot study of a 10-week infusion, LVEF increased from 22% to 28% over the first five weeks and that was maintained three weeks after the drug was discontinued (vs. no change in control patients). In addition, NYHA Class improved.
- **CABG surgery.**

➢ **DPP-4s.** Dr. Shannon said that DPP-4s may not be as effective in heart failure as GLP-1s, "I think they are extremely good ways to increase endogenous GLP-1, and that is sufficient for beta cell insulin…Whether that is sufficient for cardiac pathways is yet to be determined. Many of the long-acting analogs don't bind the receptor with the same affinity as the native peptide does." However, Mayo Clinic researchers presented a poster reporting that animal (dog) research suggests that Merck's Januvia (sitagliptin) may have positive effects in heart failure.

Atrial Fibrillation (AF) and Heart Failure

There were no new data at HFSA on Sanofi-Aventis's dronedarone, which has been submitted to the FDA – and granted priority review status – as an anti-arrhythmic for treatment of atrial fibrillation. However, speakers at a Sanofi-Aventis-sponsored symposium set the stage for its potential future use by heart failure specialists, outlining the problem of concomitant atrial fibrillation and heart failure.

Experts estimated that atrial fibrillation occurs in about one-third of all heart failure patients. There is a debate over which is a better strategy for these patients – rate control or rhythm control – and the answer appears to be that they are equally good strategies. Unfortunately, it is not clear that AF therapy improves outcomes, but therapy for heart failure helps prevent AF. Dr. Lynn Stevenson, director of the heart failure program at Brigham & Women's Hospital in Boston, said, "We remain convinced sinus rhythm is important for something."

Dr. Nacarelli warned, "Total AF prevention with anti-arrhythmics is unlikely. Consider continuing warfarin in high-risk patients." Asked how he would choose between amiodarone and dronedarone if both were available, Dr. Nacarelli said, "There is only one small head-to-head trial (DIONYSUS) of dronedarone vs. amiodarone…Amiodarone burns you over time but also gets better over time. That is where you will be happier with a safer drug (dronedarone) in two years. Surgeons like amiodarone, but they never see the side effects…Acute decompensated heart failure patients have not been studied." He said that patients treated with dronedarone may have a better long-term outcome than if they had been treated with amiodarone, but they may have more recurrences."

♦