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Study shows CHF patients fare better when cardiologists get involved

Yet some insurance plans continue to use generalists to direct treatment

It runs counter to the currents of managed care: CHF patients fare better when cardiologists get involved in their care, compared to going it alone with their primary care physicians (PCP). Investigators from Henry Ford Hospital in Detroit and the Mary Imogene Bassett Research Institute in Cooperstown, NY, followed hospitalized CHF patients who had been placed in one of three subgroups:

❒ patients treated by someone other than a cardiologist;
❒ patients whose attending physician was a cardiologist;
❒ patients who had consultation from a cardiologist but whose attending physician was not a cardiologist.[1]

The investigators' conclusions: Hospitalized patients treated by cardiologists are less likely to be readmitted and more likely to have better quality of life than those treated by physicians outside the specialty. Yet, wrote the authors, some managed care plans are placing increasing emphasis on the role of the PCP in the treatment of CHF. **(See related article, p. 111.)**

For their study, the investigators followed nearly 2,500 patients in 10 community hospitals for six months and looked at severity of illness, process of care, and clinical outcomes. After measuring length of stay

KEY POINTS

- A new study shows that cardiologist-treated patients are less likely to be readmitted and more likely to have better quality of life than those treated by physicians outside the specialty.
- Yet some managed care companies increasingly place emphasis on the role of the primary care physician (PCP) in the treatment of CHF. Others seem to be seeing the light.
- Cardiac consult with PCP at the helm is the considered solution.

(LOS), mortality, readmission, and quality of life, they found:

❒ Patients who received direct care by cardiologists have a lower mortality rate, shorter LOS, and better quality of life scores than those treated by noncardiologists.

❒ Cardiologist-treated patients were more likely to receive the recommended diagnostic tests and treatment strategies.

❒ Treatment by cardiologists was associated with higher hospital charges and slightly lower risk of readmission for CHF.

❒ Compared to treatment by noncardiologists with no cardiologist consult, consultative care by cardiologists was associated with longer LOS, higher charges, better quality of life after discharge, and lower risk of readmission for CHF.

❒ Compared to treatment by noncardiologists, neither direct nor consultative care by cardiology specialists was associated with a lower adjusted mortality risk.

❒ Patients treated or consulted by a cardiologist were more likely to have the cause of their CHF documented in their charts, to have angiotensin-converting enzyme (ACE) inhibitors prescribed, to undergo echocardiograms or radionuclide ventriculograms, and to receive dietary counseling and case management strategies.

The authors report the reason for cardiologists' greater success was having the expertise to perform many of the new treatment modalities for CHF. Lead author, **Edward F. Philbin**, MD, a cardiologist in the Section of Heart Failure and Cardiac Transplantation at Henry Ford Hospital, wrote, "Inasmuch as half of all CHF patients receive their care in nonteaching hospitals, the implications of this study are not trivial. It is not known whether more rigorous compliance with published guidelines by noncardiologists would offer the same benefits as cardiology specialty care. In our opinion, the relationship between physician specialty, process of care, and clinical outcomes requires further study before effective sweeping health manpower recommendations can be made."

Philbin says his study grew out of a project in which 10 community hospitals in upstate New York worked together on a collaborative quality improvement program. In the course of that program, he and his colleagues gathered detailed information on 2,900 patients, then went back and asked the chart abstractors whether particular patients were managed exclusively by a noncardiologist, by a cardiologist, or by a noncardiologist with a cardiologist consult. Philbin says the length of time that all patients had heart failure, preceding hospital care, was similar among the three groups, averaging three years.

He was unable to say when consultations were done in the patients' treatment because in every day treatment of these patients, there is a wide range of how consults are used. "We know it's not that simple in real life," says Philbin. "Sometimes a consult totally takes over, and a primary totally surrenders. At other times, the consult does a quick, simple test and maintains a minimal presence and has minimal influence on day-to-day decision making." Philbin says he and his colleagues didn't look at those variables, but in the group of patients managed by noncardiologists, there was no involvement by cardiologists, and in the group managed by cardiologists, there was no involvement by PCPs. "In the third group who had cardiologist consults, there was variability."

He says the differences between internists or other PCPs and cardiologists are subtle: "The question of quality of care among specialties is still controversial and unanswered. Just how one measures quality is an elusive thing, and to develop a single score for a physician's treatment of a given disease is not agreed upon because the use of a medication may be appropriate in one patient and not another."

Philbin says he's leery of going out on a limb and saying that his study proves demonstrably better care by cardiologists. He says that if you look at studies of self-reported behavior — questionnaires on ACE inhibitor use, for example — cardiologists tend to get higher scores than PCPs. They are more likely to choose the right answers on tests.

"That may be a reflection of their practice or

COMING IN FUTURE MONTHS

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- Cardiomyopathy: Dx with echo and Tx with anticoagulants
- Patient education that spans settings and gets compliance
- CHF's autoimmune response: Overdrive wears out the heart
- The prospects for metoprolol succinate

Managed care takes a fresh look at CHF

Most managed care companies attempt to take the care of all chronic disease patients out of specialists' hands and put it into the hands of PCPs, says **Edward F. Philbin**, MD, a cardiologist who practices at the Henry Ford Hospital in Detroit. But heart failure may be a unique type of chronic disease that represents a trend in the other direction, he says. There is growing evidence that disease and case management are viable strategies for delivering good CHF care, improving outcomes, and saving money. And some companies are coming to the conclusion that specialized heart failure clinics are a viable strategy.

Philbin, the lead author of the *Chest* study **(see cover story)**, says he and his colleagues did another study on 43,000 patients where they found that managed care CHF patients received better care for heart failure and at a lower cost than non-managed care CHF patients.

"Managed care sees primary care doctors as costing less money," says **Santosh G. Menon**, MD, a cardiologist in the division of cardiology at the University of Kentucky in Lexington. "But I'm not so sure that CHF treatment costs less with a primary care doctor. It's never been proven, and in fact, the long-term costs may be more."

Philbin's study showed that heart failure patients' initial treatment in the hospital is more costly when cardiologists do the treating. But once the patients have the right diagnostic tests, get started on the most efficacious drugs, and receive lifestyle and diet counseling by specialists, they may not need to be re-hospitalized as much, saving money in the long run.

"Leading managed care organizations should be experimenting with PCP education, including the use of guidelines and audits, incentives for PCPs to obtain cardiology consultations, and the use of specialty clinics devoted to CHF," says generalist **Elgin K. Kennedy**, MD, of Hillsborough, CA. He says the allure of cost-effectiveness and quality improvement is undeniable. But Kennedy adds that he doubts that the majority of managed care companies will make very many changes until such time as there is substantial proof that such changes will be truly cost-effective as opposed to just providing somewhat better quality.

[See the next issue of CHF Disease Management *for new evidence suggesting that specialized outpatient care by clinics devoted to CHF treatment may foster better practice patterns and patient care.]* ■

just a reflection of their better cognitive knowledge of the area," he says. "But when you physically measure the practices of cardiologists and of internists or other primary care doctors and what they're doing, the differences between groups is not as profound."

But Philbin says there are some differences favoring the cardiologists. "And even among cardiologists, there are differences. Heart failure cardiologists do better than general cardiologists in the area of heart failure."

CHF Disease Management asked several experts in the field for their comments on the study:

❒ **Gordon Ewy**, MD, chief of cardiology at the University of Arizona Health Sciences Center in Tucson agrees with the study's lead author. "You can't generalize and say that any cardiologist is better than any primary care doctor. Cardiologists differ. There are some whose major interest is catheterization and angioplasty, and they have very little interest in CHF. Those cardiologists may not do any better treating CHF than a primary care physician who is very interested in heart failure and keeps up on the literature. The ideal situation is to have a cardiologist interested in keeping up with the rapidly changing field of CHF management as either a consult or the primary doctor." Ewy says that CHF mortality is worse than most cancers. "If I had a cancer," he says, "I wouldn't have a primary care physician deciding how to treat it. In the same way, if I had CHF, I'd want a specialist treating that."

❒ **Bobby Miller**, supervisor of the Optum Disease Management Program in Dayton, OH, adds treatment success often depends on the knowledge base of the PCP and the level to which he or she keeps up to date on CHF.

❒ **Douglas Chapman**, MD, director of The Heart Failure Center at Alegent Medical Center in Omaha, NE, says that he strongly agrees with the investigators' findings: "It's like asking, 'How does the cardiologist and the general surgeon's approach to appendectomy differ?' One is trained to take care of the condition, and one is not. One keeps current on the disease process, and one does not." Chapman says that a physician's approach to taking care of the patient is

How should you treat comorbidities?

When it comes to controlling the many comorbidities that burden CHF patients such as renal dysfunction, pneumonia, and diabetes, is the patient better off under the care of a cardiologist or that of a primary care physician? *CHF Disease Management* asked several experts to share their thoughts on the *Chest* article (1999; 116(2):346-354), and found they had differing opinions.

"Maybe the primary care physician is better equipped to handle comorbidities than the specialist. Cardiologists tend to focus on the heart and what's going on there, where the general practitioner may look at the whole picture." — **Bobby Miller**, supervisor of the Optum Disease Management Program in Dayton, OH.

"It depends on how up to date on the literature the doctor is. For example, for renal insufficiency, it's been shown that if you add an ACE inhibitor, the patient lives longer. But if you're not up on that, and you add an ACE inhibitor and the BUN creatinine goes up, you might discontinue the ACE inhibitor. That's the wrong thing to do." — **Gordon Ewy**, MD, chief of cardiology at the University of Arizona Health Sciences Center in Tucson.

"Primary care physicians may be better at dealing with comorbidities than cardiologists. The best scenario for a nonadvanced patient may be treatment by a primary care physician in conjunction with a cardiologist, not a cardiologist taking over the care. Consultation with a cardiologist works out the best." — **Santosh G. Menon**, MD, a cardiologist in the division of cardiology at the University of Kentucky in Lexington.

The study's lead author, **Edward F. Philbin**, MD, a cardiologist at Henry Ford Hospital in Detroit says, "For the heart failure patient with comorbidities, the best way to go is probably for him to be cared for by a primary care doctor with a cardiologist consult. There's value in teamwork and continuity of care." He says he thinks primary care physicians might take better care of comorbidities such as diabetes since the specialist tends to focus on his specialty. "That's speculative, though," he says. ■

deeply rooted in training and the everyday experience of keeping up with the literature on the disease process, and PCPs don't concentrate on the one condition.

❒ **Elgin K. Kennedy**, MD, a PCP practicing in Hillsborough, CA, says it should be up to the patient. "[PCP] patients should always have the final choice whether their CHF should be managed by a PCP who may know them personally very well, or a specialist cardiologist who may know their disease very well. The American public will continue to demand the right to make their own choices."

❒ **Kenneth McDonagh**, MD, medical director of the disease management program at AstraZeneca Pharmaceutical Company in Wilmington, DE, says that more studies need to be done before this controversy can be resolved. "The authors [of the study] feel they've found something, but they don't seem to be sure how much of a difference there is [between care by a cardiologist and care by a noncardiologist] and what it means." McDonagh says that PCPs do require additional resources to provide care to their heart failure patients to put that care on par with that rendered by cardiologists, and that needs to be explored before it can be determined that CHF patients should receive all their care from cardiologists.

"My take is that the investigators' research was well-designed," he says. "They uncovered some practice differences. They found what appear to be some differences in the care of patients, including the performance of tests, counseling, and case management."

"To treat CHF patients effectively, primary care doctors have to be up on the new treatments. It's been common knowledge for the last five years that ACE inhibitors are one of the basic components of CHF treatments. The drugs have been documented as part of the [Agency of Healthcare Policy Research] guidelines for those patients since 1994, and more recently, a revised guideline was published jointly by the American Heart Association and the American College of Cardiology." McDonagh says that managed care plans have undertaken initiatives to educate PCPs on the fact that ACE inhibitors are part of the guidelines.

❒ **Evadell Tangquist**, RN, patient education coordinator for Northwest Medical Center in Thief River Falls, MN, also agrees. She says there are no cardiologists at that facility, but they have access to several in nearby Fargo, ND, so some of their patients see or consult with cardiologists. "Yes," she says, "CHF patients do better with at least a consult with a cardiologist. In my experience, I don't see the newer ACE inhibitors or beta blockers on a chart unless a patient has at least a cardiologist consult."

❒ **Santosh G. Menon**, MD, a cardiologist in the division of cardiology at the University of Kentucky in Lexington says care by a cardiologist is most helpful for the advanced CHF patient, "especially for the patient who keeps coming back to the hospital." It's advantageous to have a cardiologist seeing them and getting them on the drugs they need. What is the main difference between care by a PCP and a cardiologist? The cardiologist's treatment is more aggressive. Menon says that often PCPs underutilize ACE inhibitors, beta-blockers, and other drugs known to be beneficial to the patient. "Those drugs have been shown clinically to improve morbidity and mortality," he says, "and maximizing their use is done better by the cardiologists."

Ewy says the problem with heart failure is, once a patient has it, the condition begets more heart failure. "If you just treat the hemodynamics, it's as if you are painting the walls without getting rid of the termites. You need to treat all the neurohumoral imbalances and the new ones that come along. The literature is clear on the standard of care — so clear that there are now heart failure clinics run by nurse practitioners who simply follow guidelines. And they do well."

But he says that extant CHF guidelines are for the management of CHF due to systolic dysfunction. "The study talked about patients with ejection fractions of less than 40%, so the guidelines would apply to them." But a high percentage of patients, he says, particularly the elderly, have CHF due to diastolic dysfunction not systolic, and no guidelines exist for that. Philbin's study does not apply to all patients. The guidelines the study was based upon will be changed in the near future because of new studies on beta-blockers and spironalactone, a diuretic agent that blocks the renal tubular actions of aldosterone. **(See *CM*, September 1999, p. 102.)**

Reference

1. Philbin EF, Weil HFC, Erb TA, et al. Cardiology or primary care for heart failure in the community setting: Process of care and clinical outcomes. *Chest* 1999; 116(2):346-354. ■

Lisinopril: FDA considers approving higher doses

ATLAS study ends with FDA application

Those higher dosages of lisinopril that you've been seeing may soon gain official approval by the Food and Drug Administration (FDA). AstraZeneca Pharmaceuticals in Wilmington, DE, filed a supplemental new drug application with the agency a few months ago to request approval for the use of its long-acting ACE inhibitor Zestril (lisinopril) at doses of up to 35 mg once daily in the management of heart failure.

Lisinopril already is indicated as adjunctive therapy in the management of heart failure for patients not responding adequately to diuretics and digitalis. The drug also is indicated for treating hypertension and improving survival of hemodynamically stable patients within 24 hours of heart attack. Its usual effective dosage range CHF patients is 5 mg to 20 mg, once daily. But cardiologists have been prescribing larger doses all along, says **David S. Roffman**, PharmD, BCPS, associate professor of pharmacy practice and science at the University of Maryland's School of Pharmacy in Baltimore and therapeutic consultant for the medical system's cardiac care unit.

"Cardiologists typically give high doses of ACE inhibitors anyway," he says, "based on the premise that higher doses — if they are tolerated, and they usually are — do more for symptomatic improvement than lower doses." He says physicians have the prerogative to use meds in a way they think is appropriate for patients, irrespective of FDA-approved labeling.

"The majority of physicians will, on occasion, use a drug for a non-FDA-approved indication in a dose that is not necessarily FDA-approved because they see evidence for its benefit in the literature," says Roffman. Off-label use of drugs is

KEY POINTS

- The manufacturer of Zestril has filed a supplemental new drug application with the U.S. Food and Drug Administration (FDA) requesting approval for the use of its product at higher doses than now recommended in the management of heart failure.
- A five-year clinical trial, ATLAS (Assessment of Treatment with Lisinopril and Survival) showed a 12% risk reduction in all-cause mortality and all-cause hospitalizations when patients were treated with higher doses.
- Cardiologists typically give high doses of ACE inhibitors despite FDA approvals.

not an uncommon phenomenon. The most recognized example is the use of nitrates for heart failure; they are not labeled for the condition, yet prescribed frequently. There is literature justification for their use, so physicians don't have medical malpractice concerns.

The FDA does not require that a manufacturer change its dosage every time the literature shows an indication that's not on the label. And conversely, a manufacturer doesn't want to change its label each time, either, because of the expense involved. "Cardiologists who are aware of the burgeoning literature on improved symptoms with higher doses will, with justification, use higher doses," says Roffman.

Then why is the company going to the trouble of submitting the supplemental new drug application? "It's a good thing to educate physicians that higher doses, when tolerated, are good for patients' symptoms and even for survival," he says. And, of course, it's good for marketing.

The ATLAS trial

AstraZeneca's rationale for the label change is based on the results of a five-year clinical trial, ATLAS (Assessment of Treatment with Lisinopril and Survival) which evaluated the effect of low (2.5 mg to 5 mg) vs. high (32.5 mg to 35 mg) doses of lisinopril on mortality and morbidity in more than 3,000 patients with CHF. ATLAS study results were first presented last year at the 47th annual American College of Cardiology scientific session in Atlanta, and they indicated a 12% risk reduction in all-cause mortality and all-cause hospitalizations when patients were treated with higher doses.

Raymond Urbanski, MD, associate medical director at AstraZeneca, explained the complexity of determining ideal dosages for CHF: "For a condition like hypertension, you can monitor a patient's blood pressure and adjust the dose that way. But in patients with heart failure, you're not sure what dosages are more or less effective because you don't have such a simple marker as you do with hypertension. Instead, you have to look at different specific dosage levels and then look at outcomes data — morbidity and mortality statistics — to ascertain what doses are more efficacious."

That was the rationale for the ATLAS study. "Based on that data," he says, "it appears that higher doses [of lisinopril] produce a better outcome with regard to morbidity and mortality than lower doses." The dose-response relationship between lisinopril and its mechanism of action in CHF — its effect on the left ventricular remodeling process — is not known. It appears that lisinopril acts at the cardiac level by altering some of the neurohumeral factors that are involved in worsening heart failure. "We don't know the dose-response relationship to that," he says, "but based on the ATLAS data, it appears that higher doses are efficacious in counteracting that pathologic process, and that low doses, while effective, are not as effective as the higher doses."

Urbanski says that side effect profiles of the high and low doses are essentially the same. "There was slightly more hypotension in the higher doses in the ATLAS trial, but that's to be expected. Most ACE inhibitor side effects tend to occur early in therapy with the initial doses."

"There is symptomatic improvement when lisinopril dosage is increased to the 40 mg level," Roffman explains. "Whether that improvement could be translated to mortality in a larger study is unknown at this point, but early indications from ATLAS imply that patients who don't get systematic improvement on 20 mg of lisinopril, for example, may experience improved symptoms when the dosage is increased to 40. That is the impetus for AstraZeneca's application to the FDA for increasing the dose."

He says that while many CHF cardiologists have been prescribing 40 mg doses of Prinivil or Zestril for a long time despite FDA approvals, "unfortunately, in the community population, people are put on small doses of ACE inhibitors and left on them."

Why? In a 1996 editorial review of the then-ongoing ATLAS trial, Milton Packer, MD, lead investigator, said that the preference for low doses is based on the belief that low and high doses exert similar benefits, but that high doses produce more side effects.[1]

"Yet most studies indicate that large doses of ACE inhibitors produce greater hemodynamic and clinical effects than small doses with no additional toxicity," he wrote.

It was uncertain whether survival effects of the drugs are also related to dose, and it was that question that launched the ATLAS trial — it compared the effects of low and high doses of lisinopril on the survival of patients with heart failure. "If the study demonstrates that large doses are needed to produce optimal effects on mortality," wrote Packer, "then the low dose strategies now widely used in clinical practice may be inadvertently nullifying

the enormous potential benefits that ACE inhibitors might otherwise have."

Roffman concurs that a major concern in prescribing higher doses is that they may increase the risk of side effects. "A significant number of patients in heart failure Class III or IV have relatively low blood pressure due to poor pump function. There's a hesitancy on the part of physicians — mostly internists or family doctors — to push the drug in someone who's blood pressure is 90/60 even though the data say that most such patients tolerate higher doses without symptomatic hypotension."

Administration of lisinopril to patients with hypertension results in a reduction in blood pressure to about the same extent in both reclining and standing positions with no compensatory rapid heart beat. In patients receiving digitalis and diuretics, single doses of lisinopril result in decreases in blood pressure and systemic vascular resistance, accompanied by an increase in cardiac output but no change in heart rate.

Adverse reactions are usually mild

Roffman says another concern is that higher doses will decrease renal function in CHF patients who have some renal insufficiency to begin with. But aside from the renal concerns, he says, there is a greater overriding problem in this type of drug therapy — its underuse.

"The bigger issue is that only 30% to 50% of CHF patients are on ACE inhibitors at all" says Roffman. "Half the people who ought to be on the drugs aren't."

Originally approved by the FDA in 1987, Zestril is now the most prescribed ACE inhibitor on the American market and is available by prescription in packages of 100 tablets in strengths of 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg. In patients with heart failure and renal impairment of hyponatremia, the drug should be initiated at 2.5 mg to 5 mg once daily under close supervision, then titrated upward until blood pressure is controlled. According to AstraZeneca, Lisinopril has been well-tolerated in controlled clinical trials of patients with hypertension or CHF. The drug suppresses the renin-angiotensin-aldosterone system to reduce blood pressure, with an onset of action with one hour.

ACE inhibition limits the conversion of angiotensin I to angiotensin II, resulting in decreased plasma angiotensin II, reduced vasopressor activity, and lower aldosterone levels, according to literature distributed by AstraZeneca. Angiotensin II is a potent vasoconstrictor that increases blood pressure and fluid retention that may play a role in CHF. Adverse experiences are generally mild and transient, the most frequent being dizziness, headache, fatigue, diarrhea, upper respiratory symptoms, and cough. Lisinopril is also marketed by West Point, PA-based Merck as Prinivil.

[For information on Zestril, call (800) 456-3669, ext. 2231; www.usa.zeneca.com/pharm/pibs/pib_zestril.htm. For information on Prinivil, call (215) 652-5000; www.merck.com.]

Reference

1. Packer M. Do angiotensin-converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? *J AM Coll Cardiol* 1996; 28:1,323-1,327.

Suggested reading

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Study details risks of LVAD implantation

High rate of serious infections among findings

Acquiring a heart for transplant, no matter how badly a patient needs one, is a dicey prospect. Of the 40,000 people each year with end-stage heart failure who could be helped with a transplant, only about 3,000 manage to get one. Left-ventricular assist devices (LVAD) are used as bridges to transplant, and researchers continue to investigate their use as an alternative permanent therapy for those patients. But there's a problem: Long-term device implantation is rarely an option because of the high rate of serious infections that the devices carry.

A group of investigators at Columbia-Presbyterian Medical Center in New York City recently examined the relation between LVAD-related infection and the immune responses of LVAD recipients.[1] They compared the rate of candidal infection in 78 patients with New York Heart Association class IV heart failure who received either an LVAD or medical management.

Three months after LVAD implantation, the risk of developing candidal infection was 28% in LVAD recipients, compared with 3% in the control group. T-cell death rate was higher in LVAD recipients than in controls. The investigators concluded that LVAD implantation results in an aberrant state of T-cell activation, heightened susceptibility of some T-cells to activation-induced cell death, progressive defects in cellular immunity, and increased risk of opportunistic infection.

"It is important to emphasize that these abnormalities occur in heart failure patients only after LVAD implantation. They are specific to the device implantation. They do not occur in other patients undergoing heart surgery or bypass."

"It is important to emphasize," says **Silviu Itescu**, MD, a cardiothoracic surgeon and one of the study's authors, "that these abnormalities occur in heart failure patients only after LVAD implantation. They are specific to the device implantation. They do not occur in other patients undergoing heart surgery or bypass."

"Apoptosis is programmed cell death," says **Mehmet C. Oz**, MD, also a cardiothoracic surgeon at Columbia-Presbyterian and one of the investigators. "The cell turns off its basic life mechanism, and it dies as a result." He says that's mainly what aging is, but the phenomenon the investigators wrote about is programmed cell death of a rapidly growing, then shrinking, population of cells.

The T-cell apoptosis appears to result from excessive T-cell stimulation by the LVAD itself, almost as though the recipient's T-cells are attempting to reject the device but cannot do so and consequently enter into a pro-apoptotic pathway. These are not phenomena that are seen in transplant recipients, perhaps because they routinely receive drugs that inhibit T-cell activation. However, says Itescu, it is likely that in the absence of immunosuppression, many of these phenomena would also be seen in recipients of any organ.

Oz explains the phenomena this way: "The LVAD patients were doing two things. They were developing a hyperacute immune response — a very aggressive immunologic response — and at the same time, they were prone to certain types of infections, more than we anticipated. When we investigated this, we found that there were two T-cell lines. One T-cell line was overresponding, and because it was overresponding, the other T-cell line was underresponding." He says there's usually a balance between the different levels of immune response, but the LVAD seems to stimulate one arm more than the other.

Death of T-cells, says Itescu, promotes infection by viruses, fungi, and other opportunistic pathogens because one needs T-cells to combat these organisms. The prototypic disease where loss of T-cells leads to infection is HIV-1. In that disease, also, T-cells die through apoptosis in addition to other mechanisms. LVAD patients who undergo transplantation do not have an increased risk for infection compared to other transplant recipients. Therefore, "one can consider the immune defects and risk for infection we have described as only a problem for potential long-term LVAD use, as permanent therapy," explains Itescu. He describes therapeutic use as LVAD implantation for years, not months as with bridge-to-transplant use.

The research done by Oz and colleagues was not at the level of trying to define markers or telltales of LVAD infection. That was beyond the scope of the investigators' study. "That's not the level of our research," says Oz. "It's much more basic. We're just describing the phenomenon and epiphenomenon — what's going on and the other signs of it."

"In the short term, all patients not responding to medical therapy can benefit from LVADs," says Itescu. "There are no predictive variables that would help decide whether LVAD or medical therapy is optimal for an individual patient."

Designing a treatment strategy is perhaps the next step in this research. For that next step, researchers will look at medications that specifically block whatever is overstimulating the one arm of the T-cells," Oz says. "If we can block them from being overstimulated, the other arm won't be understimulated."

He says that participants in the study were waiting for heart transplants. Patients with LVADs are weakened, but they can survive. "They're better off without the device and the infection than with the device," he says. "Our findings don't help us decide in whom to place the device, just to deal with the problems once it's in."

"The major positive impact of using LVADs as bridges to transplant," says Itescu, "is on patient survival while on the waiting list." Without LVADs, about 30% of patients die while waiting

several months for an organ, whereas with an LVAD, waiting-list mortality is almost negligible.

"The immune problems during this short period do not generally lead to life-threatening infections since the defects need to accumulate over time," he says. "In LVAD patients with immune activation / T-cell apoptosis, we have observed an increased incidence of concomitant B cell activation and production of anti-HLA antibodies. This 'sensitized' state is associated with a greater risk of cellular rejection post-transplant. For these patients, we have developed immunosuppressive protocols pre-transplant [while on LVAD support], and now their post-transplant outcome is as good as any nonsensitized transplant recipient."

Reference

1. Ankersmit HJ, Tugulea S, Spanier T, et al. Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. *Lancet* 1999; 354:550-555. ■

Another perspective on LVAD safety

A group of investigators at Columbia-Presbyterian Medical Center in New York City that is examining the relationship between infection and immune responses involved with left-ventricular assist devices (LVADs) proposes both are specific to the implanted devices. The investigators did not focus on where the devices were surgically implanted and whether their drive lines — the tubing that drives the pump—— jut to the side (three or nine o'clock) or proceed straight downward (six o'clock). **(See related article on LVADs, p. 115.)**

But **O.H. Frazier**, MD, at the Texas Heart Institute in Houston, says the site where LVADs are placed has much to do with whether they get infected. The problem, he says, is often with the way the pumps are placed surgically, not with the pumps themselves.

"The *Lancet* article (1999; 354:550-555) is a bit misleading," he says. "I think it contains a lot of soft data. The study has to do with surgical contamination and violation of certain surgical principles." says Frazier, chief of cardiopulmonary transplantation, co-director of the Cullen Cardiovascular Research Laboratories, and director of Surgical Research at the Texas Heart Institute. "I don't want to be overly critical of the study, but no infection to speak of was seen in the initial group of patients receiving LVADs; it just was seen with extraperitoneal placement of the pumps. [The authors'] conclusions, that there are any cellular immunity implications of the pump itself, are soft. There are implications from chronic infection that can result from the chronic contamination that result from the extraperitoneal placement of the pump."

When Frazier first started working with LVADs, he placed the devices interabdominally. He says he has gone back to placing them in that position, as opposed to extraperitoneally, and you "nearly never see infection." He says the article discounts the relation of surgical technique to infection. (The study group is placing the devices extraperitoneally behind the posterior rectus sheath.) "When we first started working with these devices, we didn't see infection, and we had the pumps in as long as the authors did. Whenever you have trauma in an area of contaminated blood, you get infection. The investigators got bacterial infections that were overtreated, and they got secondary candida with the antibiotics."

Frazier started working with an interabdominal LVAD in the 1970s. The device was envisioned then as a long-term permanent pump, not as a bridge to transplant. He and others wrote the original 1976 Request For Application to the Food and Drug Administration of the National Heart, Lung, and Blood Institute for a permanent, long-term implantable LVAD. "That's where the pumps manufactured by Thermo Cardiosystems Inc. [TCI] and Novacor came from," he says. "I worked on the TCI pump [now called HeartMate] since I was a medical student with Dr. DeBakey."

The initial pump his team worked on in the '70s was an interabdominal pump. Then the team thought it might fit outside the abdomen, and their physicians placed two in that position in 1986. Both developed hematomas and got infected. The patients' blood had to be thinned in order to put them on the heart-lung machine, and they bled. "The pump worked all right, but there was hematoma for that reason," he says, "so after the first two, we didn't put any more outside the abdomen."

TCI's device was the first pump designed as a bridge to transplant approved by the FDA in 1992. Frazier published the study upon which the FDA approval was based.[1] "There were no infections in

those patients," he says. "I put the pump inside the abdomen, and the drive line came out at six o'clock." He says the drive line was stiff, and he pulled it from outside the abdomen, then straight down the left side, and out. Since the pump itself was inside the abdomen, it was protected from infection.

"When I took those patients to transplant, it was very hard to cut the drive line out," says Frazier. "I could literally lift the patient off the table; the drive line was so well adhered. I had absolutely no infections."

The Novacor pump was placed by a physician at Stanford around that same time. "The Novacor pump is a much longer, bigger, heavier pump," Frazier says. "Initially it was placed in the abdominal cavity, but it was so long, it eroded into the transverse colon. The surgeon had to do a colostomy on that patient. From that point on, the Novacor LVAD was placed extraperitoneally. It was too long to place inside the belly." The surgeons developed a technique of making a long space for it extraperitoneally. The pump took up too much of the left side of the abdomen, and its drive line couldn't exit on the left side. "The drive line came out on the right side," he says. "It was tunneled to a long distance of tissue from the body of the pump at 3 o'clock."

As the TCI pump began expanding to more and more uses, surgeons found it much easier to put it in the extraperitoneal space, rather than in the abdomen. The drive line had to be brought out at 6 o'clock because it was too stiff to turn when placed in an extraperitoneal position. It came directly out of the bottom of the pump. "The drive line went outside the body very close to where the pump was, about two inches away. So you could only place it on the left side," he says. "As a result, blood collected and got infected. They all got infected. The explanation for the infection is very logical: Trauma and contamination equals infection."

Novacor has managed to bring the drive line out through longer tunnels on the right side, and as a result, Novacor has seen fewer infections, says Frazier.

A third device made by Thoratec was designed to be used as a temporary, intermediate pump and is placed outside the body. "But it has the advantage that it can be used for small patients," says Frazier. "There are size limitations for the pumps that are placed inside the body. The Thoratec device has a low infection rate." **(See photos of the devices, inserted in this issue.)**

(Frazier has no affiliation with the companies mentioned in this article.

***Silviu Itesci**, MD, and **Mehmet C. Oz**, MD, both cardiothoracic surgeons at Columiba-Presbyterian Medical Center in New York City and two of the* Lancet *study's authors, take issue with Frazier's commentary. Itescu states, "I am not sure what the relevance of [LVAD placement] is to the infection rate, but I would emphasize the exposure of the device to circulating elements of blood as being the primary etiology of increased susceptibility to infection." Oz adds, "I may be Bud Frazier's biggest fan, but he is incorrect. The TCI database revealed infections in both groups. How we define infections among centers varies, but over the long run, they are clearly the Achilles' heel of this procedure.")*

Reference

1. Frazier OH. Thermo Cardiosystems' left ventricular assist device. *Ann Thorac Surg* 1992; 54(5):1,019-1,020. ■

NEWS BRIEFS

Company recalls Rotablator systems

In August, Boston Scientific in Natick, MA, voluntarily recalled from the market its Rotablator RotaLink Advancer and RotaLink Plus rotational atherectomy systems.

According to **Larry Best**, a company spokesman, a part of the device responsible for securing the guidewire might not perform adequately and could be unsafe. He said the recall was due only to the advancer part of the device, which acts as an air turbine that spins the catheter, and was not due to the catheter itself. Boston Scientific said that it has undertaken a program to remedy the problem then will resume manufacturing the systems.

The latest recall follows last year's recall of the same company's NIR ON Ranger with Sox coronary stent system and more recent problems with its Discovery catheter. Company officials said that the RotaLink was associated with one patient death. They said that it has received six complaints

about the device, out of approximately 35,000 units on the market. ▼

Patients keep taking drugs after angioplasty

Investigators at the Mayo Clinic in Rochester, MI, found that many heart patients who undergo angioplasty to open blocked arteries still take chest pain medications six months later despite the fact that their chest pain is alleviated. Researchers reviewed more than 3,800 cases and found that of the 99% who reported improvement in chest pain symptoms after angioplasty, 39% still took beta-blockers, 36% still took nitrates, and 57% still took calcium channel blockers. "There may be good reasons for continuing to take these drugs in some cases," said David Holmes, MD, a Mayo Clinic cardiologist, in a statement. "But we believe that there is the potential to save people from the side effects, costs, and inconvenience associated with taking these drugs. We plan to develop guidelines to identify which patients need to continue taking medications after successful angioplasty and which patients can safely discontinue these drugs." The study was published in a recent issue of *Annals of Internal Medicine.* ▼

FDA gives nod to two new products

The Food and Drug Administration (FDA) gave clearance to Minneapolis-based Medtronic in August to market its Sigma pacemakers. According to the company, the Sigma line includes enhancements not typically found in other pacemakers, such as icon-based software for easier access to a patient's cardiac activity, worldwide clinician and patient telephone support, and a system longevity of more than 10 years.

The FDA also approved the Voyager Aortic IntraClusion Device for stopped heart procedures. The device, manufactured by CardioThoracic Systems in Cupertino, CA, is recommended for use in mitral valve replacement and repair and arterial bypass graft surgery. According to a company statement, the Voyager enables surgeons to perform four functions through one incision, including internal aortic occlusion, arterial perfusion, antegrade cardioplegia delivery, and aortic venting, providing a less traumatic way of eliminating blood flow to the heart than procedures that require multiple incisions and external cross-clamping of the aorta. ▼

HT awareness, treatment, control decline

The rates of high blood pressure awareness, treatment, and control continue to fall, according to a recent report in the September issue of *Hypertension*.

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Editor: **Dorothy Pennachio**, (201) 760-8700, (dorothy.pennachio@medec.com).
Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).
Executive Editor: **Park Morgan,** (404) 262-5460, (park.morgan@medec.com).
Managing Editor: **David Flegel**, (404) 262-5537, (david.flegel@medec.com).
Production Editor: **Ann Duncan**.

Editorial Questions

For questions or comments, call **David Flegel** at (404) 262-5537.

Investigators at the Mayo Clinic and Mayo Foundation in Rochester, MN, interviewed and measured blood pressure in more than 600 subjects, all white, randomly selected for participation in the Stroke Prevention: Assessment of Risk in a Community (SPARC) study. Overall, the team found that about half of both the men and women had blood pressures of 140/90 mm Hg or above, or reported a history of hypertension.

"This study illustrates a disturbingly low awareness and control of hypertension in a community that is socioeconomically prosperous, with easy access to both primary and tertiary medical care," the research team wrote. "Continued efforts are necessary to clarify the definition of hypertension, identify prognostic indicators for target organ damage, and heighten community awareness of the risks of increased blood pressure across the spectrum of severity." ■

SourceKit

• **Edward F. Philbin**, MD, Section of Heart Failure and Cardiac Transplantation, Henry Ford Hospital, Detroit. Telephone: (313) 916-2895. E-mail: ephilbi1@hfhs.org.

• **Gordon Ewy**, MD, Chief of Cardiology, University of Arizona Health Sciences Center, Tucson, AZ. Telephone: (520) 694- 0111.

• **Bobby Miller**, Supervisor, Optum Disease Management Program, Dayton, OH. Telephone: (937) 220-9114.

• **Douglas Chapman**, MD, Director, The Heart Failure Center, Alegent Medical Center, Omaha, NE. Telephone: (402) 572-3300.

• **Kenneth McDonagh**, MD, Medical Director, disease management program, AstraZeneca Pharmaceuticals, Wilmington, DE. Telephone: (302) 886-3000. E-mail: www.astrazeneca-us.com.

• **Evadell Tangquist**, RN, Patient Education Coordinator, Northwest Medical Center, Thief River Falls, MN. Telephone: (218) 681-4240, ext. 446.

• **Elgin K. Kennedy**, MD, Hillsborough, CA. Telephone: (415) 348-3647.

• **Santosh G. Menon**, MD, Division of Cardiology, University of Kentucky, Lexington. Telephone: (606) 257-3632.

• **David S. Roffman**, PharmD, BCPS, Associate Professor of Pharmacy Practice and Science, School of Pharmacy, University of Maryland, Baltimore. Telephone: (410) 706-3215.

• **Raymond Urbanski** , MD, Associate Medical director, AstraZeneca Pharmaceuticals, Wilmington, DE. Telephone: (302) 886-3000. E-mail: www.astrazeneca-us.com.

• **Silviu Itescu**, MD, Cardiothoracic Surgeon, Columbia-Presbyterian Medical Center, New York City. Telephone: (212) 305-2500. E-mail: si5@columbia.edu.

• **Mehmet C. Oz**, MD, Cardiothoracic Surgeon, Columbia-Presbyterian Medical Center, New York City. Telephone: (212) 305-4434. E-mail: mco2@columbia.edu. ■

CE objectives

After reading *CHF Disease Management*, health care professionals will be able to:

1. Identify management, clinical, educational, and financial issues relevant to the care of CHF patients.

2. Explain how those issues affect CHF patients and the providers who care for them.

3. Describe practical ways to solve problems commonly encountered by care providers in their daily activities. ■