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Some question study results on spironolactone treatment for CHF

Trial finds new drug reduces mortality, morbidity rates

Despite promising news for patients, there are concerns that cloud the unconditional acceptance of the new CHF drug spironolactone. Some physicians call into question the conclusions of a recent study of the drug, challenging the significance of the findings and their impact on CHF treatment. Some argue that the study participants are not representative of CHF patient profiles, while others say the dosing level of ACE inhibitors was too low.

However, not all feedback on the Randomized Aldactone Evaluation Study (RALES) of spironolactone, also called Aldactone, is negative. In support of RALES, many clinicians enthusiastically embrace the positive implications of the study and are optimistic about the drug that has been shown to reduce mortality and morbidity rates.

In a double-blind study following 1,600 patients from 15 countries, RALES results found that spironolactone reduced CHF patient mortality by 30% and re-hospitalization by 35% as compared to a CHF placebo group. By blocking the chemical signal aldosterone, which causes the heart muscle to lose its ability to pump, spironolactone keeps the heart muscle from becoming stiff and fibrotic.

Lead RALES researcher **Bertram Pitt**, MD, associate chair of internal medicine and professor of cardiology at the University of Michigan Medical Center in Ann Arbor, first became interested in studying spironolactone while lecturing on diuretics. In continuous studies, spironolactone proved to act not only as a diuretic, but also had effects on the endothelium as well as other vascular benefits. Prompted by the knowledge that ACE inhibitors did not suppress aldosterone completely and that aldosterone contributed significantly to fibrosis, Pitt approached G.D. Searle & Co. of Skokie, IL, and began to test spironolactone's safety.

In what was meant to be a three-year study, RALES was cut short after only two years because of the overwhelmingly positive results in respect to CHF patient mortality and morbidity. Although the report was due to be published in the *New England Journal of Medicine (NEJM)* on Sept. 2, 1999, the journal's editors surprised everyone by

making details of the study available on their Web site in July.

As a treatment option for CHF, spironolactone is usually prescribed as the fourth or fifth drug for most CHF patients. **(See *CHF Disease Management*, September 1999, pp. 102-105.)** According to David S. Roffman, PharmD, BCPS, associate professor at the University of Maryland School of Pharmacy in Baltimore, current standard CHF treatment options are an ACE inhibitor, a diuretic, a beta-blocker, and digitalis.

The medications that were taken in the study included loop diuretics, ACE inhibitors, digitalis, aspirin, potassium supplements, and beta-blockers. At baseline, the drug doses of ACE inhibitors given daily to the placebo group were Captopril 62.1 mg, Enalapril 16.5 mg, and Lisinopril 13.1 mg. At baseline, the drug doses of ACE inhibitors given daily to the spironolactone group were Captopril 63.4 mg, Enalapril 13.5 mg, and Lisinopril 15.5 mg.

Are older patients at risk?

Rosanne M. Leipzig, MD, PhD, clinical associate professor at Mount Sinai School of Medicine and the department of geriatrics and adult development at Mount Sinai Medical Center in New York City, responded to the findings of the RALES study in a letter to the editor of the *NEJM*.

Leipzig says she was particularly concerned for older patients and cautious about adding more drugs to a treatment plan before it was absolutely necessary. "My biggest concern is we don't maximize what folks are on before we add another drug. When you add another drug, you add all the possibilities of drug interactions. Spironolactone is for people who are on the usual three drugs who are still not responding at maximum doses of those."

"These are not benign drugs," Leipzig emphasizes. Referring to the traditional CHF drug therapy regimen, she explains her philosophy. "Give them the maximal dose and make sure they get the maximum benefit before adding other drugs to those."

She admits, however, that "spironolactone is a much more benign drug than beta-blockers, which have all sorts of potential complications. Compared to other drugs, spironolactone is cheap."

In another letter to *NEJM*, Karl T. Weber, MD, a cardiologist at the University of Missouri Health Services Center, said that when properly monitored, spironolactone should reduce the risk of death among patients with CHF. "The importance of aldosterone in CHF has been overlooked in recent years because ACE-inhibitor-related reductions in angiotensin were thought to eliminate aldosterone production."

Some physicians caution against the broad use of spironolactone when treating CHF patients. Also responding in a letter to the editor of *NEJM*, Robert J. Larkin, MD; Stephen A. Atlas, MD; and Thomas J. Donohue, MD; staff members at Hospital of St. Raphael in New Haven, CT, pointed out that the average blood pressure reported in the study was 122/75, which they claim indicates that the dose of ACE inhibitors was too low.

They reason that patients with diabetes may be at a greater risk for hyperkalemia when treated with the combination of spironolactone and a high dose of an ACE inhibitor, which is considered standard. Hyperkalemia is a condition caused by excessive amounts of potassium in the blood. **(See related story, p. 27.)** Another point of contention with the RALES results, as pointed out in their letter, asserts that although Type 2 diabetes is common in CHF patients, potassium levels in diabetic patients were not considered in the subgroup analysis.

In a follow-up letter to the *NEJM* editor, lead RALES researcher Pitt claims that the data revealed no difference in the effect of spironolactone on mortality between patients on higher doses and those on lower doses of ACE inhibitors.

Regarding CHF patients who also suffer from diabetes mellitus, Pitt explains that nearly 25% of

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RALES study patients had a history of diabetes mellitus at baseline. He also notes that none of the patients receiving spironolactone died of hyperkalemia.

Two practicing geriatricians from the Universite Catholique de Louvain in Belgium question the mean age of the RALES population. In their letter to *NEJM*, Dominique Vanpee, MD, and Christian Swine, MD, write that the mean age of the study population (65 ± 12 years) is very different from that of the patients (83 ± 8 years) in their own practice. Because the prevalence and incidence of heart failure increases with age, the physicians challenge the study's implications for a much older population.

Adding to the age factor, the Belgium physicians point out that older patients have lower levels of aldosterone as well as impaired renal function, despite apparently normal levels of serum creatinine. The Belgium doctors also caution that hyperkalemia may develop in these patients after only a single dose of ACE inhibitors or spironolactone.

Pitt counters that out of the 24 patients in the study developing hyperkalemia, nine of those patients were diabetic and four were 80 or older. He concludes that there was no significant difference in the occurrence of serious hyperkalemia between the treatment groups and the subgroup of patients with diabetes.

Pitt warns clinicians "to monitor potassium and not to give spironolactone to people with renal dysfunction using a 2.5 mg per deciliter cutoff." Despite challenges to the RALES findings, "the data are still very valid. I see a big change in people's thinking."

Gerald Glick, MD, professor of medicine at Rush Medical College in Chicago, applauded the RALES findings in a letter to *NEJM* as a major breakthrough in the understanding of the pathogenesis and therapy of CHF.

"In patients with congestive heart failure, the beneficial effects of spironolactone and beta-blockade are produced by means of the same final common pathway of suppressed aldosterone effects: Spironolactone blocks aldosterone at its effector site, and beta-blockade decreases the production of aldosterone. Such a formulation would help to explain the apparently counterintuitive finding that beta-blockade, which is a negative inotropic intervention, has salutary effects in patients with congestive heart failure," he wrote.

Glick prefers the use of spironolactone. "It may be preferred to use spironolactone rather than starting with a beta-blocker to get to the same culprit, namely aldosterone, and avoid bad side effects," he says.

Glick reports no problems in the short term in prescribing spironolactone for CHF patients. "It's a valuable addition to usual drug therapy."

To clarify the debate over population concerns expressed by physicians who questioned the study's participants as not representative of typical CHF profiles, those excluded from RALES were patients with these conditions:

❒ primary operable valvular disease;

Hyperkalemia can pose threat for CHF patients

One of the biggest threats for CHF patients taking spironolactone, also known as Aldactone, is hyperkalemia, a condition caused by excessive amounts of potassium in the blood. Symptoms include diarrhea, nausea, muscle weakness, and heart irregularities.

"It can be a very serious threat," says **Rosanne M. Leipzig**, MD, PhD, clinical associate professor at Mount Sinai School of Medicine and the department of geriatrics and adult development at Mount Sinai Medical Center in New York City. "You get EKG changes, arrhythmia, or no rhythm."

Leipzig encourages clinicians to monitor a patient's potassium level carefully, defining levels of potassium that are too high. "The lab will tell you over 5 mmol per liter. Many of us will tell you 5.5 mmol per liter is all right. You start playing [with fire] when you go over that."

In the Randomized Aldactone Evaluation Study (RALES), a double-blind study conducted to analyze the effects of spironolactone on CHF patients, hyperkalemia occurred in 10 patients in the placebo group and 14 patients in the spironolactone group. Conclusions in the RALES study claim that at doses of 12.5 mg to 25 mg daily, spironolactone is effective in blocking the aldosterone receptors. Serious hyperkalemia occurred most often with doses of 50 mg or greater.

Patients in the spironolactone group took 25 mg of Aldactone once a day for two months. As long as there were no signs of hyperkalemia, the dose could be doubled after that if the CHF symptoms worsened. In cases where potassium levels got too high, it was suggested that the treating physician first adjust the other medications to correct the problem. If that did not help, then the dose of spironolactone could be reduced 25 mg once a day. ■

❒ congenital heart disease;
❒ unstable angina;
❒ primary hepatic failure;
❒ active cancer, or any life threatening disease (other than heart failure);[1]
❒ a serum creatinine concentration of more than 2.5 mg per deciliter (221 mmol per liter);
❒ a serum potassium concentration of more than 5.0 mmol per liter.

Reference

1. Pitt B, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341:709-717. ■

Molecular 'glitch' can lead to heart failure

Disorder costs $10 billion per year in medical care

A recent study by scientists at Johns Hopkins University in Baltimore and Queen's University in Kingston, Ontario, indicates that an abnormal form of the protein troponin I (TnI), part of a three-prong, regulatory "switch" that activates heart muscle contraction, is responsible for causing myocardial stunning, a common but potentially fatal form of acquired heart failure that affects almost all patients who have undergone open-heart surgery.

A function of the blood supply to the heart being shut down and then restored, stunning effects patients, especially children, who have had to be placed on heart/lung machines. Also highly susceptible are adult heart attack victims whose blood supply has been restored through drugs or angioplasty.

To make the heart of patients with stunning contract more forcefully, clinicians generally place them on an inotrope drug such as epinephrine for a day or two, until their heart begins to contract more forcefully.

Distinguished by a general weakness in the heart muscle, stunning is a frequent complicator of coronary artery disease. Present in up to 10% of heart patients, it can continue anywhere from hours to days. Though usually a temporary condition, some patients experience complications and die. Consequently, victims require careful monitoring, and must be hospitalized following surgery in intensive care for 24 hours. It's hardly surprising that the disorder costs the United States an estimated $10 billion per year in postoperative medical care.

The study, which involved injecting mice with faulty TnI, marks the first time it has been shown that a problem or "glitch" at a molecular level can lead to any type of acquired heart failure. If researchers' findings are borne out in humans, clinicians not only could gain valuable insight regarding treatment of the disorder, but could be well on their way to eliminating myocardial stunning altogether.

"Congestive heart failure is the leading cause of hospitalization in America in people over 65 years of age. Although many of those hospitalizations are associated with heart attacks, a large number also are related to cardiomyopathies such as myocardial stunning," says **Charles Inman Wilmer**, MD, director of angioplasty, cardiac disease specialist, and director of data management at the Fuqua Heart Center of Piedmont Hospital in Atlanta.

"A study such as [this] may well link what causes the heart to become hypocontractile, dysfunctional, and dilate, leading to heart failure and atrial fibrillation," he says. "If we can find out how to make patients less susceptible to this condition or discover ways to better treat those who do have it, then we can decrease the need for hospitalization for heart failure and cardiac transplants."

Part of a closely interacting complex of troponins that plays a vital role in heart contraction, TnI could be likened to a light switch, in that it is the protein which is responsible for switching the heart muscle from a relaxed position to a contracted one. "If the switch is down, the muscle is relaxed; if it's up, it is contracted. If part of that switch is broken, it's not going to work as well," says **Jennifer Van Eyk**, MD, one of the research participants and an assistant professor at Queen's University's department of physiology.

Data for the study was gathered over a period of 14 years. From earlier experiments, the researchers already were aware that animal models of stunning have damaged TnI, which, in addition to being shorter than usual, also contains fewer amino acids than usual. To determine whether TnI was, in fact, the actual cause of stunning, the team set out to mimic the change that occurs in abnormal human TnI, by creating a transgenic mouse model.

Cloning genes from the defective human protein, they injected the substitute gene into the mice. "Being able to work with lab animals into

which we actually were able to incorporate the defect, gave us an advantage over past studies on acquired disorders, where researchers had to attempt by trial and error to reproduce the physiology within the animal," says **Anne Murphy**, MD, cardiologist at Hopkins Children's Center, who lead the research team.

As the major proteolytic product of TnI in stunning is missing the 17 COOH-terminal residues, they created three independent lines of transgenic mice expressing TnI in the heart driven by the murine a-myosin heavy chain promoter.

The resultant findings, published in the Jan. 21, 2000 issue of the journal *Science*, corresponded almost to the letter with what the research team had expected: Heart cells deprived of oxygen experience a sudden increase in calcium. That high calcium level, in turn, trips the production of enzymes that are responsible for cleaving proteins.

Some 20% of the TnI in the mice studied turned out to be the shortened form. Transgenic mice also exhibited cardiac enlargement and echocardiography. In addition, in a classic response to weakened muscle, they developed ventricular dilation, as well as diminished contractility and reduced myofilament calcium responsiveness. "The force their heart muscles exerted also was far below normal," says Murphy.

"The mice resembled humans with myocardial stunning in any way that we could measure. The study not only demonstrates proof of hypothesis — that the partial breakdown in troponin actually has a causal role in bringing about cardiac dysfunction — it also provides a model in which clinicians can test a variety of new therapies," she says.

Along with revealing that as the change in TnI occurs acutely, "there's a good chance" stunning can be cured, another, highly significant implication of the study is TnI is present in a number of diseases, including, in all probability, angina, Van Eyk says.

The study also includes data dealing with human heart patients who allowed blood specimens and very small samples of heart muscle to be extracted from them, both prior to bypass surgery and 15 minutes after the heart was restarted. Blood samples also were taken one and three days following surgery.

In addition to supporting the researchers' hypothesis that patients experienced "some" breakdown of TnI, "What was [different] is that some sort of injury to their heart tissue had occurred prior to surgery," Murphy says.

Glorianne Ropchan, MD, a cardiac surgeon at Queen's University, who also was a member of the research team, sees the study as being especially timely. "Before this, no one had looked at the role of troponin in heart surgery at all. At a time when we're treating older and older people with sicker and sicker hearts, we are hoping we'll be able to use this technique, not only to evaluate how well we protect the heart, but also to make improvements in how we do protect the heart.

"We are banking on the findings being useful, not only in helping investigate modality in order to diagnose problems, but also in helping monitor patients and tailor their therapies to their own particular needs."

John Odell, MD, head of surgery at Mayo Medical School's section of thoracic and cardiovascular surgery in Rochester, MN, concurs that the findings, if correct, are exciting. "Like a lot of disease processes, myocardial stunning is one that we really haven't understood. It's interesting that they have found a molecular change in troponin that occurs in the heart's contraction. Whether we ever will be able to form a drug that actually prevents myocardial stunning, I'm not sure. But, once you've located a problem, there's no question that it's that much easier to focus on the best ways of dealing with it." ■

System offers clinics daily CHF monitoring

Automated data prevent hospitalizations

While third-party monitoring of congestive heart failure (CHF) patients is better than no monitoring, a new technology offers a way to bring it in-house with potentially impressive quality outcomes.

Mary Jo Macklem, RN, nurse clinician in the CHF Clinic of the Park Nicollet Clinic in Minneapolis, uses the system, Cardiocom, for daily patient feedback. "We can quickly review [patients'] current weight, symptoms, medications, and trends on the screen and know specifically who needs our assistance."

By using the Cardiocom CHF management program, at $50 a month per patient, health care organizations can eliminate outside monitoring fees of at least $150 a month per patient, according to **Daniel Cosentino**, president of Cardiocom, based in Excelsior, MN. Daily monitoring also

offers a high probability of preventing hospital readmissions, which average about $7,000 per episode.

Cardiocom entered the commercial market in October 1999, and already it's been installed in health care systems around the country, Cosentino says. Patients welcome the ease of use and the closer ties with their nurses. Soon, the company will expand the program to include blood-pressure and pulse-rate monitoring.

The basis of the system is a Telescale placed in the patient's home. It connects into an electrical outlet and the phone jack. Equipped with a computer chip, the Telescale transmits the patient's weight to the clinic's computer via the phone line. It also sends the patient's answers to 12 questions regarding key signs of an impending CHF crisis. Some of the questions cover medication compliance, shortness of breath, and decreased urine output. It takes patients roughly two minutes to step on the scale, dial the clinic, and answer the wellness questions. They have their choice of communication modes: voice or a numeric or Braille key pad.

"Clinicians only spend time with patients who need it the most," Cosentino says. "The daily monitoring is better than random calls that can miss patients who are headed for a crisis."

Patient data reaches the provider within 30 seconds. The system records the data and alerts staff about patients requiring intervention. It compiles customized reports to mesh with the user's existing record-keeping system. Routine reports include:

- individual patient summaries;
- trend reports on the clinic's CHF patient population;
- hospital and emergency room admissions.

Macklem uses Cardiocom for patients with the highest risk of readmission. "Most of them are elderly people who had compliance issues or who have bad vision and could not see a regular home scale. Before we introduced Cardiocom, they would not have weighed themselves every day. If they only weighed themselves once a week, they could have gone into a crisis before they weighed themselves again."

The initial concern at Park Nicollet centered on the patients' acceptance of and compliance with daily monitoring. As it turned out, "Most of the patients are thrilled with the Telescale," says Macklem. "Some even say it's like having a home visit by us each day. We can catch a change in symptoms before a crisis develops. When we call the patient, we have the footwork done."

The ease of use that patients enjoy extends to providers as well. She says the system was up and running within a few days after the phone lines were installed.

Cost details

Users pay $50 per month for each patient monitored. The minimum is 100 patients, or $5,000 a month. Here's what the fee covers:

1. Cardiocom software with free upgrades as they become available. The software can be integrated into the provider's existing network. Data are generated in a Microsoft Access database and are compatible with other commonly used software packages.

2. A computer with accessories, including the required modems, a 17" color monitor, a rewritable and recordable CD-ROM drive, and a laser printer. As the patient population increases, additional modems and memory are provided.

3. A Telescale for each patient in the program. Shipping fees for the scale are extra. The amount varies. Sometimes the delivery goes directly to patients' homes. Other providers request bulk shipment to a hospital or clinic for distribution to patients.

4. Installation and on-site training. One condition prospective users need to consider is that Medicare does not reimburse for the monitoring, Cosentino acknowledges. "But we're working on that." ■

Small hospital launches high-tech stroke solution

Program includes specialists via Internet

If administered within three hours of a stroke, the drug t-PA (tissue plasminogen activator) can reverse stroke damage that would turn an active person into an invalid. But success depends on speed and teamwork of the caliber you might expect in an Olympic relay race. "Time is brain," says **John Hartness**, MD, chairman of the stroke treatment improvement committee at Union Regional Medical Center (URMC) in Monroe, NC.

T-PA assessment and therapy is a process in which minutes count and handoffs are numerous. "I can't emphasize the team effort enough,"

Hartness explains. "If any one person is not there to do his job, it breaks down.

"The sooner t-PA starts, the greater the benefits. But after three hours [from the time of the stroke], there's more harm than good," he stresses.

That time frame is a distinct challenge for URMC. The 160-bed hospital's catchment area is largely rural. When specialists are needed, URMC's clinicians usually turn to the larger medical centers in Charlotte, 30 miles away. Monroe isn't a place where you'd look for adoption of a revolutionary and highly complicated therapy within months of its introduction.

But URMC was upgrading its stroke care procedures in 1995 as Hartness kept one eye on the t-PA clinical trials. When the guidelines emerged in December that year,[1] the hospital was positioned to consider them.

Candidates for treatment are people who sustain an ischemic stroke caused by a blood clot that becomes lodged in the brain or in an artery supplying blood to the brain. Administered intravenously, t-PA dissolves clots that block blood flow. It does not work for hemorrhagic strokes, which are caused by a ruptured blood vessel in the brain.

'Country cousins' teach city docs

An interdisciplinary committee included members from the area's stroke care network. Represented were radiology; lab; surgery; physical, occupational, and speech therapy; nursing; social services; intensive care; and the emergency department (ED), as well as the local family practitioners. The committee created technological links with the offsite specialists. "We had to tweak our processes so we wouldn't lose patients to the time barrier," Hartness recalls. The t-PA protocol went into use in June 1996.

The ED orchestrates the moves:

• Paramedics make a heads-up call to the ED when they are dispatched to a possible stroke episode. In transit, they assess the patient for signs such as facial paralysis, general weakness, and impaired speech skills. If possible, they draw a blood sample to shave minutes off procedures in the ED.

• ED staff, meanwhile, clear a large front room to accommodate the stroke care team.

• Upon receiving a call from the paramedics, ED staff telephone or page the radiologists, neurologists, and neurosurgeons, alerting them to watch for X-rays and CT scans transmitted electronically, usually over the Internet.

• Word goes out to URMC's lab and radiology technicians to stand by for tests.

• If a blood sample is not ready upon arrival, the ED nurse draws it within 10 minutes, or calls a physician if it has to be drawn from a large blood vessel. Testing rules out hypoglycemia.

• A nurse administers a stroke scale to determine the extent of brain injury.

As the specialists in Charlotte learned more about t-PA through their consultation on URMC's cases, they spread the word to their peers. Soon, Hartness and his team received invitations to come to Charlotte and tell their story.

"Here we were, the country cousins, telling the city doctors about our new stroke treatment program! It was a surprise to all of us that we were using t-PA before the centers in Charlotte. We usually expect it to be the other way around," he says.

URMC takes care of about 150 stroke episodes each year. Here are a few of their t-PA statistics:

• The therapy has been administered 11 or 12 times, according to Hartness.

• Average arrival-to-CT-read cycle is under 45 minutes.

• T-PA starts in less than 60 minutes.

• More than 50% of the t-PA recipients experience complete, or nearly complete prevention of long-term brain damage. In the clinical trials,[1] patients treated with intravenous t-PA were at least 30% more likely to have minimal to zero disability three months later.

Treatment costs are low

Recently, in a new URMC record of 25 minutes for arrival-to-CT-read, t-PA spared a 91-year-old man from spending the rest of his life paralyzed and bedridden. It saved his family the ordeal and expense of moving him to a nursing home. He didn't even need rehab after he left the hospital.

Economically, t-PA is a bargain when compared to the cost of long-term disability, Hartness explains. His point is clear in the case of another URMC stroke patient.

The age 40-something truck mechanic suffered a severe ischemic stroke but arrived in time for t-PA. He was able to walk out of the hospital and go back to work after a brief recovery period. "In that case, we saved two breadwinners — the mechanic and his wife, who would have had to quit working to take care of her husband," Hartness notes.

Hartness credits part of URMC's complication-free track record to conservative adherence to the time and patient profile guidelines. "About 80% of the hemorrhaging from the drug comes in cases where it is given outside of the guidelines. But we've also been very fortunate," he concedes. "Sooner or later, we will experience complications." Even with timely administration, the drug can cause cerebral hemorrhaging for some patients.

In the clinical trials, 6.4% of the t-PA recipients had brain hemorrhage; only 0.6% of the placebo recipients had similar problems. Three months post-stroke, mortality was 17% in the t-PA group and 21% in the placebo group. Hartness emphasizes the cerebral hemorrhage risks from using the drug more than three hours after the stroke usually outweigh potential therapeutic benefits.

Early in the stroke care initiative, the emphasis was on coordination of the clinical response, he says. "Now we're ready to get the information to the community that there is something we can do for strokes, if they can get in here fast enough." The local news media have cooperated by running newspaper, radio, and television stories. Community groups sponsor educational programs. "People are starting to get the point that they should act fast when they see the symptoms in themselves or in their loved ones," Hartness notes.

Eventually, URMC will work with the schools to introduce stroke symptom recognition into the science curricula. The goal is for children to carry the message home. With that goes the never-ending emphasis on prevention. According to Hartness, smoking is quite prevalent in the area. His observation is confirmed by a recent study[2] conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in Atlanta. Hypertension is disproportionately high among residents of southern states, especially middle-aged, non-Hispanic white men living in nonmetropolitan regions.

Doing what works locally

The stroke treatment program at URMC grew out of the VHA's Clinical Advantage initiative. VHA is a nationwide network, based in Irving, TX, whose membership comprises community-owned health care organizations and physicians. Clinical Advantage is a member resource for converting clinical knowledge into patient care practices.

The hallmark of the effort, according to VHA vice president for clinical affairs, **Stacy Cinatl**, is the interplay between standardization and flexibility. One set of practices or objectives cannot work for all VHA organizations, as the membership runs the gamut from academic medical centers to rural clinics.

Available care improvement programs include: Acute myocardial infarction, medical error reduction, and congestive heart failure. The theme is "Here's the science, find ways to make it work in your organization."

The Clinical Advantage stroke care program involves five domains:

1. **Coordination of care**
2. **Saving brain**
3. **Preventing complications**
4. **Secondary stroke prevention**
5. **Restoration of function**

Participating institutions learn how to apply proven change methodologies like rapid-cycle change as taught by the Institute for Healthcare Improvement in Boston, and PICOS, the QI improvement process introduced by General Motors in Detroit, as applied in the manufacturing world. Collaboration and information-sharing take place through VHA-sponsored chat rooms monitored by experts, and shared literature reviews, case studies, and care techniques.

Are primary care facilities next?

The experience at URMC makes a strong case for the potential of applying complex medical processes in primary care facilities. The keys are strict adherence to proven guidelines and creative partnering of human and technical resources.

"Everybody has to look at how resources are being used in their institutions. Start asking 'Who could learn new skills? How can we find the consultants to fill in for our knowledge limitations?'" Hartness suggests. "At first people here didn't think they could learn what they needed to know to use t-PA, but the enthusiasm grew when they saw that we got good results from tweaking our work processes and applying the drug protocol. Now, everyone is very proud of our success and nobody wants to be the reason it doesn't work."

Cinatl predicts that consumer demand will grow as people learn about t-PA through local media and articles like the one in a recent issue of *Good Housekeeping*.[3]

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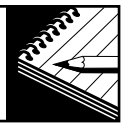
GUEST COLUMN



Does aspirin interfere with benefits of ACEI?

By **Aileen Luzier**, PharmD
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The impact of aspirin on the therapeutic benefits of angiotensin converting enzyme inhibitors (ACEI) has been a topic of intense research for nearly two decades. ACEIs are considered first-line therapy in the treatment of heart failure and are recommended for the prevention of heart failure in post-myocardial infarction patients.[1,2]

Aspirin is widely recommended for both primary and secondary prevention of cardiovascular events, particularly in ischemic heart disease — a significant etiologic factor in heart failure.[3,4] Thus many patients are appropriately treated with both of these agents. However, there is a growing body of evidence that questions the simultaneous use of ACEIs and aspirin.[5]

The weight of some recent studies supports the presence of an interaction between these agents. However, the clinical relevance of the interaction remains unanswered. The Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH) is a large clinical trial currently in progress that will provide important insight into this issue. Until the answers are available, the clinician should be aware of the potential for aspirin to attenuate the beneficial effects of ACEIs. However, given the weight of evidence that supports the use of ACEI and aspirin therapy, clinicians are obligated to use the agents together in appropriate patients. Clinicians should be encouraged to titrate ACEIs to doses recommended by current guidelines. As lower doses of aspirin theoretically may interfere less with the effects of ACEIs than higher doses, it may be prudent to use smaller doses of aspirin (80 mg to 160 mg daily) for the prevention of cardiovascular events in these patients.

The evidence for a pharmacologic interaction between ACEIs and aspirin is in the form of theoretical mechanistic considerations, animal data, small drug interaction studies, and clinical trials.

Theoretical

In addition to inhibiting the formation of angiotensin II, ACEIs also inhibit the enzyme kininase II that is responsible for the degradation of kinins. This results in potentiation of the biologic effects of kinins and enhances the production of prostaglandins.

The primary mechanism of aspirin is to decrease platelet aggregation through the inhibition of prostaglandin (and thromboxane) production. As the two agents have opposite effects on prostaglandins, concern has been raised that aspirin may nullify the beneficial effects of ACEIs.

This interaction has greater significance with the recent understanding of the biologic role of kinins in the regulation of vascular tone, myocardial contractility and ventricular remodeling, modulation of neuroendocrine activation, and influence over the response to tissue injury or stress.[6,7]

Animal studies

The interaction of aspirin and ACEIs has been investigated in animal models. Aspirin reduced endothelium-dependent relaxation induced by captopril in the canine model.[8]

The role of prostaglandins in maintaining renal function has been clearly shown; however, conflicting results have been reported on the effects of aspirin on renal responses in ACEI-treated animals.[9,10] The beneficial effects of ACE inhibition, and specifically the role of bradykinin on ventricular remodeling — the hallmark of heart failure — also has been studied in animal models. Aspirin administration was shown to

attenuate the beneficial effects of ACEIs on post-myocardial infarction ventricular remodeling.[11]

Interaction studies

Several small studies in heart failure patients have investigated the effects of the combination of aspirin and ACEIs on hemodynamics, renal function, and pulmonary dynamics. A 350 mg dose of aspirin abolished enalapril-induced decreases in left ventricular filling pressures, systemic and vascular resistances, and increases in cardiac output.[12] Subsequent studies also showed decreased vasodilatory activity of ACEIs with concomitant aspirin.[13,14]

In contrast, several studies that only assessed peripheral hemodynamics (rather than central hemodynamics or cardiac output) did not demonstrate an interaction. Aspirin did not influence the mean blood pressure response to 25 mg of captopril or 5 mg to 10 mg of enalapril when administered at a dose of 236 mg and 250 mg, respectively.[15,16] Other investigations have demonstrated that co-administration of aspirin and ACEIs can be detrimental to renal function in patients with heart failure.[17,18]

A series of studies by Guazzi and fellow researchers has investigated the interaction in heart failure patients using pulmonary function testing. Several issues support this methodology. The lungs are an important site for prostaglandin production, release, and metabolism, and ACEIs improve pulmonary function and thus exercise performance in heart failure patients, an effect thought to be due to prostaglandin activation. Guazzi has demonstrated a counteracting effect of aspirin (325 mg) on ACEI-induced improvements, assessed through changes in exercise tolerance, pulmonary carbon monoxide diffusion, and oxygen consumption.[19,20]

The interaction was not observed with losartan, an angiotensin II antagonist that does not influence bradykinin or prostaglandin production. In addition, the interaction was demonstrated with chronic dosing of the agents, in contrast to the acute dosing used by many of the previously mentioned studies.

Clinical trials

Subanalyses of large clinical trials also have suggested a negative interaction between aspirin and ACEIs. Enalapril did not improve survival among a subgroup of heart failure patients taking aspirin in the SOLVD trial.[21]

Similarly, patients in the CONSENSUS II trial who were taking aspirin had a smaller mortality benefit from enalapril compared to those who were not taking aspirin.[22] In contrast to this data, a subanalysis of the Benzafibrate Infarction Prevention (BIP) study observed lower five-year mortality in coronary artery disease patients who

Expert commentary

David S. Roffman, PharmD, BCPS, associate professor at University of Maryland's School of Pharmacy in Baltimore and a therapeutic consultant for the cardiac care unit in the university's medical system, has a slightly different take on the data discussed by Aileen Luzier, PharmD. **(See article, p. 33.)**

"My bias is that the degree of the significance of this interaction is not fully understood," Roffman says. "Dr. Luzier states that upfront in talking about the one study that may provide some more evidence one way or the other.

"I'm not sure that particular trial will provide all the answers, because it's not a head-to-head study of small dose vs. large dose in the face of ACEIs [angiotensin converting enzyme inhibitors].

"But I think the conclusion I would make at this point, in terms of clinical utility of these two drugs together, is that the weight of the evidence of the effectiveness of aspirin and the effectiveness of ACEIs in people with coronary disease and CHF is so clear that even if there is a potential reduction in the benefit, we are obliged to still use the two drugs together.

"There are not enough data that say the reduction of the effect of ACEIs by aspirin is significant enough an outcome that we shouldn't do this. The question is, 'Should we or should we not?'

"If there is a dose-related argument here, which I admit may be part of the reason the data are a little confusing, given what we know about the beneficial effects of aspirin and the beneficial effects of ACEIs in people with heart failure of ischemic etiology, there is little choice but to use both drugs." ■

were treated with both aspirin and ACEIs.[23]

Lower mortality (24% vs. 34%, p=0.001) was also observed in a subgroup of patients with congestive heart failure who received the combination vs. those who only received ACEI therapy.

Why discrepancies in literature?

There may be several explanations for the discrepancies in the literature. The dose of aspirin used may influence the results. Aspirin exhibits dose-dependent inhibition of platelet thromboxane A2 synthesis. At low doses (£100 mg / day) aspirin selectively inhibits platelet thromboxane A2 synthesis.[24]

Higher doses (³160 mg / day) reduce renal and systemic prostaglandin synthesis.[25] If prostaglandins are partially responsible for the clinical effects of ACEIs, higher daily doses of aspirin should be more prone to blunting their effects than lower doses.

Differences may be related to the different populations studied, as the role of kinins may be more significant in post-myocardial infarction and heart failure patients (CONSENSUS II and SOLVD, respectively) than in chronic ischemic heart disease (BIP registry). Also, it must be emphasized that the clinical trial data presented are retrospective subanalyses and caution must be exercised in their interpretation.

At this time, there are considerable data to support the presence of an interaction between these agents. However, it is difficult to draw any conclusions about the clinical significance of the interaction.

Until answers are provided by large controlled clinical trials of long-term therapy that directly addresses this question, clinicians are obligated to use the agents concurrently.

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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. ■