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Even though tolvaptan failed to reduce mortality or morbidity, 'I have something new to offer patients,' said Dr. Marvin A. Konstam.

## Novel Drug Eases Symptoms of HF

BY MARY ANN MOON  
Contributing Writer

NEW ORLEANS — The investigational agent tolvaptan relieves core symptoms of acute decompensated heart failure without inducing adverse effects, but has no impact on all-cause mortality, according to researchers in the EVEREST clinical trials.

The oral vasopressin antagonist also had no effect on the combined end point of cardiovascular mortality or subsequent hospitalization for worsening heart failure, study investigators reported at the annual meeting of the American College of Cardiology.

One day into therapy, after one dose, significantly more patients reported improvement in dyspnea scores after taking tolvaptan, compared with placebo. Changes in body weight due to improvements in fluid overload were also significant at day 1 and day 7 of therapy, and were sustained during a median 9.9 months of follow-up, study investigator Dr. Marvin A. Konstam reported at the meeting.

"I, as a clinician, can say I have something new to offer patients," said Dr. Konstam, chief of cardiology and professor of medicine at Tufts–New England Medical Center, Boston, in a press conference. However, Dr. Konstam acknowledged he was "disappoint-

ed" that the agent failed to reduce mortality or heart failure–related morbidity either during hospitalization or at 1-year follow-up.

In an editorial accompanying simultaneous publication of trial data, Dr. Clyde W. Yancy of Baylor Heart and Vascular Institute, Dallas, applauded the "noteworthy findings" on symptomatic improvement, but said the lack of impact on global clinical status, subsequent hospitalizations, or mortality must temper enthusiasm for the EVEREST findings.

"To the extent that it helps patients do better, that's a good thing," he said.

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## Medical Therapy As Good as PCI in Stable Disease

COURAGE shows medical strategy works.

BY BETSY BATES  
Los Angeles Bureau

NEW ORLEANS — Percutaneous coronary intervention adds no benefit to optimal medical therapy for extensive but stable coronary artery disease, according to results of the COURAGE trial, and that finding has set off a debate about the medical necessity of PCI in many patients.

As an initial management strategy, PCI added to optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial did not reduce the rates of death, nonfatal MI, or hospitalization for acute

coronary syndromes during a mean follow-up of 4.6 years, Dr. William E. Boden reported at the annual meeting of the American College of Cardiology.

"I think we can say with some degree of conviction that if you opt for an initial strategy of medical therapy, you are not putting patients in harm's way," Dr. Boden said at a press conference preceding his formal presentation.

"What was remarkable was how well optimal medical therapy did in this trial."

At the press conference, Dr. Boden said, "Historically, there has been an unproven assumption that if you have significant

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## Aliskiren, First in Class, Approved for Hypertension

BY DIANA MAHONEY  
New England Bureau

For the first time in more than a decade, there's a new weapon available for the battle against hypertension.

Aliskirin, the first in a new class of orally administered drugs called direct renin inhibitors, received Food and Drug Administration approval last month on the basis of the results of multiple clinical trials showing its safety and efficacy alone and in combination with established antihypertensive drugs.

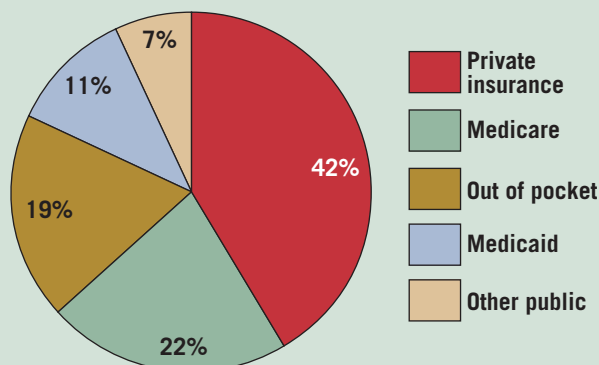
Like other antihypertensive

agents, aliskiren (Tekturna) targets the renin-angiotensin system (RAS), which plays an important role in blood pressure regulation, water and salt balance, and tissue growth control. It differs from other agents by targeting the RAS at the point of activation by inhibiting renin in the synthesis of angiotensin I and II, leading to reductions in plasma renin activity, according to a statement issued by Novartis, the manufacturer of the drug. (ACE inhibitors and angiotensin receptor blockers disrupt feedback inhibition of renin release from the kidney, and di-

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### VITAL SIGNS

#### More Private Insurance Dollars Were Spent On Prescriptions in 2006



Total Spent on Prescriptions: \$213.7 billion

Note: Percentages do not add up to 100 because of rounding.  
Source: Centers for Medicare and Medicaid Services

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# No Slowing of Disease Progression

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thing,” said Dr. Yancy at the ACC press conference. He called the lack of safety signals in the follow-up study “comforting.”

But neither physician suggested that the trial points to an improvement in the progression of heart disease in a patient group Dr. Konstam termed “daunting.”

He specifically said it should not be used indiscriminately or indefinitely in patients with worsening heart failure, although he said he might reinstate it if a patient’s fluid overload worsened upon discontinuation of short-term use of the drug.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial comprised two identical short-term trials (required to meet regulatory requirements for two independent confirmatory studies) and one long-term safety trial. All were conducted at 359 sites in North America, South America, and Europe between 2003 and 2006, and all were funded by Otsuka Inc., the drug’s manufacturer.

In the two short-term trials, the clinical effects of tolvaptan were compared with those of placebo when added to optimal medical therapy during hospitalization for acute decompensated heart failure (HF) with impaired left ventricular ejection fraction (LVEF). In trial A, 1,018 subjects were randomly assigned to receive tolvaptan and 1,030 to receive placebo, while in trial B the numbers were 1,054 and 1,031, respectively, wrote Dr. Mihai Gheorghade of Northwestern University, Chicago, and associates (JAMA 2007;297:1332-43).

In both short-term trials, patients in the active drug group showed decreases in body weight as early as the first day of treatment, which persisted as long as the drug was administered (7 days or until hospital discharge, whichever came first). Dyspnea and rales, fatigue, jugular venous distension, and pedal edema all improved in a similar fashion.

Tolvaptan improved or normalized serum sodium concentrations in hyponatremic patients. It also allowed all patients to reduce their use of furosemide.

“These positive effects were achieved without adversely affecting heart rate, blood pressure, or serum electrolytes,” and there was no adverse effect on liver or renal function, the investigators wrote.

The long-term trial was primarily designed to assess the drug’s safety in the same patients from hospital discharge through 1-year of follow-up. Unlike other agents previously used to treat the disorder, “Long-term tolvaptan treatment had no effect, either favorable or unfavorable, on all-cause mortality or the combined end point of cardiovascular mortality or subsequent hospitalization for worsening HF,” wrote Dr. Konstam, the lead investigator in this trial, and his associates.

“Overall, the benefits on short-term symptoms, together with the demonstrable short-term and long-term safety profile, support the usefulness of tolvaptan treatment for patients manifesting volume overload during hospitalization for HF,” they wrote (JAMA 2007;297:1319-31).

Tolvaptan’s safety record stands in contrast to nesiritide, which has been associated with increased mortality and renal dysfunction two meta-analyses.

In his editorial comment, Dr. Yancy noted that in the short-term trials, improvements in dyspnea and edema with tolvaptan were “modest” relative to placebo and were mainly driven by decreases in

body weight. There were no differences in global clinical status, nor in rates of recurrent HF hospitalization or mortality. And rates of adverse events—especially thirst and dry mouth—were “high” in all three EVEREST trials, he said.

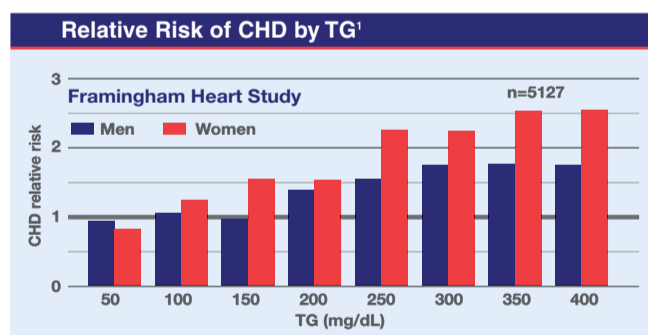
Moreover, the trial results apply only to patients with profiles like those of the study subjects, and cannot be extrapolated to other groups such as heart failure patients with preserved left ventricular ejection fraction and nonhospitalized heart failure patients.

Betsy Bates contributed to this report from New Orleans.

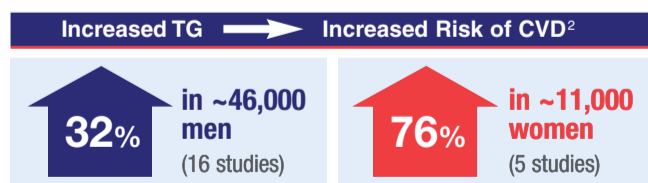


## Elevated Triglycerides Make a Difference in Women’s Risk of CHD

While great attention and clinical efforts have been directed toward LDL-C-lowering, the Framingham Heart Study 30-year follow-up clearly showed that elevated triglycerides (TG) are also associated with an increased relative risk of coronary heart disease (CHD) — especially in women.<sup>1</sup>



In addition, meta-analyses demonstrated that every 1 mmol/L (89 mg/dL) increase in TG increased cardiovascular disease (CVD) risk by:<sup>2</sup>



### CHD is the #1 Killer of Women

The effect of elevated TG in women is important to keep in mind in view of the fact that CHD is the single leading cause of death among American women, claiming nearly 500,000 lives each year.<sup>3</sup> Menopausal women are particularly at risk, with CHD rates 2 to 3 times those of women the same age who are premenopausal.<sup>3</sup>

### CHD Risks With Diabetes or Metabolic Syndrome\* in Women: Role of TG and HDL-C

Of the estimated 16 million Americans with diabetes, more than half are women.<sup>4</sup> In women, diabetes is a powerful risk factor for CHD, increasing CHD risk 3-fold to 7-fold compared to a 2-fold to 3-fold increase in men.<sup>5</sup> It has also been shown that metabolic syndrome is associated with a 2-fold risk of CHD mortality in women.<sup>6</sup> **It is important to note that the most common pattern of dyslipidemia in patients with type 2 diabetes is elevated TG levels and decreased HDL-C levels.<sup>7</sup>**

\*At least 3 of the 5 criteria: abdominal obesity with waist circumference >102 cm in men and >88 cm in women; triglycerides ≥150 mg/dL; HDL-C <40 mg/dL in men and <50 mg/dL in women; blood pressure ≥130/85 mmHg; fasting glucose ≥110 mg/dL.<sup>8</sup>

### More Aggressive Guidelines for TG and HDL-C

While LDL-C lowering is recognized as the primary lipid target to reduce CHD morbidity and mortality, it does not remove all risk.<sup>9</sup> Recent data has shed more light on the role of increased TG and decreased HDL-C in CHD risk. It is critical that these lipid abnormalities be considered and managed, in addition to LDL-C. In fact, the current National Cholesterol Education Program (NCEP) guidelines recommend more aggressive TG and HDL-C target goals.<sup>8</sup> The American Heart Association (AHA) and American Diabetes Association (ADA) recommend similar aggressive goals for TG (<150 mg/dL) and HDL-C (>50 mg/dL) in CVD prevention for women.<sup>10,11</sup>

### You Can Help Make a Difference

A majority of women are still not aware of the substantial CHD risks posed by abnormal lipid levels.<sup>12</sup> As a physician, you can help make a difference by raising your female patients’ awareness of these issues, and by helping them achieve optimal lipid levels, as recommended by the NCEP, the AHA and the ADA.

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