

# Atrial Natriuretic Peptide Reduces Infarct Size

BY BRUCE JANCIN  
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CHICAGO — Carperitide infusion as adjunctive therapy for acute MI reduced infarct size, boosted left ventricular ejection fraction, and sharply decreased the incidence of cardiac death and rehospitalization for heart failure in a large placebo-controlled, randomized trial, Dr. Masafumi Kitakaze reported at the annual scientific sessions of the American Heart Association.

"I think reduction of infarct size has been kind of a dream for cardiologists. In dog experiments, rat experiments, there [is] a bunch of drugs that have been able to reduce infarct size, but until now there is no drug that has done so in humans. So the current study may open a new era of adjunctive therapy in patients with acute MI," said Dr. Kitakaze, director of the cardiovascular division of the National Cardiovascular Center, Suita, Japan.

In a parallel study that together with the carperitide trial is known as the Japan-



Several drugs have reduced infarct size in animals, but until now none have done so in humans.

DR. KITAKAZE

Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by ANP or Nicorandil (J-WIND), nicorandil resulted in a significantly improved ejection fraction and a threefold reduction in the incidence of coronary revascularization of nonculprit lesions, added Dr. Kitakaze, chair of J-WIND.

J-WIND involved 1,216 patients with a first acute MI at 65 hospitals in Japan. The left anterior descending coronary artery was the infarct-related vessel in roughly half of cases. Within 4 hours after early revascularization by percutaneous intervention, half of participants were randomized to carperitide, also known as human atrial natriuretic peptide, at 0.025 mcg/kg per minute for 3 days or placebo. The other half was randomized to placebo or a 0.067 mg/kg bolus of nicorandil followed by 24 hours at 1.67 mcg/kg per minute. Then, nearly one-half of patients in the nicorandil arm were continued on oral nicorandil long-term.

The two primary end points were infarct size as estimated by the area under the curve for creatine kinase and left ventricular ejection fraction (LVEF) measured by ventriculography. Infarct size was reduced by 14.7% in the carperitide arm relative to placebo, while LVEF increased by an absolute 5.1%. Both effects were statistically significant. They were clinically significant as well, as evidenced by a 73% reduction in the combined secondary end point of cardiac death or hospitalization for heart failure in the carperitide group, Dr. Kitakaze said.

Mean LVEF in the control arm was about 42%. With carperitide it climbed to

47%. "That's very important because over 45% we don't call it heart failure, while below 45% we think of it as ventricular dysfunction. So the carperitide group just crosses over the normal/abnormal line," he continued.

In addition, reperfusion injury—defined as new-onset severe arrhythmia, ST-elevation ECG changes, or recurrent chest pain after successful percutaneous coronary intervention—was reduced by 26% in the carperitide arm compared with controls.

In contrast, intravenous nicorandil did not influence infarct size, reperfusion injury, or cardiovascular events. However, patients who got oral nicorandil did experience significantly improved left ventricular function and a reduced incidence of revascularization of nonculprit lesions, suggesting the drug may provide some cardiovascular protection, he said.

J-WIND was funded by the Japanese Ministry of Health, Labor, and Welfare.

Carperitide is marketed in Japan for the

treatment of acute heart failure. It is being developed for western markets, where it remains investigational, by Astellas in partnership with Daiichi Suntory Pharma. Nicorandil is an adenosine triphosphate-sensitive potassium channel activator widely prescribed for chronic stable angina. Side effects with either agent were minimal, Dr. Kitakaze added.

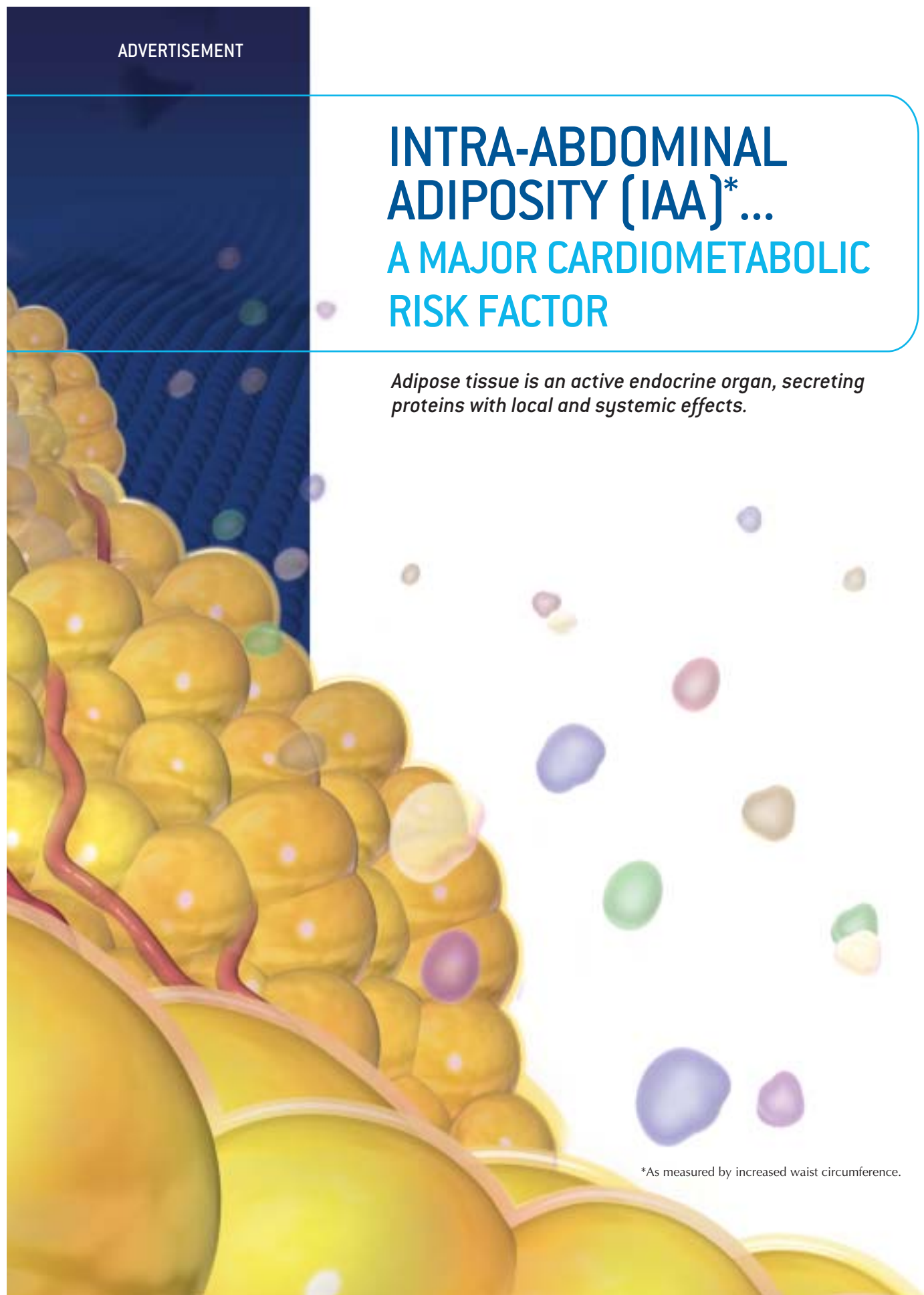
Discussant Dr. Robert Harrington urged restraint in interpreting the J-WIND results in light of the lengthy list of once-promis-

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## INTRA-ABDOMINAL ADIPOSITY (IAA)\* ... A MAJOR CARDIOMETABOLIC RISK FACTOR

*Adipose tissue is an active endocrine organ, secreting proteins with local and systemic effects.*

\*As measured by increased waist circumference.



ing drugs with a variety of proposed mechanisms for reducing infarct size, none of which have come to fruition.

"I caution us with the following: Despite great biological belief and promise and preclinical work that suggested upwards of 50% reduction in infarct size in animal models and then in early human experiments, absolutely no benefit has been seen for these [earlier] agents in clinical trials enrolling more than 100,000 patients," stressed Dr. Harrington, professor of medicine at Duke University, Durham, N.C., and director of the Duke Clinical Research Institute.

Contemporary guideline-driven therapy

for acute MI is so effective that a ceiling may be near. The way to make a major difference in MI today is not by focusing on shaving a sliver off 30-day mortality or final infarct size, but by preventing MI from occurring in the first place, he argued.

Dr. Harrington pointed to the landmark INTERHEART study led by Dr. Salim Yusuf of McMaster University, Hamilton, Ont., which has convincingly shown that 90% of the population-attributable risk for first-time MI worldwide is contained in familiar risk factors such as smoking, hypertension and hyperlipidemia (Lancet 2004; 364[9437]: 937-52). ■

# High LVEF Hikes Risk in Older Women With ACS

BY BRUCE JANCIN  
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CHICAGO — Sometimes a woman's heart can be too strong for her own good.

Data from the Global Registry of Acute Coronary Events (GRACE) indicate that elderly women with supernormal left ventricular systolic function as defined by an

ejection fraction (EF) greater than 65% at the time they present with an acute coronary syndrome (ACS) have a twofold greater mortality risk than those presenting with a normal EF, Dr. Fadi A. Saab reported at the annual scientific sessions of the American Heart Association.

The highest mortality of all in the GRACE analysis was seen in elderly women with an EF below 55%, as would be expected. Depressed left ventricular systolic function complicating ACS is well established as the most powerful predictor of poor outcome, both during acute hospitalization and at 6 months.

However, the elevated risk associated with supernormal EFs came as a surprise to the investigators. A plot of in-hospital mortality against EF deciles in the more



**'This is the first time this J-shaped association [between mortality and EF deciles] has been described.'**

DR. SAAB

than 5,100 women over age 65 with ACS in GRACE describes a J-shaped curve with a nadir at an EF of 60%-69%. "We believe this is the first time this J-shaped association has been described," noted Dr. Saab of the University of Michigan, Ann Arbor.

GRACE is an ongoing Sanofi-Aventis-sponsored observational study at 112 hospitals in 14 countries. An EF below 55% was present in 2,987 elderly female ACS patients in GRACE, a normal EF of 55%-65% in 1,483, and a supernormal EF in 657.

In a multivariate logistic regression analysis adjusted for age, medical history, Killip class at presentation, in-hospital complications such as heart failure or atrial fibrillation, in-hospital management, and medical therapies, an EF greater than 65% was an independent predictor of poor outcomes. It was linked to a 2.4-fold greater risk of in-hospital mortality than in patients with a normal EF, a 2.0-fold greater 6-month mortality, and a 2.5-fold increased risk of cardiac arrest/ventricular fibrillation.

Dr. Saab said one possible explanation for the observed association between supernormal EF and poor outcomes is that elderly women with a hypertrophic heart and a very high EF may be particularly susceptible to oxygen supply-mediated myocardial ischemia, with resultant QT prolongation and an increase in serious arrhythmias, although he was quick to add that this is speculation.

Session cochair Dr. Galen S. Wagner noted that the GRACE investigators haven't looked at elderly male ACS patients with supernormal EFs. "We know that elderly women do badly if their hearts are too strong, but we really don't know what it means when elderly men have hearts that are too strong," observed Dr. Wagner of Duke University, Durham, N.C. ■

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## INCREASED ACTIVITY OF THE ENDOCANNABINOID SYSTEM (ECS) IS ASSOCIATED WITH INCREASED WAIST CIRCUMFERENCE<sup>1,2</sup>

## INCREASED WAIST CIRCUMFERENCE, A MARKER FOR IAA, IS AN ESTABLISHED CARDIOMETABOLIC RISK FACTOR<sup>3</sup>

- Significantly increases the risk of myocardial infarction, death from cardiovascular disease, and all-cause mortality<sup>4</sup>
- Has been found to be an independent predictor of type 2 diabetes<sup>5</sup>

## ADIPOSE TISSUE IS A HIGHLY ACTIVE ENDOCRINE ORGAN<sup>6</sup>

- Fat cells (adipocytes) produce adiponectin<sup>6</sup>
  - In type 2 diabetes and obesity, adiponectin levels are reduced<sup>6</sup>

## TARGETING THE ECS MAY PLAY A POTENTIAL ROLE IN THE CONTROL OF MAJOR CARDIOMETABOLIC RISK FACTORS SUCH AS IAA\*

**IF YOU ARE INTERESTED IN LEARNING MORE ABOUT THE ECS, PLEASE CALL 1-800-815-0298 TO RECEIVE A MONOGRAPH.**

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