Heart Failure TODAY

WINTER ISSUE

A REMINDER
February 9-15 is Heart Failure Awareness Week

HOW DIAGNOSTICS CAN HELP TREAT PATIENTS WITH HEART FAILURE

❄

IDENTIFYING PATIENTS THAT COULD BENEFIT FROM HIGH-DOSE BETA BLOCKERS

❄

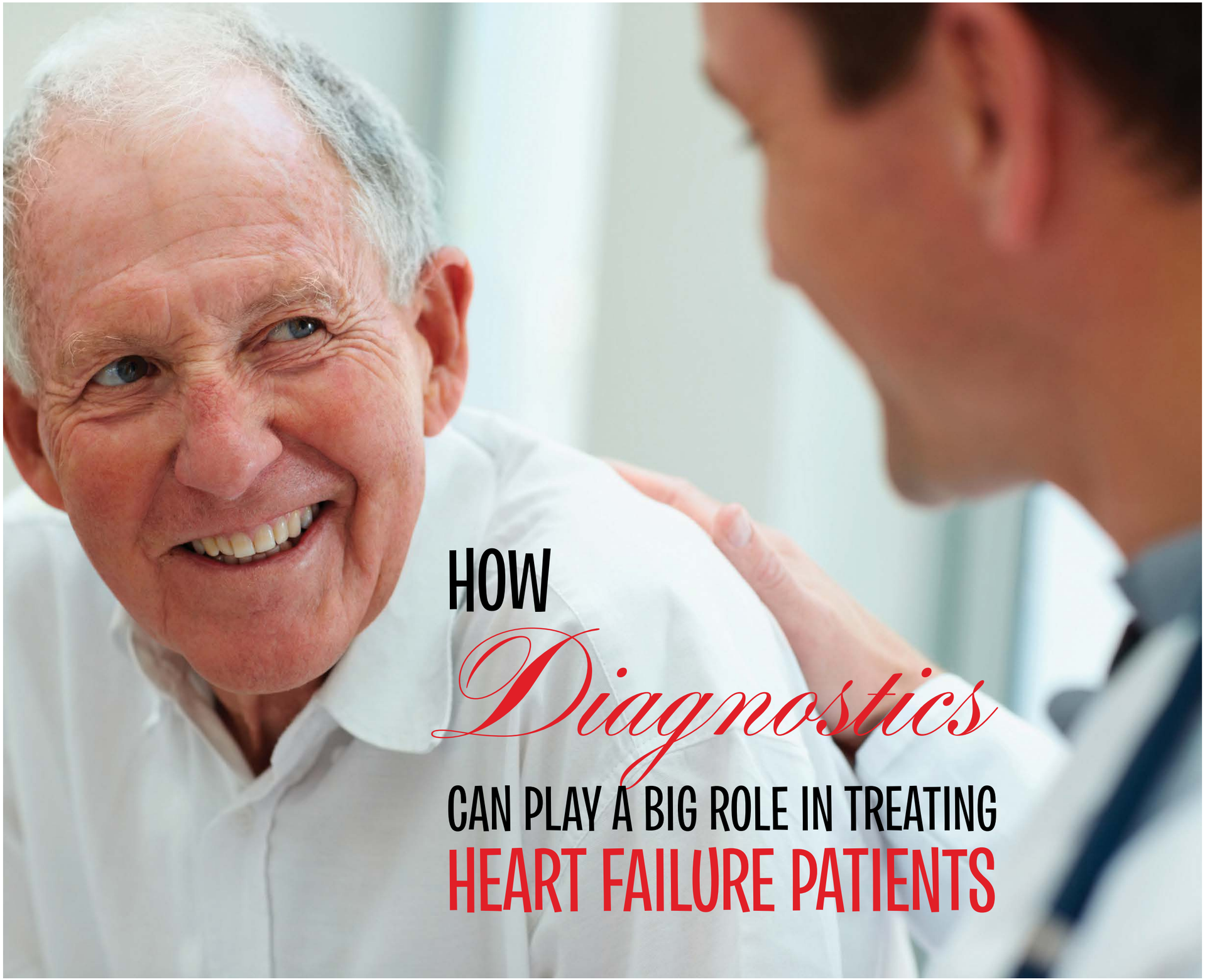
WHY CARDIOLOGISTS ARE SELLING THEIR PRACTICES

WHICH HEART FAILURE PATIENTS BENEFIT FROM *Exercise*

❄

OBESITY & HEART FAILURE

Heart Failure TODAY is a publication of Critical Diagnostics, makers of the Presage® ST2 Assay. This information is to educate our readers and is not intended as medical advice or a substitute for consulting a physician. The Presage® ST2 Assay is CE Marked and has received 510(k) clearance from the US FDA for use in risk stratification of chronic heart failure patients. The American College of Cardiology Foundation (ACCF) and the American Heart Association (ACC) jointly publish the ACCF/AHA Guideline. For simplicity purposes you will note we call it the ACC/AHA Guideline.



HOW *Diagnostics* CAN PLAY A BIG ROLE IN TREATING HEART FAILURE PATIENTS

Diagnostics represent the foundation of a successful healthcare system, providing the critical information physicians need to care for their patients. While diagnostics represent only 2 percent of the world's healthcare spending, it influences 60 percent of all healthcare decisions.

Diagnostics are helping bring the promise of "personalized medicine" – the right treatment, for the right patient, at the right time – to the management of heart failure patients. At the forefront of that effort is the cardiac biomarker ST2.

A recently published prospective, randomized, controlled study,[1] shows that patients above the FDA-cleared ST2 threshold of 35 ng/mL and who were taking low doses of beta blocker were almost seven times as likely to experience a cardiovascular event–such as an unplanned hospitalization–than patients who had low ST2 levels and were on high-doses of beta blocker.

The study also proved that patients above the 35 ng/mL threshold who were taking low doses of beta blocker were almost three times as likely to experience a cardiovascular event as those above the FDA-cleared ST2 threshold on high-doses of beta blockers.

Beta blockers are used by tens of millions of Americans to treat high blood pressure and other heart ailments, such as heart failure, yet despite their proven benefit and vigorous support in clinical practice guidelines, the actual dose of beta blocker achieved in standard practice is considerably lower than the guideline-recommended dose, due to potential side effects, the cost of medication, and poor understanding of whether higher doses of beta blocker are providing added benefit to a particular patient.

A multivariable model was created with both baseline ST2 levels and final achieved beta blocker dose. Model variables included age, gender, ischemic cardiomyopathy, atrial fibrillation or flutter, NYHA class III or IV, baseline heart rate, baseline NT-proBNP and baseline eGFR (estimated glomerular filtration rate). When all clinical and laboratory characteristics were included into a model predictive

(continued on page 20)

1"Soluble Concentrations of the Interleukin Receptor Family Member ST2 and Beta Blocker Therapy in Chronic Heart Failure," Circulation: Heart Failure.

WHY THE RISK OF HEART DISEASE IS HIGHEST IN *Winter*

Winter can be a killer. Literally. Compared to the summer months, people are 26 to 36 percent more likely to die in winter from a heart attack, stroke, heart failure, or some other circulatory disease, say Drs. Bryan Schwartz and Robert Kloner of the Heart Institute at Good Samaritan Hospital in Los Angeles.

The researchers examined some 1.7 million death certificates from 2005 to 2008 collected at seven U.S. locations that ranged from hot to cold: Texas, Arizona's Maricopa County, Georgia, California's Los Angeles County, Washington, Pennsylvania and Massachusetts. Geography had nothing to do with it. No matter where the data were from, the pattern was the same: Many more deaths in the winter than in the summer.

"We thought the winter peak would be more prominent in cold climates like Massachusetts," said Schwartz, "but the death rates were similar. That means that temperature is a small factor – or not a factor at all."

One possible explanation is the higher incidence of influenza and depression. Flu season peaks in the winter, and, as Schwartz points out, during winter's shorter days, people tend to feel more down and discouraged. They may exercise less and not be as careful about what they eat.

For example, "a patient who already has congestive heart failure might not be as adherent to a low-salt diet. That can be enough to promote fluid retention and worsening heart failure and eventually death."

OR IT COULD BE...

In a separate study, as reported at a European Society of Cardiology conference in 2013, Swiss researchers looked at cross-sectional data from 10 population-based studies over seven countries, encompassing over 100,000 participants.

Findings of the analysis revealed that many heart disease risk factors, such as blood pressure, total cholesterol and waist circumference, were higher in January and February but lower in July and August, compared with the annual average.

Waist circumference was around 1 cm smaller in summer compared with winter, while total cholesterol was on average 0.24 mmol/L lower in summer than in winter. The results also showed that systolic blood pressure levels were 3.5 mmHg lower in summer compared with the winter months.

Study author Dr. Pedro Marques-Vidal of the Institute of Social and Preventive Medicine at the University of Lausanne, Switzerland, noted, "Although this difference is almost irrelevant for an individual, it is considerable for a whole population because the whole blood pressure distribution is shifted to higher values, increasing cardiovascular risk."

Dr. Marques-Vidal's recommendation? People need to make an extra effort to exercise and eat healthily during the winter months to protect their health.

FAT CHANCE

The debate over why there are more deaths in winter doesn't end there. A new study suggests one reason may be that the cold weather causes brown fat to accelerate the build-up of plaque in blood vessels.

Researchers from Sweden and China made this breakthrough discovery while studying mice, as reported last July in the online issue of *Cell Metabolism*. Like humans, mice have two types of body fat: white fat and brown fat. White fat stores calories, such as in the flab that accumulates around waists and hips, while brown fat burns calories to generate heat.

Cold temperatures trigger brown fat to generate heat. This was thought to be "healthy" for the body because it also helps reduce white flabby fat. But what author Yihao Cao, of the Karolinska Institutet and Linköping University in Sweden and colleagues found was that exposure to cold accelerated the formation of fatty deposits or atherosclerotic plaques in the mice, which can lead to heart attack and brain hemorrhaging.

It seems that the lower temperatures activated the breakdown of fatty acids in the mice's brown fat, causing levels of small low-density lipoprotein (LDL) remnants in the blood to rise, thus encouraging more of it to deposit as plaque.

And not only did the lower temperature accelerate plaque build-up, but also it made the plaque less stable. Unstable plaque is more likely to rupture and leak stored fat into the blood, causing blockages in vessels in the heart and brain.

At first, the researchers thought the mice would get thinner and healthier when the cold temperatures activated the brown fat.

"Instead, we found that they ended up having more fat stored in the blood vessels," says Cao. "This came as a surprise and was the opposite of what we thought would happen.

"If the same is true of humans, then perhaps we should be advising people with cardiovascular diseases to avoid getting cold and to don warm clothes when they step outside in the winter months," he adds.

THE JANUARY EFFECT

Death and length of stay in hospital are highest in heart failure patients admitted in the month of January, (as well as on a Friday and overnight) according to research presented at the Heart Failure Congress 2013 in Lisbon this past May.

The analysis looked at nearly one million hospitalizations for congestive heart failure over a 14-year period in the state of New York from 1994 to 2007.

One theory the scientists were able to disprove is that the holiday spike was caused by alcohol and drug use. The findings did, however, suggest that staffing may have an impact on seasonal variations in mortality and length of stay.

"The fact that patients admitted right before the weekend and in the middle of the night do worse and are in hospital longer suggests that staffing levels may contribute to the findings," says the study's author, as well the cold weather, he adds.

It may also have something to do with the shock of opening post-Christmas credit card bills.

For a FREE downloadable copy of this or past issues of *Heart Failure TODAY*:
www.criticaldiagnostics.com/US/News/archive.htm

IN-HOSPITAL SERIAL TESTING OF ST2

SPOTS HIGH RISK PATIENTS AND THOSE LIKELY TO BENEFIT MOST FROM BETA BLOCKERS

Patients hospitalized for acute heart failure with elevated ST2 levels who had more than a 42 percent drop in ST2 levels within 48 hours from admission, lowered their risk of 1-year mortality more than three fold, versus those that showed a smaller change.[1]

These were the results of a University Hospital Basel study[2] of just over 200 acute heart failure patients followed over a three-and-a-half year period, showing that in-hospital testing of the cardiac biomarker ST2 may help to identify a high-risk population with particular benefit from tailored therapy at discharge.

Patients who didn't show at least a 20 percent drop in their ST2 levels within 48 hours of admission had an alarming better-than-even (50/50) chance of dying within one year, whereas patients whose ST2 level decreased by at least 42% had only about a one in seven chance of dying within one year.

Powerfully, it was also shown that if these high-risk patients received more intensive outpatient therapy their risk of adverse events was reduced to be comparable to that of the low risk group.

(continued from page 20)

1The Presage® ST2 Assay has received 510(k) clearance from the U.S. FDA for use in risk stratification of chronic heart failure patents.
2"Heart Failure Therapy Induced Early ST2 Changes May Offer Long-term Therapy Guidance."

OBESITY & HEART FAILURE

THE FAT OF THE MATTER

Nearly 78 million American adults are obese. Obesity is a major public health problem, ranking fifth on the World Health Organization's list of leading risk factors for mortality. Not too surprisingly, this worldwide epidemic is also closely linked to the rise in the incidence of cardiovascular disorders, particularly heart failure.

A 2010 review in the *Journal of the American College of Cardiology* cited obesity as an increasingly important risk factor for heart failure, noting the metabolic abnormalities associated with obesity appear to stress the circulatory system and set the stage for heart failure.

Weight control affects cardiac function, says Thomas H. Marwick, Ph.D., professor of medicine at the University of Queensland at Princess Alexandra Hospital in Brisbane, Australia. A study compared the left ventricles of normal-weight people, with the left ventricles of severely obese people, and found that in the obese participants, there was a very weakened ability of cardiac muscle to contract and a diminished ability of cardiac muscle to fully relax.

The full-relax is important for enabling the ventricle to be refilled with blood during rest periods between the heartbeats. The study showed impairments of left ventricular function in mildly obese, as well as overweight, subjects. "The study showed a direct relationship between the level of obesity and the degree of myocardial dysfunction," remarks Marwick. And this finding was independent of other risk factors. "We think this indicates a direct metabolic effect of obesity on the heart muscle."

Every 1-point rise in a person's body mass index increases the risk for heart failure by 5 to 7 percent, according to a study published in 2002 in the *New England Journal of Medicine*. Obese people – those with a BMI above 30 – were found to be twice as likely to develop heart failure as normal-weight subjects. The statistical relationship between heart failure and obesity remained strong even when other obesity-related risk factors for heart failure, such as high blood pressure and diabetes, were accounted for.

"Obesity is at least as great a risk factor for heart failure as it is for heart attack or stroke," stated John McMurray, professor of cardiology at the Western Infirmary, Glasgow, in a presentation at the Heart Failure Congress in 2009 in his discussion of the findings from Euroaspire, Europe's largest survey of cardiovascular risk factors in coronary patients, which found that the prevalence of obesity had increased from 25 percent in 1997 to 38 percent in just ten years – and this in people who had already had at least one heart attack.

As America's waistline increases, so too does the cost to the healthcare system. Reuters reports that the price tag for obesity in the U.S. is close to $200 billion a year, exceeding smoking as public health enemy number one when it comes to cost. A 2012 study in the *American Journal of Preventive Medicine* estimated that by 2030 obesity will rise from 34.5% of the adult population to 42%, with related health care spending forecast to rise to an astounding $550 billion.

Making the cost impact all the more troubling is the fact that, unlike smokers, obese people tend to live almost as long as those who keep their weight under control. "Smokers die early enough that they save Social Security, private pensions, and Medicare trillions of dollars," notes Eric Finkelstein of Duke University, paradoxically.

There is hope, though. If adults across America could reduce their body mass index by just 5 percent, savings in health care costs could be as much as 7.9 percent – and millions could avoid a stroke or cardiovascular disease – notes a Robert Wood Johnson Foundation Health Group study. Fat chance of that happening, say most of the critics.

Why

MORE AND MORE CARDIOLOGISTS ARE SELLING THEIR PRACTICES

Almost 1 in every 7 cardiologists is seeking to sell his or her practice, according to a report from staffing firm Jackson Healthcare, who surveyed physicians across all areas of medicine.[1]

Physicians in private practice still outnumber those employed, but this could change as less than half the survey respondents with an ownership stake say they plan to remain in private practice. The main reasons cited to sell were reimbursement cuts (79 percent) and the cost of maintaining their practices (64 percent).

The survey found physicians increasingly influenced by the Affordable Care Act (ACA). Fifty-seven percent cited complexities of healthcare reform as a reason to sell. Resource constraints also factored into decisions to sell. Twenty-four percent of physicians thinking of selling said they lacked the resources to comply with the ACA.

Many fear that as their incomes fall, percent said that they would rather focus more of their time on the practice of medicine without the administrative and legal burdens associated with running a business. While many cardiologists are selling their practice or giving it serious consideration, the majority are not looking to leave the profession. Of those that sold or plan to sell, 84 percent plan to work for their buyers.

About two-thirds of over 500 respondents currently owned or had an ownership stake in a practice. Of those, more than half were actively looking for a buyer, passively willing to sell, or planning to retire or quit the field. Internal medicine specialists—that included cardiologists—led the list by physician type for actively seeking a buyer.

More than half of those in the process of selling or actively in search of a buyer considered a hospital or a healthcare system as a good choice. And hospitals are receptive, according to the report. Twenty percent of respondents who sold a practice in the past three years had been approached by a hospital, up from 15 percent who sold three or more years ago.

"There's been a steady increase in practice acquisitions by hospitals since the ACA passed in 2010," noted the report. "For the first time, we see many of these purchases are being initiated by the physicians."

So is life any better on the other side? Many who sold their practice reported satisfaction with the move. Sixty percent were satisfied or very satisfied with their situation, 55 percent didn't miss ownership and 76 percent would make the same decision again.

1TREND WATCH 2013: Physician Practice Acquisitions

ST2 Helps Assess Heart Failure Risk And Identify Patients Likely To Benefit From Exercise

Levels of the biomarker ST2 are predictive of long-term outcomes for people suffering with heart failure, and identify those patients who may benefit from exercise.

Duke Clinical Research Institute investigators evaluated 912 subjects, part of a large, multicenter, randomized study of exercise training in well-treated ambulatory heart failure patients. The subjects were followed for 32 months.

In multivariable models, ST2 remained a significant predictor of outcomes after adjustment for clinical variables and the natriuretic peptide biomarker NT-proBNP. This association was particularly strong for cardiovascular death and heart failure hospitalization, consistent with ST2's role as a cardiovascular risk marker.

A doubling of ST2 levels above the baseline more than doubled the risk of cardiovascular death or heart failure re-hospitalization.[1]

Almost all the patients in this study (95 percent) were receiving beta blockers and three-quarters were also on ACE inhibitors. Besides medication, exercise is another treatment option often recommended for heart failure patients to help improve symptoms and lower risk of adverse outcomes or death, but it has never been clear which patients would benefit most from exercise. "Of the endpoints tested," note the authors, "there was a statistical interaction between exercise training and the outcome of all-cause mortality, such that patients with lower ST2 levels were more likely to have a benefit of exercise training than were patients with higher levels."

> Patients with both elevated levels of ST2 and NT-proBNP had a nearly six-fold increased risk of death during the course of long-term follow up, compared to those with neither marker elevated.

Researchers also found that increased levels of ST2 were strong predictors of cardiovascular events.

They note: "Elevation of ST2 was significantly associated with long-term outcomes . . . These associations were relatively robust for disease specific endpoints (cardiovascular death and heart failure hospitalization) in traditional multivariable modeling, persisting even after comprehensive covariate adjustment, including demographics, clinical variables, and NT-proBNP."

ST2 was recently included in the 2013 ACC/AHA Guideline For The Management of Heart Failure, recognizing ST2 as *"not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in [its] prognostic value."*

This study supports that recommendation. When considered along with NT-proBNP, as four groups based on NT-proBNP levels above or below the median level for NT-proBNP, and ST2 levels above or below the standard FDA-cleared 35 ng/mL cutpoint, patients with both markers elevated had nearly a six-fold increased risk of death during the course of long-term follow up, compared to those with neither marker elevated.

"To our knowledge, this is the most robust test of this novel biomarker to date with regard to covariate adjustment in a large, multicenter cohort of ambulatory heart failure patients," noted G. Michael Felker, MD, MS, one of the authors.

The results of this study were in sharp contrast to a study that used the same cohort of subjects to analyze another

(continued on page 21)

1"Soluble ST2 in Ambulatory Patients with Heart Failure: Association with Functional Capacity and Long-Term Outcomes," *Circ*, October, 2013

ST2 PROVES VALUABLE IN HELPING RISK ASSESS HEART FAILURE PATIENTS WITH *Renal Insufficiency*

Results of a recent study demonstrated that the prognostic value of ST2 was not adversely influenced by impaired renal function. In patients with renal insufficiency, even when a comprehensive multivariable analysis incorporating other popular biomarkers was performed, ST2 remained as an independent prognostic marker.[1]

Heart failure is on the rise in our aging society. According to a 2013 Centers For Disease Control report, "The State of Aging And Health in America 2013," the growth in the number and proportion of older adults is unprecedented in the history of the United States. Two factors – longer life spans and aging baby boomers – will combine to double the population of Americans aged 65 year or older during the next 25 years. Given that over 80% of heart failure patients are 65 years of age or older,[2] it's no wonder, then, that, according to the American Heart Association, the number of Americans with heart failure is expected to jump from just over 5 million today to 8 million in 2030.

Furthermore, two out of three older Americans have multiple chronic conditions. A study of over 100,000 heart failure patients reported that over 60% also had kidney disease.[3] The intersection of cardiac and renal insufficiency (kidney failure) is so prevalent it is often referred to as cardio-renal syndrome.

Ever since the introduction of the natriuretic peptide biomarkers, BNP and NT-proBNP, into clinical practice, confusion has existed about their utility in the context of renal disease. Multiple factors are known to affect circulating levels of natriuretic peptides, complicating their interpretation. The *Achilles heel* of the NT-proBNP molecule is the impact of kidney disease in the heart failure patient population.

Investigators in this study followed 879 heart failure patients over a median period of three-and-a-half years. NT-proBNP was significantly impacted by renal function. Notably, in New York Heart Association (NYHA) functional class III-IV patients, in whom accurate risk stratification is most crucial, NT-proBNP serum concentration were significantly increased with worsening eGFR (Estimated Glomerular Filtration Rate, a measure of how well the kidneys are working), whereas ST2 concentrations were not affected by worsening eGFR.

Net reclassification improvement (reclassification according to predefined risk categories) also significantly improved after the inclusion of ST2. Reclassification with the models containing ST2 was even better among patients with renal insufficiency than in the global population, showing a net reclassification of 16.6 percent as compared with the baseline model.[4]

The authors also noted that ST2 provides independent and incremental prognostic information on top of clinical data as well as high-sensitivity troponin, cystatin C, and NT-proBNP in patients with heart failure and renal insufficiency, whereas NT-proBNP, eGFR, and cystatin C lost their significance when high-sensitivity troponin and ST2 were introduced into the multivariable analysis.

"Renal insufficiency is frequent in heart failure patients and the majority of current biomarkers, including

(continued on page 21)

1 "Soluble ST2 Serum Concentration And Renal Function in Heart Failure," *Journal of Cardiac Failure*
2 "Epidemiology of Chronic Kidney Disease in Heart Failure," *Heart Fail Clin*, 2008 October; 4(4): 387-399.
3 From the Acute Decompensated Heart Failure National Registry (ADHERE).
4 Baseline model includes age, gender, ischemic etiology of heart failure, LVEF, NYHA functional class, diabetes mellitus, eGFR, ACEI or ARB treatment, b-blocker treatment, sodium, and hemoglobin.

Diabetes

AND

HEART FAILURE

People with diabetes are 38% more likely to die early and have a 73% higher chance of being admitted to hospital for heart failure than others, according to a U.K. report.

The review of more than two million people found just over a quarter of admissions to hospital for heart failure were among people with diabetes. Furthermore, diabetics admitted to hospital for heart failure had more than quadruple the odds of dying in the following year compared with the general population.

"There is no great mystery about why the rate is so high, as we know that half of people with diabetes have high blood pressure and a quarter have high cholesterol," says Barbara Young, Director of Diabetes UK.

In the Framingham study, diabetic men aged 45 to 74 had better than twice the risk of developing heart failure as their non-diabetic cohorts, and women had an alarming fivefold increased risk.[1]

As the authors pointed out, this excessive risk appeared to be caused by factors other than accelerated atherogenesis and coronary heart disease. Even when patients with prior coronary or rheumatic heart disease were excluded, the diabetic subjects had a four- to fivefold increased risk of congestive heart failure.

Moreover, the increased risk of heart failure in the diabetic patients persisted after taking into account age, blood pressure, weight and cholesterol values as well as coronary heart disease.

Women with diabetes appeared to be especially vulnerable and, irrespective of coronary disease status, had twice the frequency of congestive heart failure as men.

1 "Role of diabetes in congestive heart failure: The Framingham study," William B. Kannel, MD, FACC, et al., *Amer. J. Cardiology.*

A PATENT ON *Prevention*

Patents are the lifeblood of innovation. Without innovation, science becomes stagnant. In the cardiac biomarker world, much of the advancements took place over a decade ago, with the introduction of the natriuretic peptide biomarkers like BNP and NT-proBNP. But while natriuretic peptide biomarkers have proven quite useful as a diagnostic tool, they have never seen the body of clinical evidence needed to support their use in treating these patients. Now one new biomarker for prognosis of HF patients, ST2, is taking the medical world by storm.

The evidence on the use of ST2 across all four stages of heart failure was compelling enough that the ACC/AHA Guideline includes ST2 in its latest update, calling it, "not only predictive of hospitalization and death in patients with HF [heart failure] but also additive to natriuretic peptide levels in [its] prognostic value."

"Having ST2 included in the 2013 ACC/AHA Guidelines is unprecedented," notes David Geliebter, CEO of Critical Diagnostics, makers of Presage™ ST2 Assay. "We only received FDA clearance in December of 2011. No cardiac biomarker that we know of has ever achieved this acceptance so quickly."

Specifically, ST2 was included as level IIbA for additive risk stratification in acute HF as a biomarker of myocardial fibrosis. An "A" Level of Evidence is the highest classification possible, meaning that data were derived from multiple randomized clinical trials or meta-analysis, and a IIb Class of Recommendation corresponds to 'May Be Considered' for the purpose risk stratification.

"Data from this second generation Framingham cohort showed that otherwise healthy individuals with the highest levels of ST2 in their blood had the greatest risk of developing heart failure years before the presence of any symptoms."

Critical Diagnostics recently announced that the United States Patent and Trademark Office issued a 10th patent in connection with its ST2 assay covering "Methods for Treatment of Cardiovascular Disease."

"We are very pleased that the USPTO recognized the novelty and utility of our biomarker, ST2," states James Snider, President of Critical Diagnostics. "Broadly speaking, this patent expands upon our issued patent to include utility in primary disease prevention around a method for treating patients to reduce their risk of developing a cardiovascular condition."

In May, 2013 the company revealed publication of a study that, for three years, followed a cohort of 1,834 otherwise healthy individuals, where those with high levels of the biomarker ST2 present in their blood were almost twice as likely to develop hypertension than those with low ST2 levels. Hypertension (high blood pressure) affects some 67 million people in the U.S. and is the leading cause of heart failure.

This study came out of the far-reaching Framingham Heart Study, under the direction of the National Heart Institute (now known as the National Heart, Lung, and Blood Institute) which, in 1948, embarked on an ambitious effort to identify causes of heart disease and stroke, about which little was known at the time. In 1971, the Study enrolled a second generation – just over 5,000 of the original participants' adult children and their spouses - to participate in similar examinations.

Data from this second generation Framingham cohort showed that otherwise healthy individuals with the highest levels of ST2 in their blood had the greatest risk of developing heart failure years before the presence of any symptoms. In fact, ST2 was, by far, the most predictive of any biomarker tested, including such established biomarkers as the natriuretic peptides and troponin.

It was another study, this one conducted through the Mayo Clinic and Foundation, that once again proved the remarkable accuracy of ST2 in predicting the risk of heart failure and mortality in the general population. The study of 1,831 healthy individuals from Olmsted County, Minnesota, who were followed for approximately a decade, showed that those with the highest ST2 concentrations were at

(continued on page 21)

HOW DIAGNOSTICS CAN PLAY A BIG ROLE IN TREATING HEART FAILURE PATIENTS

(continued from page 3)

of CV [cardiovascular] events, only ST2 was independently predictive of cardiovascular events.

"Our proof-of-concept analysis suggests that biomarker concentrations may identify a risk that may theoretically be mitigated by specific drug therapy, raising the possibility that higher dose BB [beta blocker] therapy may be particularly efficacious in the face of an elevated sST2," say the authors, adding, "Another hypothesis-generating inference from this data may be that a low sST2 value may be protective against CV events in patients with other poor prognostic markers such as low achieved BB dose or high baseline NT-proBNP values."

The ad-hoc look at beta blockers came out of a bigger biomarker-guided therapy study of chronic heart failure patients with left ventricular systolic dysfunction followed over a 10-month period, which demonstrated that of all biomarkers tested, only serial testing of ST2 added prognostic information to baseline concentrations and predicted change in left ventricular function.

As a baseline value added to traditional clinical and biochemical characteristics including NT-proBNP, ST2 added independent information in predicting total cardiovascular events, but, more importantly, as a serial biomarker measured every three months during the treatment period of the study, only ST2 provided incremental prognostic information. Patients with persistently elevated ST2 levels were at more than three-and-a-half times the risk of experiencing a cardiovascular event, such as an unplanned hospitalization, than patients who had low ST2 levels.

"Beyond the baseline measurement, only sST2 appeared to provide incremental prognostic information and reflect changes in myocardial remodeling over time," state the authors. "A novel biomarker's dynamic ability to reflect the underlying HF [heart failure] biology makes it an ideal candidate for potentially monitoring and guiding HF management. In the present analysis, sST2 [soluble ST2) appeared to add prognostic information above the natriuretic peptides across multiple time points of measurement, and indicate significant dynamic change of the biomarker in parallel with risk for adverse events and myocardial remodeling."

Furthermore, there was a direct relationship between the percent of time spent with ST2 below its FDA cleared threshold of 35 ng/mL and cardiovascular event rates. The time that patients spent with ST2 levels below 35 ng/mL was directly related to improving cardiac function as measured by decreasing left ventricular end diastolic volume index, even after adjusting for relevant baseline characteristics. These findings strongly suggest that managing patients to a ST2 level below 35 ng/mL may be an appropriate treatment strategy, versus managing patients to a specific dosing regimen.

Note the authors: "More time spent in sST2 response predicted decreasing LVEDi [left ventricle end diastolic volume index] after adjusting for relevant baseline characteristics."

"Concentrations of sST2 are increasingly accepted to reflect important prognostic information not already revealed by natriuretic peptides," remark the authors, "In the present analysis, sST2 appeared to add prognostic information above the natriuretic peptides across multiple time points of measurement, and indicate significant dynamic change of the biomarker in parallel with risk for adverse events and myocardial remodeling."

ST2 was recently included in the 2013 ACC/AHA Guideline For The Management of Heart Failure, recognizing ST2 as *"not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in [its] prognostic value."* The guideline gives ST2 its highest classification ("A") for the body of evidence supporting its recommendation.

Says David Geliebter, CEO of Critical Diagnostics: "As these studies show, ST2 can be an important element in delivering more efficient and effective care to the millions of people suffering from heart failure."

IDENTIFYING PATIENTS THAT COULD BENEFIT FROM HIGH-DOSE BETA BLOCKERS

(continued from page 7)

The study also demonstrated that ST2 measurements were independent predictors of one-year mortality, even after a rigorous multivariate analysis adjusting for important risk factors (blood urea nitrogen, systolic blood-pressure and serum creatinine), traditional markers of inflammation (total white cell count and high-sensitive C-reactive protein), plus the cardiac biomarker BNP, as well as the cumulative diuretic dose administered during the first 48 hours.

The strongest effect in mitigating risk by intensified outpatient care was seen with the addition of beta blockers, but similar trends were observed with diuretics, and with renin-angiotensin-aldosterone system (RAAS) inhibitor drugs, the most common being ACE inhibitors.

"This most recent study provides compelling evidence that risk shown by either baseline ST2 or change in ST2 is both accurate and can be attenuated," notes James Snider, President of Critical Diagnostics. "Patients shown to be high risk by ST2, but who receive more intensive follow-up therapy have significantly better outcomes, comparable to low ST2 patients, suggesting that ST2 monitoring may be an effective tool to assess therapeutic effectiveness."

This study expands on recent work done at Massachusetts General Hospital ("Soluble Concentrations of the Interleukin Receptor Family Member ST2 and Beta Blocker Therapy in Chronic") published in October 2013 in *Circulation: Heart Failure*, of beta blocker interaction with baseline ST2 measurements in ambulatory heart failure patients, by extending therapy interaction analysis to the in-patient environment and with serial testing. That study showed that at baseline, patients with elevated ST2 levels who were taking low doses of beta blocker were almost seven times as likely to experience a cardiovascular event, such as an unplanned hospitalization, than patients who had low ST2 levels and were on high-doses of beta blocker.

This study also confirms similar findings in two other studies.

S. Boisot et al ("Serial Sampling of ST2 Predicts 90-day Mortality Following Destabilized Heart Failure," *Journal of Cardiac Failure*, 2008) prospectively determined the prognostic utility of serial sampling ST2 for predicting 90-day mortality in 150 acutely destabilized patients with heart failure admitted to a Veteran Affairs Medical Center in San Diego, and found that percent change in ST2 concentrations during acute heart failure treatment was predictive of 90-day mortality and was independent of BNP or NT-proBNP levels.

Results reported by Benoit et al ("ST2 in Emergency Department Patients With Noncardiac Dyspnea") in the *Academy of Emergency Medicine* in October, 2013, from a prospective observational cohort study of 82 patients with dyspnea secondary to acute heart failure and acute coronary syndrome that presented to the Department of Emergency Medicine, University of Cincinnati, showed that patients with non-cardiac dyspnea who died or required readmission to the hospital within 180 days had higher levels of ST2 compared with non-admitted survivors.

"What we are witnessing is the evolution of diagnostics from a lower value, high volume business into one of the key drivers of improved patient outcomes, and ST2 is helping to lead that change," says David Geliebter, Founder and CEO of Critical Diagnostics. "In the future, patients will receive more targeted therapies, and their doctors will have a higher degree of certainty than ever before that their patients are receiving the right treatment, all while reducing overall healthcare costs."

ST2 HELPS ASSESS HEART FAILURE RISK AND IDENTIFY PATIENTS LIKELY TO BENEFIT FROM EXERCISE

(continued from page 13)

analysis pointed out, "In a final model adjusting for all predictors of the primary endpoint in the HF-ACTION dataset as a whole . . . as well as NT-proBNP, there was no evidence for an independent association between galectin-3 and outcomes . . . Given the unique nature of the randomized intervention in the HF-ACTION study (exercise training), we examined the interaction between baseline galectin-3 levels and treatment assignment. There was no significant interaction between galectin-3 levels and exercise training for any of the 3 study endpoints [all-cause death or hospitalization, cardiovascular death or cardiovascular hospitalization, and for cardiovascular death or heart failure hospitalization.]"

"The ability of a biomarker to identify low risk as well as high risk patients with heart failure is very important," says Critical Diagnostics' President James Snider. "As noted in this study, patients identified as low risk by ST2 showed a significant benefit from exercise as part of their care plan, and is thus another example of how ST2 can provide information to the physician helpful in guiding care and management of their heart failure patients."

"We want to get to a place with heart failure where we have a better understanding of what is happening in the heart at a molecular level, and we want to be able to better identify the sickest patients who are at greatest risk for being hospitalized and would benefit most from intensive therapies," said Dr. Ahmad, MD, MPH, who led the HF-ACTION study, in a report published in March, 2012, on the Duke Clinical Research Institute's website. "ST2 is one of the exciting new emerging tools in heart failure. It may give us unique insights into the pathophysiology of heart failure, and provide independent prognostic information about patient outcomes."

ST2 PROVES VALUABLE IN HELPING RISK ASSESS HEART FAILURE PATIENTS WITH RENAL INSUFFICIENCY

(continued from page 14)

natriuretic peptides and troponins, are substantially affected by it," remarks Antoni Bayes-Genis, MD, PhD, FESC, one of the authors of the paper. "Here we provide evidence that ST2 remains stable in moderate to severe renal dysfunction – even in the sickest class III-IV heart failure patients. Thus ST2 may be the best option for the practicing clinician in this subgroup of patients."

"While natriuretic peptide biomarkers such as BNP and NT-proBNP have become the accepted standard for diagnosing heart failure, their use presents challenges, particularly in this comorbidity 'grey zone,' where interpretation of results can be muddled," comments David Geliebter, CEO of Critical Diagnostics. "This study proves yet again that ST2 is the most powerful chronic heart failure risk stratification tool available, and that unlike natriuretic peptide markers, ST2 is not adversely affected by confounding factors such as age, body mass index and impaired renal function."

A PATENT ON PREVENTION

(continued from page 19)

the most risk of heart failure or death over this same period of time.

"The implications of these findings from both Framingham and Olmsted are enormous," notes David Geliebter, CEO of Critical Diagnostics. "They mean that the onset of hypertension or heart failure are not a certainty, that with this knowledge in hand, physicians may be able to offer their patients tailored treatment options as part of a preventative approach to medicine that can postpone or even prevent such life-threatening disorders."

CRITICAL DIAGNOSTICS

3030 BUNKER HILL STREET
SUITE 117A
SAN DIEGO, CA 92109

THE PRESAGE® ST2 ASSAY is a simple blood test that aids physicians in risk assessment of chronic heart failure patients. Elevated ST2 levels are indicative of increased risk of an adverse event, hospitalization or death.

FROM THE 2013 ACC/AHA GUIDELINE FOR HEART FAILURE MANAGEMENT:

ST2 is "not only predictive of hospitalization and death in patients with HF [heart failure] but also additive to natriuretic peptide levels in [its] prognostic value."

THE PRESAGE ST2 ASSAY IS AVAILABLE FROM THESE PREFERRED LABORATORIES:

ARUP® LABORATORIES

ORDERING INFORMATION
Test Code: 2002268

MAYO CLINIC
Mayo Medical Laboratories

ORDERING INFORMATION
Test ID: ST2S

Quest Diagnostics®

ORDERING INFORMATION
Test Code 91523