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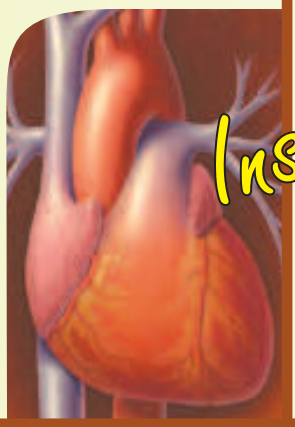

Insight HEART

Vol: 9 No: 2; 2013

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American College of Cardiology Recommends

Five Things Physicians and Patients Should Question

1 Don't perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present.

Asymptomatic, low-risk patients account for up to 45 percent of unnecessary "screening." Testing should be performed only when the following findings are present: diabetes in patients older than 40-years-old; peripheral arterial disease; or greater than 2 percent yearly risk for coronary heart disease events.

2 Don't perform annual stress cardiac imaging or advanced non-invasive imaging as part of routine follow-up in asymptomatic patients.

Performing stress cardiac imaging or advanced non-invasive imaging in patients without symptoms on a serial or scheduled pattern (e.g., every one to two years or at a heart procedure anniversary) rarely results in any meaningful change in patient management. This practice may, in fact, lead to unnecessary invasive procedures and excess radiation exposure without any proven impact on patients' outcomes. An exception to this rule would be for patients more than five years after a bypass operation.

3 Don't perform stress cardiac imaging or advanced non-invasive imaging as a pre-operative assessment in patients scheduled to undergo low-risk non-cardiac surgery.

Non-invasive testing is not useful for patients undergoing low-risk non-cardiac surgery (e.g., cataract removal). These types of tests do not change the patient's clinical management or outcomes and will result in increased costs.

4 Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms.

Patients with native valve disease usually have years without symptoms before the onset of deterioration. An echocardiogram is not recommended yearly unless there is a change in clinical status.

5 Don't perform stenting of non-culprit lesions during percutaneous coronary intervention (PCI) for uncomplicated hemodynamically stable ST-segment elevation myocardial infarction (STEMI).

Stent placement in a noninfarct artery during primary PCI for STEMI in a hemodynamically stable patient may lead to increased mortality and complications. While potentially beneficial in patients with hemodynamic compromise, intervention beyond the culprit lesion during primary PCI has not demonstrated benefit in clinical trials to date.

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Ranolazine for the Treatment of Heart Failure With Preserved Ejection Fraction:Background, Aims, and Design of the RALI-DHF Study

Introduction

The prevalence of heart failure (HF) has reached epidemic proportions in Western countries. Diastolic heart failure (DHF) currently accounts for >50% of all patients with HF. Diastolic heart failure is also referred to as HF with preserved ejection fraction (HFpEF). Patients with HFpEF suffer from symptoms of congestive heart failure (dyspnea on exertion, ankle swelling, hepatomegaly, etc.) due to an impaired relaxation and increased stiffness of the left ventricle (LV). Injuries sustained by the myocardium leading to interstitial fibrosis and myocyte hypertrophy, impaired intracellular calcium homeostasis, reduced elastic recoil due to isomeric changes in sarcomeric proteins, and various neurohormonal activation are involved in HFpEF.

The physical limitations (exercise intolerance) and psychological strain in HFpEF are substantial, and the prognosis is as ominous as that of patients suffering from systolic heart failure (SHF), with 5-year mortality of about 50%. Diastolic LV dysfunction is not unique to patients with HFpEF, but also occurs in patients with SHF; and in this latter group, the degree of diastolic LV dysfunction correlates even better with symptoms than the left ventricular ejection fraction (LVEF).

Whereas in SHF a variety of evidence-based therapeutic options for the improvement of symptoms and prognosis are available, the treatment options for patients with DHF are limited. Currently, there is no specific treatment for impaired LV relaxation that results in symptomatic improvement and/or prognostic relevance for these patients. The piperazine derivative ranolazine, marketed as Ranexa for the treatment of chronic angina, is an anti-ischemic agent that has been shown in preclinical and clinical studies to selectively inhibit the late sodium current ($I_{Na,late}$) in cardiac myocytes. This might be of particular importance in patients with HF and diastolic dysfunction; it is known that in the failing heart, the late sodium current ($I_{Na,late}$) is increased, leading to an Na^+ accumulation in cardiac myocytes. The increased Na^+ concentration reverses the mode direction of the Na^+/Ca^{2+} exchanger, contributing to a Ca^{2+} overload in the cell. Increased diastolic Ca^{2+} impairs relaxation leading to diastolic dysfunction. By inhibiting the $I_{Na,late}$, ranolazine is expected

Table 1. Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) Inclusion Criteria

1. Males or females age ≥40 years
2. Clinical symptoms of heart failure (NYHA class II-III) at time of screening (eg, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema)
3. LVEF ≥50% at screening
4. With:
   a. E/E'>15 measured by tissue Doppler echocardiography at screening or
   b. NT-proBNP >220 pg/mL at screening and
   c. Average resting LVEDP ≥18 mm Hg (refer to continued eligibility criteria), and
   d. Average resting time constant of relaxation (τ) ≥50 ms at time of cardiac catheterization (refer to continued eligibility criteria).
5. For female patients: must be post- menopausal (no menses for last 24 mo) or sterilized; or if of child-bearing potential, is not breastfeeding, has a negative pregnancy test at time of study, has no intention of becoming pregnant during the study, and is using a safe contraceptive regimen.
6. Signed informed consent. Continued eligibility criteria: Patients must continue to meet eligibility criteria and have an average (of 3 measurements) resting LVEDP ≥18 mm Hg and resting τ ≥50 ms at time of cardiac catheterization to receive study drug.

Abbreviations: E/E′, ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; NT-proBNP, N-terminal pro-type brain natriuretic peptide; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2. Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) Exclusion Criteria

1. Acute cardiac decompensation requiring mechanical ventilation
2. Hypotension with systolic/diastolic BP <90/50 mm Hg, respectively
3. Primary hypertrophic or restrictive cardiomyopathy or systemic illness associated with infiltrative heart disease (eg, cardiac amyloidosis)
4. Pericardial constriction
5. Hemodynamically significant uncorrected obstructive or regurgitant valvular disease
6. Cor pulmonale or other causes of right heart failure not associated with LV dysfunction
7. MI, UA, or CABG surgery within 90 days prior to screening, or PCI within 30 days prior to screening
8. Stroke within 90 days prior to screening
9. Clinically significant pulmonary disease in opinion of the investigator, or requiring home oxygen or oral steroid therapy
10. History of serious cardiac dysrhythmias, including AF with resting heart rate >100 bpm
11. Need for treatment with class I or III antiarrhythmic medications
12. Implantable pacemaker, cardioverter-defibrillator, or LVAD
13. Clinically significant chronic hepatic impairment (Child-Pugh class B [moderate] or class C [severe])
14. Severe renal insufficiency defined as creatinine clearance ≤ 30 mL/min as calculated by Cockcroft-Gault formula or MDRD equation
15. History of congenital or a family history of long QT syndrome, or acquired QT-interval prolongation
16. Inability to exercise due to comorbidities that affect performance of CPET (eg, osteoarthritis, PVD)
17. Current treatment with potent and moderate CYP3A inhibitors
18. Current treatment with potent CYP3A inducers
19. Prior treatment with ranolazine
20. Participation in another trial of an investigational drug or device within 30 days prior to screening
21. Other conditions that in the opinion of investigator may increase risk to the patient (eg, weight < 60 kg), prevent compliance with study protocol, or compromise the quality of the clinical trial.

Abbreviations: AF, atrial fibrillation; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CPET, cardiopulmonary exercise test; CYP3A, cytochrome P450, family 3, subfamily A; LV, left ventricular; LVAD, left ventricular assist device; MDRD, Modified Diet in Renal Disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; UA, unstable angina.

to prevent (or reduce) sodium accumulation in the myocyte. This should improve calcium extrusion through the Na^+/Ca^{2+}- exchanger and thereby improve relaxation of the myocardium. Data from in vitro and animal studies indicate that ranolazine improves diastolic function of the myocardium. We published results of a study that confirms the improvement of diastolic function by ranolazine in ex vivo (isolated) human myocardium from patients suffering from HF and diastolic dysfunction, and more recently in another study using right atrial trabeculae from patients with chronic atrial fibrillation.

Ranolazine significantly reduced the increased diastolic tension in isolated myocardial muscle strips by ~30%. This effect was more pronounced at higher stimulation rates of the muscle strips, and especially in the myocardium with severe diastolic dysfunction. This is important because patients with HFpEF typically decompensate at high heart rates (eg, during new onset of atrial fibrillation). Mechanistically, we could show that ranolazine inhibits the $I_{Na,late}$ and thereby reduces intracellular diastolic sodium and calcium concentrations. Neither the sarcoplasmic reticulum calcium content nor the systolic function of the myocardium was significantly affected. In a canine model of chronic HF, ranolazine significantly decreased the LV end-diastolic pressure (LVEDP) as a parameter for diastolic dysfunction. Furthermore, ranolazine has been shown to improve diastolic function in patients with ischemic heart disease.

The primary objective of the RALI-DHF trial is to determine if ranolazine, compared with placebo, will be more effective in improving diastolic function in patients with HFpEF.

Methods

Study Design and Patient Selection

The RALI-DHF study is a prospective, single-center, randomized, double-blind, placebo-controlled proof-of-concept study to investigate the effect of ranolazine on diastolic function in patients with HFpEF. The trial is funded by a grant from Gilead Sciences Palo Alto, Inc. (Foster City, CA). The ClinicalTrials.gov registration number is NCT01163734.

Patients with clinical symptoms of HF undergoing cardiac catheterization as part of the routine diagnostic procedure

for standard care will be screened for inclusion into the study. Twenty patients who fulfill the inclusion and exclusion criteria will be randomized to receive ranolazine or placebo in a 1.5:1 ratio (12 patients will receive ranolazine and 8 patients will receive placebo). Inclusion and exclusion criteria are listed in Tables 1 and 2.

Study Conduct and Procedures

Patients with clinical symptoms of HF will be consented and screened for eligibility. Complete medical history and physical examination will be recorded at screening. Echocardiography will be performed to determine cardiac dimensions, regional and global contractility, and cardiac valve functions. The measured and calculated parameters that are obtained by standard 2-D images, pulsed-wave and continuous-wave Doppler tracings, and tissue Doppler are listed in Table 3.

Blood samples will be collected to determine the level of N-terminal pro-type brain natriuretic peptide (NTpro- BNP) at screening. Other laboratory measurements include complete blood count, red blood cells, hemoglobin, hematocrit, platelet count, white blood count, coagulation test/international normalized ratio, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, blood urea nitrogen, creatinine, gamma-glutamyl transferase, potassium, and sodium.

Table 3. Hemodynamic Data and Echocardio - graphic Parameters

Hemodynamic Data and Pressure Measurements

- Time constant of relaxation (τ)
- Relaxation time
- Left ventricular end-diastolic pressure (LVEDP)
- Left ventricular end-systolic pressure (LVESP)
- dP/dt minimum
- Pulmonary capillary wedge pressure (PCWP)
- Pulmonary artery pressure (systolic/diastolic/mean)
- Systemic vascular resistance (SVR)
- Pulmonary vascular resistance (PVR)
- Cardiac output (CO) and cardiac index (CI)
- Right atrial pressure (RAP)

Echocardiographic Parameters

- Left ventricular end-diastolic volume/index (LVEDV)
- Left ventricular end-systolic volume/index (LVESV)
- Left ventricular stroke volume
- Left ventricular ejection fraction (LVEF; Simpson method)
- Mitral E wave velocity
- Mitral A wave velocity
- Mitral E/A ratio
- Mitral annular velocity (E/E′, tissue Doppler)
- E/E′ ratio

A standard 12-lead electrocardiogram (ECG) will be performed and reviewed for any clinically significant abnormalities to ensure patient safety. A symptom-limited cardiopulmonary exercise test (CPET) will be performed using a bicycle ergometer. The following parameters will be measured: peak oxygen uptake (Pk VO_2), maximal oxygen uptake (VO_2 max), anaerobic threshold, respiratory exchange ratio (RER), oxygen saturation (SpO_2), exercise duration, and ventilation/carbon dioxide production ratio (V_E/V_{CO_2}).

Patients who fulfill the inclusion and exclusion criteria will be randomized prior to catheterization. The cardiac catheterization itself is part of the diagnostic procedure of the standard of care for these patients. A catheter will be introduced into the right ventricle and into the pulmonary artery for measurement and analysis of right heart pressures. A conductance catheter will be advanced into the LV for measurement of LV pressures and pressure/volume relations. A transient pacemaker probe will be introduced into the right atrium for pacemaker stimulation. If clinically indicated, coronary angiography will be performed before any pressures and hemodynamic data are measured. Once all catheters are in stable position, 3 sets of pressures and hemodynamic assessments will be will be performed at 120 bpm and 3 sets of pressures and hemodynamic assessments will again be obtained. The parameters that will be obtained are listed in Table 3.

Administration of the study drug (placebo or ranolazine) will be initiated if the continued eligibility criteria (average resting LVEDP ≥18 mm Hg and τ ≥50 ms) are met. The study treatment will begin with an initial intravenous (IV) bolus injection at T = 0 minutes of 92 mg ranolazine or placebo (Figure 1). The initial 92 mg of study drug will be administered as 10-mL loading bolus over a period of 2 minutes. A second bolus injection of 92 mg ranolazine or placebo at the same dilution will be administered 15

minutes (T = 15 min) after initial bolus injection. Continuous infusion of ranolazine or placebo at a dose of 92 mg/hour (23 mL/h) will start at T = 20 minutes (5 min after the start of second bolus injection) and continue through to 24 hours (T = 24 h). To assess pharmacokinetic (PK) parameters, PK blood samples will be drawn at T = 10 minutes, T = 20 minutes (prior to continuous infusion), and T = 30 minutes.

The catheter probes stay in place during the initiation of the IV study drug administration. All invasive measurements will be repeated at 30 minutes after initiation of the first loading bolus (T = 30 min) at resting (3 sets) and paced (3 sets) conditions. Three measurements will be taken, and the average of the 3 will represent the value for that variable measured. When all assessments are complete, the catheters are removed and the patient is transferred to the cardiac ward for monitoring (continuous 3-lead ECG monitoring via telemetry, vital signs every 4 h). The IV study drug infusion will be continued through to 24 hours (T = 24 h). One hour prior to the end of the 24-hour infusion, patients will be started on oral study drug 1000 mg twice daily and will be continued until the end of the study on day 14. All echocardiography measurements will be repeated at T = 22 hours (within 60 min prior to administration of oral study drug). The 12-lead ECG will be repeated at this time point. Patients may be discharged at any time after T = 24 hours at the investigator's judgment per standard of care. Oral treatment will last for 13 days. Patients will be instructed to take 2 intact tablets of the study medication with water every day at 12-hour intervals (in the morning and in the evening).

Patients will be required to return to clinic for the end of study visit on day 14 (+2 d). The end-of-study visit procedures (specifically, echocardiography and CPET) will be performed within 2 to 6 hours after the morning dose.

The following assessments will be performed: complete PE including vital signs and weight measurements, 12-lead ECG, echocardiography (prior to CPET), NT-pro-BNP determination and safety labs, CPET, serum pregnancy test (for females aged < 65 years), adverse events, and concomitant medications.

Approximately 14 days after the end-of-study visit, the patient will be contacted either by phone or in person to assess and record –adverse-event and concomitant medication status since the last visit (day 28 safety follow-up contact). The schedule of study events is depicted in Figure 2.

Endpoints

The study will include the following exploratory endpoints:

1. Change from baseline to 30 minutes from initiation of study drug bolus No. 1 (T = 30 min) in cardiac catheterization hemodynamic parameters at both resting and paced conditions:

- Time constant of relaxation (τ).

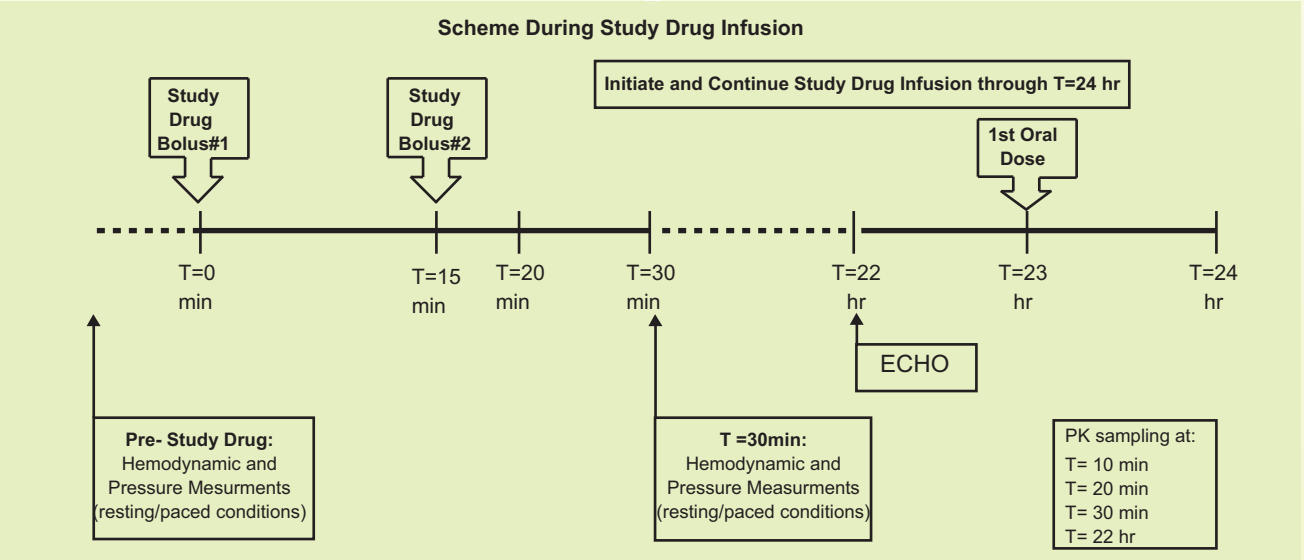


Figure 1. Schema during study-drug infusion. Abbreviations: ECHO, echocardiography; PK, pharmacokinetic.

- LVEDP
- dP/dt min (minimal rate of LV pressure change).

2. Change from baseline to day 14 in:

- Mitral E wave velocity/mitral annular velocity (E/E′) ratio assessed by tissue Doppler echocardiography.
- VO max assessed by CPET.
- NT-pro-BNP.

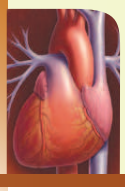
Baseline is defined as the average of 3 measurements of each hemodynamic parameters taken at rest conditions and during pacing prior to start of study-drug infusion.

Schedule of events

Assesment	Day - 1 Screen	Day - 1 Pre Cath	Day - 1 Cardiac Cath	Day -2 End of infusion	Day 2-13 Oral Dosing	Day -14 End of Study	Day -28 Phone Contact
Informed Consent	X						
IEC	X	X					
Medical History	X						
Physical Exam [a]	X					X	
Vital Signs[b]	X	X ---------- X				X	
ECS[c]	X	X[d] ---------- X				X	
Local Safety Labs	X					X	
NT - pro - BNP	X					X	
Pregnancy test	X					X	
ECHO[e]	X			X		X	
CPET	X					X	
Randomization		X[g]					
Hemodynamic / Pressure Measures			X[f]				
Study Drug Administration			X[h] ---------- X		X[i] ---------- X		
PK Sampling[j]			X[j] ---------- X				
Concomtant Meds	X ---------- X						
Adverse Events	X ---------- X						

a. Include height and weight with height measured at Screening only.
b. Continuous vital signs monitoring until end of catheterization procedure. Record VS at T=0, every 15 min through T = 2 hr, T= 4hr, then every 4 hrs until end of 24-hr sudy drug infusion.
c. Standard 12-lead ECG at Screening, End of infusion and Day 14 end of study.
d. Continuous 3-lead ECG monitoring via cardiac monitors and telemetry until end of 24-hr study drug infusion.
e. Include standard 2-D, pulsed wave Doppler and Tissue Doppler imaging.
f. Measured at resting and paced conditions before start of study drug infusion and at 30 minutes after start of study drug intiation; measurements will occur in sets of 3.
g. Occurs prior to catheterization procedures; obtain study drug prior to proccedure
h. iv loading bolus No. 1 at T=0, iv loading bolus No. 2 at T=15 min, followed by initiation of iv continuous infusion at T=20 min (92 mg/hr) for 24-hours at a rate of 23 ml/hr.
i. Oral treatment to begin 1 hour before end of 24-hr infusion and continue until Day 14.
j. PK sampling will occur at T=10 min, T=20 min, T=30 min (prior to hemodynamic measures), and T=22 hours (prior to ECHO)

Figure 2. Schedule of events. Abbreviations: cath, catheterization; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; ECHO, echocardiography; iv, intravenous; NT-proBNP, N-terminal pro-type brain natriuretic peptide; PK, pharmacokinetic.



Detailed analyses of hemodynamic data and pressure measurements, echocardiography, and CPET parameters will be performed, pending on blinded review of the distributions of each measurement.

Statistical Considerations

The current study is considered exploratory, and therefore the sample size selection is based on practical considerations.

All statistical tests for treatment difference between ranolazine vs placebo will be performed using 2-sided hypothesis tests at 5% significance level with no adjustment for multiple comparisons. Descriptive summaries will show counts and percentages for categorical variables and sample size, mean, SD, or SEM, minimum, median, and maximum for continuous variables by treatment. The Wilcoxon rank sum test will be applied to evaluate whether the reductions from baseline in primary and secondary efficacy endpoints are statistically significantly different between placebo vs ranolazine. The Cochran-Mantel-Haenszel test may be used to compare categorical variables between randomized treatments: row mean scores test for ordered categorical variables and general association test for nominal categorical variables. Analysis of variance, including effects for treatment, may be used to analyze continuous variables. All patients who receive $\geq$1 dose of randomized study medication will be included in the analyses for both efficacy and safety endpoints. Patients will be assigned to treatment group according to the treatment actually received.

Discussion

Despite the high prevalence, morbidity, and poor prognosis of HFpEF, its treatment is still poorly defined. Compared with trials in patients with reduced EF, fewer trials have included patients with HFpEF, and often the results have been disappointing. Thus far, there has been no specific treatment for impaired LV relaxation. In preclinical studies we could demonstrate, that ranolazine improves relaxation in myocardium from patients with HF and diastolic dysfunction due to normalization of altered intracellular sodium and calcium homeostasis. The RALI-DHF study provides a bench-to-bedside translational approach to evaluate if ranolazine, compared with placebo, will be more effective in improving diastolic function in patients with HFpEF by inhibiting the $I_{Na,late}$, as described in the background section of this paper. However, diastolic heart failure is not only caused by an abnormal Ca^{2+} and Na^{+} homeostasis. Increased interstitial deposition of collagen and modified matricellular proteins also contributes to increased myocardial stiffness and slowed LV relaxation. It is not expected that ranolazine will affect this structural pathophysiology. Therefore, the chances for a positive result will depend on the relative contribution of the dysregulated cellular Na^{+} and Ca^{2+} homeostasis to the mechanism underlying diastolic dysfunction. Furthermore, it has to be considered that the results in isolated myocardium might not reflect the in vivo situation in patients with HFpEF.

The RALI-DHF study is considered exploratory, and therefore the sample size (20 patients) is based on practical considerations. If ranolazine significantly improves diastolic function in this proof-of-concept study, a larger, multicenter trial will be warranted to confirm whether ranolazine, over a longer period of treatment, provides meaningful clinical benefit for these patients.

Diastolic LV dysfunction is not unique to patients with HFpEF; it also occurs in patients with HF and reduced EF, and in these patients parameters of diastolic dysfunction even correlate better with symptoms than LVEF. Dyspnea and edema of the lower extremities are symptoms of CHF that is caused by increased left atrial and LV filling pressures. Therefore, it is also reasonable to investigate the effect of ranolazine on diastolic function in patients with SHF. A separate clinical study, RALI-SHF, will be also initiated to address this issue.

In conclusion, ranolazine by inhibiting $I_{Na,late}$ has been shown to improve diastolic function in isolated human myocardium and animal models as shown previously. In summary, RALI-DHF is designed to investigate the effect of ranolazine on LV diastolic function in patients with HFpEF.

Ref: Ranolazine for the Treatment of Heart Failure With Preserved Ejection Fraction: Background, Aims, and Design of the RALI-DHF Study. Claudius Jacobshagen, Luiz Belardinelli, Gerd Hasenfuss, Lars S. Maier. Clin. Cardiol. 34, 7, 426–432 (2011)

Insight HEART
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Cardiology News

Energy Drinks May Prolong QT Interval, Raise BP

Tossing back one to three energy drinks may result in more than just a buzz. A small-meta analysis found that immediately afterward, subjects had increased systolic blood pressure and, more troubling, they also had, on average, a 10-msec prolongation in their QT interval. Three studies with a pooled sample of 93 subjects had QT/QTc data. Six studies with a pooled sample of 132 subjects had blood-pressure data, and seven studies investigated heart rate. The patients, who were all young (aged 18 to 45) and healthy, underwent ECG and blood-pressure testing before and just after drinking one to three cans of energy drink. Shortly after drinking the energy drinks, the pooled subjects had a systolic blood pressure increase of an average 3.5 mm Hg. In a clinical setting, physicians are usually concerned if a patient has a QT-interval increase of about 30 msec from baseline. Diastolic BP and heart rate increased nonsignificantly.

EPI-NPAM 2013; New Orleans, LA, March 21, 2013. Abstract P324.

Statins Tied to Lower Liver Cancer Risk With Hep C

Clinical improvements seen with the addition of ivabradine to standard heart-People with chronic hepatitis C are less likely to develop liver cancer if they are taking statins, research from Taiwan suggests. Previous studies have come to ambiguous and conflicting conclusions on the question of statins' cancer-preventing abilities. At the National Taiwan University College of Public Health in Taipei, Dr. Pau-Chung Chen and colleagues used nationwide data to track nearly 261,000 people with hepatitis C from 1999 through 2010. The researchers said statins may prevent the hepatitis C virus from replicating or slow the growth of malignant cells. But they can't prove the drugs stopped people from getting cancer. One limitation, they noted, is that they weren't able to measure other health and lifestyle factors that influence people's risk of liver cancer, including their weight and whether they smoked or drank heavily.

J Clin Oncol 2013.

Mitral Valve Disease in the Elderly: Repair or Replace?

For elderly patients with mitral valve disease, surgery offers better survival than medical treatment, and repair seems better than replacement for most patients, a longitudinal analysis suggests. This study included 47,279 patients, of whom 17,360 (36.7%) had mitral valve repair and 29,919 (63.3%) had valve replacement. Comorbidities were common: 60.4% had heart failure, 17.5% had renal insufficiency, 17.6% had COPD, and 48.5% had atrial fibrillation. Operative mortality was 3.9% with repair and 8.9% with replacement. During a median follow-up of five years, survival estimates were better after repair (90.9% at one year, 77.1% at five years, and 53.6% at 10 years) than for patients undergoing replacement (82.6% at one year, 64.7% at five years, and 37.2% at 10 years). When patients were stratified into age groups, survival estimates were higher for patients under 75 years old than for old patients, but the patterns were consistent: higher survival rates after repair than after replacement. Female gender and the presence of comorbidities predicted lower likelihood of mitral valve repair, whereas younger age, elective admission status, and greater annual mitral procedure volume predicted higher likelihood of mitral valve repair. These findings go counter to current guidelines that favor medical management of elderly asymptomatic or mildly symptomatic patients.

Circulation, Apr, 2013.

Editorial Note

Dear Doctor,

We are happy to present the 29th issue of "Insight Heart". It is a small endeavor to provde you compiled & updated information on cardiovascular diseases and its management. This issue is focused on " ***Ranolazine for the Treatment of Heart Failure***". We will appreciate your thoughtful comments.

Thanks and regards.