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trial that demonstrated a significant improvement in a composite of heart failure (HF) status and clinical events by using implant-based remote-monitoring to assist physicians in the management of patients with advanced HF.

The ability to more closely monitor these tenuous patients has long been hypothesized as a way to improve a wide variety of HF endpoints. Certain clinical events or characteristics, such as arrhythmia or increased heart rate at rest, may precipitate worsening HF, leading to hospital admission or death [Opasich C et al. *Am J Cardiol 2001*]. Home-monitoring (HM) data provides access to these early predictive changes of worsening HF and thereby may enable intervention prior to hospitalization [Sack S et al. *Eur J Heart Fail* 2011].

IN-TIME was designed to evaluate the impact of physician access to these predictive parameters (eg, heart rate, atrial fibrillation burden) in relative "real-time" to influence changes in therapeutic treatment. No specific guidance was provided to physicians; treatment decisions were left to each physician's clinical judgment. The primary endpoint was the modified Packer score—a clinical composite score based on mortality, overnight hospitalization for worsening HF, NYHA class status, and changes in the patient's global self-assessment score. Secondary endpoints included all-cause total mortality and the number of overnight hospitalizations due to worsening HF.

The trial was conducted among 36 international investigational centers. Inclusion criteria included a history of HF ≥3 months, NYHA Class II or III symptoms for 1 month prior to screening, left ventricular ejection fraction ≤35% within 3 months prior to screening, indication for diuretic therapy and an indication for an implantable cardioverter defibrillator (ICD; with or without cardiac resynchronization therapy). All patients received a device with remote-monitoring capability at the time of ICD implantation. Although remote monitoring data were collected for all patients, these were not available to treating physicians until the study was completed in the control group.

Of the 716 patients enrolled, 52 were excluded during an initial run-in; 664 were subsequently randomized to either HM (n=333) or a control group with standard HF care (n=331). Baseline characteristics were similar in both arms, except for a slightly lower utilization of angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker in the control arm (86.4% vs 92.2%). A total of 82 patients (30 in the HM arm and 52 in the control arm) did not complete 12 months of follow-up. This difference was primarily related to the excess of mortality in the control arm compared to HM arm (control 27 vs HM 10).

At 12 months, significantly fewer patients in the HM group compared with the control group had reached the primary endpoint, worsening of HF according to modified Packer score (18.9% vs 27.5%; p<0.05). A significantly

reduced rate was found in the secondary endpoint of all-cause mortality (HR, 0.36; 95% CI, 0.17 to 0.74; p=0.004). The increase in mortality was largely cardiovascular in cause (HR, 0.37; 95% CI, 0.16 to 0.83; p=0.012).

IN-TIME has contributed important data regarding the efficacy of telemonitoring in patients with HF. Further analyses are needed to better understand its impact on how physicians responded to these data and the consequent changes in conventional therapies. Prof. Hindricks summarized by stating that IN-TIME is the first implant-based, telemonitoring, randomized trial to show significant survival benefits of this type of monitoring in advanced HF patients. The decrease in mortality will require further studies for validation since there were a small number of deaths (37 total) in this trial, and it was not powered to evaluate this endpoint.

Losartan Reduces Aortic Dilatation Rate in Adults With Marfan Syndrome

Written by Maria Vinall

Results from the Cozaar in Marfan Patients Reduces Aortic Enlargement trial [COMPARE; Groenink M et al. *Eur Heart J* 2013] reported by Maarten Groenink, MD, PhD, Academic Medical Centre, Amsterdam, The Netherlands, demonstrated that the angiotensin receptor blocker, losartan, significantly reduced the rate of aortic enlargement after 3 years in patients with Marfan syndrome (MFS).

MFS is a connective tissue disorder caused by a mutation in fibrillin-1 that is associated with structural dysfunction in the aortic wall and biochemical changes including over expression of TGF β [Cohn RD et al. *Nat Med* 2007]. Patients with MFS are at an increased risk of sudden death due to aortic dissection or rupture. Clinical management includes prophylactic aortic root replacement and pharmacologic therapy (β-blockers and possibly losartan).

COMPARE was a multicenter, open-label, randomized, controlled trial designed to assess the effect of the addition of losartan to the standard of care on the rate of aortic dilatation at any level in adult patients with MFS. The study included adults aged ≥18 years with MFS (as classified by the 1996 Ghent criteria) with an aortic root diameter <50 mm, no aortic dissection and ≤1 vascular prosthesis. Subjects received losartan (100 mg QD) along with their previous medication (n=116) or remained on their previous medication only (n=117). Magnetic resonance imaging was performed at inclusion and after 3 years of follow-up. The primary endpoint was aortic dilatation rate at any of the predefined aortic levels at follow-up. Secondary endpoints included

changes in the incidence of cardiovascular mortality, aortic dissection, aortic volume, and prophylactic aortic surgery [Radonic T et al. *Trials* 2010].

Subjects (53% women in the control group; 41% in the treatment group) were aged 20 to 50 years (mean age 37 years); most (~73%) were on β-blockers. A significant proportion of patients in both groups had already undergone aortic root replacement (31% of controls and 23% in the treatment group). At baseline, subjects had a mean aortic root measurement of 44 to 45 mm.

After 3 years aortic root enlargement was significantly less in the losartan group than in the control group (0.77 vs 1.35 mm; p=0.014; Figure 1), and 50% of losartan patients showed no growth of the aortic root compared with 31% of controls (p=0.022).

Figure 1. Aortic Root Dilatation Rate
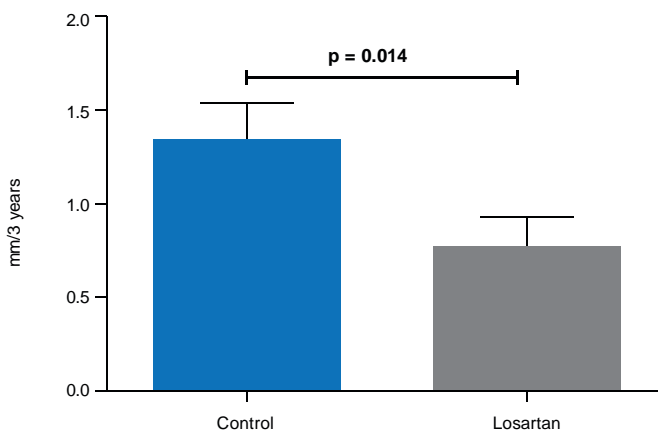
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All subgroups benefited from losartan regardless of age, sex, the presence of fibrillin-1 mutation, β-blocker use, mean aortic pressure, or aortic root size. There were no differences in aortic dilatation rate beyond the aortic root. There were no significant differences in combined clinical endpoints between the two groups. There were no cardiovascular deaths in either arm.

In a small subset of patients treated with prior aortic root replacement, patients treated with losartan (n=26) had significantly lower dilatation rates of the aortic arch compared with controls (n=31; 0.50 vs 1.01 mm; p=0.033; Figure 2).

The results of the COMPARE trial suggest that the addition of losartan to standard care in patients with MFS reduces the rate of aortic dilatation and may also reduce the rate of aortic arch dilatation among patients who have already had aortic root replacement. Study limitations include being open-label and not achieving target inclusion population.

Figure 2. Dilatation Rate of the Aortic Arch After Prophylactic Aortic Root Replacement
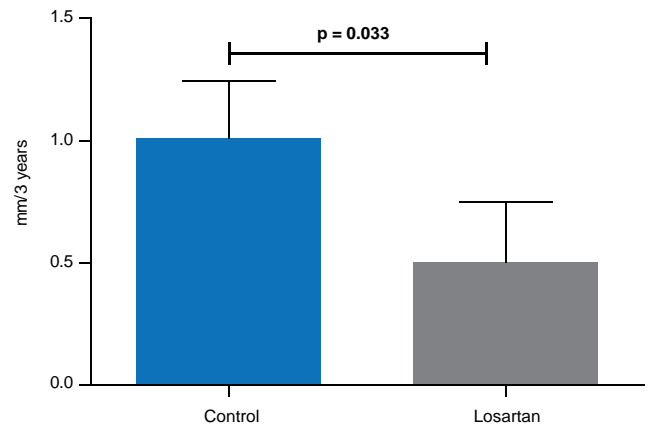
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Omecamtiv Mecarbil: Phase 2 Study Shows No Improvement in Dyspnea AHF but Trend for Further Exploration

Written by Toni Rizzo

The Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure trial [ATOMIC-AHF; NCT01300013], presented by John R. Teerlink, MD, University of California San Francisco, San Francisco, California, USA, was a Phase 2 dose ranging study which aimed to evaluate the safety, pharmacokinetics and pharmacodynamics (PK/PD), and efficacy of intravenous (IV) omecamtiv mecarbil (OM) in patients with acute heart failure (AHF). The investigators hypothesized that ≥1 dose of IV OM would be well tolerated and improve dyspnea in patients with left ventricular systolic dysfunction hospitalized for AHF.

The study employed a sequential dosing design. Patients presenting with AHF were randomized 1:1 to IV OM versus IV placebo (pooled placebo, n=303) and divided into 3 cohorts, with each cohort receiving increasing OM doses (Table 1).