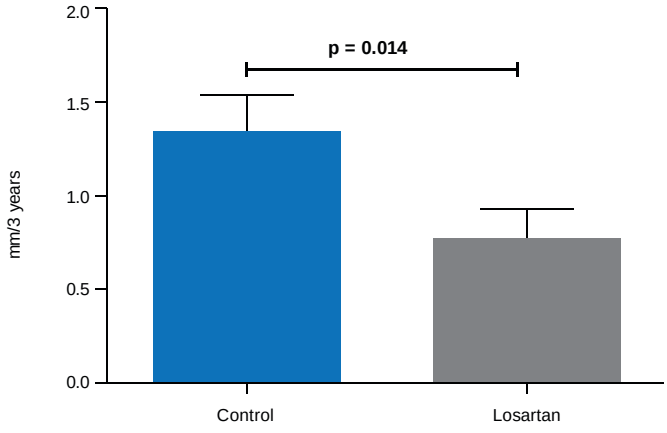
changes in the incidence of cardiovascular mortality, aortic dissection, aortic volume, and prophylactic aortic surgery [Radonic T et al. *Trials* 2010].

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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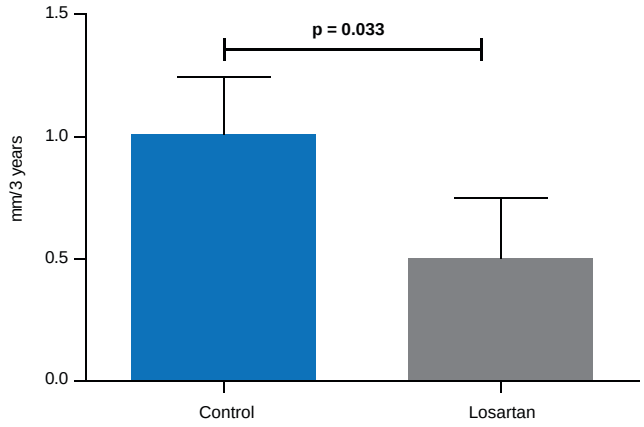
All subgroups benefited from losartan regardless of age, sex, the presence of fibrillin-1 mutation, β-blocker use, mean aortic pressure, or aortic root size. There were no differences in aortic dilatation rate beyond the aortic root. There were no significant differences in combined clinical endpoints 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).

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Table 1. Sequential Omecamtiv Mecarbil Dosing Cohorts

Dosing	Cohort 1 (n=103)	Cohort 2 (n=99)	Cohort 3 (n=101)
Dose	7.5 mg/h, 0-4 hours 1.5 mg/h, 4-48 hours	15 mg/h, 0-4 hours 3 mg/h, 4-48 hours	20 mg/h, 0-4 hours 4 mg/h, 4-48 hours
Target	115 ng/mL	230 ng/mL	310 ng/mL
C_{max}	30-250 ng/mL	75-500 ng/mL	125-700 ng/mL
SET	~3-28 ms	~8-55 ms	~14-78 ms

SET=systolic ejection time.

The primary efficacy endpoint was dyspnea symptom response through 48 hours, evaluated by a 7-point Likert scale. Responders were defined as minimally, moderately, or markedly better at 6 hours and moderately or markedly better at both 24 and 48 hours, without worsening HF or death from any cause by 48 hours. Secondary endpoints included death and/or worsening HF within 7 days, dyspnea area under the curve (AUC), dyspnea by 7-point Likert scale at each assessment, Patient Global Assessment response through 48 hours, change from baseline in NT-proBNP, length of hospital stay, and days alive out of hospital until Day 30. PK/PD were evaluated up to Day 6 after discharge.

Baseline characteristics were well balanced between the OM and placebo groups. Analysis of dyspnea response demonstrated no significant difference between any of the OM cohorts and the pooled placebo group (overall p=0.33).

An exploratory analysis comparing the individual OM groups versus their respective placebo groups found a trend toward a beneficial dyspnea response between OM at the highest dose (Cohort 3) and placebo (51% vs 37%; RRR, 1.41; 95% CI, 1.02 to 1.93; p=0.03).

The risk of worsening HF was similar between groups with OM versus placebo with relative risks of 0.68 (95% CI, 0.38 to 1.21; p=0.179) in Cohort 1; 0.49 (95% CI, 0.24 to 0.98; p=0.034) in Cohort 2; and 0.55 (95% CI, 0.28 to 1.09; p=0.075) in Cohort 3. There were no significant differences between the OM cohorts and the pooled placebo group in the other secondary endpoints.

Adverse event rates were similar between the OM and placebo groups with the exception of myocardial injury which was more frequent with OM (2.3% vs 1.0%); however, these events were characterized by the authors as primarily low level elevations in troponin concentration. Systolic ejection time significantly increased with OM versus placebo (p≤0.005).

In the ATOMIC-AHF trial OM did not significantly improve dyspnea response compared with pooled placebo in patients with left ventricular systolic dysfunction hospitalized for AHF. However, this Phase 2 dose-ranging study found a trend towards reduction of worsening HF with OM (Table 2) with a trend toward improved dyspnea response in the highest dose compared with placebo. OM was associated with increased rates of myocardial injury. Overall these results suggest that further study with this compound in AHF should be considered with a careful evaluation of safety and clinical outcomes to better understand the implications of the associated troponin elevations.

Table 2. Worsening Heart Failure

Within 7 Days of IP Initiation	Pooled Placebo (n=303)	Cohort 1 OM (n=103)	Cohort 2 OM (n=99)	Cohort 3 OM (n=101)
Death or WHF*				
Yes, n (%)	52 (17)	13 (13)	9 (9)	9 (9)
RR		0.67	0.54	0.54
(95% CI)		(0.38–1.18)	(0.28–1.04)	(0.27–1.08)
p Value		0.151	0.054	0.067
WHF*				
Yes, n (%)	51 (17)	13 (13)	8 (8)	9 (9)
RR		0.68	0.49	0.55
(95% CI)		(0.38–1.21)	(0.24–0.98)	(0.28–1.09)
p Value		0.179	0.034	0.075

*Worsening heart failure (WHF) is defined as clinical evidence of persistent or deteriorating HF requiring at least one of the following treatments: initiation, reinstitution or intensification of intravenous (IV) vasodilator; initiation of IV positive inotropes, or IV vasopressors; initiation of ultrafiltration, hemofiltration, or dialysis; initiation of mechanical ventilatory or circulatory support.

Saxagliptin and Alogliptin Noninferior for CV Ischemic Events in Patients at High Risk With T2DM and Coronary Disease

Written by Emma Hitt, PhD

Antihyperglycemic therapies have been shown to reduce microvascular events (ie, blindness, amputation, and kidney failure); however, their impact on macrovascular events (ie, cardiovascular [CV] death, myocardial infarction [MI], and stroke) has not been well established. In addition, concerns of increased risk of CV events with some antihyperglycemic therapies prompted the United States Food and Drug Administration and European Medicines Agency to require demonstration of CV safety for all new diabetes therapies [Food and Drug Administration. Guidance for Industry. 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf]. As a result, well-powered trials of CV outcomes in high-risk patients with type 2 diabetes mellitus (T2DM) are being conducted to establish CV safety with new antihyperglycemic drugs.

Saxagliptin and alogliptin, both selective dipeptidyl peptidase 4 (DPP-4) inhibitors, are incretin-based antihyperglycemic therapies that improve glycemic control in T2DM. A meta-analysis of the Phase 2-3 clinical development trials of saxagliptin suggested it may reduce