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

the risk of major adverse cardiac events (MACE) in T2DM but these overall findings were based on few outcomes [Frederich R et al. *Postgrad Med* 2010].

The purpose of the SAVOR-TIMI 53 and EXAMINE trials was to determine if treatment with saxagliptin or alogliptin, respectively, would be noninferior to placebo for MACE in patients with T2DM at heightened risk of CV events [Scirica BM et al. *Am Heart J* 2011; White WB et al. *N Engl J Med* 2013].

Saxagliptin treatment in patients with T2DM and stable atherosclerotic vascular disease or risk factors does not increase the risk of MACE. Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus TIMI 53 trial [SAVOR-TIMI 53; Scirica BM et al. *N Engl J Med* 2013].

In the international, Phase 4 SAVOR-TIMI 53 trial, 16,492 patients with T2DM and a history of or at risk for CV events were randomized to receive saxagliptin 5 mg daily (2.5 mg in patients with an estimated GFR of ≤50 mL/minute) or placebo for a median follow-up of 2.1 years [Scirica BM et al. *N Engl J Med* 2013]. Eligible patients with established CV disease had to be aged ≥40 years, with documented coronary, cerebrovascular, or peripheral artery atherosclerosis. Patients with risk factors were eligible if they were aged ≥55 (males) or ≥60 (females) years, and had a history of dyslipidemia, hypertension, or active tobacco use. Patients were ineligible if already treated with incretin-based therapy within the last 6 months, or had a history of end-stage renal disease, long-term dialysis, renal transplantation, or serum creatinine levels of ≥6.0 mg/dL (530 µmol/L).

The primary endpoint was a composite of CV death, nonfatal MI, or nonfatal ischemic stroke. Secondary endpoints included the primary endpoint plus hospitalization due to heart failure (HF), coronary revascularization, or unstable angina, and each component of the composite CV endpoints.

The occurrence of the primary endpoint at 2 years was similar in both study arms (7.3% saxagliptin vs 7.2% placebo; HR, 1.00; 95% CI, 0.89 to 1.12; superiority p=0.99; noninferiority p<0.001). The broader secondary endpoint was also similar (12.8% with saxagliptin vs 12.4% with placebo; HR, 1.02; 95% CI, 0.94 to 1.11; superiority p=0.66; noninferiority p<0.001).

Individual CV outcomes were consistently similar between both treatment arms with the exception of hospitalization for HF, which occurred more frequently in the saxagliptin arm (3.5%) compared with the placebo arm (2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; p=0.007). *Major* hypoglycemic events (defined when the event required a third party to intervene actively) occurred more frequently with saxagliptin (2.1% vs 1.7%; p=0.047); however, *hospitalization* for hypoglycemia was similar in both arms (p=0.33). Cases of acute and chronic pancreatitis (p=0.77), and pancreatic cancer (p=0.095), were infrequent and similar between both arms.

In the EXAMINE trial, alogliptin therapy in patients with T2DM with recent acute coronary syndrome (ACS) similarly did not increase the risk of MACE. William B. White, MD, University of Connecticut School of Medicine, Farmington, Connecticut, USA, presented data from the Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome [EXAMINE; White WB et al. *N Engl J Med* 2013].

In the international, double-blind EXAMINE trial, 5380 patients with T2DM and recent ACS (acute MI or hospitalization for unstable angina within 15 to 90 days) were randomized to receive alogliptin QD (n=2701) or placebo QD (n=2679) and followed for a median of 18 months. All patients were currently on antidiabetic treatment with an agent other than a DPP-4 inhibitor or glucagon-like peptide-1 analog (ie, incretin-based therapy). Exclusion criteria included type 1 diabetes, unstable cardiac disorders such as HF, refractory angina, uncontrolled arrhythmias, severe valvular heart disease, uncontrolled hypertension, and recent dialysis.

The primary endpoint of the EXAMINE trial was a composite of CV death, nonfatal MI, and nonfatal stroke. The secondary endpoint included the primary endpoint plus urgent revascularization due to unstable angina within 24 hours after hospitalization.

The primary endpoint was similar between groups (11.3% with alogliptin vs 11.8% with placebo; HR, 0.96; upper boundary of one-sided repeated CI, 1.16; superiority p=0.32; noninferiority p<0.001). The incidence of the secondary endpoint was also similar (12.7% vs 13.4%; HR, 0.95; upper boundary of one-sided repeated CI, 1.14; superiority p=0.26). In addition, there was no significant difference between alogliptin and placebo for CV death (p=0.21), nonfatal MI (p=0.47), nonfatal stroke (p=0.71), or all-cause death (p=0.23). Hospitalization for HF was not part of the primary endpoint.

The incidence of hypoglycemia was similar (~6.6%) between study arms, as was the incidence of acute (~0.4%) and chronic (~0.2%) pancreatitis. There were no reports of pancreatic cancer occurring during the trial.

Dr. Bhatt concluded that SAVOR-TIMI 53 demonstrated noninferiority of saxagliptin for major ischemic events in patients with T2DM with heightened CV risk. Similarly, Dr. White noted that the EXAMINE trial found that MACE rates were not increased with alogliptin compared with placebo in patients with T2DM and recent ACS. In both trials, the rates of pancreatitis and pancreatic cancer were reassuring. Dr. Bhatt also pointed out that further study to elucidate the mechanism behind the unexpected increased incidence of hospitalization for HF in the saxagliptin arm observed in the SAVOR-TIMI 53 study is needed.

Science Advisor's Note: Hospitalization for HF was not reported in the primary EXAMINE publication but was recorded as an exploratory CV endpoint [White WB et al. *Am Heart J* 2011;162:2634-53 (Appendix A)]. Given the results of SAVOR-TIMI 53, further description of this endpoint in EXAMINE will be important in determining whether this is a class effect and clarifying the underlying mechanism.

No Improvement With CRT in Patients With HF and QRS <130 msec

Written by Toni Rizzo

The current 2012 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) recommend cardiac resynchronization therapy (CRT) for symptomatic HF and a QRS complex ≥120 msec [McMurray JJV et al. *Eur Heart J* 2012]. Although CRT is not currently recommended for HF patients with a QRS complex <120 msec, many such patients have evidence of mechanical dyssynchrony by echocardiography.

The Echocardiography Guided Cardiac Resynchronization Therapy study [EchoCRT; Ruschitzka F et al. *N Engl J Med* 2013] was a prospective, multicenter, randomized, clinical trial designed to evaluate the effect of CRT on morbidity and mortality in patients with symptomatic HF, a QRS complex <130 msec, and evidence of mechanical dyssynchrony. On March 13, 2013, the trial was stopped for futility at the recommendation of the Data and Safety Monitoring Board. The results of the trial were presented by Johannes Holzmeister, MD, University of Zurich, Zurich, Switzerland.

At enrollment, patients had NYHA Class III to IV HF, stable pharmacologic therapy, left-ventricular systolic dysfunction and dilation (ejection fraction ≤35%; left-ventricular end diastolic diameter ≥55 mm), QRS <130 msec, and ventricular dyssynchrony by tissue Doppler imaging and speckle-tracking radial strain on echocardiography. Of the 855 eligible patients, 809 had a successful implantation with a Lumax HF-T CRT-D device and underwent randomization [CRT turned "on" group (n=404); CRT turned "off" group (n=405)].

The primary efficacy endpoint was all-cause mortality or first hospitalization for worsening HF. The primary safety endpoint was freedom from complications due to the CRT-D system at 6 months. Baseline characteristics were similar in both groups, with the exception of chronic kidney disease, which was more common in the CRT group. Utilization of standard HF therapies was very high in both groups (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker 95%, β-blocker 96% to 98%, and aldosterone antagonist 59% to 60%).

The study terminated at a median follow-up of 19.4 months. The primary efficacy endpoint occurred in 28.7% of patients in the CRT group and 25.2% of patients in the control group (HR, 1.20; 95% CI, 0.92 to 1.57; p=0.15; Table 1). Secondary efficacy endpoints including all-cause mortality (Table 2), cardiovascular mortality, and hospitalization for worsening HF occurred more frequently in the CRT group. It is important to interpret the secondary outcomes with caution, especially in the context of the early termination of the trial.

Table 1. Risk of Death or Hospitalization for HF Among All Patients

Endpoint	Control Group (n=405) Number (%) With Event	CRT Group (n=404) Number (%) With Event	Adjusted HR (95% CI) p Value
Primary Endpoint Composite			
Death or WHF hospitalization	102 (25.2%)	116 (28.7%)	1.20 (0.92–1.57); 0.15
Primary Endpoint Components			
WHF hospitalization	90 (22.2%)	99 (24.5%)	1.16 (0.87–1.55); 0.25
All-cause mortality	26 (6.4%)	45 (11.1%)	1.81 (1.11–2.93); 0.02
Other CV Endpoints			
CV hospitalization	137 (33.8%)	147 (36.4%)	1.11 (0.88–1.40); 0.36
CV mortality	17 (4.2%)	37 (9.2%)	2.26 (1.27–4.01); 0.004

CRT=cardiac resynchronization therapy; CV=cardiovascular; WHF=worsening heart failure.

4 deaths in the control group and 1 death in CRT group were after (L)VAD /Transplant and were excluded from analysis; HR (95% CI) from Cox model adjusted for country and p value from stratified log-rank test.

Table 2. All-Cause Mortality Components

Reason	Control Group (n=405) Number (%) With Event	CRT Group (n=404) Number (%) With Event
Cardiovascular/vascular	17 (4.2%)	37 (9.2%)**
Death due to heart failure	10 (2.5%)	17 (4.2%)
Death due to arrhythmic events	4 (1.0%)	14 (3.5%)*
Death due to nonischemic dysrhythmia	0	2 (0.5%)
Death due to symptomatic heart block/bradycardia/PEA	0	4 (1.0%)
Sudden cardiac death	4 (1.0%)	8 (2.0%)
Presumed cardiovascular death	1 (0.3%)	5 (1.2%)
Fatal stroke	1 (0.3%)	1 (0.3%)
Other vascular death	1 (0.3%)	0
Noncardiovascular	9 (2.2%)	8 (2.0%)

CRT=cardiac resynchronization therapy; PEA=pulseless electrical activity.

Statistically significant difference of *p<0.05, **p<0.01; 4 deaths in the control group and 1 death in CRT group were after (L)VAD/Transplant and were excluded from analysis; p value from stratified log-rank test.