reduced LV remodeling in patients with type 2 diabetes mellitus (T2DM), independent of blood pressure (BP), age, and sex, according to Roland E. Schmieder, MD, University of Erlangen-Nurnberg, Erlangen, Germany.

The ROADMAP study showed the angiotensin receptor blocker olmesartan 40 mg compared with placebo reduced clinic BP more (by 3.1/1.9 mm Hg), and fewer patients developed microalbuminuria (8.2% and 9.8% respectively) [Haller H et al. *N Engl J Med* 2011]. Time to onset of microalbuminuria increased by 23% with olmesartan (95% CI, 0.63 to 0.94; p=0.01). Nonfatal cardiovascular (CV) events were reduced with olmesartan, but fatal CV events were higher with the drug (15 vs 3 with placebo; p=0.01), explained by more CV deaths in patients with coronary heart disease in the olmesartan group (11 vs 2 with placebo; p=0.02).

In the present analysis, 1513 patients (777 taking olmesartan, 736 placebo) had interpretable ECGs at baseline and at the last assessment. A significant reduction in the prevalence of Cornell voltage QRS duration product, the primary ECG parameter of LV remodeling and hypertrophy, was found in olmesartan-treated patients with a BP <130/80 mm Hg (RR, 39.2%; p=0.0081) and >130/80 mm Hg (RR, 45.6%; p=0.0406).

The reduction in Cornell voltage QRS duration product was independent of age. The risk reduction was 37.9% (p=0.0347) for patients aged >58 years, and 42.3% for patients ≤58 years (p=0.0121). The reduction was also independent of sex, with the risk reduction in men 46.5% (p=0.0448) and 36.3% in women (p=0.0136).

The significant reduction in LV remodeling in these patients with T2DM was most striking in patients with a longer duration of diabetes, taking antidiabetic medication at baseline, who were obese, and had an HbA1C level that was elevated at baseline or increased during the study. These reductions are summarized in Table 1.

Table 1. Reduction in Left Ventricular Remodeling With Olmesartan by Patient Characteristic

Patient Characteristic	Relative Risk Reduction (%)	p Value vs Placebo
Diabetes duration >5 years	37.7	0.0039
Antidiabetic drug at baseline	41.5	0.0008
Obese (BMI >28 kg/m^2)	44.2	0.0011
HbA1C at baseline >7.0%	46.1	0.0023
HbA1C increased during study	52.6	0.0010

BMI=body mass index.

Cardiac structural adaptation, known to develop early in patients with hypertension and diabetes, was delayed by olmesartan, compared with placebo, as measured by LV remodeling on ECG.

LEADER Study: Testing the Cardiovascular Safety of Liraglutide

Written by **Mary Mosley**

Liraglutide, an analogue for human glucagon-like peptide 1, is approved for patients with type 2 diabetes mellitus (T2DM) and is associated with HbA1C reductions of 1.0% to 1.5% and moderate weight loss. Diabetes is associated with a 2-fold increased risk of cardiovascular (CV) events. The ongoing Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation trial [LEADER; NCT01179048] is evaluating the CV safety of liraglutide, in accordance with requirements of the United States Food and Drug Administration. The study design and characteristics of the enrolled patients were reviewed by Steven P. Marso, Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA.

From 2010 to 2012 at 410 sites in 32 countries, 9340 patients with T2DM and a HbA1C ≥7.0% with (≥50 years) or without (≥60 years) prior CV disease (CVD) were randomized to liraglutide (0.6 to 1.8 mg QD) or placebo, plus standard of care. The patients will be followed for at least 3.5 years and up to 5 years in the event-driven trial. The patients are treated with oral antidiabetic agents, basal or premix insulin, or both. The primary outcome is the time to the first occurrence of CV death, stroke, or nonfatal myocardial infarction (MI).

A unique aspect of LEADER, stated Dr. Marso, is the number of adjudicated endpoints in the trial, including all-cause mortality, acute coronary syndromes, cerebrovascular disease, heart failure, neuropathy, nephropathy, retinopathy, pancreatitis, cancers, and thyroid disease.

The analysis of the primary endpoint is a 2-step process. Noninferiority of liraglutide will be established if the upper 2-sided 95% CI for the relative risk of the primary endpoint is <1.3. Superiority of liraglutide compared with placebo will be assessed only if noninferiority is established, and superiority will be established if the hazard ratio of the upper range of the 2-sided 95% CI is <1.0.

The majority of the patients (81.7%) had prior CVD. The proportion with reduced renal function was 19.9% (n=1854) with an estimated glomerular filtration rate (eGFR) 30 to 59 mL/min/1.73 m^2, and 1.9% with an eGFR <30 mL/min/1.73 m^2 (n=177).

The patients had a mean age of 64.3 years, a mean body mass index of 32.5 kg/m^2; 36% in the overall group were women (33.5% prior CVD; 45.4% no prior CVD groups), and about 12% were current smokers. Table 1 presents key diabetes-related clinical characteristics and Table 2 details CV risk factors at baseline.

Table 1. Clinical Characteristics in the LEADER Trial

Baseline Characteristics and Treatment History	Total (n=9340)	Previous CVD (n=7592)	No Previous CVD (n=1748)
Mean HbA1C, % ± SD	8.7±1.5	8.7±1.5	8.8±1.6
Mean diabetes duration, years ± SD	12.7±8.0	12.8±8.1	12.3±7.5
No glucose-lowering therapy (diet only), n (%)	504 (5.4)	405 (5.3)	99 (5.7)
Insulin use, n (%)	3905 (41.8)	3260 (42.9)	645 (36.9)

CVD=cardiovascular disease; SD=standard deviation.

Table 2. Risk Factors for CVD at Baseline in LEADER

CVD Risk Factors, n (%)	Total (n=9340)	Previous CVD (n=7592)	No Previous CVD (n=1748)
Hyptertension	8408 (90.0)	6888 (90.7)	1520 (87.0)
Hyperlipidemia	7191 (77.0)	6135 (80.8)	1056 (60.4)
Coronary artery disease	5303 (56.8)	5288 (69.7)	17 (1.0)
Congestive heart failure	1599 (17.1)	1562 (20.6)	37 (2.1)
Peripheral artery disease	1644 (17.6)	1394 (18.4)	250 (14.3)

CVD=cardiovascular disease.

The LEADER trial is expected to demonstrate conclusive evidence regarding the CV safety of liraglutide compared with standard of care for a global population of patients with T2DM. Results are anticipated in 2016.

Cardiovascular Safety of Linagliptin Demonstrated in Pooled Analysis

Written by **Mary Mosley**

The cardiovascular (CV) safety of linagliptin, a dipeptidyl peptidase-4 inhibitor, in patients with type 2 diabetes mellitus (T2DM) has been supported by a pooled comprehensive analysis of prospectively adjudicated CV events in Phase 3 studies. Odd Erik Johansen, MD, Boehringer-Ingelheim, Asker, Norway, presented the analysis.

The present analysis expands on a previous assessment that showed the CV safety of linagliptin, and a hint of a benefit [Johansen OE et al. *Cardiovasc Diabetol* 2012], by including recently completed trials with linagliptin. The possibility of CV benefit was also shown in a head-to-head comparison of linagliptin and glimeperide in a noninferiority trial [Gallwitz B et al. *Lancet* 2012]. CV benefit with linagliptin is being tested prospectively in the CAROLINA study [NCT01243424] against glimepiride and in the CARMELINA study [NCT01897532] against placebo.

The pooled analysis included 9459 patients from 19 United States or multinational, multicenter, double-blind, parallel-group studies. Of these, 5847 patients were randomized to receive linagliptin and 3612 to a comparator for at least 12 weeks and up to 2 years. A prospectively defined, blinded, and independent adjudication of events was used. The primary composite endpoint was CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina pectoris.

In the pooled analysis, the patients were aged ~60 years, ~45% were women, and ~60% were white. Most patients had normal or mild estimated glomerular filtration rate and had high (~73%) prior use of a CV medication (aspirin, lipid-lowering agent, or antihypertensive). About a quarter (24.5% linagliptin, 29.0% placebo) of the patients had a Framingham Risk Score >15%.

The drug exposure and the incidence of primary, secondary, and tertiary outcomes in the pooled analysis are detailed in Table 1. Linagliptin, versus the combined comparators, reduced the primary outcome (HR, 0.78; 95% CI, 0.55 to 1.12) and the secondary outcome of CV death, stroke, or MI (HR, 0.74; 95% CI, 0.49 to 1.13). Significant reductions were achieved with linagliptin versus the combined comparators for nonfatal stroke (HR, 0.34; 95% CI, 0.15 to 0.75; p<0.05), and transischemic attack (HR, 0.09; 95% CI, 0.01 to 0.75; p<0.05).

Table 1. Drug Exposure, Incidence, and Incidence Rates of Cardiovascular Endpoints

	Linagliptin (n=5847)		Total Comparators (n=3612)	
Median exposure (range), days	175 (1776)		182 (1804)	
Cumulative drug exposure, patient-years	4421.3		3254.7	
	Incidence n (%)	**Incidence Rate (per 1000 years)**	**Incidence n (%)**	**Incidence Rate (per 1000 years)**
Primary Endpoints				
CV death, stroke, MI, or UAP with hospitalization	60 (1.0)	13.4	62 (1.7)	18.9
Secondary Endpoints				
CV death, stroke, or MI	42 (0.7)	9.3	46 (1.3)	14.0
Tertiary Endpoints				
CV death	11 (0.2)	2.4	8 (0.2)	2.4
Nonfatal MI	23 (0.4)	5.1	20 (0.6)	6.1
Nonfatal stroke	9 (0.2)	2.0	19 (0.5)	5.8
TIA	1 (0.02)	0.2	8 (0.2)	2.4
UAP with hospitalization	22 (0.4)	1.9	16 (0.4)	4.8
Total mortality	18 (0.3)	4.0	16 (0.4)	4.8

CV=cardiovascular; MI=myocardial infarction; TIA=transischemic attack; UAP=unstable angina pectoris.

A placebo cohort analysis included 7746 patients from 18 United States or multinational, double-blind, parallel-group studies, of whom 5071 were randomized to