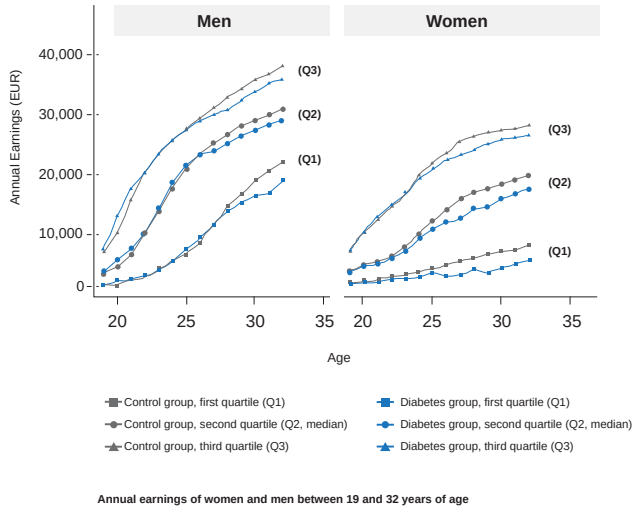
Figure 1. Earnings Through Early Adulthood in Patients With T1DM in Sweden



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Long-Term Ranibizumab Effective in Diabetic Macular Edema

Written by Emma Hitt, PhD

In patients with diabetic macular edema (DME), long-term intravitreal injections of ranibizumab maintains best-corrected visual acuity (BCVA) and central retinal subfield thickness (CRT) improvements over 36 months, with no new or increased safety concerns. Anna Boixadera, MD, Hospital Vall D'Hebron, Barcelona, Spain, presented the final analysis of the 36-month study comprising: A 12 Month Core Study to Assess the Efficacy and Safety of Ranibizumab (Intravitreal Injections) in Patients With Visual Impairment Due to Diabetic Macular Edema and a 24 Month Open-Label Extension Study [RESTORE; NCT00687804].

In patients with diabetes, the most common cause of vision loss is macular edema, which is a leading cause of visual impairment in the working-age population [Ciulla TA et al. *Diabetes Care* 2003]. The RESTORE core trial demonstrated that ranibizumab treatment as monotherapy or in combination with laser therapy was superior to laser therapy alone in patients with visual impairment due to DME over 12 months [Mitchell P et al. *Ophthalmology* 2011]. The purpose of the extension study was to evaluate the long-term efficacy and safety of ranibizumab 0.5 mg intravitreal injections [Boixadera A, Garcia-Arumi J. EASD 2013 (abstr 54)].

In the open-label, multicenter RESTORE extension study, 240 patients were eligible to receive ranibizumab as needed according to prespecified BCVA stability and DME progression-based retreatment criteria for 24 months. Laser therapy was allowed. The extension study was completed by 208 patients, and 19% and 25% of patients did not require ranibizumab injections during the extension study. The mean age of participants ranged from 61.7 to 63.8 years and the mean duration of DME ranged from 1.5 to 1.7 years.

The most common ocular adverse events (AEs) during the 36-month RESTORE core and extension studies were cataracts (16.3%) and eye pain (15.4%). Serious ocular AEs were reported in 2.4% to 4.1% of patients; there were no incidents of retinal tear or detachment, and no reports of endophthalmitis during the 36 months. The most frequent nonocular AEs included nasopharyngitis (23.3%) and hypertension (13.3%). The most frequent nonocular serious AEs included coronary artery disease and cerebrovascular accident (1.7% each).

The mean BCVA gain and CRT reductions observed from baseline to Month 12 were maintained through Month 36 in patients treated with prior ranibizumab in both the core and extension phase (+8.0 letters, –145.9 µm [prior ranibizumab], +6.7 letters, –142.1 µm [prior ranibizumab plus laser]). In addition, patients who had received laser monotherapy in the core study experienced progressive BCVA improvement (+6.0 letters) and CRT reduction (–142.7 µm) during the extension trial (Months 12 to 36) with ranibizumab treatment. The mean change in the Visual Functioning Questionnaire scores over the 36 months for the ranibizumab monotherapy, ranibizumab plus laser therapy, and laser monotherapy arms were +12.2, +7.8, and +8.4, respectively, for near activities and +2.6, +4.1, and +3.5, respectively, for distance activities, and the mean change in the composite score was +5.0, +4.3, and +3.9, respectively.

Prof. Boixadera stated that, in her opinion, the data from the RESTORE core and extension studies indicate that there are no new or increased safety issues with long-term intravitreal ranibizumab injections. In addition, patients could maintain their BCVA and CRT improvements gained in the first year of ranibizumab treatment with decreasing frequency of ranibizumab injections in subsequent years.

Left Ventricular Remodeling Reduced With Olmesartan in ROADMAP

Written by Mary Mosley

A prespecified analysis of left ventricular hypertrophy (LVH) as evaluated by electrocardiography (ECG) from the Olmesartan Medoxomil in Diabetes Mellitus study [ROADMAP] showed that olmesartan significantly

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.