

## **WCIR Presentation- C-peptide levels and CVD outcomes in the VADT**

**Aims:** Low C-peptide levels, indicating beta-cell dysfunction, are associated with increased within-day glucose variation and hypoglycaemia. Low C-peptide levels in type 2 diabetes patients may also indicate a more type 1 diabetes phenotype. In advanced type 2 diabetes, disturbances in glucose regulation such as hypoglycemia and glucose fluctuation predict increased cardiovascular (CVD) risk. The present study examined the association between low C-peptide levels and CVD risk and whether it can be explained by visit-to-visit glucose variation and severe hypoglycaemia.

**Methods:** Fasting C-peptide levels at baseline, composite CVD outcome, severe hypoglycaemia, and visit-to-visit fasting glucose coefficient of variation (CV) and average real variability (ARV) were assessed in 1,565 Veterans Affairs Diabetes Trial participants.

**Results:** Among type 2 diabetes patients, those in the lower quartile of C-peptide levels were thinner, had lower triglyceride levels, higher HDL and higher HbA1c. In contrast, those with higher C-peptide levels had characteristics consistent with more insulin resistance. There was a U-shaped relationship between C-peptide and CVD risk with increased risk with declining levels in the low range (<0.50 nmol/l, HR 1.30 [95%CI 1.05-1.60], p=0.02) and with rising levels in the high range (>1.23 nmol/l, 1.27 [1.00-1.63], p=0.05). C-peptide levels were inversely associated with the risk of severe hypoglycemia (OR 0.68 [0.60-0.77]) and visit-to-visit glucose variation (CV, standardized beta-estimate -0.12 [SE 0.01]; ARV, -0.10 [0.01]) (all p<0.0001). The association of low C-peptide levels with CVD risk was independent of cardiometabolic risk factors (1.48 [1.17-1.87, p=0.001) and remained associated with CVD when tested in the same model with severe hypoglycaemia and glucose CV.

**Conclusions:** Low C-peptide levels were associated with increased CVD risk in advanced type 2 diabetes. The association between low C-peptide and CVD risk was independent of increases in glucose variation or severe hypoglycaemia. C-peptide levels may predict future glucose control patterns and CVD risk, and identify phenotypes influencing clinical decision making in advanced type 2 diabetes.