

## Neutrophil-to-lymphocyte ratio predicts cardiovascular events in patients with type 2 diabetes: post hoc analysis of SUSTAIN 6 and PIONEER 6

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**Funding Acknowledgement:** Type of funding sources: Private company. Main funding source(s): Novo Nordisk A/S

**Background:** Inflammation plays an important role in atherosclerosis. The neutrophil-to-lymphocyte ratio (NLR) may serve as a clinically useful biomarker of inflammation and cardiovascular (CV) disease, although this relationship has not been studied in people with type 2 diabetes (T2D).

**Purpose:** This post hoc analysis investigated the relationship between NLRs and CV outcomes in T2D CV outcomes trials for two formulations of semaglutide, a glucagon-like peptide-1 receptor agonist.

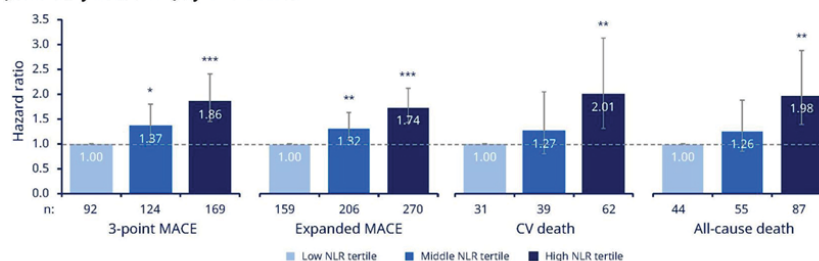
**Methods:** In pooled analyses of the SUSTAIN 6 and PIONEER 6 trials, 6,480 patients with T2D at high CV risk received placebo or semaglutide (once-weekly subcutaneously up to 1.0 mg, or once-daily orally up to 14 mg). NLRs were calculated from complete blood counts at randomisation. Adjudicated outcomes included 3-point major adverse CV events (MACE: composite of CV death, non-fatal myocardial infarction [MI] or non-fatal stroke; primary outcome), expanded MACE, CV death and all-cause death (secondary outcomes). Patient characteristics and CV outcomes were analysed according to baseline NLR tertiles using pooled trial data. Estimation of hazard ratios (HRs) for all outcomes across NLR tertiles used a Cox proportional hazards model. A Cox spline regression with continuous NLR as covariate adjusted for treatment was used to predict the event rate of first MACE at 2 years.

**Results:** Overall, baseline NLR was recorded in 6,364 patients. Mean

baseline NLRs were 1.5, 2.2 and 3.6 in the low, middle and high tertiles, respectively. Patients in the high NLR tertile were older (66.6 years), more likely to be male (70.0%), had longer duration of diabetes (15.3 years), higher body weight (93.3 kg), lower diastolic blood pressure (75.5 mmHg) and estimated glomerular filtration rate (70.4 mL/min/1.73m<sup>2</sup>) vs those in the lower NLR tertiles (all  $p < 0.0001$ ). Higher NLR was associated with an increased risk of MACE (HR [95% confidence interval (CI)]: 1.37 [1.05; 1.80;  $p = 0.02$ ] and 1.86 [1.45; 2.41;  $p < 0.0001$ ] for the middle and high tertiles, respectively, vs the low tertile). The high NLR tertile was also associated with a 74% increased risk of expanded MACE and twofold risk for CV death and all-cause death vs the low NLR tertile (Figure 1). Spline regression indicated that NLR values  $> 5$  increased the risk of first MACE substantially (Figure 2). Further analysis of NLR and MACE by tertiles showed a more pronounced association in patients without prior MI and/or stroke (HR [95% CI]: 1.64 [1.07; 2.56];  $p = 0.03$  and 2.09 [1.38; 3.21];  $p = 0.0006$  in the middle and high tertiles, respectively, vs the low tertile).

**Conclusion:** Baseline NLR predicts MACE, CV death and all-cause death in patients with T2D and high CV risk. NLR is readily accessible from routinely obtained and inexpensive blood counts; it could offer a convenient, clinically useful inflammatory biomarker for CV risk prediction in this population.

**Hazard ratios for 3-point MACE (primary outcome), expanded MACE, CV death and all-cause death (secondary outcomes) by NLR tertiles**

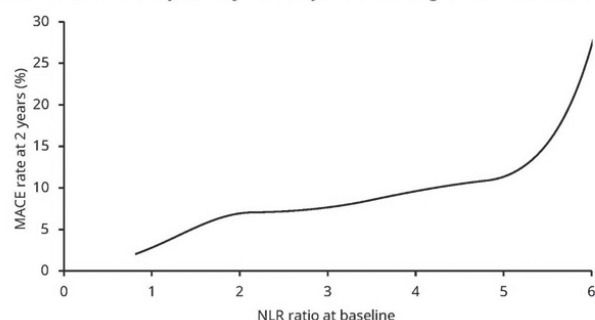


\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.0001$  vs the low NLR tertile. Error bars represent 95% confidence intervals. Low NLR tertile: patients with  $\text{NLR} \leq 1.88$  at BL (mean 1.5); middle NLR tertile: patients with  $\text{NLR} > 1.88$  to  $\leq 2.65$  at BL (mean 2.2); high NLR tertile: patients with  $\text{NLR} > 2.65$  at BL (mean 3.6). The dashed line shows the reference value (low NLR tertile). 3-point MACE included a composite of CV death, non-fatal MI or non-fatal stroke, and was the primary outcome in both SUSTAIN 6 and PIONEER 6. Expanded MACE (CV death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina, hospitalisation for heart failure, and, in SUSTAIN 6 only, revascularisation [coronary or peripheral]), CV death and all-cause death were secondary outcomes. All outcomes were adjudicated by an external EAC except for peripheral revascularisation. Adjusted hazard ratios across NLR tertiles were computed using a Cox regression model with treatment (semaglutide, placebo) and NLR tertiles as fixed factors, stratified by trial.

BL, baseline; CV, cardiovascular; EAC, event adjudication committee; MACE, major adverse cardiovascular events; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio.

Figure 1

**Predicted MACE rate by all subjects at 2 years according to NLR at baseline**



The event rate of first MACE at 2 years was predicted using the NLR baseline value in a quadratic spline function, using a Cox regression model adjusted for treatment. MACE, major adverse cardiovascular events; NLR, neutrophil-to-lymphocyte ratio.

Figure 2