Abstract: **4348**

Cluster analysis of cardiovascular risk phenotypes in patients with type 2 diabetes and established atherosclerotic cardiovascular disease: a potential approach to precision medicine

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Introduction: Phenotypic heterogeneity among patients with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) is ill defined although likely there are multiple subtypes.

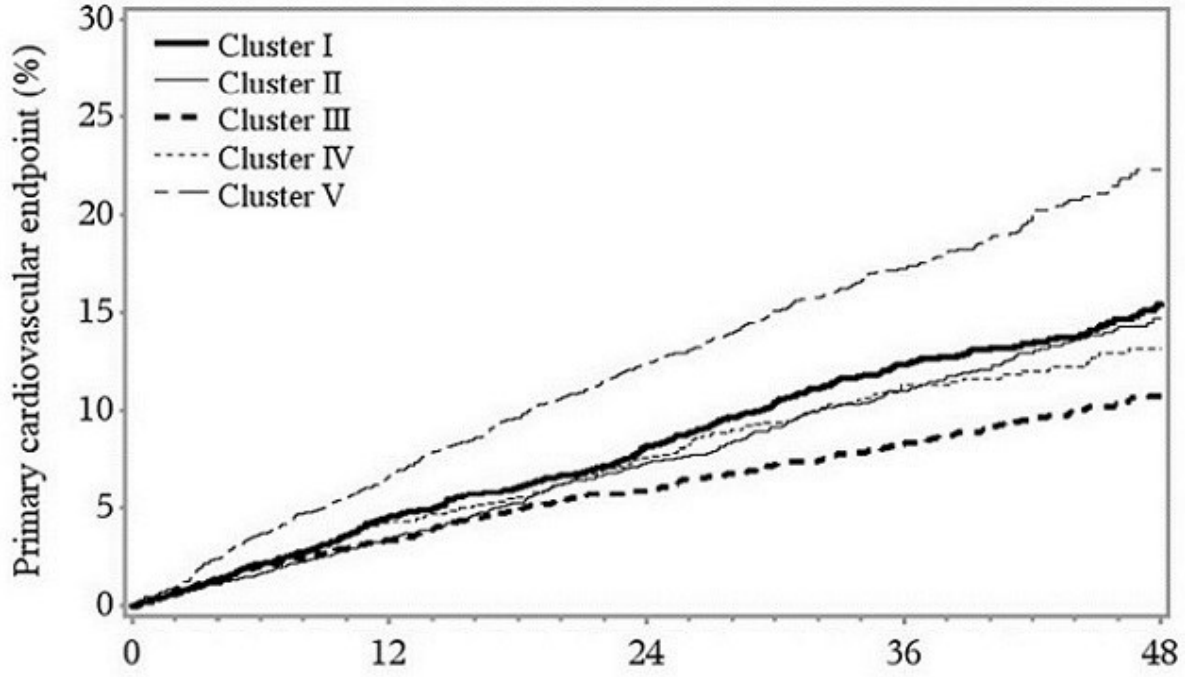
Purpose: We aimed to use a data agnostic machine learning algorithm to identify potentially different phenotypes among patients with T2DM and ASCVD.

Methods: We used data from the 14,671 patients with T2DM and ASCVD enrolled in TECOS, a cardiovascular (CV) safety outcome trial comparing sitagliptin vs placebo with median 3.0 years follow-up. Hierarchical clustering of 40 potentially prognostic baseline variables was conducted. The primary composite outcome (CV death, nonfatal MI/stroke or unstable angina hospitalization) across these clusters was then assessed using Cox proportional models. We also examined whether a differential treatment effect of sitagliptin across the clusters affected clinical outcomes.

Results: Five distinct patient clusters were identified. Cluster I included older men with a high prevalence of prior coronary artery disease. Cluster II primarily included women with non-coronary ASCVD. Cluster III comprised Asian patients with a low BMI. Cluster IV included younger males with a high BMI. Cluster V consisted of patients with heart failure. The primary composite outcome occurred in 11.9%, 10.6%, 8.7%, 11.0%, and 16.7% of patients in clusters I to V respectively. The CV risk for the highest vs lowest risk clusters (cluster V vs III) was statistically significant (HR 2.65; $p \leq 0.001$; Figure). No heterogeneity of sitagliptin vs. placebo on CV risk across the clusters was evident (interaction P value = 0.54).

Conclusions: In a contemporary cohort of patients with T2DM and ASCVD, cluster analysis identified five clinically distinct groups with varying CV risk, suggesting the need for improved CV phenotyping in T2DM patients to personalize patient care and optimize clinical trial designs.

Figure. Kaplan-Meier estimated cumulative incidence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina endpoint by cluster



At risk					
Cluster V	2539	2256	2041	955	335
Cluster IV	1616	1500	1408	710	265
Cluster III	3791	3532	3351	1980	718
Cluster II	3440	3187	2941	1346	452
Cluster I	3285	3018	2829	1398	511