Outcomes of Type 2 Diabetes (T2D) Clustering Replicated in the DEVOTE and LEADER Trials

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Aim

- Type 2 diabetes (T2D) is a heterogeneous disease. Multiple studies have therefore attempted to characterize more precise T2D patient populations.[1,2]
- Individuals in the Swedish All New Diabetics in Scania (ANDIS) cohort with newly diagnosed diabetes were grouped by 6 demographic and clinical variables (autoantibodies, sex, age at diagnosis, body mass index (BMI), hemoglobin A_{1c} (HbA_{1c}), and HOMA estimates of beta cell function and insulin resistance) to show 4 distinct T2D subtypes with differential risk for nephropathy.[2] (Cluster 1 was essentially identical to type 1 diabetes).
  - Cluster 2 (SIDD- severe insulin-deficit diabetes)
  - Cluster 3 (SIRD- severe insulin-resistant diabetes)
  - Cluster 4 (MOD- mild obesity-related diabetes)
  - Cluster 5 (MARD- mild age-related diabetes).
- The objective of this study was to test the predictive validity of the same clustering system for advanced T2D in the DEVOTE trial and the LEADER trial for predicting time to first episode of severe hypoglycemia (SH), time to first major adverse cardiovascular event (MACE), time to cardiovascular (CV) death, and time to all-cause mortality.

Methods

- Data came from the DEVOTE and LEADER trials. DEVOTE was a large, geographically diverse cardiovascular outcomes trial in advanced T2D patients at high risk of CV events.[3] For confirmation, all analyses were replicated in the LEADER trial, likewise a cardiovascular outcomes trial in advanced T2D patients.[4]
- Individuals enrolled in the DEVOTE and LEADER trials were included in the analysis if they had data on three key variables for clustering (BMI, HbA_{1c}, and age at diagnosis, calculated as baseline age in years minus years since diagnosis). C-peptide and auto-antibodies were not measured in the DEVOTE and LEADER trials.
- Participants were assigned to one of the four clusters described in the ANDIS cohort based on baseline HbA_{1c}, BMI, and calculated age at diagnosis. The Euclidean distance to exact cluster centers were calculated and participants were assigned to the cluster for which the distance was the smallest.
- Time-to-event analysis was used to compare differences in outcomes between the four clusters. Specifically Kaplan-Meyer curves were depicted and p-values for the log-rank test were determined.

Results

- The analysis included:
  - 7,673 participants in the DEVOTE trial with a mean age of 65.0 years, mean T2D duration of 16.4 years, and mean HbA_{1c} of 8.4%.
  - 9,340 participants in the LEADER trial with mean age of 64 years, mean T2D duration of 12.8 years, and mean HbA_{1c} of 8.7%.
- The four T2D clusters from the ANDIS cohort were represented in the DEVOTE trial as (a similar distribution was seen in the LEADER trial):
  - SIDD-like: 16.7% (N = 1,261)
  - SIRD-like: 24.5% (N = 1,847)
  - MOD-like: 26.8% (N = 2,632)
  - MARD-like: 34.9% (N = 2,632).
- The four replicated clusters showed differences in baseline characteristics consistent with the original ANDIS clusters despite clustering on a subset of the variables (**Figure 1**). For example, patients in the SIDD-like cluster had higher HbA_{1c}, and lower BMI. No other cluster had this profile.
- Differences in HbA_{1c} and BMI were retained over time [**Figure 2**].

Figure 1 Comparison of baseline characteristics of T2D Clusters in the DEVOTE trial (top row), the LEADER trial (bottom row).

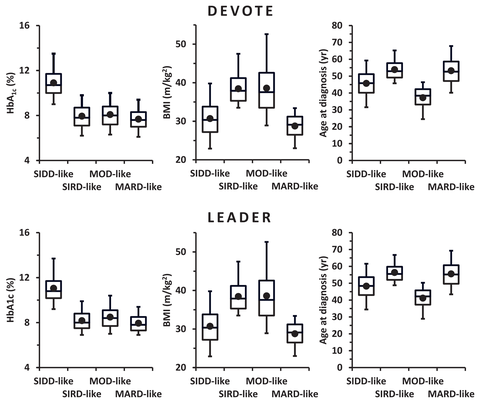
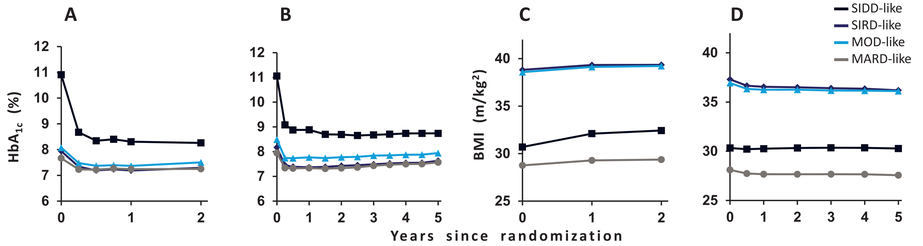
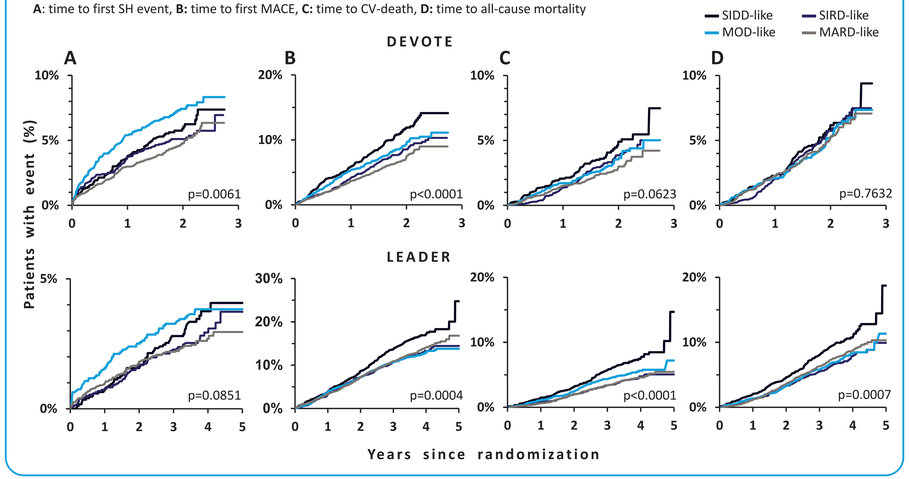


Figure 2 Mean HbA_{1c} and BMI over time in DEVOTE (A & C) and LEADER (B & D) according to T2D cluster



Key Result

Figure 3 Time to first event for the four T2D clusters: Upper panel DEVOTE data, lower panel LEADER data.
A: time to first SH event, **B:** time to first MACE, **C:** time to CV-death, **D:** time to all-cause mortality



- There was significant difference ($p<0.05$) across the T2D clusters in time to first SH and time to first MACE in the DEVOTE trial, and time to first MACE, time to first CV death and time to all-cause mortality in the LEADER trial [**Figure 3**].
- In the DEVOTE trial, the proportion of MACE incidence and CV death was highest among Cluster 2 SIDD (12.0% and 4.8% respectively) and lowest among the Cluster 4 MARD (7.7% and 3.2%, respectively). The LEADER trial showed similar trends.
- The results were not modified by sex or insulin use at baseline.

Discussion

- The data replicate patterns of previous T2D clusters derived in a predominantly northern European cohort early in T2D,[2] and further replicated in Chinese and US populations.[5]
- T2D clusters in DEVOTE and LEADER represent a geographically-diverse population with higher HbA_{1c}, greater CVD risk, and longer disease duration (mean diabetes duration: 16.4 years).
- Overall, the SIDD-like cluster appeared to have to highest risk of MACE, CV and all-cause mortality and may benefit from early intervention.
- The SIDD-cluster has previously shown significantly higher rates of retinopathy compared the other clusters in the ANDIS cohort.[2]
- To reduce disparity in survival outcomes, more work is needed to understand if and how optimal treatment regimens may differ according to subgroups.
- T2D clusters that are optimized by incorporation of treatment response variables over longitudinal follow-up could inform future treatment algorithms for clinical practice.

Conclusion

- Clusters derived from early T2D can be replicated in long-standing T2D and may confer information about time to first SH, MACE, CV mortality, and all-cause mortality.
- Patients with T2D, a high HbA_{1c} and low BMI (i.e. the SIDD-like phenotype) show significantly shorter time to first MACE and CV-death compared to other subgroups of T2D.
- The consistency of clusters across different populations adds to the evidence that T2D is not a homogeneous disease, but instead may have different prognoses and require different treatment according to specific disease subtypes.

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References: (**1**) Li L, Cheng W-Y et al. Sci Transl Med 2015; 7 (311): 311ra174-311ra174. (**2**) Ahlqvist E et al. Lancet Diabetes Endocrinol 2018; 6 (5): 361-9. (**3**) Marso SP et al. Am Heart J 2016; 179: 175-183. (4) Marso SP et al. New Eng J Med. 2016; 375 (4): 311-22. (5) Zou Xet al. Lancet Diabetes Endocrinol 2019; 7 (1): 9-11.