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# Validation of distinct type 2 diabetes clusters and their association with diabetes complications in the DEVOTE, LEADER and SUSTAIN-6 cardiovascular outcomes trials

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## Abstract

**Aims:** To validate the clusters of Swedish individuals with recent-onset diabetes at differential risk of complications, which were identified in a previous study, in three global populations with long-standing type 2 diabetes (T2D) who were at high cardiovascular risk, and to test for differences in the risk of major diabetes complications and survival endpoints.

**Materials and methods:** We assigned participants from recent global outcomes trials (DEVOTE [n = 7637], LEADER [n = 9340] and SUSTAIN-6 [n = 3297]) to the previously defined clusters according to age at diabetes diagnosis, baseline glycated haemoglobin (HbA1c) and body mass index (BMI). Outcomes were assessed using Kaplan–Meier analysis and log-rank tests.

**Results:** The T2D clusters were consistently replicated across the three trial cohorts. The risk of major adverse cardiovascular events and cardiovascular death differed significantly, in all trials, across clusters over a median follow-up duration of 2.0, 3.8 and 2.1 years, respectively, and was highest for the cluster of participants with high HbA1c and low BMI ($P < 0.05$ in DEVOTE and LEADER). In LEADER and SUSTAIN-6, the risk of nephropathy differed across clusters ($P < 0.0001$ and $P = 0.003$, respectively). The risk of severe hypoglycaemia differed in DEVOTE ($P = 0.006$).

**Conclusions:** Previously identified clusters can be replicated in three geographically diverse cohorts of long-standing T2D and are associated with cluster-specific risk profiles for additional clinical and survival outcomes, providing further validation of the clustering methodology. The external validity and stability of clusters across cohorts provides a premise for future work to optimize the clustering approach to

yield T2D subgroups with maximum predictive validity who may benefit from subtype-specific treatment paradigms.

**KEYWORDS**
cardiovascular disease, diabetes complications, GLP-1, hypoglycaemia, insulin analogues, type 2 diabetes

## 1 | INTRODUCTION

Type 2 diabetes (T2D) remains a major challenge to the health of a large and rapidly increasing part of the global population.[1] Despite the availability of a range of pharmacological treatments, a sizeable proportion of affected individuals develop severe and potentially fatal complications, including cardiovascular disease, renal disease and hypoglycaemia.[2–4] Considering the marked heterogeneity of the disease in terms of its clinical presentation, multifactorial risk factors and diverse outcomes and disease course, characterizing distinct subgroups of individuals with T2D may allow a more targeted and individualized therapeutic approach to improve patient outcomes and decrease costs.[5,6]

Recently, Ahlqvist et al[7] identified five clinically relevant and distinct phenotypic clusters in a large cohort of Swedish individuals with adult-onset diabetes (the All New Diabetes in Scania [ANDIS] cohort, 8980 individuals) using data-driven clustering based on six clinically available and diabetes-associated variables. Four clusters resembled T2D phenotypes and were characterized by age at diagnosis, β-cell function and insulin resistance (represented by homeostatic model assessment [HOMA] indices), body mass index (BMI), and glycated haemoglobin (HbA1c). A fifth cluster was defined by autoantibodies and resembled autoimmune type 1 diabetes. The identified subgroups showed disparate patterns in initiation of therapies and risk of early complications of diabetes, suggesting that these efforts to identify homogenous subgroups within the broader patient population may ultimately be used to improve unequal prognosis within the same disease classification.

Developing robust methodologies for identifying phenotypic T2D clusters marks an important milestone. Validation by replicating the clusters in additional and different diabetes cohorts, including geographically diverse populations, is needed to establish the generalizability of the clustering methodology. In the study by Ahlqvist et al,[7] the ANDIS clusters were replicated accurately in two additional cohorts, including a smaller cohort of individuals with long-standing T2D. Additionally, Dennis et al[8] successfully replicated the ANDIS clusters in the T2D populations of the ADOPT and RECORD clinical trials with focus on glycaemia-related and renal outcomes. Moreover, clustering was recently attempted in a cohort of individuals with type 1 diabetes or T2D from Germany.[9] To date, however, no study has investigated how the clustering approaches perform and aid in the prediction of long-term diabetes-related complications that account for the major morbidity and mortality of the disease, including cardiovascular risk and iatrogenic outcomes such as severe hypoglycaemia, in cohorts of individuals with advanced T2D and high risk of associated comorbidities. These validation studies are needed to establish fundamentally the merit of a compiled clustering approach, prior to further work characterizing and refining the resulting T2D clusters for optimal clinical utility. Accordingly, to validate and test the applicability of the ANDIS clustering approach in geographically diverse cohorts of individuals with advanced diabetes and high cardiovascular risk, we aimed to identify the same distinct subgroups of participants in the DEVOTE,[10] LEADER[11] and SUSTAIN-6[12] cardiovascular outcomes trials (CVOTs). These trials provide data from controlled, global investigations of a modern, long-acting basal insulin (insulin degludec)[10] and two widely prescribed subcutaneous glucagon-like peptide 1 analogues (liraglutide[11] and semaglutide[12]). Further, to test the utility of the clusters in predicting the risk of diabetes-related outcomes, we explored the association between the identified clusters and cardiovascular events (including major adverse cardiovascular events [MACE], cardiovascular death, non-fatal stroke and heart failure), all-cause death, new or worsening nephropathy and severe hypoglycaemia.

## 2 | MATERIALS AND METHODS

### 2.1 | Study populations

We performed clustering analyses on baseline data from a total of 20 274 participants recently enrolled in three randomized, double-blind, controlled, parallel-group multinational CVOTs in adults with long-standing T2D, all treated on a background of standard of care. The populations were enriched for cardiovascular risk, which in this study is graded as high (at least 50 years of age and established cardiovascular or chronic kidney disease) or medium (at least 60 years of age and presence of specific cardiovascular risk factors). The CVOTs formally confirmed the cardiovascular safety of insulin degludec (DEVOTE, conducted from October 2013 to October 2016; 7637 participants), liraglutide (LEADER, conducted from September 2010 to December 2015; 9340 participants) and semaglutide (SUSTAIN-6, conducted from February 2013 to March 2016; 3297 participants). In DEVOTE, the comparator was insulin glargine U100; LEADER and SUSTAIN-6 were placebo-controlled. Participants with available information on the selected clustering variables (see below) were included in the analyses.

Across the trials, more than 80% of the enrolled participants were classified as having high cardiovascular risk, the mean age was

64 years or older and the mean duration of diabetes was 12 years or longer. The mean HbA1c level was 8.4% in DEVOTE and 8.7% in both LEADER and SUSTAIN-6. The median follow-up time was 2.0, 3.8 and 2.1 years in DEVOTE, LEADER and SUSTAIN-6, respectively. Additional details are available in the original publications.[10–12]

## 2.2 | Cluster validation

We adopted the clustering methodology used by Ahlqvist et al[7]; however, the presence of glutamic acid decarboxylase antibodies (GADA), which was used to identify and classify individuals with autoimmune type 1 diabetes as severe autoimmune diabetes (cluster 1), was not available in our T2D-only cohorts. Moreover, we did not include HOMA indices because, in contrast to the ANDIS cohort, our cohorts included a high number of individuals treated with insulin; this may confound the interpretation of the indices, which were based on insulin measurements. Thus, our clustering was based on HbA1c level and BMI at baseline (defined as trial entry), and age at T2D diagnosis.

Rather than a *de novo* clustering analysis, we performed a validation study of the T2D clusters from the ANDIS cohort. In the clustering process, the three variables for each participant were first scaled and centred. Second, participants were assigned to one of four clusters based on the smallest Euclidean distance to the same cluster centres identified by Ahlqvist et al[7] (nearest centroid). To fully evaluate the accuracy of the clustering in our cohorts, we computed the subject-specific ratio between the smallest and the second smallest Euclidian distance to the ANDIS cluster centres; a ratio close to zero indicates a low distance to a cluster and therefore a strong participant-cluster association, whereas a ratio close to 1 indicates a weak association. Acknowledging the cohort differences between the present study and the study by Ahlqvist et al,[7] we chose letter-based cluster labels, which correspond to the replicated ANDIS labels as follows: Cluster A, severe insulin-deficient diabetes (ANDIS cluster 2); Cluster B, severe insulin-resistant diabetes (cluster 3); Cluster C, mild obesity-related diabetes (cluster 4); and Cluster D, mild age-related diabetes (cluster 5).

## 2.3 | Associations of clusters and outcomes

We assessed the following outcomes by cluster for each of the three trials separately: three-component MACE (primary outcome in all three CVOTs; components were the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); cardiovascular death separately; all-cause death; heart failure requiring hospitalization; severe hypoglycaemia (hypoglycaemic episodes classified as severe according to contemporary American Diabetes Association [ADA] definitions[13]); and new or worsening nephropathy for LEADER and SUSTAIN-6 (composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease or death attributable to renal disease). The outcomes had been confirmed by adjudication performed by an external, independent committee in a blinded manner.

For each outcome, the risk was assessed using Cox regression and Kaplan–Meier analysis. Associations between clusters and outcome events were evaluated using a log-rank test. All analyses were performed using R (version 3.5.1).[14]

# 3 | RESULTS

## 3.1 | Cluster characteristics

Using three T2D-related participant characteristics (HbA1c and BMI at baseline, and age at T2D diagnosis), participants in the DEVOTE, LEADER and SUSTAIN-6 populations were assigned to four distinct clusters (Clusters A to D; Figure 1) mapped to the ANDIS parameters. Across the three populations (Table 1), a noticeably worse degree of glycaemic control characterized Cluster A (mean HbA1c at baseline 10.9% to 11.1% compared with ~ 7.7% to 8.5% in the other three clusters). Clusters B and C were characterized by greater baseline BMI (~ 37–39 vs. ~ 28–30 kg/m$^2$ in the other two clusters) and the age of T2D diagnosis in Clusters B and D clusters (~ 53–56 years) were higher than in the other clusters and consistently lowest in Cluster C (~ 37–41 years). The number of participants in each cluster was very similar across the three trial populations; more than one-third of the participants was assigned to Cluster D, a quarter was assigned to Cluster B and around one-fifth was assigned to each of Clusters A and C. The sex distribution did not differ markedly across the clusters. Further, Cluster C was characterized by many participants with long-standing (>10 years) T2D. For LEADER and SUSTAIN-6, Clusters B and D were defined by a higher prevalence of insulin-naïve individuals, whereas for DEVOTE, all clusters had a low prevalence of such individuals. The prevalence of participants at high cardiovascular risk (as compared to participants with medium cardiovascular risk) was higher in Cluster C than in the other clusters (~ 88%–90% vs. ~ 79%–84% of the participants), whereas there did not appear to be a consistent difference in renal function across clusters in any of the trials.

## 3.2 | Risk–cluster association

We evaluated the risk of multiple outcomes in the three trials (Figures 2 and 3, and Table 2). Overall, cardiovascular event risk differed across clusters, as evident from the clear and early separation of the cumulative incidence curves. Specifically, the risk of MACE and cardiovascular death was highest in Cluster A in all three trials; the differences were statistically significant in DEVOTE and LEADER ($P = 0.026$ and $P < 0.0001$, respectively). The risk of all-cause death in LEADER was greatest in Cluster A ($P < 0.001$). The risk of heart failure (Table S1) also differed across clusters ($P < 0.006$), most prominently in SUSTAIN-6, where the risk was markedly greater for Cluster C compared to the other clusters ($P = 0.006$). For both LEADER and SUSTAIN-6, the risk of new or worsening nephropathy differed across clusters ($P < 0.0001$ and $P = 0.003$, respectively). In DEVOTE only, the risk of severe hypoglycaemia differed across the clusters ($P = 0.006$).

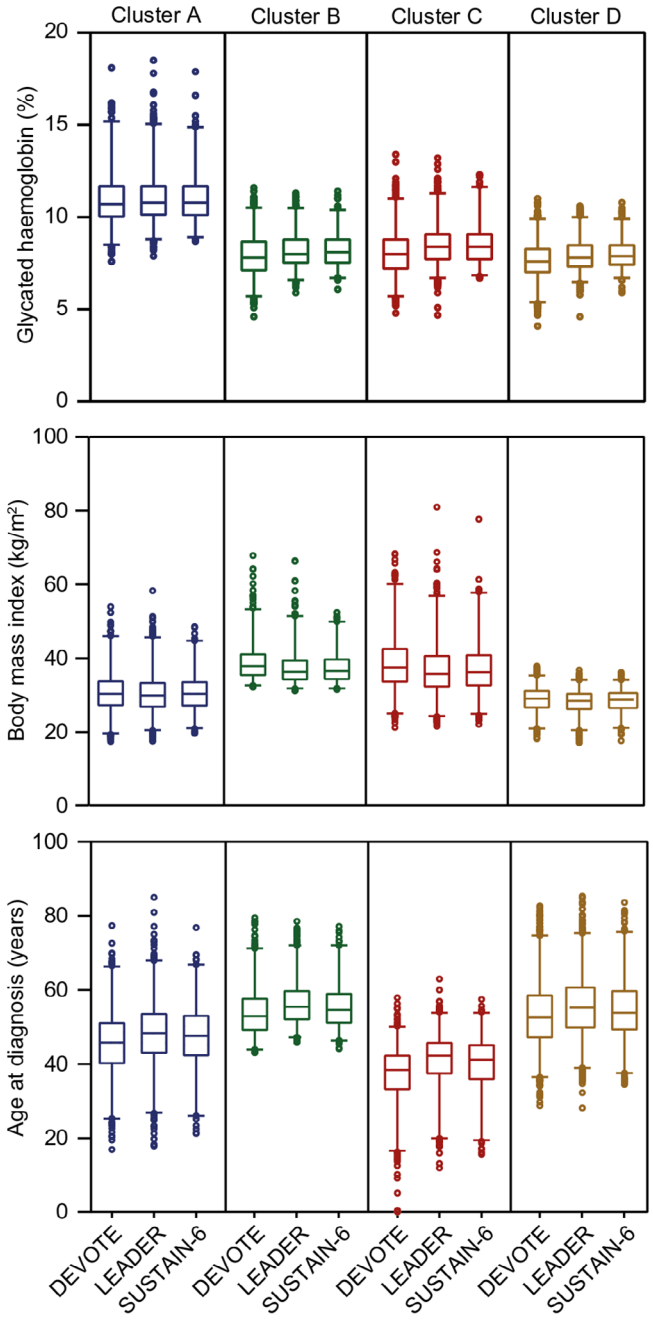



**FIGURE 1** Clustering parameters (glycated haemoglobin and body mass index at baseline, and age at diabetes diagnosis) by cluster assignment in the DEVOTE, LEADER and SUSTAIN-6 trials. Boxes are the median, and 25th and 75th percentiles; whiskers are the 1st and 99th percentiles. Values outside these percentiles are represented by open circles. Cluster labels correspond to the ANDIS labels as follows: Cluster A, severe insulin-deficient diabetes; Cluster B, severe insulin-resistant diabetes; Cluster C, mild obesity-related diabetes; and Cluster D, mild age-related diabetes. Baseline was defined as trial entry

### 3.3 | Clustering performance

The performance of the clustering was assessed by the ratio between the smallest and the second smallest Euclidian distance to the cluster centres (Figure S1), where a smaller distance ratio indicates a more unique participant-to-cluster association. Considering the somewhat large number of participants with a relatively high distance ratio, outcomes were reassessed when excluding data for participants with a distance ratio greater than 0.8 (ie, those most difficult to assign to a single cluster). In these sensitivity analyses (Figures S2 and S3 [dashed lines] and Table S1), the risk–cluster associations and the associated statistical significances were consistent with those of the original analyses with a single exception: in the sensitivity analysis, the risk for nephropathy in SUSTAIN-6 did not statistically significantly differ across clusters.

## 4 | DISCUSSION

In the present study, we applied recent phenotypic clustering approaches[7] to three populations of individuals with T2D enriched for high cardiovascular and/or renal risk who were enrolled in controlled CVOTs (DEVOTE,[10] LEADER[11] and SUSTAIN-6[12]), based on a subset of readily available clinical measures obtained before exposure to trial treatment. The main aim was to provide additional external and broad validation of the methodology originally developed by Ahlqvist et al.[7] Our cohorts were geographically more diverse and characterized by more advanced diabetes compared with the cohorts of the previous studies using the methodology (ie, the ANDIS cohort and cohorts from the follow-on studies[8,9]). We demonstrate similar results to those obtained with the six-variable clustering approach in the ANDIS study by clustering based on three variables, which should be clinically available in all individuals with T2D. As an additional novel aspect, we showed that the approaches can be used to differentiate the risk of diabetes outcomes in global T2D populations.

The validity of the ANDIS clustering approach was confirmed by our findings. Despite the different cohorts and the longer duration of the follow-up in the outcome trials, the distribution of trial participants across the corresponding clusters generally align between the ANDIS cohort and our cohorts. While differences across the studied cohorts between the ANDIS study and our investigation preclude a direct comparison of the identified risks, there appeared to be a general alignment between the risk of cardiovascular and renal disease across clusters in DEVOTE, LEADER and SUSTAIN-6 and the risk of early complications (Clusters A and B), as shown for the ANDIS cluster. An interesting finding of the study was that Cluster A, the insulinopenic subgroup defined by high HbA1c and low BMI, showed the highest incidence of cardiovascular events, even though long-term insulin resistance and hyperinsulinaemia are known cardiovascular risk factors. It is possible that these results are attributable to the differences between the study populations, where the insulinopenic group from the trials (Cluster A) may not have exhibited the degree of insulin deficiency of the severe insulin-deficient diabetes cluster in the Ahlqvist et al cohort. In addition, HbA1c was appreciably higher in Cluster A compared with the other clusters across all study populations (~ 11% in Cluster A, compared with <8.5% in the other subgroups), which may have accelerated cardiovascular risk through

**TABLE 1** Participant characteristics at baseline by cluster

| | DEVOTE | | | | LEADER | | | | SUSTAIN-6 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D |
| Women, n (%) | 479 (33.8) | 682 (38.1) | 675 (42.3) | 984 (35.8) | 570 (32.6) | 832 (37.5) | 747 (39.7) | 1176 (34.0) | 222 (36.6) | 336 (41.9) | 283 (43.1) | 454 (37.0) |
| Men, n (%) | 937 (66.2) | 1107 (61.9) | 919 (57.7) | 1763 (64.2) | 1178 (67.4) | 1388 (62.5) | 1136 (60.3) | 2285 (66.0) | 384 (63.4) | 465 (58.1) | 374 (56.9) | 772 (63.0) |
| Age, years (SD) | 62.01 (6.69) | 66.48 (6.36) | 61.39 (6.69) | 67.58 (7.32) | 62.2 (6.87) | 65.55 (6.22) | 60.15 (6.38) | 66.78 (7.13) | 61.84 (6.41) | 65.96 (6.53) | 60.33 (6.57) | 67.42 (7.22) |
| Adults, age < 60 years, n (%) | 490 (34.6) | 217 (12.1) | 659 (41.3) | 362 (13.2) | 601 (34.4) | 329 (14.8) | 894 (47.5) | 490 (14.2) | 217 (35.8) | 113 (14.1) | 301 (45.8) | 150 (12.2) |
| Elderly, age ≥ 60 years, n (%) | 926 (65.4) | 1572 (87.9) | 935 (58.7) | 2385 (86.8) | 1147 (65.6) | 1891 (85.2) | 989 (52.5) | 2971 (85.8) | 389 (64.2) | 688 (85.9) | 356 (54.2) | 1076 (87.8) |
| HbA1c, % (SD) | 10.91 (1.4) | 7.94 (1.09) | 8.08 (1.16) | 7.67 (0.98) | 11.05 (1.36) | 8.17 (0.92) | 8.49 (1.03) | 7.95 (0.8) | 10.99 (1.25) | 8.23 (0.89) | 8.51 (1.02) | 7.98 (0.78) |
| Age at T2D diagnosis, years (SD) | 45.68 (8.38) | 53.87 (6.08) | 37.2 (7.04) | 53.18 (8.47) | 48.26 (8.44) | 56.36 (5.61) | 41.17 (6.66) | 55.56 (7.98) | 47.42 (8.27) | 55.58 (5.76) | 40.17 (6.9) | 54.87 (8.07) |
| Diabetes duration, years (SD) | 16.33 (8.36) | 12.62 (6.16) | 24.19 (9.17) | 14.39 (7.64) | 13.94 (7.86) | 9.19 (5.51) | 18.99 (9.03) | 11.22 (6.72) | 14.42 (7.66) | 10.38 (5.81) | 20.16 (9.02) | 12.55 (7.16) |
| Insulin-naïve, n (%) | 271 (19.1) | 303 (16.9) | 127 (8.0) | 514 (18.7) | 862 (49.3) | 1364 (61.4) | 750 (39.8) | 2179 (63.0) | 203 (33.5) | 373 (46.6) | 183 (27.9) | 621 (50.7) |
| BMI, kg/m$^2$ (SD) | 30.71 (5.25) | 38.84 (4.57) | 38.6 (7.21) | 28.77 (3.24) | 30.33 (5.17) | 37.3 (4.24) | 36.94 (6.81) | 28.11 (3.04) | 30.59 (4.88) | 37.49 (4.15) | 37.21 (6.86) | 28.47 (2.97) |
| Body weight, kg (SD) | 87.49 (18.48) | 111.23 (17.06) | 111.16 (24.65) | 82.03 (14.12) | 84.83 (17.97) | 105.51 (15.76) | 105.07 (23.38) | 79.14 (12.78) | 85.44 (16.51) | 105.52 (15.73) | 104.89 (24.06) | 79.76 (12.38) |
| Smoking status | | | | | | | | | | | | |
| Current smoker, n (%) | 191 (13.5) | 166 (9.3) | 146 (9.2) | 337 (12.3) | 236 (13.5) | 222 (10.0) | 232 (12.3) | 433 (12.5) | 91 (15.0) | 84 (10.5) | 97 (14.8) | 131 (10.7) |
| Previous smoker, n (%) | 570 (40.3) | 868 (48.5) | 687 (43.1) | 1189 (43.3) | 760 (43.5) | 1147 (51.7) | 845 (44.9) | 1580 (45.7) | 247 (40.8) | 384 (47.9) | 245 (37.3) | 518 (42.3) |
| Never smoked, n (%) | 655 (46.3) | 755 (42.2) | 761 (47.7) | 1221 (44.4) | 752 (43.0) | 851 (38.3) | 806 (42.8) | 1448 (41.8) | 268 (44.2) | 332 (41.4) | 315 (47.9) | 577 (47.1) |
| Cardiovascular risk[a] | | | | | | | | | | | | |
| High, n (%) | 1197 (84.5) | 1500 (83.8) | 1440 (90.3) | 2296 (83.6) | 1393 (79.7) | 1753 (79) | 1652 (87.7) | 2773 (80.1) | 507 (83.7) | 661 (82.5) | 579 (88.1) | 982 (80.1) |
| Medium, n (%) | 213 (15) | 286 (16.0) | 150 (9.4) | 444 (16.2) | 355 (20.3) | 467 (21) | 231 (12.3) | 688 (19.9) | 99 (16.3) | 140 (17.5) | 78 (11.9) | 244 (19.9) |
| Blood pressure | | | | | | | | | | | | |
| Systolic, mmHg (SD) | 136.36 (19.03) | 135.55 (17.7) | 135.93 (18.21) | 134.86 (17.51) | 135.43 (18.23) | 136.34 (17.14) | 135.86 (18.23) | 135.92 (17.58) | 134.61 (17.81) | 136.8 (16.81) | 136.76 (17.28) | 134.75 (16.89) |
| Diastolic, mmHg (SD) | 78.19 (10.47) | 76.02 (10.35) | 75.53 (10.65) | 75.63 (10.02) | 77.91 (10.18) | 77.7 (10.22) | 77.3 (10.61) | 76.2 (9.97) | 77.14 (9.88) | 77.88 (9.78) | 78.09 (10.25) | 75.88 (9.98) |
| Pulse rate, bpm (SD) | 74.97 (11.57) | 72.15 (11.13) | 73.22 (11.52) | 72.59 (11.06) | 74.48 (11.41) | 72.27 (11.36) | 72.88 (10.71) | 71.69 (11.56) | 73.79 (11.14) | 71.73 (10.74) | 73.04 (10.82) | 70.85 (10.82) |
| Glomerular filtration rate, mL/min/1.73 m$^2$ (SD)[b] | 73.44 (21.93) | 65.43 (20.78) | 67.34 (22.73) | 67.14 (20.61) | 83.93 (22.72) | 78.92 (20.29) | 80.86 (23.51) | 78.07 (21.3) | 79.29 (28.92) | 74.89 (25.21) | 75.16 (27.82) | 75.9 (25.41) |
| Renal impairment, n (%)[c] | 430 (30.6) | 759 (42.8) | 656 (41.6) | 1058 (38.8) | 336 (19.2) | 488 (22) | 447 (23.8) | 790 (22.9) | 146 (24.1) | 245 (30.6) | 195 (29.7) | 319 (26.0) |
| Region | | | | | | | | | | | | |
| Asia, n (%) | 220 (15.5) | 20 (1.1) | 51 (3.2) | 349 (12.7) | 220 (12.6) | 25 (1.1) | 68 (3.6) | 396 (11.4) | – | – | – | – |

(Continues)

**TABLE 1** (Continued)

| | DEVOTE | | | | LEADER | | | | SUSTAIN-6 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D |
| Europe, n (%) | 141 (10.0) | 211 (11.8) | 152 (9.5) | 367 (13.4) | 370 (21.2) | 953 (42.9) | 578 (30.7) | 1384 (40.0) | 65 (10.7) | 177 (22.1) | 110 (16.7) | 278 (22.7) |
| North America, n (%) | 835 (59.0) | 1452 (81.2) | 1264 (79.3) | 1663 (60.5) | 500 (28.6) | 775 (34.9) | 765 (40.6) | 798 (23.1) | 212 (35.0) | 368 (45.9) | 305 (46.4) | 386 (31.5) |

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

[a]Cardiovascular risk was classified as high for participants aged ≥50 years enrolling with established cardiovascular and/or chronic kidney disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease, chronic heart failure [New York Heart Association class II or III], or chronic kidney disease); medium cardiovascular risk corresponds to participants aged ≥60 years with cardiovascular risk factors (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction, ankle/brachial index <0.9).

[b]Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

[c]Renal impairment was defined as an estimated glomerular filtration rate of ≤60 mL/min/1.73 $m^2$; participants with end-stage renal disease were not enrolled in any of the trials. Baseline was defined as trial entry.

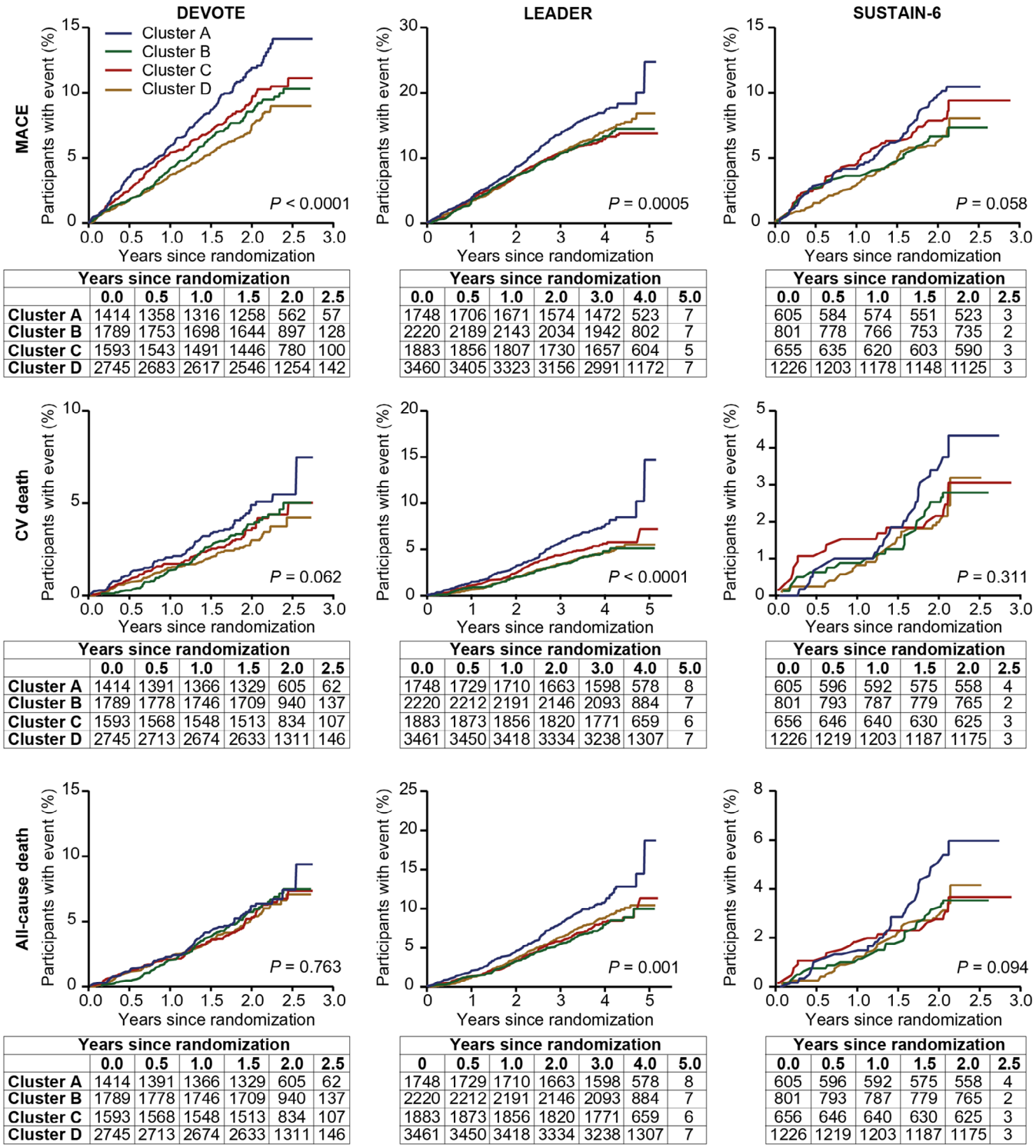
mechanisms not directly mediated by insulin resistance or hyperinsulinaemia.

In the present study, we also evaluated the risk of severe hypoglycaemia, relevant primarily for persons treated with an insulin. As evident from the early and clear separation of the incidence curves (Figure 3), the risk of severe hypoglycaemia differed between clusters in DEVOTE where all participants were treated with insulin, probably reflecting the low incidence of severe hypoglycaemic episodes in LEADER and SUSTAIN-6. In DEVOTE, the risk of severe hypoglycaemia was greatest in Cluster C. This was also observed for LEADER, but the differences were not statistically significant. For DEVOTE, the observation may relate to the lower prevalence of insulin-naïve individuals in this cluster and to the fact that DEVOTE (but not LEADER and SUSTAIN-6) was a treat-to-target trial, which required sufficiently high doses of basal insulin to achieve the prespecified HbA1c target.

The generalizability of risk stratification shown in the present study should be considered in the context of the fact that the results were observed for individuals participating in controlled clinical trials. Moreover, in real-world clinical settings, competing risks may have a greater influence than in relatively short-term clinical trials. Thus, while we demonstrate that it is possible to associate the validated clusters with selected unique risk patterns, further investigations are needed to fully establish the legitimacy of these findings and their clinical applicability.

Ahlqvist et al elucidated single nucleotide polymorphisms as associated with the clusters[7]; currently, however, the broad clinical applicability of genotypic clustering is low. Conversely, T2D subgroups may be more easily applied in clinical practice if they rely on fewer variables while maintaining accuracy and predictive validity for other long-term outcomes. In this context, we were able to replicate the ANDIS clusters based on three variables compared with the five relevant for T2D in the original work by Ahlqvist et al.[7] In particular, the GADA variable was disregarded in our analyses, because all three cohorts comprised patients with T2D exclusively. Moreover, this variable was suspected to be of limited utility as the prevalence of GADA is likely to be lower among the included patients with long-standing diabetes compared with the ANDIS cohort with recent-onset diabetes. Similarly, HOMA estimations of insulin resistance were discarded because of their limited utility; interpretation is not straightforward among a population with long-standing diabetes lacking universal insulin naivety.

This carries important implications for the scalability and clinical utility of clustering-based approaches in patient stratification, because the C-peptide or insulin measurements required for the HOMA variables used in the study by Ahlqvist et al[7] have not been fully standardized or recommended in general clinical practice. Thus, while the HOMA indices may be more available clinically in the future and acknowledging their relevance to the pathophysiology of diabetes, our results suggest that the clustering approaches can provide adequately robust and clinically useful patient stratification without those variables. Future studies may help to elucidate if there are other clinical markers, such as measures of renal function, which may be more




| MACE | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 1414 | 1358 | 1316 | 1258 | 562 | 57 | |
| Cluster B | 1789 | 1753 | 1698 | 1644 | 897 | 128 | |
| Cluster C | 1593 | 1543 | 1491 | 1446 | 780 | 100 | |
| Cluster D | 2745 | 2683 | 2617 | 2546 | 1254 | 142 | |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 3.0 | 4.0 | 5.0 |
| Cluster A | 1748 | 1706 | 1671 | 1574 | 1472 | 523 | 7 | |
| Cluster B | 2220 | 2189 | 2143 | 2034 | 1942 | 802 | 7 | |
| Cluster C | 1883 | 1856 | 1807 | 1730 | 1657 | 604 | 5 | |
| Cluster D | 3460 | 3405 | 3323 | 3156 | 2991 | 1172 | 7 | |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 605 | 584 | 574 | 551 | 523 | 3 | |
| Cluster B | 801 | 778 | 766 | 753 | 735 | 2 | |
| Cluster C | 655 | 635 | 620 | 603 | 590 | 3 | |
| Cluster D | 1226 | 1203 | 1178 | 1148 | 1125 | 3 | |

| CV death | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 1414 | 1391 | 1366 | 1329 | 605 | 62 | |
| Cluster B | 1789 | 1778 | 1746 | 1709 | 940 | 137 | |
| Cluster C | 1593 | 1568 | 1548 | 1513 | 834 | 107 | |
| Cluster D | 2745 | 2713 | 2674 | 2633 | 1311 | 146 | |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 3.0 | 4.0 | 5.0 |
| Cluster A | 1748 | 1729 | 1710 | 1663 | 1598 | 578 | 8 | |
| Cluster B | 2220 | 2212 | 2191 | 2146 | 2093 | 884 | 7 | |
| Cluster C | 1883 | 1873 | 1856 | 1820 | 1771 | 659 | 6 | |
| Cluster D | 3461 | 3450 | 3418 | 3334 | 3238 | 1307 | 7 | |

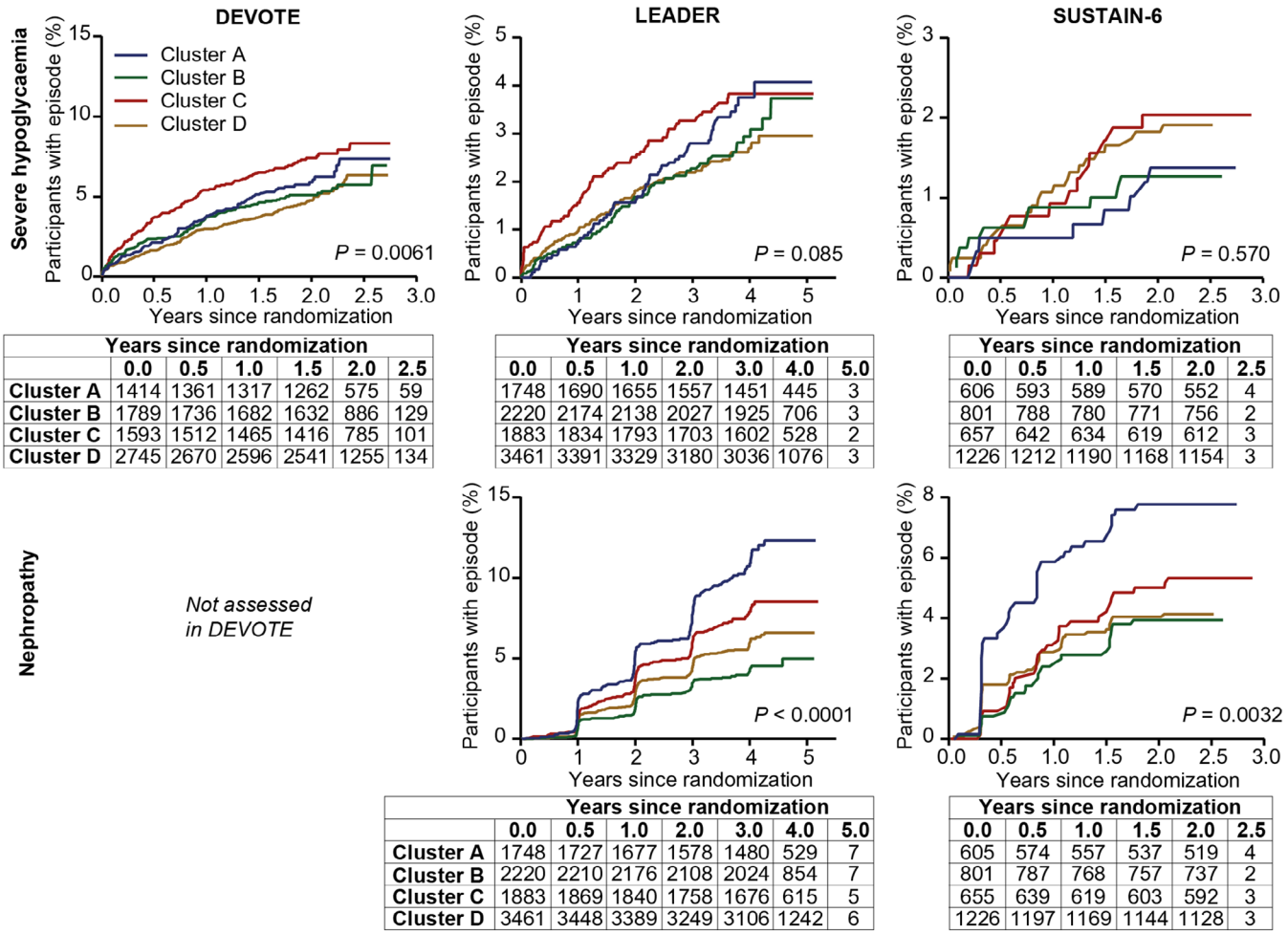
| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 605 | 596 | 592 | 575 | 558 | 4 | |
| Cluster B | 801 | 793 | 787 | 779 | 765 | 2 | |
| Cluster C | 656 | 646 | 640 | 630 | 625 | 3 | |
| Cluster D | 1226 | 1219 | 1203 | 1187 | 1175 | 3 | |

| All-cause death | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 1414 | 1391 | 1366 | 1329 | 605 | 62 | |
| Cluster B | 1789 | 1778 | 1746 | 1709 | 940 | 137 | |
| Cluster C | 1593 | 1568 | 1548 | 1513 | 834 | 107 | |
| Cluster D | 2745 | 2713 | 2674 | 2633 | 1311 | 146 | |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Cluster A | 1748 | 1729 | 1710 | 1663 | 1598 | 578 | 8 |
| Cluster B | 2220 | 2212 | 2191 | 2146 | 2093 | 884 | 7 |
| Cluster C | 1883 | 1873 | 1856 | 1820 | 1771 | 659 | 6 |
| Cluster D | 3461 | 3450 | 3418 | 3334 | 3238 | 1307 | 7 |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | |
| Cluster A | 605 | 596 | 592 | 575 | 558 | 4 | |
| Cluster B | 801 | 793 | 787 | 779 | 765 | 2 | |
| Cluster C | 656 | 646 | 640 | 630 | 625 | 3 | |
| Cluster D | 1226 | 1219 | 1203 | 1187 | 1175 | 3 | |

**FIGURE 2** Cumulative risk of a major adverse cardiovascular event (MACE), cardiovascular (CV) death and all-cause death by cluster in the DEVOTE, LEADER and SUSTAIN-6 trials. First occurrence of a MACE was the three-component primary outcome in each trial; components comprised CV death, non-fatal myocardial infarction and non-fatal stroke. All outcomes had been confirmed by adjudication performed by external, independent medical experts. Full lines represent analyses based on all eligible participants; dashed lines represent analyses based on all except the 20% of the participants who were most difficult to assign to a single cluster (see text). *P* values are from a log-rank test for the analysis of all participants. Participants at risk, shown in the tables, are for the full analysis. The median follow-up time was 2.0, 3.8 and 2.1 years in DEVOTE, LEADER and SUSTAIN-6 respectively. N, number of participants; %, proportion of participants




| Severe hypoglycaemia | Years since randomization | | | | | |
|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 |
| Cluster A | 1414 | 1361 | 1317 | 1262 | 575 | 59 |
| Cluster B | 1789 | 1736 | 1682 | 1632 | 886 | 129 |
| Cluster C | 1593 | 1512 | 1465 | 1416 | 785 | 101 |
| Cluster D | 2745 | 2670 | 2596 | 2541 | 1255 | 134 |

| | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Cluster A | 1748 | 1690 | 1655 | 1557 | 1451 | 445 | 3 |
| Cluster B | 2220 | 2174 | 2138 | 2027 | 1925 | 706 | 3 |
| Cluster C | 1883 | 1834 | 1793 | 1703 | 1602 | 528 | 2 |
| Cluster D | 3461 | 3391 | 3329 | 3180 | 3036 | 1076 | 3 |

| | Years since randomization | | | | | |
|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 |
| Cluster A | 606 | 593 | 589 | 570 | 552 | 4 |
| Cluster B | 801 | 788 | 780 | 771 | 756 | 2 |
| Cluster C | 657 | 642 | 634 | 619 | 612 | 3 |
| Cluster D | 1226 | 1212 | 1190 | 1168 | 1154 | 3 |

| Nephropathy | Years since randomization | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Cluster A | 1748 | 1727 | 1677 | 1578 | 1480 | 529 | 7 |
| Cluster B | 2220 | 2210 | 2176 | 2108 | 2024 | 854 | 7 |
| Cluster C | 1883 | 1869 | 1840 | 1758 | 1676 | 615 | 5 |
| Cluster D | 3461 | 3448 | 3389 | 3249 | 3106 | 1242 | 6 |

| | Years since randomization | | | | | |
|---|---|---|---|---|---|---|
| | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 |
| Cluster A | 605 | 574 | 557 | 537 | 519 | 4 |
| Cluster B | 801 | 787 | 768 | 757 | 737 | 2 |
| Cluster C | 655 | 639 | 619 | 603 | 592 | 3 |
| Cluster D | 1226 | 1197 | 1169 | 1144 | 1128 | 3 |

**FIGURE 3** Cumulative risk of severe hypoglycaemia and new or worsening of nephropathy by cluster in the DEVOTE, LEADER and SUSTAIN-6 trials. New or worsening of nephropathy was defined as occurrence of one of the following: new onset of persistent macroalbuminuria or doubling of the serum creatine concentration or of creatine clearance; continuous renal replacement therapy; death attributable to renal disease. Hypoglycaemic episodes were classified as severe according to contemporaneous American Diabetes Association criteria. All outcomes had been confirmed by adjudication performed by external, independent medical experts. Full lines represent analyses based on all eligible participants; dashed lines represent analyses based on all except the 20% of the participants who were most difficult to assign to a single cluster (see text). *P* values are from a log-rank test for the analysis of all participants. Participants at risk, shown in the tables, are for the full analysis. The median follow-up time was 2.0, 3.8 and 2.1 years in DEVOTE, LEADER and SUSTAIN-6, respectively. N, number of participants; %, proportion of participants

readily available in clinical settings to help further distinguish diabetes subtypes.

The advances made by Ahlqvist et al[7] represented an important early step in identifying clusters of apparent clinical relevance and implicated a series of key scientific steps by which the computational clustering approach can be systematically validated, optimized and ultimately translated to the clinical care of patients with T2D. The generation of evidence supporting the scalability and stability of the computational clustering approach across different populations of patients with T2D represents the first step in this workflow. After careful external validation, there remain important research questions that warrant thorough investigation before the T2D clusters can be translated to daily clinical practice. Thus, we propose that the present study is the first of multiple steps towards moving the T2D clusters to the clinic and that the findings provide a premise for future studies to test specifically how clusters can be refined via integration of different variables to optimize cardiovascular outcome prediction beyond existing tools and dictate treatment response.

A key endeavour, for example, will be to identify additional clustering variables for improved risk prediction. Early work in this area by Dennis et al[8] showed that using prognostic markers such as glomerular filtration rate and age at diagnosis alone could outperform clustering in stratifying high-risk individuals for diabetic nephropathy outcomes. As this was an external validation study, we did not perform a *de novo* clustering analysis and instead used the cluster centres from the previous study of interest in order to test whether previously identified clusters were stable in our cohort; therefore, including novel variables in this analysis was not feasible given the constraints of the

**TABLE 2** Outcomes by trials and clusters

| | DEVOTE | | | | LEADER | | | | SUSTAIN-6 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D | Cluster A | Cluster B | Cluster C | Cluster D |
| **First MACE** | | | | | | | | | | | | |
| Participants, n | 1414 | 1789 | 1593 | 2745 | 1748 | 2220 | 1883 | 3460 | 605 | 801 | 655 | 1226 |
| Events, n (%) | 164 (0.12) | 156 (0.09) | 150 (0.09) | 203 (0.07) | 295 (0.17) | 289 (0.13) | 237 (0.13) | 473 (0.14) | 61 (0.1) | 54 (0.07) | 54 (0.08) | 84 (0.07) |
| Mean follow-up time, years | 1.85 | 1.96 | 1.93 | 1.93 | 3.54 | 3.65 | 3.64 | 3.62 | 1.98 | 2.02 | 1.99 | 2.02 |
| *P* value (log-rank) | | <0.0001 | | | | 0.0005 | | | | 0.058 | | |
| **Cardiovascular death** | | | | | | | | | | | | |
| Participants, n | 1414 | 1789 | 1593 | 2745 | 1748 | 2220 | 1883 | 3461 | 605 | 801 | 656 | 1226 |
| Events, n (%) | 64 (0.05) | 70 (0.04) | 59 (0.04) | 82 (0.03) | 130 (0.07) | 101 (0.05) | 102 (0.05) | 158 (0.05) | 23 (0.04) | 22 (0.03) | 17 (0.03) | 28 (0.02) |
| Mean follow-up time, years | 1.93 | 2.02 | 2.00 | 1.97 | 3.73 | 3.84 | 3.81 | 3.81 | 2.05 | 2.07 | 2.06 | 2.07 |
| *P* value (log-rank) | | 0.062 | | | | <0.0001 | | | | 0.311 | | |
| **All-cause death** | | | | | | | | | | | | |
| Participants, n | 1414 | 1789 | 1593 | 2745 | 1748 | 2220 | 1883 | 3461 | 605 | 801 | 656 | 1226 |
| Events, n (%) | 82 (0.06) | 106 (0.06) | 87 (0.05) | 144 (0.05) | 193 (0.11) | 171 (0.08) | 151 (0.08) | 305 (0.09) | 33 (0.05) | 28 (0.03) | 21 (0.03) | 40 (0.03) |
| Mean follow-up time, years | 1.93 | 2.02 | 2.00 | 1.97 | 3.73 | 3.84 | 3.81 | 3.81 | 2.05 | 2.07 | 2.06 | 2.07 |
| *P* value (log-rank) | | 0.763 | | | | 0.001 | | | | 0.094 | | |
| **Severe hypoglycaemia** | | | | | | | | | | | | |
| Participants, n | 1414 | 1789 | 1593 | 2745 | 1748 | 2220 | 1883 | 3461 | 606 | 801 | 657 | 1226 |
| Events, n (%) | 84 (0.06) | 94 (0.05) | 117 (0.07) | 134 (0.05) | 57 (0.03) | 60 (0.03) | 67 (0.04) | 87 (0.03) | 8 (0.01) | 10 (0.01) | 13 (0.02) | 23 (0.02) |
| Mean follow-up time, years | 1.86 | 1.95 | 1.90 | 1.92 | 3.43 | 3.57 | 3.50 | 3.58 | 2.03 | 2.05 | 2.03 | 2.05 |
| *P* value (log-rank) | | 0.0061 | | | | 0.085 | | | | 0.570 | | |
| **New or worsening nephropathy** | Not assessed | | | | | | | | | | | |
| Participants, n | | | | | 1748 | 2220 | 1883 | 3461 | 605 | 801 | 655 | 1226 |
| Events, n (%) | | | | | 178 (0.1) | 90 (0.04) | 141 (0.07) | 196 (0.06) | 46 (0.08) | 31 (0.04) | 34 (0.05) | 50 (0.04) |
| Mean follow-up time, years | | | | | 3.57 | 3.77 | 3.69 | 3.72 | 1.95 | 2.03 | 2 | 2.01 |
| *P* value (log-rank) | | | | | | <0.0001 | | | | 0.0032 | | |

Abbreviations: MACE, major adverse cardiovascular event.

*Note:* First occurrence of a MACE was the three-component primary outcome in each trial; components comprised cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Hypoglycaemic episodes were classified as severe according to contemporaneous American Diabetes Association criteria. New or worsening of nephropathy was defined as occurrence of one of the following: new onset of persistent macroalbuminuria or doubling of the serum creatine concentration or of creatine clearance; continuous renal replacement therapy; death attributable to renal disease. All outcomes had been confirmed by adjudication performed by external, independent medical experts.

validation methods. It is likely, however, that the integration of additional risk-associated and easy-to-measure biomarkers could improve risk stratification; the predictive performance of the resulting T2D subgroups should then be compared against existing cardiovascular risk engines and other such prediction algorithms to demonstrate proof of enhanced, population-specific estimations.

In addition, current treatment guidelines (eg, the ADA/European Association for the Study of Diabetes consensus report[15]) focus on risk prevention that is individualized to patient priorities (eg, reducing cardiorenal risk, hypoglycaemia risk, body weight or the cost of therapy). However, data to guide the individualization of diabetes therapy is currently lacking. Accordingly, a more in-depth and precise understanding of diabetes subtypes is central for efforts to achieve the promise of precision medicine in this complex disease to benefit individuals with diabetes as well as the healthcare system. Foremost, it remains unclear if the subgroups are useful beyond risk stratification, specifically, how such groups may receive and respond to various therapies. Maximally useful subtypes should capture heterogeneity that describes not only who is at risk, but also, within risk strata, for whom a given therapy is likely to be associated with meaningful benefit. To this end, there is a need to establish whether treatment responses to different drug classes differ across diabetes subtypes.

As the field evolves to explore how phenotypic clusters of patients with T2D can be refined and optimized, there may be multiple opportunities to guide treatment decisions. Algorithms allowing the clinician to base decisions regarding new or adjusted therapy choices on cluster-based predictions and prognoses could become relevant. For example, one application of cluster-specific T2D therapy could be to first use a few clinical measurements to assign a newly diagnosed individual to a well-established phenotypic cluster with a preferred treatment regimen. Second, longitudinal outcome follow-up after selected time points comparing predicted and actual outcomes could provide information for the clinician to accurately adjust the drug class, posology or co-medication to further optimize the long-term outcomes for people with diabetes. Our results suggest that well-established cardiovascular, renal and hypoglycaemia-related outcomes may be relevant to follow and adjust treatment based on response. More specifically, our findings suggested that careful prospective attention to cardiovascular risk is especially warranted for Cluster A (characterized by Ahlqvist et al as severe insulin-deficient diabetes[7]), which appears to be associated with significantly higher risk of MACE compared with individuals in the other clusters. However, these outcomes are probably not all equally relevant for every subgroup of individuals with T2D, considering that the trial populations used in the present evaluation were all enriched for cardiovascular risk and characterized by long-standing diabetes. Evaluation of disease-specific complications and all relevant outcomes, such as diabetic retinopathy, may also help to guide medical management of subgroups. Finally, the clusters may be refined to incorporate additional patient data, including biological and non-biological features that are known to influence treatment results, thereby generating subgroups that carry inherent prescriptive relevance.

In conclusion, the present study supports the validity of recent clustering approaches in deriving distinct subtypes of diabetes. The consistency of clusters across global populations underscores that T2D is a heterogeneous disease with different prognoses that may require different treatment according to specific disease subtypes. Our findings add to the promise that a subgroup-centric and risk-based approach for the management of diabetes is feasible to help improve patient outcomes and to further optimize the cost–benefit balance of current and future diabetes treatment. With this evidence of external validity and phenotypic stability, further investigations are needed to improve the clustering approach, including exploration of how novel data may be incorporated to improve risk prediction and even guide cluster-specific treatment selection, thereby increasing clinical actionability and accelerating translation to the day-to-day clinical care of the diverse population of patients with T2D.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the interpretation of data for the manuscript, drafted and critically revised the manuscript, provided final approval of the version to be published and agreed to be accountable for all aspects of the manuscript. All authors are responsible for the integrity of the work as a whole.

## DATA ACCESSIBILITY

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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