Online-Only Supplemental Material

A Type 2 Diabetes Subtype Responsive to ACCORD Intensive Glycemia Treatment

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Supplemental Approaches

Clustering

Early-Time-Weighted Dynamic Time Warping (etwDTW)

Dynamic time warping (DTW) has been used extensively for time series pattern matching and in speech recognition and image analysis.[1] DTW works by generating a non-linear, multiple alignment map to compare two trajectories and calculates the cost of each point alignment. The alignment with the minimum cost is considered to be the optimal alignment. Compared to point-to-point alignment, multiple alignments are more robust to minor structural distortions.[2] Consequently, the cost metric is a more relevant dissimilarity measure than the sum of linear point to point Euclidean distance. etwDTW calculated Euclidean distance between each combination of points along two trajectories, creating an M x N matrix, where M is the number of points in one trajectory and N is the number of points in the second trajectory. The minimum cost is determined from the optimal path in the *M* x *N* matrix. etwDTW sums the Euclidean distance of the previously aligned points for each alignment. This aggragated distance matrix was then used to calculate minimum cost of pairwise trajectory alignment and has the effect of weighting the cost of earlier differences in the trajectories more than differences observed later in the trajectories.

Hierarchical clustering with Ward's method was used to cluster patient HbA1c trajectories based on etwDTW dissimilarity for each of the nine outcomes[3,4]. Clustering was performed in an unsupervised manner. Post-clustering, cophenetic distances of the clustering dendrograms were calculated, and these were summed for all nine outcome dendrograms to generate a cophenetic dissimilarity matrix[5]. Hierarchical clustering with Ward's method was used again to cluster patient HbA1c trajectories based on cophenetic dissimilarity. The optimal number of clusters (k) was determined by comparing the risk of outcomes for each split in the dendrogram using Cox proportional hazards. The optimal k was the number of clusters preceding a non-significant split ($P>.05$) (Fig. 1). For each cluster, composite trajectories were created by averaging the HbA1c values across all individuals at each time point within the cluster. For each cluster, composite trajectories were created by averaging the HbA1c values across all individuals at each time point within the cluster.

Table S1. Characterization of clinical groups

	Intensive arm (N = 4,946)					Standard arm (N = 5,119)
	All Clinical Groups	*Clinical Group 1 (C1) (N = 1538)*	*Clinical Group 2 (C2) (N=1266)*	*Clinical Group 3 (C3) (N= 775)*	*Clinical Group 4 (C4) (N=1367)*	
MACE[1]	470 (9.50)	168 (10.92)	135 (10.66)	125 (16.13)	42 (3.07)	543 (10.61)
Cardiovascular mortality	159 (3.21)	53 (3.45)	38 (3.00)	57 (7.35)	11 (0.80)	144 (2.81)
Total mortality[2]	338 (6.83)	114 (7.41)	86 (6.79)	106 (13.68)	32 (2.34)	327 (6.39)
Congestive heart failure[3]	226 (4.57)	67 (4.36)	61 (4.82)	57 (7.35)	41 (3.00)	212 (4.14)
Non-fatal myocardial infarction[3]	281 (5.68)	115 (7.48)	76 (6.00)	63 (8.13)	27 (1.98)	344 (6.72)
Non-fatal stroke[3]	77 (1.56)	12 (0.78)	36 (2.84)	24 (3.10)	5 (0.37)	94 (1.84)
Total stroke[4]	85 (1.71)	16 (1.04)	38 (3.00)	25 (3.23)	6 (0.44)	106 (2.07)
Expanded macrovascular events	1115 (22.54)	363 (23.60)	304 (24.01)	210 (27.10)	238 (17.41)	1229 (24.00)
Coronary heart disease[3]	547 (11.06)	201 (13.07)	155 (12.24)	126 (16.26)	65 (4.75)	627 (12.25)
Race						

White	3093 (62.54)	979 (67.55)	751 (56.80)	365 (47.70)	998 (71.92)	3199 (62.49)
Other	1853 (37.46)	559 (32.45)	515 (43.20)	410 (52.30)	369 (28.08)	1920 (37.50)
Gender						
Female	1903 (38.48)	557 (37.97)	498 (39.40)	354 (47.70)	494 (32.09)	1966 (38.41)
Male	3043 (61.52)	981 (62.03)	768 (60.60)	421 (52.30)	873 (67.91)	3153 (61.59)
Blood pressure arm						
Intensive BP	1128 (22.81)	352 (22.89)	275 (21.72)	203 (26.19)	298 (21.80)	1183 (23.11)
Lipid Fibrate	1323 (26.75)	410 (26.66)	357 (28.20)	179 (23.10)	377 (27.58)	1390 (27.15)
Lipid Placebo	1340 (27.09)	427 (27.76)	315 (24.88)	193 (24.90)	405 (29.63)	1369 (26.74)
Standard BP	1155 (23.25)	349 (22.60)	319 (25.20)	200 (25.81)	287 (20.99)	1177 (23.00)
Baseline cardiovascular risk	1751 (35.40)	527 (34.27)	473 (37.36)	330 (42.58)	421 (30.80)	1782 (34.81)
Baseline HbA1c % (mean ± sd)	8.27 ± 1.01	8.13 ± 0.94	8.34 ± 1.00	8.86 ± 0.99	8.04 ± 0.98	8.29 ± 1.00
Baseline Age, years (mean ± sd)	62.73 ± 6.63	63.23 ± 6.64	62.60 ± 6.57	61.97±7.12	62.73 ±6.33	62.72 ± 6.60
Baseline years with diabetes, years (mean ± sd)	10.71 ± 7.55	10.44 ± 7.37	11.45 ± 7.41	13.77 ± 8.14	8.58 ± 6.82	10.85 ± 7.60
Baseline diabetes medications (insulin excluded)						
≥1	4127 (83.44)	1315 (85.50)	1092 (86.26)	585 (75.48)	1135 (83.02)	4248 (82.98)
≥2	2495 (50.44)	851 (55.33)	713 (56.32)	352 (45.42)	579 (42.36)	2554 (49.89)
≥3	546 (11.04)	206 (13.39)	170 (13.43)	59 (7.61)	111 (8.12)	557 (10.88)
Baseline insulin	1686 (34.09)	465 (30.23)	472 (37.29)	458 (59.10)	291 (21.29)	1831 (35.77)

[1]MACE=major cardiovascular events and included cardiovascular death or first occurrence of a non-fatal heart attack or non-fatal stroke. Based on this definition, each individual can only have a single MACE event but will also be represented in the corresponding constituent outcomes (e.g., non-fatal stroke). [2] Death due to any cause.[3]Represents first events. [4]Fatal or first non-fatal stroke.

Table S2: Clinical and demographic factors considered in analyses.

Demographic and Trial specific Variables	Baseline Age
	Sex
	Education
	Smoking status
	Network
	Alcohol use
	Intensive blood pressure trial arm
	Fibrate trial arm
Medications	Loop diuretic
	Thiazide
	Potassium sparing diuretic
	Potassium
	Angiotensin II receptor blockers
	Ace inhibitor
	Dihydropyridine-calcium channel blockers
	Non- Dihydropyridine-calcium channel blockers
	Alpha Blocker
	Central agent
	Beta Blocker
	Vasodilator
	Reserpine
	Other blood pressure medication
	Digitalis
	Antiarrhythmic

	Nitrate
	Other cardiovascular medication
	Sulfonylurea
	Biguanide
	Meglitinide
	AG inhibitor
	NPHL insulin
	TZD
	Regular insulin
	LA insulin
	Other bolus insulin
	Premix insulin
	LA and/or other bolus insulin
	NPHL, regular, and/or premix insulin
	Any insulin use
	Other diabetes medication
	Bile sequestrant
	Statin
	Fibrate
	Other lipid medication
	Cholesterol ABI
	Niacin
	Anti-coagulant
	Anti-inflammatory
	Platelet AGI
	Cox2
	Aspirin
	Thyroid medication
	Progestin
	Estrogen
	Oral asthma medication
	Anti-depressant
	Inhaled asthma medication
	Oral steroid
	Anti-psychotic
	Osteoporosis medication
	Fluid retention
	Other medication
	Vitamins
	Over the counter medication
	Herbal
Other Clinical Factors	Years with diabetes
	Years with dyslipidemia
	Hypertension
	CVD history at baseline
	Micro or macro albuminuria with past 2 years
	LVH by ECG or echocardiogram with past 2 years
	≥50% stenosis of coronary, carotid, or lower extremity artery in past 2 years.
	Eye disease
	Neuropathology
	Serum creatinine
	Glomerular filtration rate
	Diastolic blood pressure
	Systolic blood pressure
	Waist (cm)
	BMI

Table S3: Covariates selected in GWAS.

Covariate	Beta	Std. Error	z-value	p-value
PC1	-0.858	0.122	-4.910	9.11E-07
PC2	-0.293	0.060	1.895	0.058
PC3	0.108	0.064	1.247	0.213
Sex	-0.344	0.107	-3.219	0.001
Years with Diabetes	-0.197	0.061	-3.245	0.001
BMI	0.161	0.053	3063	0.002

Baseline Sulfonylurea	-0.505	0.106	-4.750	2.04E-06
Baseline Biguanide	-0.396	0.103	-3.838	1.24E-04
Baseline Thiazolidinedione	-0.442	0.129	-3.429	6.07E-04
Any Insulin Use at Baseline	-0.824	0.146	-5.636	1.74E-08

Pathway Analysis

Traditionally, pathway analysis has been used to identify common ontologies and/or biological associations from gene expression data. These ontologies may describe a gene-set with a common function or known biological pathways known to be affected by differential gene expression. The software package eXploring Genomic Relations (XGR) shifts this approach from the gene to the SNP-level.[9] XGR provides both an enrichment analysis and a functional interaction network analysis. The SNP-based enrichment analysis identifies enriched ontologies by comparing a user-defined set of variants, and XGR also incorporates information from SNPs which are in strong LD to the provided set. XGR SNP enrichment analysis takes advantage of the Gene Ontology's (GO) graph structure and controls for the overrepresentation in a GO term to avoid producing false-positive results[10]. Permutation testing is then used to determine statistical significance.

Network analysis was also performed using XGR to identify gene networks that may be impacted by the SNPs detected in the GWAS. First, a distance window (*D*) of 50 Kb is placed around each input SNP. Those SNPs located within *D* and with an R^2>0.8 to the input SNPs are then added to the list of input SNPs. The software then scores SNPs by taking the difference between their p-values and a genome-wide significance threshold ($5x10^{-8}$). The SNPs are then weighted by their R^2 values. Next, genes are scored by their proximity to the listed SNPs, weighted by the SNP scores, based on the method described in Fang et al.[9]

SNP enrichment analysis was performed using XGR's SNP-based enrichment tool with both those SNPs that reached suggestive significant ($p<5.0x10^{-6}$) in the GWAS and those used in the polygenic score (PS). Three ontology terms were significantly enriched (FDR $p < 0.05$) for the suggestive significant SNPs in the GWAS: disposition ($p<5.0x10^{-6}$), disease ($p<5.0x10^{-6}$), and material property ($p<5.0x10^{-6}$).

Development of model for clinical group prediction

Polygenic Scores (PS)

Several approaches to constructing polygenic scores (PS) were investigated. In order to reduce correlation between significant variants, a "clumping" procedure was first performed to select the best variants from a list of all significant variants.[11] Here, all variants with a p-value less than a pre-defined threshold and not already within a clump are considered "index" SNPs. *P* value thresholds were taken from a sequence of length *S* iterating from the maximum to minimum GWAS p-value. A sliding window of *D*kb is then set around each index SNP in order to define LD blocks. All SNPs within the LD block with R^2 value >*r* with the index SNP were selected. The most significant SNP within each LD block is then selected as the best "proxy" SNP and retained in the PS. The unique combination of p_1, *r*, and *D* values used are given in Table S4. CT-PS were generated for each unique combination of p_1, *r*, *D*, and chromosome, the set of significant variants were weighted by their respective log odds ratio taken from the association tests. The sum of each weighted, significant variant then represents the CT-PS for each individual. An additional "stacked" approach, SCT-PS, was constructed using the workflow described in Prive, Aschard, and Blum[12] and the *bigsnpr* R package v1.3.0.[13] This procedure is similar to the CT-PS. The grid search implemented described above resulted in 32,200 unique PS values for each individual. With the SCT-PS procedure, a penalized regression was used to find the optimal combination of PS values to create a final SCT-PS, used for predictive modeling. The parameter values for constructing PS are shown in Table S4.

Table S4. Parameter Values for Constructing the PS.

D (window size)	r (R^2 Threshold)	S (number of unique p-value thresholds)
5000	0.01	50
10000	0.01	50
20000	0.01	50
50000	0.01	50
1000	0.05	50
2000	0.05	50
4000	0.05	50
10000	0.05	50

500	0.10	50
1000	0.10	50
2000	0.10	50
5000	0.10	50
250	0.20	50
500	0.20	50
1000	0.20	50
2500	0.20	50
100	0.50	50
200	0.50	50
400	0.50	50
1000	0.50	50
62	0.80	50
125	0.80	50
250	0.80	50
625	0.80	50
52	0.95	50
105	0.95	50
210	0.95	50
526	0.95	50

Model training

The CT-PS and SCT-PS with and without baseline clinical variables were used to construct multiple models in order to evaluate which approach performed best to predict individual clinical group membership. The cohort randomized to receive intensive glycemia treatment and that consented to genetic studies was divided into a training set (N=2,270) and a test set (N=1,169). A 10-fold cross-validation procedure was performed for each modeling approach to prevent overfitting on the training set. The baseline clinical variables and the pairwise interaction terms between the CT-PS and SCT-PS and each baseline clinical variables were included in the variable selection procedure using least absolute shrinkage and selection operator (LASSO) was used to select an optimal subset of the covariates for each model.[14] Selected variables were then used in a generalized linear model (GLM) with a logit link function (i.e, logistic regression). Each model was evaluated using CT/SCT-PS only, baseline clinical variables only, or the CT/SCT-PS and baseline clinical variables. Model performance was assessed based on the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and balanced accuracy. PPV is the ratio of true positives out of all identified positives. NPV is the ratio of true negatives out of all identified negatives.

Assessment of model for clinical group prediction

Propensity Score Matching

Propensity Score Matching is a method to adjust for confounding effects across treatment groups or studies.[15] Here, we used propensity score matching to adjust for age, sex, race, and years since a T2D diagnosis. All matching was conducted using the R package, *MatchIt* v3.0.2.[16] First, the pairwise distances, based on the adjusting variables, between each individual and each individual in the other cluster were calculated. Next, each individual was paired with its nearest neighbor, if not already chosen. The matched pairs then represented the matched subset. This process resulted in 2,060 individuals which were then split into a training and test set of 1,368 and 692 indviduals each. A GLM using both the SCT-PS and clinical variables chosen in the full model was trained on the matched training set and then predicted the match test set .

Effect of sample size adjustment on observed risk differences

The SCT-PS only and SCT-PS with clinical features were considered the best models for predicting C4 based on performance and model parsimony (Table S12). These models were applied to the intensive arm test set (*N*=1,169, 33%) and standard arm (*N*=5,119, 100%) to determine if individuals predicted to be in the C4 subtype demonstrated a reduction in CVD risk between glycemia treatment arms. Because models were applied to only the withheld test set in the intensive arm (*N*=1,169, 33%) and the complete standard arm (*N*=5,119, 100%), the number of predicted C4 individuals in the standard arm (N=1,532) was nearly four times that of the predicted C4 in the intensive arm

(N=389). To determine the whether the sample size imbalance led to a bias in the observed risk differences, meta-analyzed risk was calculated for 20 iterations of various sample sizes.

Direct Prediction of CVD Outcomes

In order to compare the efficacy of predicting cluster membership as a proxy for risk of an adverse outcome compared to predicting CVD outcomes directly, SCT-PS model with baseline clinical variables and a GLM of only baseline clinical values were assessed to determine if they could be trained to predict MACE and total mortality.

Comparison to 2-SNP Genetic Risk Score (GRS) from Shah et al.

We previously published a genetic risk score (GRS) consisting of two SNPs, rs9299870 and rs57922, that demonsrated predictivity for risk of cardiovascular mortality and displayed an interaction with glycemic control in ACCORD.[17] These findings were replicated in two different cohorts, suggesting that this approach may be useful for identifying patients likely to be harmed or likely to benefit from intensive glycemia treatment.

Here, we take a fundamentally different approach to identify distinct groups with different glycemic responses to intensive glycemia treatment in ACCORD. We then demonstrate that these groups have modified risk of adverse outcomes (Figs 2,4). Next, we constructed a PS, using a new SCT-PS approach, to predict membership in C4, a group with reduced risk risk of adverse outcomes in the intensive glycemia arm. We then demonstrate evidence of a causal relationship between the SCT-PS, median HbA1c, and CVD risk using Mendelian randomization (Fig. S14). In addition the predicted C4 from the SCT-PS that received intensive glycemia treatment displayed benefit over predicted C4 recieving standard glycemia treatment (Fig. 4A). We then sought to compare the performance of the SCT-PS model developed here, with the 2-SNP GRS presented in Shah et al across all race and across individuals self identified as White (GRS=0).[17] Here, to compare different scores, we applied the models across all individuals in the discovery and test sets. However, the hazard ratios for the SCT-PS were similar between these results and the test set, reducing concerns of overfitting. In addition, due to different QC approaches during the merging of the two genotype platforms (see: “Genotyping Array and Quality Control”, above), in the comparison of White individuals presented below (Fig. S20), the cohort here had 196 fewer individuals than the original Shah et al. paper, resulting in slight discrepancies between the two analyses.

Supplemental Results

Clustering

Aggregated trajectories for clusters

After identifying the optimized number of clinical groups (see main text), representative composite HbA1c trajectories were created for each clinical group by averaging all individual HbA1c trajectories within the respective cluster (Fig. 2A). Variability of underlying clinical group can be see in Figs. S1-S2.

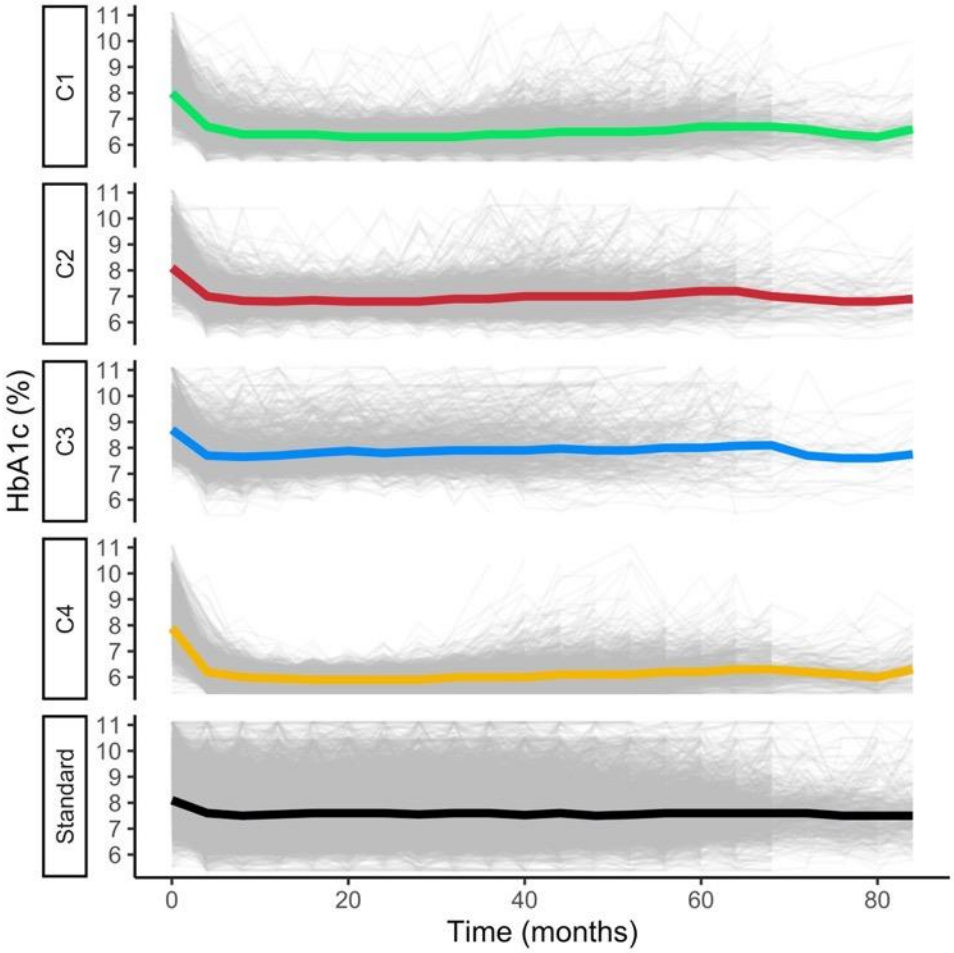

Figure S1. Individual HbA1c trajectories for intensive clinical groups and standard arm

Mean HbA1c (%) trajectories are shown for the clinical groups and the standard arm with constituent trajectories in the background.

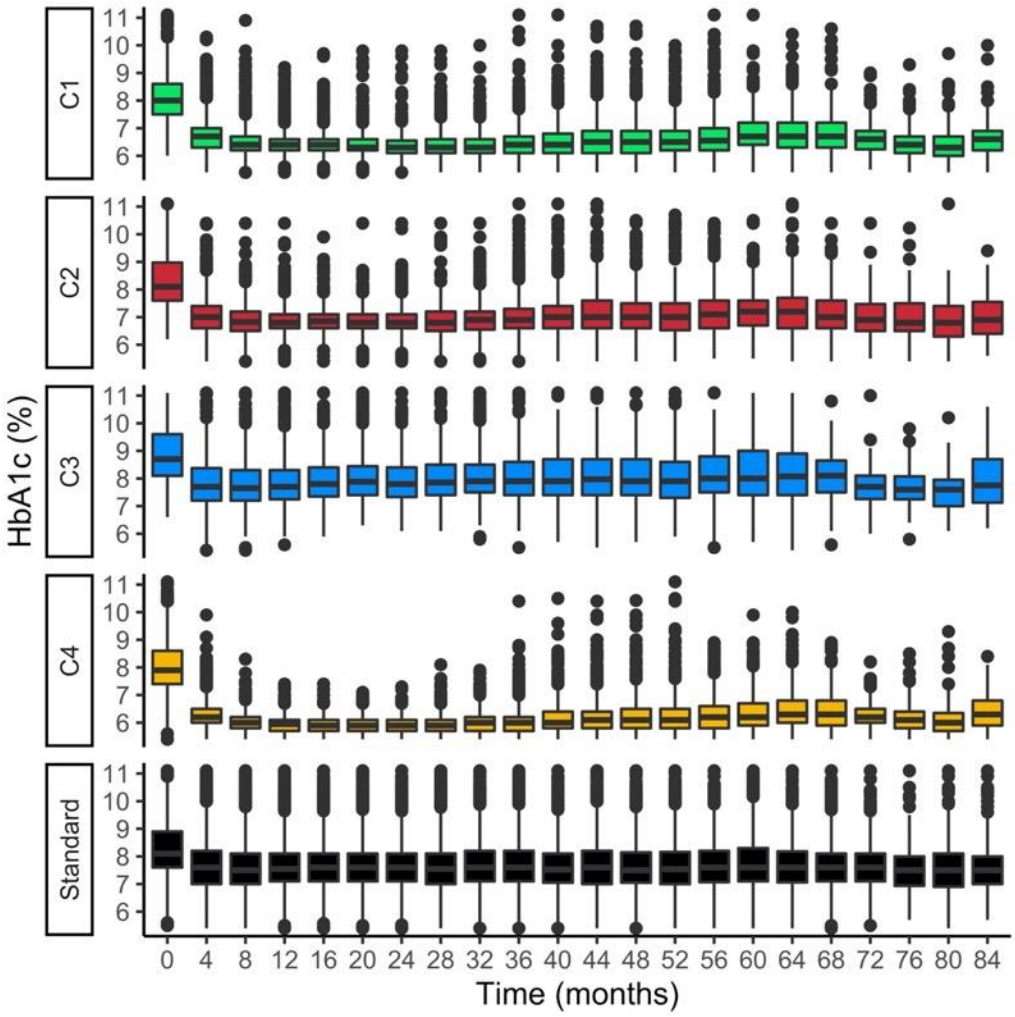

Figure S2. HbA1c distribution across time for intensive clinical groups and standard arm
Each boxplot presents the distribution of HbA1c (%) observed in the clinical groups and the standard arm at a specific point in time.

Distribution of baseline HbA1c seen in clusters

As reported in the main text, four clinical groups were identified with different incidence rates for adverse outcome. As seen in Figure S3, despite significant differences in HbA1c at baseline for the clinical groups and the standard arm ($P<.05$), there is substantial overlap between the observed distributions.

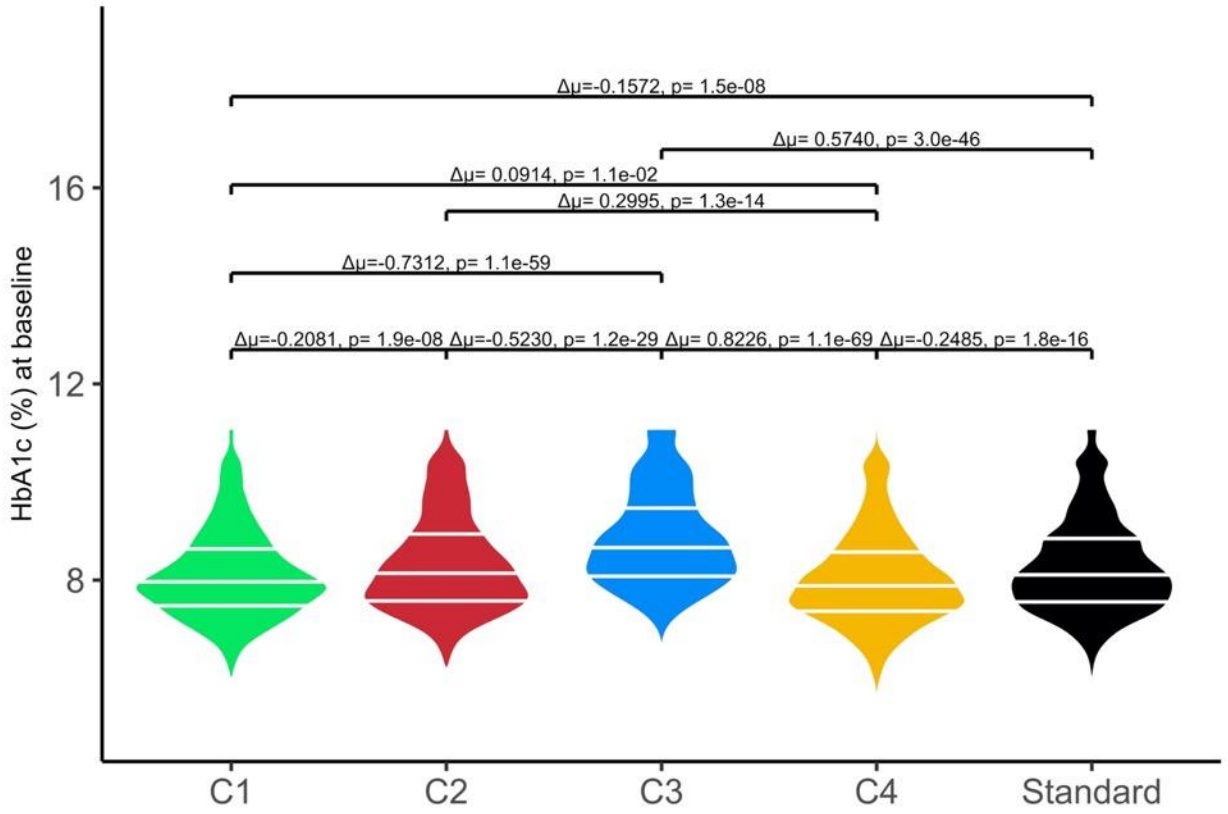

Figure S3. HbA1c distribution for individuals in clinical groups and standard arm at baseline.
HbA1c (%) differences between the clinical groups and the standard arm were compared using Student's t-test. Only significant mean differences ($\Delta\mu$) are reported ($P < .05$). As reported in the main text, four clinical groups were identified with different incidence rates for adverse outcome. Despite significant differences in HbA1c at baseline for the clinical groups and the standard arm (P<.05), there is substantial overlap between the observed distributions.

Permutation testing for composite trajectory representation

Composite trajectories were tested for how well they represented their underlying HbA1c trajectories using permutation testing, as described in the main text. HbA1c composite trajectories for C1, C2 and C4 were significantly representative of the underlying values ($P \leq .0001$) (Figure S4 A, B, D). However, the composite trajectory for C3 was not significantly different from randomly selected trajectories (P>.0001), indicating increased HbA1c variability in this group (Figure S4C). The results also suggest that C1, C2, C4 are distinct clinical groups, C3 represents patients that were the most different from other clinical groups, but not necessarily similar to each other.

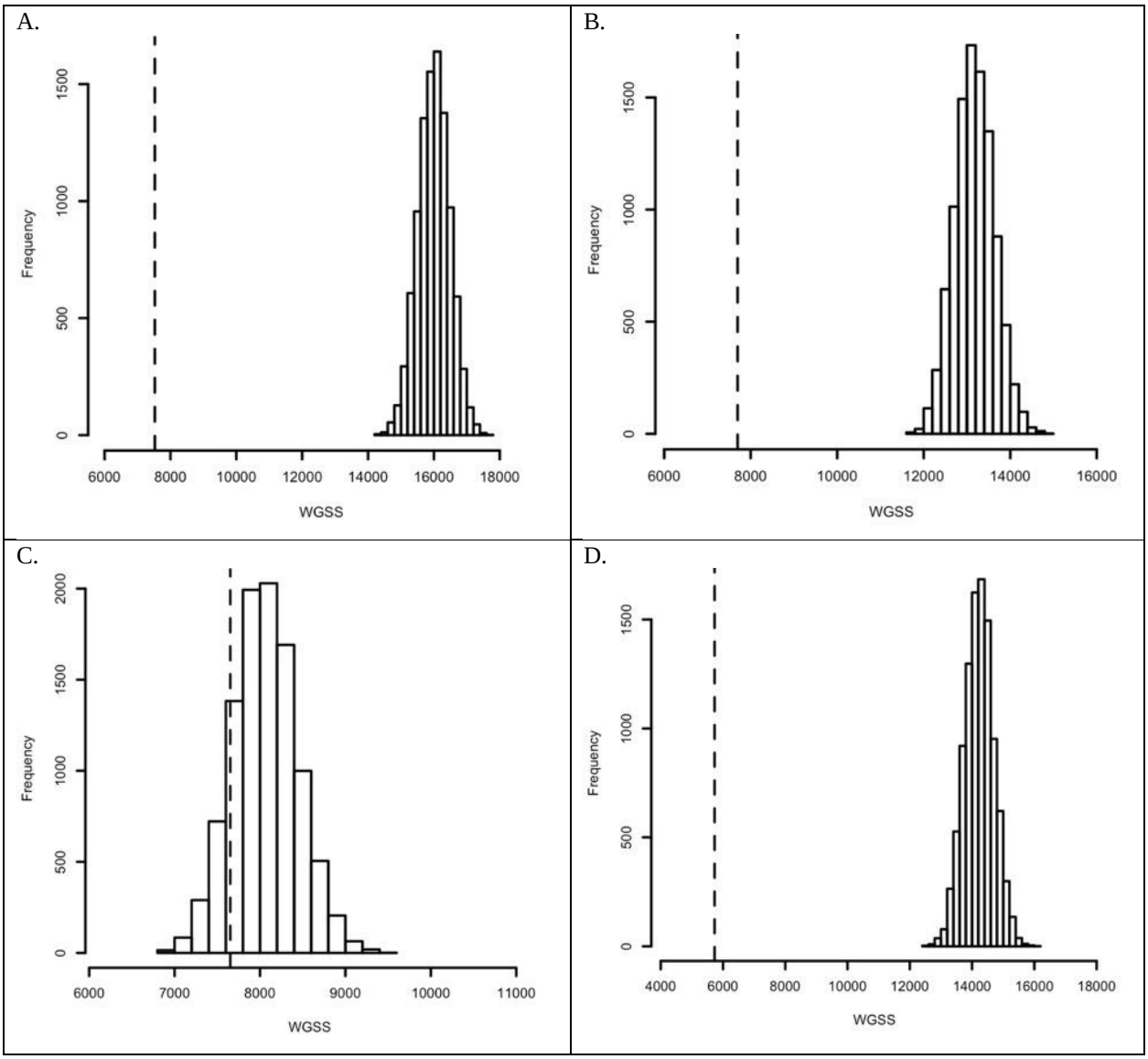

Fig S4. Permuted within group sum of squares (WGSS) distributions.
Composite trajectories were tested for how well they represented their underlying HbA1c trajectories using permutation testing, as described in the main text. For each clinical group, (A) C1, (B) C2, (C) C3 and (D) C4 the distributions of within group sum of squares (WGSS) were computed between the composite trajectory and 10,000 equally sized and random subsets of HbA1c trajectories. The dashed lines represent the actual WGSS between member trajectories of the clinical groups and their respective composite trajectories. A dashed line that overlaps less than 5% of the distribution indicates that the composite trajectory is significantly more representative of the trajectories in that clinical group than would be expected by chance. WGSS distributions for C1, C2, and C4 were statistically significant with $P \leq .0001$.

Risk of outcomes in clinical groups compared to standard treatment.
Risks of microvalscular events between HbA1c clusters
The C4 cluster demonsrated reduced risk of all evaluated microvascular outcomes (HR=0.86, P=0.0152) while elevated risk was observed for both C2 (HR=1.16, P=0.023) and C3 (HR=1.30, P<0.0001) (Fig. S5).

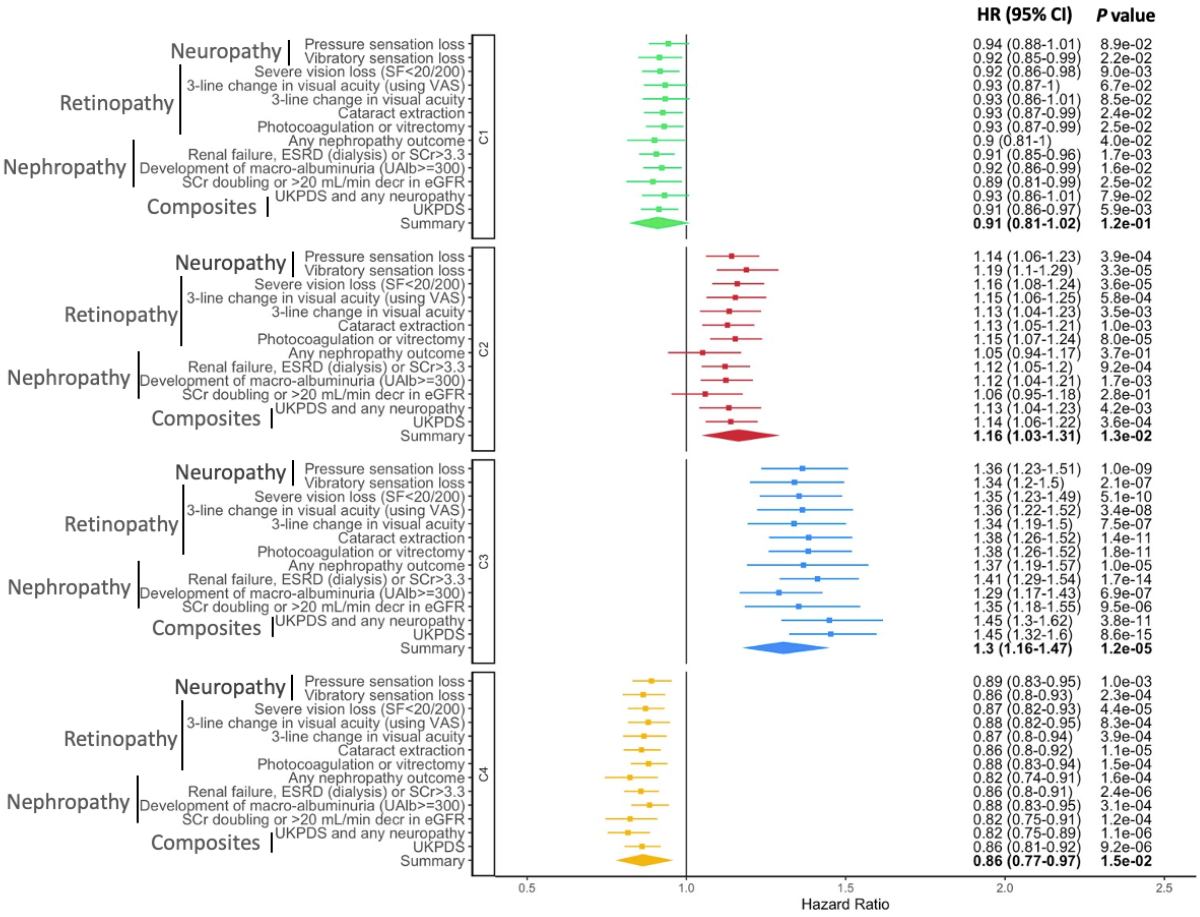

Fig S5. Risk of microvascular outcomes in clinical groups compared to standard treatment.
Cox proportional hazards models were used to calculate the risk of outcomes in all clinical groups compared to standard treatment group. Overall risk of microvascular outcomes was calculated using *R metafor package* after adjusting for covariance of all outcomes. In the plot, SF, VAS, ESRD, SCr, UAlb, eGFR and UKPDs are abbreviations for Snellen fraction, visual acuity scale, end-stage renal disease, serum creatinine, urine albumin, estimate glomerular filtration rate and UKPDS composite (i.e. retinopathy requiring photocoagulation, vitreous hemorrhage and renal failure), respectively.

Risks of hypoglycemia between HbA1c clusters

All intensive arm clinical groups had a significantly increased risk of both severe and any hypoglycemic event than individuals in the standard arm ($q < 0.05$) (Figure S6). Although C4 had significantly reduced risks for CVD events (Figure 3, main text) (meta-analyzed HR=0.0.52, P=1.47x10^{-69}), these individuals still had elevated risks of having any hypoglycemic event (HR=2.18, P=3.5x10^{-18}) or a severe hypoglycemic event (HR=1.89, P=1.3x10^{-8})(Fig. S6A). This suggests that although intensive glycemia treatment increased risk of hypoglycemia, this was not the driver of the observed increased risk of CVD related outcomes in the intensive arm. Notably, individuals in C3, which had increased risk of CVD related outcomes compared to standard treatment, that experienced hypoglycemic events had any hypoglycemic event on average 0.92 years and for severe hypoglycemia, 1.02 years earlier than individuals in standard arm (q<0.0001)(Fig. S6B-C). Of the individuals that experienced a hypoglycemic event in the C4 intensive treatment group and those receiving standard treatment, there were no significant differences observed between the time to their first hypoglycemic event (q>0.05).

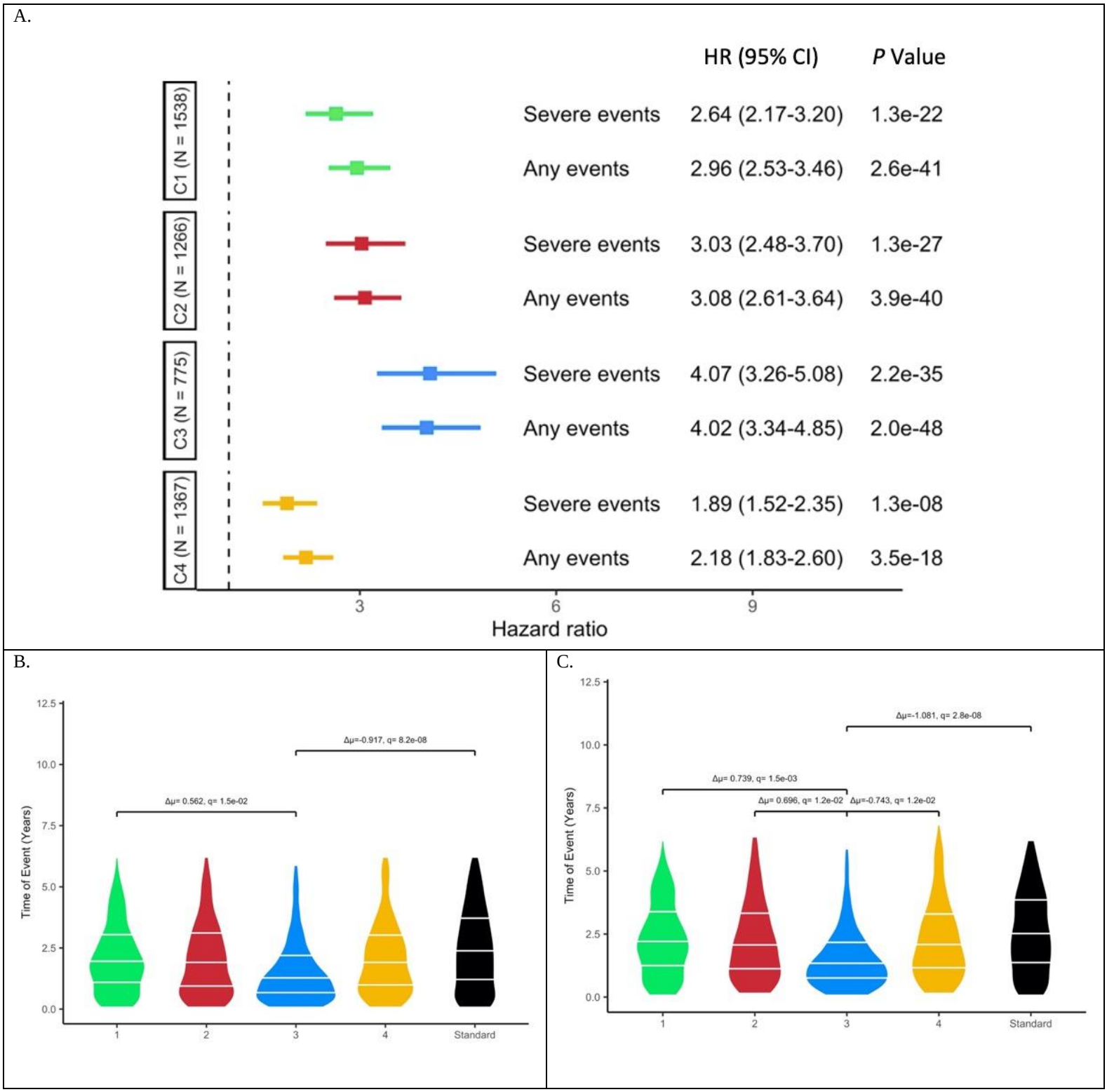

Figure S6. Risks of hypoglycemia between HbA1c clusters.
Cox proportional hazards models were used for to evaluate the time-to-event for hypoglycemia for each cluster and the standard arm. In only those individuals that experienced a hypoglycemic event, a separate analysis was performed using a Student's t-test to compare the mean time to either a hypoglycemic or severe hypoglycemic

event. All tests were adjusted for multiple comparisons using an FDR approach.[18] (A) Hazard ratios (HR) for etwDTW HbA1c clinical groups for time to any hypoglycemic event and severe hypoglycemic events compared to standard arm were computed using Cox proportional hazards models. (B) Distribution of time to first hypoglycemic events and (C) severe hypoglycemic events in individuals that had at least one hypoglycemic event. '$\Delta\mu$' represents the mean time difference. '*q*' is the FDR adjusted *P* value obtained from respective pairwise comparisons using Student's t-test.

Comparison of risk outcomes based on rudimentary binning of HbA1c trajectories

Outcome risk categorization based on median HbA1c quartiles within 1 year of baseline

To evaluate whether etwDTW clustering of HbA1c trajectories provided additional value compared to stratification by early quartiles of HbA1c, individuals were categorized into four groups based on only on median HbA1c quartiles observed within the first year. The composite HbA1c trajectories for these quartiles are shown in Fig. S7A. This method of classification did identify individuals with reduced risk of MACE (Fig. S7B), but failed to identify a group of individuals within the intensive arm with significantly lower risk for total mortality (Fig. S7C).

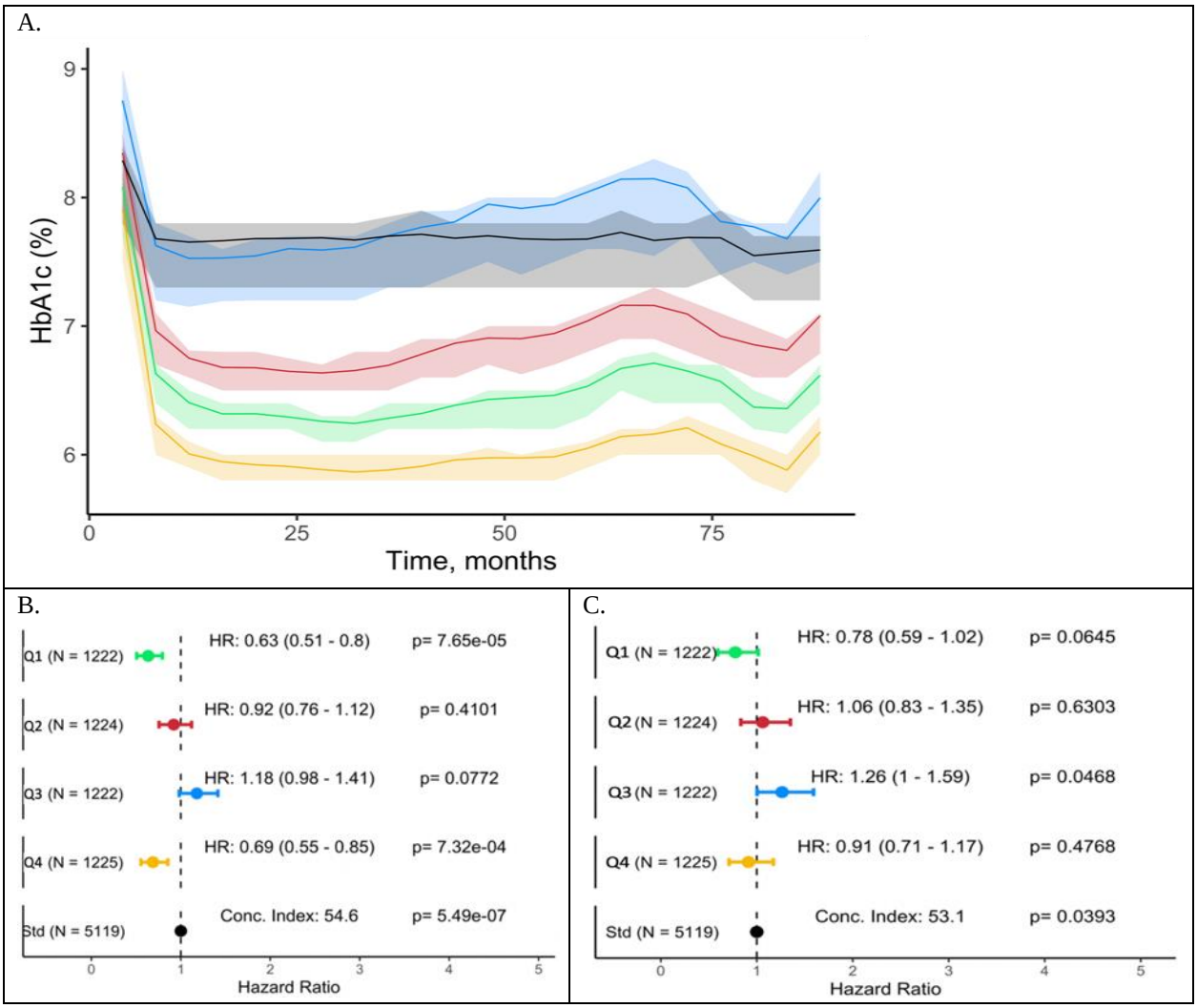

Figure S7. Classification using median HbA1c quartiles within first year of baseline.

To evaluate whether etwDTW clustering of HbA1c trajectories provided additional value compared to stratification by early quartiles of HbA1c, individuals were categorized into four groups based on only on median HbA1c quartiles observed within the first year. (A) Mean composite HbA1c trajectories with standard errors representing underlying quartiles are shown in Panel A for each median HbA1c. (B) Hazard ratios (HR) for MACE for each

quartile and (C) total mortality for each quartile are shown compared to standard treatment. These HR were calculated for each quartile using Cox proportional hazards models with the standard arm as reference.

Outcome risk categorization based on median HbA1c quartiles across the entire trajectory

Individuals within the intensive arm were also categorized into four groups using median HbA1c quartiles across the entire trajectory. For this comparison, baseline HbA1c values were excluded. Similar to categorization using baseline HbA1c quartiles (Fig. S7A), this approach identified individuals with reduced risk of MACE (Fig. S8B), but failed to identify a group of individuals within the intensive arm with significantly lower risk for total mortality (Fig. S8C), compared to individuals in the standard glycemia treatment arm.

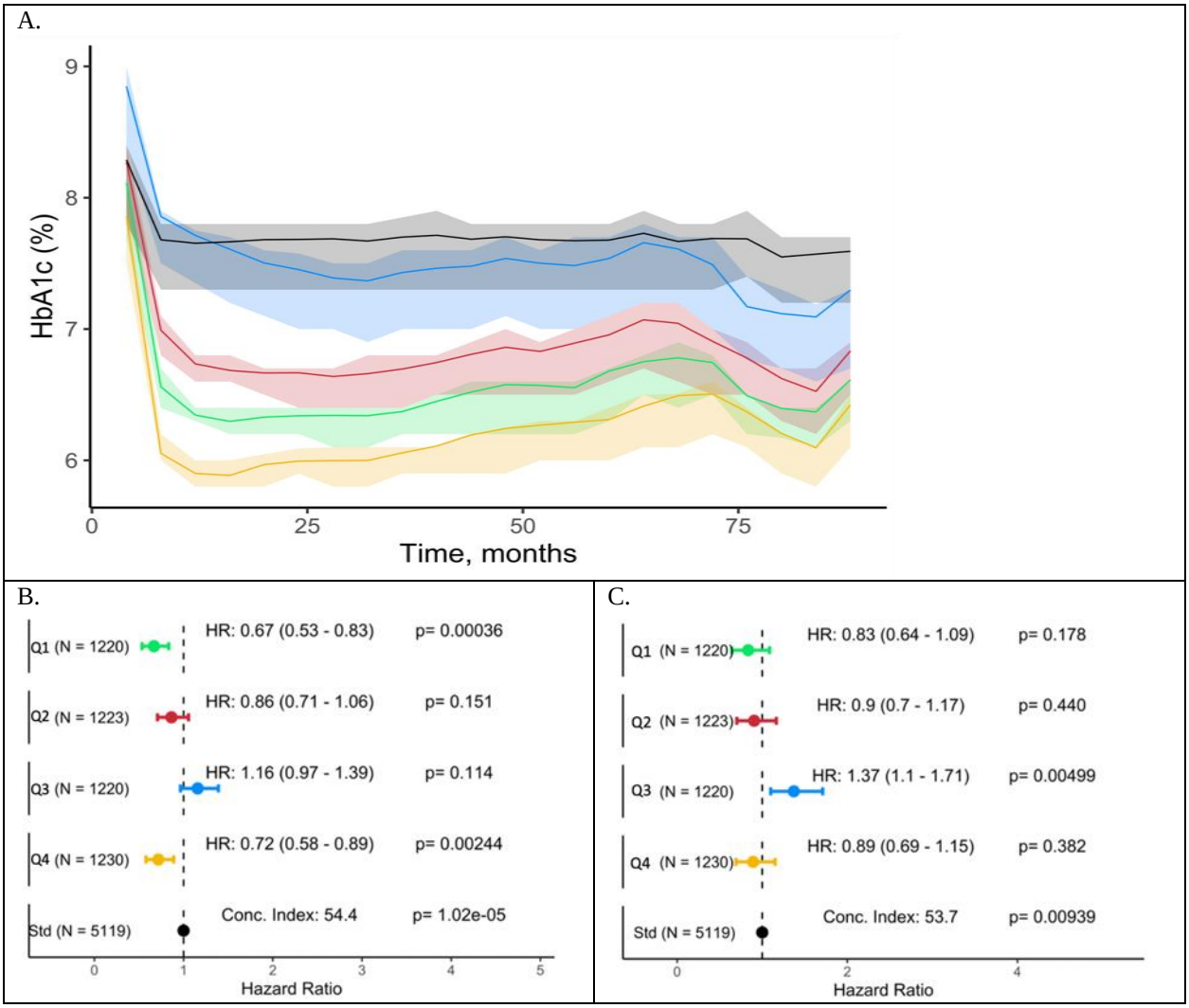

Figure S8. Classification using median HbA1c quartiles across entire HbA1c after baseline measurements. Individuals within the intensive arm were also categorized into four groups using median HbA1c quartiles across the entire trajectory. For this comparison, baseline HbA1c values were excluded. (A) Mean composite HbA1c trajectories with standard errors representing underlying quartiles are shown in Panel A for each median HbA1c. (B) Hazard ratios (HR) for MACE for each quartile and (C) total mortality for each quartile are shown compared to standard treatment. These HR were calculated for each quartile using Cox proportional hazards models with the standard arm as reference.

Baseline clinical and demographic differences between HbA1c clinical groups

Significant differences ($q < 0.01$) for medications, medications adjusted with duration of T2D, and clinical and demographic differences are reported in Tables S5-S8.

Table S5. Baseline medication differences between clinical groups (q<0.01)

Variable	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Ace inhibitors	C2	C4	57.5	51.39	0.781 (0.67-0.911)	1.68e-03	6.69e-03
if any insulin	C3	C1	59.1	30.23	3.334 (2.787-3.994)	2.45e-39	9.37e-38
if any insulin	C2	C1	37.28	30.23	1.372 (1.172-1.606)	8.41e-05	4.33e-04
if any insulin	C3	C4	59.1	21.29	0.187 (0.154-0.227)	6.88e-65	6.57e-63
if any insulin	C2	C4	37.28	21.29	0.455 (0.383-0.54)	3.56e-19	6.80e-18
if any insulin	C1	C4	30.23	21.29	0.624 (0.527-0.739)	4.67e-08	4.06e-07
if any insulin	C2	C3	37.28	59.1	2.43 (2.025-2.92)	1.86e-21	4.45e-20
Beta-blockers	C2	C4	30.73	25.29	0.763 (0.643-0.905)	1.93e-03	7.54e-03
Beta-blockers	C3	C4	35.06	25.29	0.627 (0.518-0.76)	1.83e-06	1.25e-05
Biguanides	C3	C1	58.97	65.8	0.747 (0.625-0.892)	1.29e-03	5.37e-03
Biguanides	C2	C3	68.25	58.97	0.669 (0.555-0.805)	2.16e-05	1.25e-04
Biguanides	C2	C4	68.25	60.86	0.724 (0.616-0.849)	7.87e-05	4.18e-04
Lispro or Aspart Insulins	C3	C1	16.65	6.44	2.903 (2.201-3.839)	5.61e-14	6.70e-13
Lispro or Aspart Insulins	C3	C4	16.65	5.19	0.274 (0.201-0.371)	8.67e-17	1.27e-15
Lispro or Aspart Insulins	C2	C3	9.08	16.65	1.999 (1.527-2.618)	4.61e-07	3.39e-06
Lispro or Aspart Insulins	C2	C4	9.08	5.19	0.548 (0.402-0.743)	1.20e-04	5.90e-04
either othbol_insulin or la_insulin	C3	C1	17.81	7.28	2.758 (2.115-3.604)	7.99e-14	8.98e-13
either othbol_insulin or la_insulin	C2	C3	9.72	17.81	2.013 (1.55-2.617)	1.59e-07	1.27e-06
either othbol_insulin or la_insulin	C3	C4	17.81	6	0.295 (0.22-0.392)	1.23e-16	1.68e-15
either othbol_insulin or la_insulin	C2	C4	9.72	6	0.593 (0.442-0.791)	4.23e-04	1.88e-03
Loop diuretics	C3	C1	12.94	8.34	1.632 (1.235-2.152)	5.34e-04	2.32e-03
Loop diuretics	C3	C4	12.94	6.6	0.475 (0.352-0.641)	1.16e-06	8.20e-06
Nitrates	C2	C4	6.24	3.53	0.549 (0.378-0.79)	1.38e-03	5.62e-03
Nitrates	C3	C4	6.87	3.53	0.495 (0.331-0.74)	5.93e-04	2.52e-03
NPH or L Insulins	C3	C1	54.19	26.46	3.288 (2.744-3.943)	5.85e-38	1.86e-36
NPH or L Insulins	C2	C3	34.2	54.19	2.276 (1.896-2.734)	1.21e-18	1.93e-17
NPH or L Insulins	C3	C4	54.19	18.29	0.189 (0.155-0.23)	1.08e-61	6.86e-60
NPH or L Insulins	C2	C1	34.2	26.46	1.444 (1.228-1.699)	8.87e-06	5.47e-05
NPH or L Insulins	C2	C4	34.2	18.29	0.431 (0.359-0.515)	3.89e-20	8.25e-19
NPH or L Insulins	C1	C4	26.46	18.29	0.622 (0.52-0.742)	1.67e-07	1.28e-06
either nphl_insulin, reg_insulin, or premix_insulin	C3	C1	59.1	30.17	3.344 (2.795-4.006)	1.64e-39	7.81e-38
either nphl_insulin, reg_insulin, or premix_insulin	C2	C1	37.2	30.17	1.371 (1.171-1.606)	8.61e-05	4.33e-04
either nphl_insulin, reg_insulin, or premix_insulin	C2	C3	37.2	59.1	2.439 (2.032-2.93)	1.34e-21	3.64e-20
either nphl_insulin, reg_insulin, or premix_insulin	C3	C4	59.1	21.29	0.187 (0.154-0.227)	6.88e-65	6.57e-63
either nphl_insulin, reg_insulin, or premix_insulin	C1	C4	30.17	21.29	0.626 (0.528-0.741)	5.76e-08	4.78e-07
either nphl_insulin, reg_insulin, or premix_insulin	C2	C4	37.2	21.29	0.456 (0.384-0.542)	5.12e-19	8.88e-18
Premixed Insulins	C3	C1	16.13	9.62	1.806 (1.397-2.331)	5.84e-06	3.72e-05
Premixed Insulins	C3	C4	16.13	8.19	0.464 (0.353-0.609)	3.18e-08	2.89e-07
Premixed Insulins	C2	C3	10.66	16.13	1.611 (1.239-2.093)	3.55e-04	1.65e-03
Regular Insulins	C2	C4	11.45	7.39	0.617 (0.472-0.804)	3.78e-04	1.72e-03
Regular Insulins	C2	C3	11.45	19.1	1.825 (1.423-2.342)	2.19e-06	1.45e-05
Regular Insulins	C3	C4	19.1	7.39	0.338 (0.257-0.442)	3.81e-15	4.86e-14

Variable	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Regular Insulins	C3	C1	19.1	9.69	2.2 (1.72-2.816)	3.44e-10	3.46e-09
Sulfonylureas	C1	C4	58.84	50.69	0.719 (0.621-0.833)	1.08e-05	6.44e-05
Sulfonylureas	C2	C3	58.69	44.39	0.562 (0.469-0.673)	3.86e-10	3.69e-09
Sulfonylureas	C3	C1	44.39	58.84	0.558 (0.469-0.664)	5.62e-11	5.96e-10
Sulfonylureas	C2	C4	58.69	50.69	0.724 (0.62-0.844)	3.94e-05	2.15e-04
Thiazolidinediones	C2	C4	24.01	18.14	0.701 (0.581-0.847)	2.26e-04	1.08e-03
Thiazolidinediones	C1	C4	24.64	18.14	0.678 (0.566-0.811)	2.26e-05	1.27e-04

Table S6. Baseline medication differences between clinical groups after adjusting for years with type 2 diabetes (q<0.01).

Variable	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
if any insulin	C3	C4	59.1	21.29	0.266 (0.216-0.328)	1.41e-35	1.73e-34
if any insulin	C1	C4	30.23	21.29	0.749 (0.622-0.9)	2.05e-03	3.57e-03
if any insulin	C3	C1	59.1	30.23	2.749 (2.263-3.344)	3.18e-24	3.58e-23
if any insulin	C2	C4	37.28	21.29	0.583 (0.484-0.702)	1.31e-08	3.16e-08
if any insulin	C2	C3	37.28	59.1	2.165 (1.781-2.633)	9.53e-15	3.71e-14
Beta-blockers	C3	C4	35.06	25.29	0.674 (0.55-0.826)	1.44e-04	2.98e-04
Biguanides	C2	C4	68.25	60.86	0.722 (0.612-0.851)	1.07e-04	2.23e-04
Biguanides	C1	C4	65.8	60.86	0.8 (0.687-0.933)	4.47e-03	7.56e-03
Biguanides	C2	C3	68.25	58.97	0.714 (0.591-0.864)	5.07e-04	9.41e-04
Lispro or Aspart Insulins	C3	C1	16.65	6.44	2.249 (1.686-3.007)	3.81e-08	8.93e-08
Lispro or Aspart Insulins	C3	C4	16.65	5.19	0.422 (0.304-0.581)	1.63e-07	3.71e-07
Lispro or Aspart Insulins	C2	C3	9.08	16.65	1.76 (1.335-2.321)	6.09e-05	1.29e-04
either othbol_insulin or la_insulin	C3	C1	17.81	7.28	2.142 (1.625-2.829)	6.99e-08	1.61e-07
either othbol_insulin or la_insulin	C2	C3	9.72	17.81	1.767 (1.351-2.313)	3.30e-05	6.99e-05
either othbol_insulin or la_insulin	C3	C4	17.81	6	0.451 (0.331-0.612)	3.83e-07	8.46e-07
Loop diuretics	C3	C4	12.94	6.6	0.566 (0.411-0.779)	4.84e-04	9.17e-04
Nitrates	C3	C4	6.87	3.53	0.546 (0.356-0.837)	5.48e-03	9.23e-03
NPH or L Insulins	C3	C1	54.19	26.46	2.702 (2.225-3.285)	1.43e-23	1.56e-22
NPH or L Insulins	C2	C4	34.2	18.29	0.537 (0.444-0.65)	1.77e-10	4.44e-10
NPH or L Insulins	C3	C4	54.19	18.29	0.269 (0.218-0.333)	4.84e-34	5.78e-33
NPH or L Insulins	C1	C4	26.46	18.29	0.742 (0.613-0.897)	2.16e-03	3.75e-03
NPH or L Insulins	C2	C3	34.2	54.19	2.003 (1.651-2.432)	1.94e-12	7.28e-12
NPH or L Insulins	C2	C1	34.2	26.46	1.351 (1.137-1.606)	6.35e-04	1.14e-03
either nphl_insulin, reg_insulin, or premix_insulin	C3	C1	59.1	30.17	2.759 (2.271-3.356)	2.23e-24	2.58e-23
either nphl_insulin, reg_insulin, or premix_insulin	C3	C4	59.1	21.29	0.266 (0.216-0.328)	1.41e-35	1.73e-34
either nphl_insulin, reg_insulin, or premix_insulin	C2	C4	37.2	21.29	0.585 (0.486-0.704)	1.59e-08	3.80e-08
either nphl_insulin, reg_insulin, or premix_insulin	C2	C3	37.2	59.1	2.173 (1.788-2.644)	6.82e-15	2.69e-14
either nphl_insulin, reg_insulin, or premix_insulin	C1	C4	30.17	21.29	0.751 (0.625-0.903)	2.34e-03	4.05e-03
Potassium supplements	C2	C1	1.18	2.8	0.41 (0.219-0.725)	3.25e-03	5.60e-03
Premixed Insulins	C3	C1	16.13	9.62	1.478 (1.133-1.923)	3.76e-03	6.40e-03
Regular Insulins	C3	C4	19.1	7.39	0.506 (0.379-0.674)	3.38e-06	7.34e-06
Regular Insulins	C3	C1	19.1	9.69	1.752 (1.356-2.263)	1.73e-05	3.71e-05
Regular Insulins	C2	C3	11.45	19.1	1.565 (1.208-2.026)	6.74e-04	1.21e-03
Sulfonylureas	C2	C3	58.69	44.39	0.609 (0.506-0.732)	1.39e-07	3.19e-07
Sulfonylureas	C1	C4	58.84	50.69	0.718 (0.618-0.833)	1.23e-05	2.65e-05
Sulfonylureas	C3	C1	44.39	58.84	0.625 (0.523-0.748)	3.04e-07	6.75e-07
Sulfonylureas	C2	C4	58.69	50.69	0.714 (0.61-0.837)	3.15e-05	6.72e-05

Variable	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Thiazolidinediones	C2	C4	24.01	18.14	0.75 (0.618-0.91)	3.51e-03	6.02e-03
Thiazolidinediones	C1	C4	24.64	18.14	0.716 (0.596-0.859)	3.34e-04	6.86e-04

Table S7. Other clinical and demographic differences between clinical groups at baseline (q<0.01)

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
How many alcoholic drinks do you consume in a typical week?		C2	C4	0.822	1.185	0.363 (0.571-0.155)	6.45e-04	3.07e-03
How many alcoholic drinks do you consume in a typical week?		C3	C4	0.8	1.185	0.385 (0.626-0.144)	1.75e-03	6.74e-03
CVD History	Yes	C3	C1	42.58	34.27	1.423 (1.192-1.698)	9.56e-05	6.46e-04
CVD History	Yes	C2	C4	37.36	30.8	0.746 (0.635-0.877)	3.86e-04	2.07e-03
CVD History	Yes	C3	C4	42.58	30.8	0.6 (0.5-0.721)	4.46e-08	7.61e-07
Has the participant ever been told by a physician that s/he has depression	No	C3	C4	71.87	78.71	1.447 (1.18-1.773)	3.64e-04	2.07e-03
Has the participant ever been told by a physician that s/he has depression	No	C3	C1	71.87	78.02	0.72 (0.591-0.878)	1.11e-03	4.92e-03
Has the participant ever been told by a physician that s/he has eye disease	No	C3	C1	62.32	70.81	0.682 (0.569-0.819)	3.83e-05	3.16e-04
Has the participant ever been told by a physician that s/he has eye disease	No	C3	C4	62.32	72.35	1.582 (1.311-1.908)	1.64e-06	1.83e-05
Has the participant ever been told by a physician that s/he has eye disease	No	C2	C3	68.93	62.32	0.745 (0.618-0.9)	2.18e-03	8.21e-03
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C3	C1	70.25	80.31	0.579 (0.474-0.706)	7.21e-08	1.12e-06
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C3	C4	70.25	81.05	1.812 (1.476-2.225)	1.35e-08	2.59e-07
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C2	C3	76.64	70.25	0.719 (0.588-0.881)	1.39e-03	5.72e-03
Feeling score of (0-100)		C3	C4	73.874	76.763	2.889 (4.326-1.452)	8.38e-05	5.78e-04
Feeling score of (0-100)		C3	C1	73.874	76.401	2.527 (1.106-3.947)	4.99e-04	2.46e-03
Gender	Female	C3	C4	45.68	36.14	0.673 (0.562-0.805)	1.50e-05	1.35e-04
Gender	Female	C3	C1	45.68	36.22	1.481 (1.243-1.765)	1.15e-05	1.10e-04
11 gm Filament (number of applications detected)	Reduced (1-7)	C2	C3	14.65	20.37	1.569 (1.237-1.988)	1.94e-04	1.23e-03
11 gm Filament (number of applications detected)	Reduced (1-7)	C3	C4	20.37	14.47	0.624 (0.494-0.789)	7.50e-05	5.28e-04
12 gm Filament (number of applications detected)	Absent	C3	C1	7.05	2.42	3.25 (2.122-5.029)	7.84e-08	1.12e-06
12 gm Filament (number of applications detected)	Absent	C2	C3	3.42	7.05	2.324 (1.539-3.529)	6.45e-05	4.75e-04
12 gm Filament (number of applications detected)	Absent	C3	C4	7.05	2.87	0.357 (0.232-0.544)	1.94e-06	2.09e-05
Has the participant ever been told by a physician that s/he has heartfailure/CHR	No	C3	C4	93.81	97.15	2.248 (1.462-3.479)	2.38e-04	1.46e-03
Have you experienced shortness of breath while lying, sitting or with minimal exertion?	No	C3	C4	66.81	74.02	1.416 (1.154-1.735)	8.27e-04	3.83e-03
Have you experienced shortness of breath while lying, sitting or with minimal exertion?	No	C3	C1	66.81	73.2	0.737 (0.605-0.899)	2.48e-03	9.15e-03
Participant height (cm)		C3	C1	169.085	170.579	1.493 (0.623-2.364)	7.81e-04	3.67e-03
Participant height (cm)		C3	C4	169.085	170.653	1.568 (2.451-0.685)	5.08e-04	2.46e-03

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Does the participant live with one or more other adults?	No	C3	C4	25.16	18.67	0.683 (0.553-0.844)	4.11e-04	2.15e-03
Does the participant live with one or more other adults?	No	C3	C1	25.16	19.31	1.405 (1.143-1.725)	1.21e-03	5.24e-03
Grade Pre-tibial edema based on today's visit. (Left Foot)	1	C3	C1	15.23	11.31	1.817 (1.279-2.595)	9.25e-04	4.16e-03
Grade Pre-tibial edema based on today's visit. (Left Foot)	1	C3	C4	15.23	12.36	0.548 (0.383-0.78)	9.02e-04	4.12e-03
Grade Pre-tibial edema based on today's visit. (Left Foot)	2+ or higher	C3	C4	6.84	3.95	0.39 (0.245-0.619)	6.70e-05	4.82e-04
Grade Pre-tibial edema based on today's visit. (Left Foot)	None	C2	C4	73.46	69.35	0.681 (0.536-0.864)	1.65e-03	6.51e-03
MNSI score		C3	C1	2.34	2.029	0.31 (0.462-0.159)	5.82e-05	4.49e-04
MNSI score		C2	C3	2.057	2.34	0.282 (0.44-0.125)	4.44e-04	2.26e-03
Has the participant ever been told by a physician that s/he has neuropathy/nerve problems	No	C3	C1	68.13	75.03	0.711 (0.588-0.861)	4.47e-04	2.26e-03
Has the participant ever been told by a physician that s/he has neuropathy/nerve problems	No	C3	C4	68.13	77.91	1.65 (1.353-2.01)	7.11e-07	8.53e-06
Has the participant ever been told by a physician that s/he has protein in his/her urine	No	C3	C4	75.74	83.1	1.575 (1.267-1.956)	4.00e-05	3.16e-04
Has the participant ever been told by a physician that s/he has protein in his/her urine	No	C3	C1	75.74	81.14	0.726 (0.59-0.894)	2.51e-03	9.15e-03
Race	White	C1	C4	63.65	73.01	1.544 (1.319-1.81)	7.41e-08	1.12e-06
Race	White	C2	C3	59.32	47.1	0.61 (0.51-0.731)	7.97e-08	1.12e-06
Race	White	C3	C4	47.1	73.01	3.038 (2.527-3.657)	4.67e-32	5.04e-30
Race	White	C2	C4	59.32	73.01	1.855 (1.575-2.186)	1.46e-13	4.30e-12
Race	White	C3	C1	47.1	63.65	0.508 (0.426-0.605)	3.73e-14	1.34e-12
Has the participant experienced retinopathy (a type of vision problem)?	No	C3	C1	80.46	89.68	0.474 (0.366-0.613)	1.36e-08	2.59e-07
Has the participant experienced retinopathy (a type of vision problem)?	No	C2	C3	87.98	80.46	0.563 (0.434-0.729)	1.39e-05	1.29e-04
Has the participant experienced retinopathy (a type of vision problem)?	No	C2	C4	87.98	93.07	1.834 (1.378-2.455)	3.70e-05	3.16e-04
Has the participant experienced retinopathy (a type of vision problem)?	No	C3	C4	80.46	93.07	3.259 (2.437-4.385)	2.95e-15	1.19e-13
Grade Pre-tibial edema based on today's visit. (Right Foot)	1	C3	C4	15.74	12.29	0.525 (0.367-0.748)	3.79e-04	2.07e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	1	C3	C1	15.74	11.96	1.783 (1.257-2.541)	1.26e-03	5.38e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	2+ or higher	C3	C4	5.68	3.8	0.451 (0.278-0.731)	1.21e-03	5.24e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	None	C2	C4	73.3	69.71	0.688 (0.541-0.874)	2.26e-03	8.40e-03
Visual Acuity Score (0-100) Left Side		C2	C3	73.493	70.921	2.572 (1.162-3.981)	3.56e-04	2.07e-03
Visual Acuity Score (0-100) Left Side		C3	C1	70.921	73.433	2.512 (1.133-3.891)	3.65e-04	2.07e-03
Visual Acuity Score (0-100) Left Side		C3	C4	70.921	74.255	3.335 (4.73-1.94)	3.00e-06	3.13e-05
Visual Acuity Score (0-100) Right Side		C3	C1	70.805	73.493	2.688 (1.324-4.052)	1.16e-04	7.66e-04
Visual Acuity Score (0-100) Right Side		C2	C3	73.315	70.805	2.51 (1.097-3.922)	5.05e-04	2.46e-03

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Visual Acuity Score (0-100) Right Side		C3	C4	70.805	74.412	3.606 (4.996-2.216)	4.06e-07	5.26e-06
Participant eligible for BP and Lipid Trials	Yes	C3	C4	22.32	30.94	1.559 (1.273-1.916)	2.03e-05	1.78e-04
Participant eligible for BP and Lipid Trials	Yes	C3	C1	22.32	28.48	0.722 (0.589-0.882)	1.56e-03	6.33e-03
Has the participant ever been told by a physician that s/he has a foot ulcer requiring antibiotics	No	C3	C1	92.26	95.97	0.501 (0.347-0.723)	2.11e-04	1.31e-03
Has the participant ever been told by a physician that s/he has a foot ulcer requiring antibiotics	No	C3	C4	92.26	96.42	2.257 (1.533-3.339)	3.95e-05	3.16e-04
Has the participant experienced vision loss (a type of vision problem)?	No	C3	C1	80.99	86.46	0.667 (0.522-0.855)	1.31e-03	5.48e-03
Has the participant experienced vision loss (a type of vision problem)?	No	C3	C4	80.99	87.55	1.651 (1.275-2.137)	1.37e-04	8.87e-04
Waist circumference (cm)		C1	C4	106.909	108.489	1.58 (2.567-0.592)	1.72e-03	6.71e-03
Waist circumference (cm)		C3	C4	105.402	108.489	3.087 (4.312-1.863)	8.45e-07	9.78e-06
Waist circumference (cm)		C2	C4	105.54	108.489	2.949 (3.974-1.924)	1.88e-08	3.38e-07
Participent weight (kg)		C2	C4	91.903	95.57	3.666 (5.041-2.292)	1.82e-07	2.46e-06
Participent weight (kg)		C2	C1	91.903	94.133	2.23 (0.87-3.59)	1.32e-03	5.48e-03
Participent weight (kg)		C3	C4	91.805	95.57	3.765 (5.401-2.129)	6.86e-06	6.73e-05
Years since Diabetes Diagnosis		C2	C1	11.447	10.443	1.003 (1.557-0.449)	3.90e-04	2.07e-03
Years since Diabetes Diagnosis		C1	C4	10.443	8.582	1.862 (1.343-2.381)	2.46e-12	6.12e-11
Years since Diabetes Diagnosis		C2	C3	11.447	13.772	2.325 (3.032-1.618)	1.49e-10	3.22e-09
Years since Diabetes Diagnosis		C2	C4	11.447	8.582	2.865 (2.316-3.414)	3.99e-24	2.59e-22
Years since Diabetes Diagnosis		C3	C4	13.772	8.582	5.19 (4.51-5.87)	4.29e-47	6.94e-45
Years since Diabetes Diagnosis		C3	C1	13.772	10.443	3.328 (4.012-2.644)	5.69e-21	2.63e-19

Table S8. Other clinical and demographic differences between clinical groups at baseline after adjusting for years with type 2 diabetes (q<0.01).

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
How many alcoholic drinks do you consume in a typical week?		C2	C4	0.822	1.185	0.363 (0.571-0.155)	6.45e-04	3.59e-03
How many alcoholic drinks do you consume in a typical week?		C3	C4	0.8	1.185	0.385 (0.626-0.144)	1.75e-03	7.74e-03
CVD History	Yes	C3	C1	42.58	34.27	1.423 (1.192-1.698)	9.56e-05	7.46e-04
CVD History	Yes	C2	C4	37.36	30.8	0.746 (0.635-0.877)	3.86e-04	2.45e-03
CVD History	Yes	C3	C4	42.58	30.8	0.6 (0.5-0.721)	4.46e-08	9.16e-07
Has the participant ever been told by a physician that s/he has depression	No	C3	C1	71.87	78.02	0.72 (0.591-0.878)	1.11e-03	5.69e-03
Has the participant ever been told by a physician that s/he has depression	No	C3	C4	71.87	78.71	1.447 (1.18-1.773)	3.64e-04	2.45e-03
What is the particiapnt's highest level of education?	High school grad (or GED)	C3	C4	26.49	26.99	1.571 (1.191-2.073)	1.40e-03	6.56e-03
What is the particiapnt's highest level of education?	Some college or technical school	C3	C1	31.01	35.26	0.66 (0.511-0.853)	1.46e-03	6.80e-03
What is the particiapnt's highest level of education?	Some college or technical school	C3	C4	31.01	31.89	1.586 (1.211-2.076)	7.89e-04	4.28e-03

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
What is the particiapnt's highest level of education?	College graduate or more	C3	C4	23	28.46	1.907 (1.44-2.529)	6.79e-06	8.11e-05
What is the particiapnt's highest level of education?	College graduate or more	C2	C4	24.66	28.46	1.549 (1.208-1.99)	5.82e-04	3.29e-03
Has the participant ever been told by a physician that s/he has eye disease	No	C2	C3	68.93	62.32	0.745 (0.618-0.9)	2.18e-03	9.45e-03
Has the participant ever been told by a physician that s/he has eye disease	No	C3	C4	62.32	72.35	1.582 (1.311-1.908)	1.64e-06	2.21e-05
Has the participant ever been told by a physician that s/he has eye disease	No	C3	C1	62.32	70.81	0.682 (0.569-0.819)	3.83e-05	3.55e-04
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C3	C1	70.25	80.31	0.579 (0.474-0.706)	7.21e-08	1.35e-06
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C2	C3	76.64	70.25	0.719 (0.588-0.881)	1.39e-03	6.56e-03
Has the particiapnt ever had eye surgery, including laser photocoagulation?	No	C3	C4	70.25	81.05	1.812 (1.476-2.225)	1.35e-08	3.11e-07
Feeling score of (0-100)		C3	C1	73.874	76.401	2.527 (1.106-3.947)	4.99e-04	2.91e-03
Feeling score of (0-100)		C3	C4	73.874	76.763	2.889 (4.326-1.452)	8.38e-05	6.67e-04
Gender	Female	C3	C4	45.68	36.14	0.673 (0.562-0.805)	1.50e-05	1.54e-04
Gender	Female	C3	C1	45.68	36.22	1.481 (1.243-1.765)	1.15e-05	1.25e-04
11 gm Filament (number of applications detected)	Reduced (1-7)	C3	C4	20.37	14.47	0.624 (0.494-0.789)	7.50e-05	6.10e-04
11 gm Filament (number of applications detected)	Reduced (1-7)	C2	C3	14.65	20.37	1.569 (1.237-1.988)	1.94e-04	1.43e-03
12 gm Filament (number of applications detected)	Absent	C3	C4	7.05	2.87	0.357 (0.232-0.544)	1.94e-06	2.52e-05
12 gm Filament (number of applications detected)	Absent	C2	C3	3.42	7.05	2.324 (1.539-3.529)	6.45e-05	5.46e-04
12 gm Filament (number of applications detected)	Absent	C3	C1	7.05	2.42	3.25 (2.122-5.029)	7.84e-08	1.35e-06
Has the participant ever been told by a physician that s/he has heartfailure/CHR	No	C3	C4	93.81	97.15	2.248 (1.462-3.479)	2.38e-04	1.69e-03
Have you experienced shortness of breath while lying, sitting or with minimal exertion?	No	C3	C4	66.81	74.02	1.416 (1.154-1.735)	8.27e-04	4.42e-03
Participant height (cm)		C3	C1	169.085	170.579	1.493 (0.623-2.364)	7.81e-04	4.28e-03
Participant height (cm)		C3	C4	169.085	170.653	1.568 (2.451-0.685)	5.08e-04	2.91e-03
Does the participant live with one or more other adults?	No	C3	C4	25.16	18.67	0.683 (0.553-0.844)	4.11e-04	2.54e-03
Does the participant live with one or more other adults?	No	C3	C1	25.16	19.31	1.405 (1.143-1.725)	1.21e-03	6.06e-03
Grade Pre-tibial edema based on today’s visit. (Left Foot)	1	C3	C4	15.23	12.36	0.548 (0.383-0.78)	9.02e-04	4.75e-03
Grade Pre-tibial edema based on today’s visit. (Left Foot)	1	C3	C1	15.23	11.31	1.817 (1.279-2.595)	9.25e-04	4.81e-03
Grade Pre-tibial edema based on today’s visit. (Left Foot)	2+ or higher	C3	C4	6.84	3.95	0.39 (0.245-0.619)	6.70e-05	5.56e-04
Grade Pre-tibial edema based on today’s visit. (Left Foot)	None	C2	C4	73.46	69.35	0.681 (0.536-0.864)	1.65e-03	7.47e-03
MNSI score		C2	C3	2.057	2.34	0.282 (0.44-0.125)	4.44e-04	2.68e-03
MNSI score		C3	C1	2.34	2.029	0.31 (0.462-0.159)	5.82e-05	5.05e-04

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Network	5	C2	C4	14.06	8.71	0.519 (0.383-0.701)	2.03e-05	1.98e-04
Network	5	C3	C4	17.29	8.71	0.333 (0.235-0.471)	5.47e-10	1.42e-08
Network	5	C3	C1	17.29	10.14	2.152 (1.539-3.022)	8.36e-06	9.34e-05
Network	6	C3	C4	18.58	12.36	0.441 (0.316-0.612)	1.12e-06	1.56e-05
Network	7	C3	C4	15.87	11.05	0.461 (0.327-0.647)	8.38e-06	9.34e-05
Network	7	C1	C4	14.3	11.05	0.646 (0.489-0.851)	1.92e-03	8.43e-03
Network	7	C2	C4	14.53	11.05	0.637 (0.477-0.85)	2.22e-03	9.51e-03
Has the participant ever been told by a physician that s/he has neuropathy/nerve problems	No	C3	C1	68.13	75.03	0.711 (0.588-0.861)	4.47e-04	2.68e-03
Has the participant ever been told by a physician that s/he has neuropathy/nerve problems	No	C3	C4	68.13	77.91	1.65 (1.353-2.01)	7.11e-07	1.07e-05
Has the participant ever been told by a physician that s/he has protein in his/her urine	No	C3	C4	75.74	83.1	1.575 (1.267-1.956)	4.00e-05	3.55e-04
Race	White	C3	C4	47.1	73.01	3.038 (2.527-3.657)	4.67e-32	6.06e-30
Race	White	C3	C1	47.1	63.65	0.508 (0.426-0.605)	3.73e-14	1.61e-12
Race	White	C1	C4	63.65	73.01	1.544 (1.319-1.81)	7.41e-08	1.35e-06
Race	White	C2	C4	59.32	73.01	1.855 (1.575-2.186)	1.46e-13	5.69e-12
Race	White	C2	C3	59.32	47.1	0.61 (0.51-0.731)	7.97e-08	1.35e-06
Has the participant experienced retinopathy (a type of vision problem)?	No	C2	C3	87.98	80.46	0.563 (0.434-0.729)	1.39e-05	1.46e-04
Has the participant experienced retinopathy (a type of vision problem)?	No	C2	C4	87.98	93.07	1.834 (1.378-2.455)	3.70e-05	3.52e-04
Has the participant experienced retinopathy (a type of vision problem)?	No	C3	C1	80.46	89.68	0.474 (0.366-0.613)	1.36e-08	3.11e-07
Has the participant experienced retinopathy (a type of vision problem)?	No	C3	C4	80.46	93.07	3.259 (2.437-4.385)	2.95e-15	1.44e-13
Grade Pre-tibial edema based on today's visit. (Right Foot)	1	C3	C1	15.74	11.96	1.783 (1.257-2.541)	1.26e-03	6.23e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	1	C3	C4	15.74	12.29	0.525 (0.367-0.748)	3.79e-04	2.45e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	2+ or higher	C3	C4	5.68	3.8	0.451 (0.278-0.731)	1.21e-03	6.06e-03
Grade Pre-tibial edema based on today's visit. (Right Foot)	None	C2	C4	73.3	69.71	0.688 (0.541-0.874)	2.26e-03	9.56e-03
Visual Acuity Score (0-100) Left Side		C3	C4	70.921	74.255	3.335 (4.73-1.94)	3.00e-06	3.77e-05
Visual Acuity Score (0-100) Left Side		C3	C1	70.921	73.433	2.512 (1.133-3.891)	3.65e-04	2.45e-03
Visual Acuity Score (0-100) Left Side		C2	C3	73.493	70.921	2.572 (1.162-3.981)	3.56e-04	2.45e-03
Visual Acuity Score (0-100) Right Side		C3	C4	70.805	74.412	3.606 (4.996-2.216)	4.06e-07	6.33e-06
Visual Acuity Score (0-100) Right Side		C3	C1	70.805	73.493	2.688 (1.324-4.052)	1.16e-04	8.86e-04
Visual Acuity Score (0-100) Right Side		C2	C3	73.315	70.805	2.51 (1.097-3.922)	5.05e-04	2.91e-03
Participant eligible for BP and Lipid Trials	Yes	C3	C4	22.32	30.94	1.559 (1.273-1.916)	2.03e-05	1.98e-04
Participant eligible for BP and Lipid Trials	Yes	C3	C1	22.32	28.48	0.722 (0.589-0.882)	1.56e-03	7.18e-03

Variable Description	Variable Status	Group 1	Group 2	Proportion or Mean in group 1	Proportion or Mean in group 2	Odds Ratio or Mean Difference	*P* value	q-value
Has the participant ever been told by a physician that s/he has a foot ulcer requiring antibiotics	No	C3	C1	92.26	95.97	0.501 (0.347-0.723)	2.11e-04	1.52e-03
Has the participant ever been told by a physician that s/he has a foot ulcer requiring antibiotics	No	C3	C4	92.26	96.42	2.257 (1.533-3.339)	3.95e-05	3.55e-04
Has the participant experienced vision loss (a type of vision problem)?	No	C3	C4	80.99	87.55	1.651 (1.275-2.137)	1.37e-04	1.03e-03
Has the participant experienced vision loss (a type of vision problem)?	No	C3	C1	80.99	86.46	0.667 (0.522-0.855)	1.31e-03	6.35e-03
Waist circumference (cm)		C1	C4	106.909	108.489	1.58 (2.567-0.592)	1.72e-03	7.71e-03

Table S9. On-trial differences in lipids and blood pressure between C4 and other clusters in the intensive glycemia trial arm.

Risk Factor[1]	non-C4 mean	C4 mean	*P* value	FDR *P* value
HbA1c (%)	6.94	6.03	<2.00E-16	<2.00E-16
SBP (mm Hg)	128.59	125.71	1.03E-10	7.21E-10
LDL (mg/dL)	99.16	94.91	7.54E-06	4.52E-05
Total Cholesterol (mg/dL)	174.84	170.37	0.0005	0.0027
DBP (mm Hg)	70.32	69.52	0.0106	0.0425
HDL (mg/dL)	43.72	42.83	0.0174	0.0523
Triglycerides (mg/dL)	160.64	162.71	0.2282	0.4455
VLDL (mg/dL)	31.42	31.83	0.2228	0.4455

SBP=systolic blood pressure; DBP=diastolic blood pressure, LDL=low density lipoprotein, HDL=high density lipoprotein, VLDL= very low density lipoprotein. [1]Variables were measured by taking each individuals median value while on-trial.

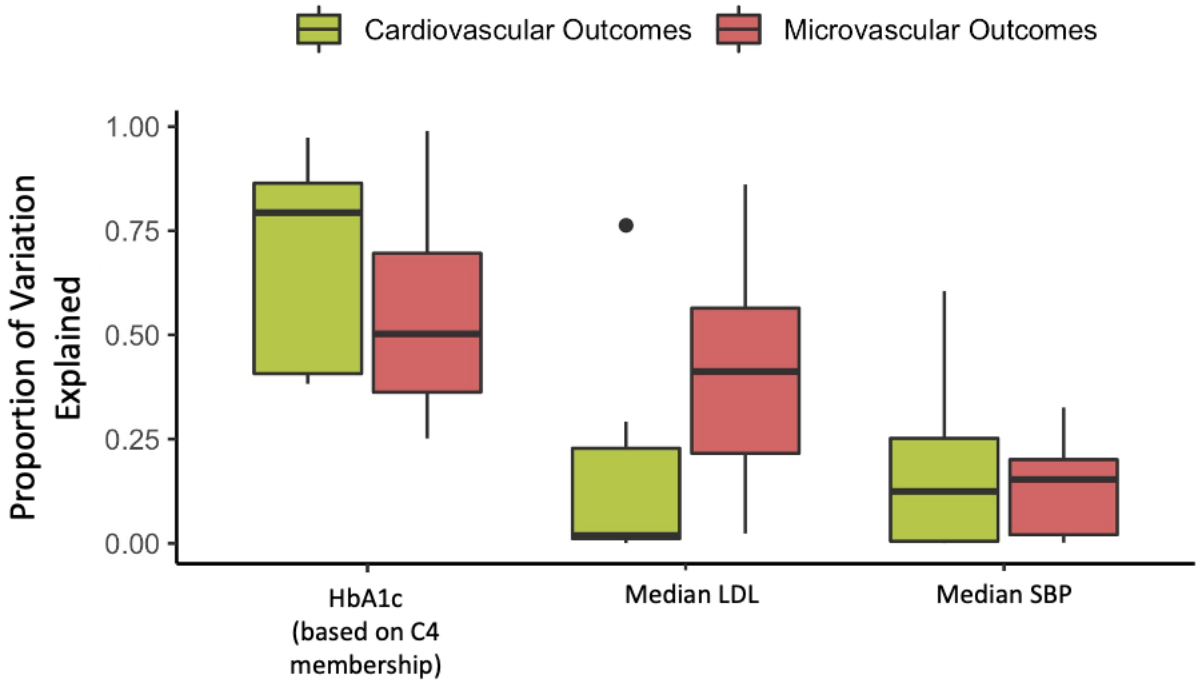

Figure S9. Variation explained for cardiovascular and microvascular outcomes by on-trial risk factors. Risk of outcomes were calculated using Cox proportional hazards models based on C4 membership, median low-density lipoprotein (LDL) and median systolic blood pressure (SBP). Using Wald's Chi-square tests, the proportion of variation explained for each risk factor was obtained for all cardiovascular (CVD) and microvascular outcomes. The range of Chi-square proportions for each risk factor across outcomes are shown in each boxplot. Hba1c was estimated based on cluster membership compared to median on-trial LDL and SBP. Stratifying by HbA1c explained more variation in both CVD and microvascular outcomes than LDL or SBP. Interestingly, LDL appears to be a more informative risk factor for microvascular outcomes than for CVD outcomes.

Genome-wide Association Tests and Variable Selection

When comparing the low-risk, intensive clinical group (C4) to the other intensive clinical groups (C1, C2, and C3), four genotyped variants reached suggestive significance ($P < 5.0x10^{-6}$). These variants and their base position, log odds ratio, and *P* values are presented in Table S10. No genotyped variants reached genome-wide significance ($P < 5.0x10^{-8}$). The most significant loci, rs220721, is located within *MAS1* ane had a 1.38 fold increase in the low risk cluster and a MAF of 27%. The SNP, rs1793004, is located within *NELL1* had a 0.74 fold decrease in the low risk clinical group and a MAF of 30%. The third SNP, rs6921353, is located in an intronic region 6Mbp downstream of *IGF2R* and associated with a 0.75 fold decrease within the low risk clinical group and a MAF of 34%. A visual representation of the GWAS results are presented in a Manhattan plot in Figure 3A, in the main text. A quantile-quantile (Q-Q) plot for every p-value is shown in Figure S8. The Q-Q plot shows the expected *P* values based on a normal distribution compared to the observed *P* values.

Table S10. GWAS results for SNPs that reached suggestive significance ($P<5x10^{-6}$).

SNP	Type[1]	Chr	Pos	Gene	A1	A2	OR	P-value
rs220721	GENO	6	159907588	MAS1	T	C	1.38	4.34E-07
rs77989944	IMPU	6	1312510	FOXQ1	T	C	0.74	4.35E-07
rs7772415	IMPU	6	166300093	-	A	G	0.73	4.38E-07
rs3926288	IMPU	6	166299490	-	A	G	0.73	5.48E-07
rs9347360	IMPU	6	159914023	MAS1	C	T	1.37	7.03E-07
rs220724	IMPU	6	159905236	MAS1	A	G	1.37	8.45E-07
rs10214855	IMPU	6	159911681	MAS1	A	G	1.36	1.03E-06
rs2024585	IMPU	6	159913985	MAS1	A	G	1.37	1.08E-06
rs2719207	IMPU	8	129395437	CCDC26	G	C	1.43	1.14E-06

rs2579861	IMPU	8	129389629	CCDC26	C	T	1.43	1.28E-06
rs2568406	IMPU	8	129390326	CCDC26	A	G	1.43	1.34E-06
rs6921526	IMPU	6	166297374	-	G	A	0.75	1.58E-06
rs1793004	GENO	11	20677383	NELL1	C	G	0.74	1.82E-06
rs220734	IMPU	6	159893659	MAS1	G	A	1.37	1.97E-06
rs220734	IMPU	6	159893659	AL035691.1	G	A	1.37	1.97E-06
rs1617707	IMPU	11	20678515	NELL1	G	A	0.74	2.26E-06
rs6921353[2]	GENO	6	166297303	PRR18[2]	G	A	0.75	2.44E-06
rs1328399	IMPU	6	152837599	LINC02840	T	C	1.42	2.47E-06
rs6456073	IMPU	6	166296031	-	T	G	0.74	3.04E-06
rs4505826	META	4	95485799	UNC5C	A	G	1.36	3.29E-06
rs17307880	IMPU	6	152848750	LINC02840	T	G	1.41	3.39E-06
rs6936214	IMPU	6	159958355	-	G	A	1.33	3.50E-06
rs10710587	IMPU	4	102189067	-	GT	G	0.75	3.52E-06
rs4709387	IMPU	6	159961484	-	C	T	1.35	3.55E-06
rs6918897	IMPU	6	159919903	-	G	A	1.34	3.63E-06
rs6455671	IMPU	6	159924005	-	G	T	1.33	3.71E-06
rs10050886	META	5	172148456	STK10	A	G	1.57	3.73E-06
rs1270874	GENO	10	29550935	SVIL	A	C	1.33	3.73E-06
rs202225334	IMPU	6	159924025	-	G	GA	1.33	3.73E-06
rs75730240	IMPU	6	159924028	-	A	AC	1.33	3.73E-06
rs9457791	IMPU	6	159966886	-	C	T	1.33	4.21E-06
rs10845619	META	12	12729394	APOLD1	A	G	1.43	4.36E-06
rs12922741	IMPU	16	27168591	LINC02129	G	A	0.76	4.36E-06
rs172698	IMPU	6	159901528	MAS1	G	A	1.35	4.36E-06
rs172698	IMPU	6	159901528	AL035691.1	G	A	1.35	4.36E-06
rs170220	IMPU	6	159901671	MAS1	G	A	1.35	4.37E-06
rs170220	IMPU	6	159901671	AL035691.1	G	A	1.35	4.37E-06
rs9456483	IMPU	6	159959968	-	G	A	1.33	4.60E-06
rs1001357	IMPU	6	159952077	-	C	A	1.33	4.66E-06
rs66801308	IMPU	6	159926605	-	T	G	1.33	4.66E-06
rs1793005	IMPU	11	20677212	NELL1	C	G	0.75	4.75E-06
rs6939598	IMPU	6	159950510	-	T	G	1.33	4.81E-06
rs62571397	IMPU	9	134798135	COL5A1	T	C	1.48	4.84E-06
rs62571397	IMPU	9	134798135	-	T	C	1.48	4.84E-06
rs220726	IMPU	6	159903111	MAS1	A	T	1.35	4.91E-06

[1] GENO=genotyped across all subjects; IMPU=imputed across all subjects; META=genotyped in some subjects and imputed in others. They were analyzed separately and meta-analyzed together.

[2]rs6921353 is located in an intronic region 8Kb upstream of *PRR18*

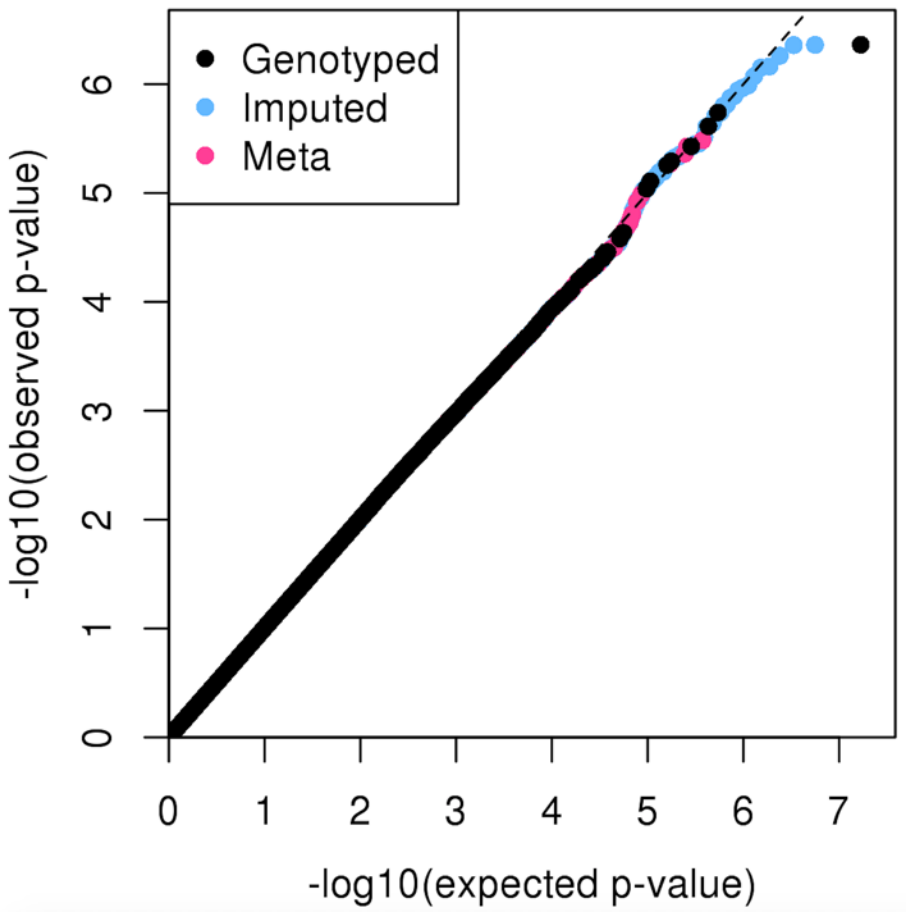

Figure S10. Q-Q plot for observed *P* values

Pathway Analysis

The SNP-based network analysis resulted in two significant genes: *SFT2D1* (FDR *P* = .008) and *PRR18* (FDR *P* = .008). Interestingly, 155 ontology terms were significantly enriched (q<0.05) based on the SNPs selected into the PS (Table S10).

Table S11. Ontology terms associated with SNPs in PS based on enrichment analysis (FDR *P* < .05).

Ontology Term	Z-score	*P* value	FDR *P* value	Num. of SNPs
body mass index	11	1.40E-27	1.60E-24	722
body height	10.9	1.00E-26	5.40E-24	409
inflammatory bowel disease	10.5	8.10E-25	3.00E-22	454
lipid measurement	9.81	2.60E-22	7.10E-20	857
rheumatic disease	9.59	2.20E-21	4.90E-19	667
lipoprotein measurement	8.97	5.50E-19	1.00E-16	674
ulcerative colitis	8.95	1.20E-18	1.80E-16	266
forced expiratory volume	8.8	2.40E-18	3.20E-16	647
Crohn's disease	8.84	2.60E-18	3.20E-16	317
physical activity measurement	8.47	7.20E-17	7.90E-15	190
high density lipoprotein cholesterol measurement	8.15	7.20E-16	7.10E-14	320
obesity	7.85	9.50E-15	8.70E-13	99
multiple sclerosis	7.53	9.00E-14	7.50E-12	187
triglyceride measurement	7.47	1.20E-13	9.10E-12	302
rheumatoid arthritis	7.37	2.60E-13	1.90E-11	240
waist circumference	7.21	8.80E-13	6.00E-11	155
systemic lupus erythematosus	7.15	1.10E-12	7.10E-11	277
glucose measurement	7.12	1.50E-12	9.00E-11	183
kidney disease	7.09	1.70E-12	9.90E-11	233

metabolic syndrome	6.81	1.00E-11	5.60E-10	54
blood metabolite measurement	6.54	6.70E-11	3.50E-09	163
neuropsychological test	6.45	1.30E-10	6.50E-09	80
total cholesterol measurement	6.35	2.10E-10	9.80E-09	251
intraocular pressure measurement	6.28	3.00E-10	1.40E-08	268
inflammatory skin disease	6.19	5.10E-10	2.30E-08	277
membranous glomerulonephritis	5.8	7.80E-10	3.30E-08	21
intestinal disease	6.12	9.50E-10	3.60E-08	87
malabsorption syndrome	6.12	9.50E-10	3.60E-08	87
celiac disease	6.12	9.50E-10	3.60E-08	87
psoriasis	6.08	1.00E-09	3.70E-08	232
serum metabolite measurement	6.1	1.10E-09	3.70E-08	91
spondyloarthropathy	6.06	1.20E-09	4.10E-08	169
ankylosing spondylitis	6.06	1.20E-09	4.10E-08	169
coronary heart disease	5.96	1.90E-09	6.30E-08	349
fasting blood glucose measurement	5.89	3.50E-09	1.10E-07	70
hip circumference	5.89	3.60E-09	1.10E-07	100
attention deficit hyperactivity disorder	5.82	4.80E-09	1.40E-07	183
chronic kidney disease	5.77	6.70E-09	1.90E-07	127
hair morphology	5.71	6.70E-09	1.90E-07	34
body ratio measurement	5.48	3.20E-08	8.60E-07	166
BMI-adjusted waist circumference	5.33	7.40E-08	0.000002	96
low density lipoprotein cholesterol measurement	5.23	1.20E-07	0.000003	200
endocrine neoplasm	5.21	1.30E-07	3.3E-06	162
sclerosing cholangitis	5.18	1.50E-07	3.8E-06	138
cis/trans-18:2 fatty acid measurement	5.1	1.80E-07	4.5E-06	31
mean arterial pressure	4.99	4.00E-07	9.5E-06	127
waist-hip ratio	4.96	4.80E-07	0.000011	137
cardiac arrest	4.92	4.90E-07	0.000011	34
sudden cardiac arrest	4.92	4.90E-07	0.000011	34
glycerophospholipid measurement	4.61	8.70E-07	0.000019	16
conduct disorder	4.81	9.10E-07	0.00002	40
information processing speed	4.72	9.70E-07	0.00002	23
fetal hemoglobin measurement	4.41	2.3E-06	0.000047	15
thyroid disease	4.56	0.000003	0.000062	89
metabolic disease	4.51	3.7E-06	0.000072	617
trans/trans-18:2 fatty acid measurement	4.5	3.7E-06	0.000072	35
glycoprotein measurement	4.51	3.9E-06	0.000075	102
age at menarche	4.48	4.4E-06	0.000083	117
age at menopause	4.39	6.5E-06	0.00012	61
function	4.08	7.9E-06	0.00014	12
liver neoplasm	4.33	8.6E-06	0.00016	85
open-angle glaucoma	4.28	0.00001	0.00018	53
QRS complex	4.24	0.000012	0.00021	42
stroke	4.24	0.000013	0.00021	94
coronary artery disease	4.2	0.000014	0.00024	265
C-reactive protein measurement	4.2	0.000015	0.00025	75
type I diabetes mellitus	4.19	0.000015	0.00025	110
A1C measurement	4.16	0.000017	0.00027	59
BMI-adjusted waist-hip ratio	4.15	0.000018	0.00028	102
very low density lipoprotein cholesterol measurement	4.04	0.000018	0.00028	17
puberty	3.85	0.000022	0.00033	11
height growth measurement	3.85	0.000022	0.00033	11
Sarcoidosis	3.97	0.000032	0.00048	26
cirrhosis of liver	4	0.000034	0.0005	73
optic disc measurement	3.99	0.000035	0.00052	70
ACPA-positive rheumatoid arthritis	3.76	0.000041	0.00058	12
allergy	3.91	0.000049	0.0007	170
diastolic blood pressure	3.88	0.000054	0.00076	330
ventricular rate measurement	3.84	0.000055	0.00076	28

thyroid neoplasm	3.78	0.00006	0.00081	19
thyroid carcinoma	3.78	0.00006	0.00081	19
platelet aggregation	3.69	0.000061	0.00081	13
motor neuron disease	3.72	0.0001	0.0013	93
amyotrophic lateral sclerosis	3.72	0.0001	0.0013	93
free cholesterol measurement	3.6	0.00011	0.0014	16
systemic scleroderma	3.66	0.00012	0.0015	41
Connective tissue disease with eye involvement	3.66	0.00012	0.0015	41
scleroderma	3.66	0.00012	0.0015	41
neoplasm of mature B-cells	3.65	0.00013	0.0016	125
bladder carcinoma	3.58	0.00013	0.0016	19
MHC class I polypeptide-related sequence B measurement	3.34	0.00016	0.0019	9
alcohol dependence measurement	3.56	0.00018	0.0021	41
sex interaction measurement	3.55	0.00019	0.0022	63
emphysema pattern measurement	3.42	0.00019	0.0022	13
chronic hepatitis B infection	3.42	0.00019	0.0022	13
HOMA-B	3.38	0.00024	0.0028	15
complement C4 measurement	3.26	0.00026	0.0029	10
Hashimoto's thyroiditis	3.26	0.00026	0.0029	10
hair color	3.38	0.00027	0.003	18
microbiome measurement	3.42	0.0003	0.0033	89
gut microbiome measurement	3.42	0.0003	0.0033	89
cutaneous psoriasis measurement	3.07	0.00043	0.0045	8
Hypertriglyceridemia	3.07	0.00043	0.0045	8
oppositional defiant disorder measurement	3.22	0.00049	0.0051	20
docosapentaenoic acid measurement	3.16	0.00054	0.0057	15
QRS amplitude	3.19	0.00058	0.006	25
psoriasis vulgaris	3.13	0.00069	0.0071	23
glomerular filtration rate	3.17	0.00072	0.0073	110
attempted suicide	3.11	0.00077	0.0077	27
carbohydrate measurement	2.95	0.00085	0.0084	10
myositis	3.02	0.00093	0.0092	19
Chronic Hepatitis C infection	2.98	0.001	0.01	17
hematocrit	3.04	0.0011	0.01	97
optic disc size measurement	3.01	0.0011	0.01	28
overweight body mass index status	2.98	0.0011	0.01	23
peripheral nervous system disease	2.92	0.0011	0.01	13
neuroblastoma	2.92	0.0011	0.01	13
response to risperidone	2.92	0.0011	0.01	13
serum creatinine measurement	3.03	0.0011	0.011	95
chronic lymphocytic leukemia	3	0.0012	0.011	56
blood urea nitrogen measurement	2.96	0.0013	0.012	33
male reproductive system disease	2.95	0.0015	0.014	214
age at assessment	2.89	0.0017	0.015	51
alcohol dependence	2.87	0.0019	0.017	90
optic cup area measurement	2.81	0.002	0.017	26
N-glycan measurement	2.68	0.002	0.017	9
acquired metabolic disease	2.68	0.002	0.017	9
amyloidosis	2.68	0.002	0.017	9
AL amyloidosis	2.68	0.002	0.017	9
Rare familial disorder with hypertrophic cardiomyopathy	2.68	0.002	0.017	9
seasonal gut microbiome measurement	2.8	0.0022	0.018	37
RR interval	2.71	0.0022	0.018	14
D dimer measurement	2.67	0.0022	0.018	10
non-alcoholic fatty liver disease	2.77	0.0023	0.019	31
panic disorder	2.67	0.0023	0.019	11
drinking behavior	2.8	0.0024	0.02	142
brain volume measurement	2.77	0.0026	0.02	73
biliary liver cirrhosis	2.74	0.0027	0.021	47

omega-6 polyunsaturated fatty acid measurement	2.72	0.0028	0.022	40
estrogen-receptor negative breast cancer	2.7	0.003	0.024	46
genomic measurement	2.65	0.0033	0.025	31
refractive error measurement	2.66	0.0035	0.027	77
lean body mass	2.51	0.0041	0.031	14
telomere length	2.55	0.0042	0.032	26
alcohol drinking	2.59	0.0044	0.033	129
heart failure	2.55	0.0045	0.033	36
aortic aneurysm	2.45	0.0046	0.034	12
Vitiligo	2.53	0.0048	0.036	42
adhesion molecule measurement	2.4	0.0049	0.036	10
response to beta blocker	2.51	0.005	0.037	35
chin morphology measurement	2.46	0.0053	0.039	24
HIV-1 infection	2.47	0.0062	0.044	96
phospholipid measurement	2.4	0.0065	0.046	44
melanoma	2.38	0.0067	0.048	25
large artery stroke	2.37	0.0068	0.048	22

Development of model for clinical group prediction

Polygenic Scores (PS)

All SNPs, weights, and code for generating new predictions for the CT-PS and SCT-PS can be found at www.github.com/rotroff-lab/accord-C4-ps.

A comparison between the GWAS effect sizes and the SCT-PS effect sizes is given in Figure S11. Boxplots of SCT-PS (Fig. S12) by cluster assignment show that C4 has a significantly higher mean SCT-PS than the other groups.

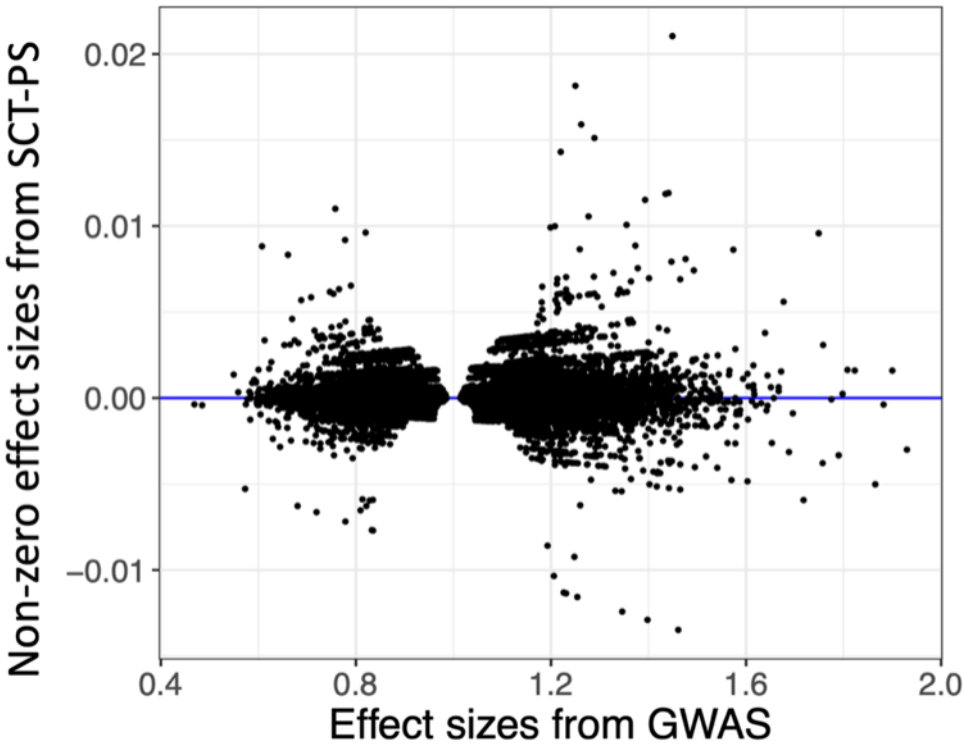

Figure S11. Comparison between effects sizes from GWAS and SCT- PS.

Non-zero effect sizes are compared between SCT-PS (y-axis) and genome-wide association study (GWAS) (x-axis).

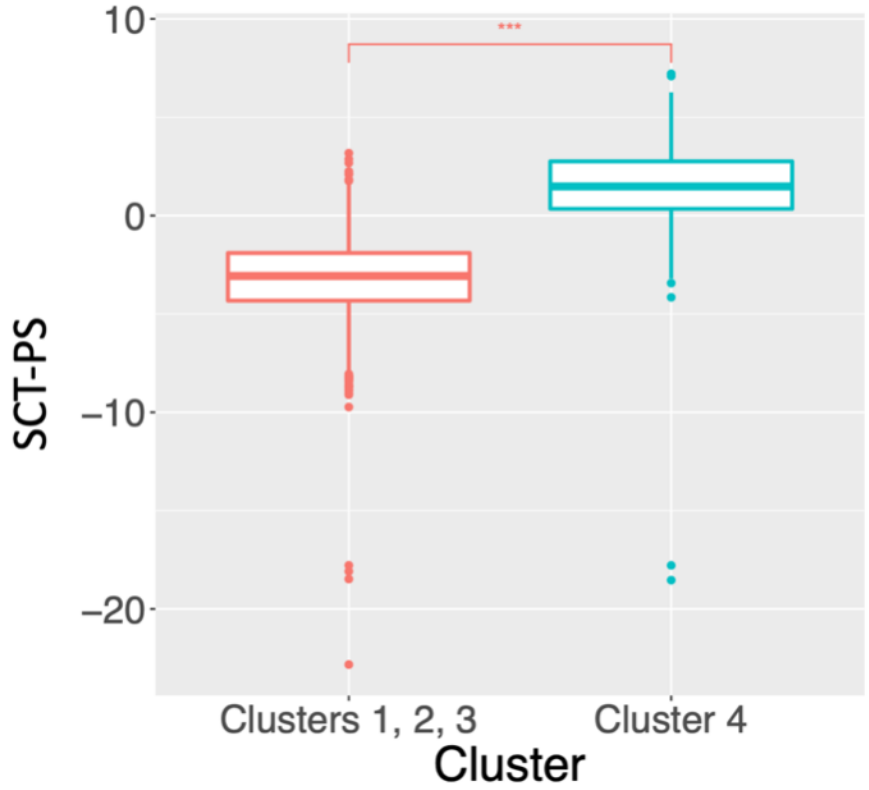

Figure S12. Box plots for SCT-PS by clinical group assignment.

Model training

The CT-PS and SCT-PS with and without baseline clinical variables were used to construct multiple models in order to evaluate which approach performed best to predict individual clinical group membership. The cohort randomized to receive intensive glycemia treatment and that consented to genetic studies was divided into a training set (N=2,270) and a test set (N=1,169). A 10-fold cross-validation procedure was performed for each modeling approach to prevent overfitting on the training set. The baseline clinical variables and the pairwise interaction terms between the CT-PS and SCT-PS and each baseline clinical variables were included in the variable selection procedure using least absolute shrinkage and selection operator (LASSO) was used to select an optimal subset of the covariates for each model.[14] Selected variables were then used in a generalized linear model (GLM) with a logit link function (i.e, logistic regression). Each model was evaluated using CT/SCT-PS only, baseline clinical variables only, or the CT/SCT-PS and baseline clinical variables. Model performance was assessed based on the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and balanced accuracy. PPV is the ratio of true positives out of all identified positives. NPV is the ratio of true negatives out of all identified negatives.

Covariates were selected using LASSO and are shown in Table S12. Testing accuracy metrics for each model are shown in Table S13. Boxplots of the 10-fold cross-validation results between each model are shown in Figure S13. Models that incorporated the PS either with or without baseline clinical factors outperformed models with only clinical variables (Table S13). GLMs incorporating PS and clinical factors negligibly outperformed models with PS only, with AUCs of 0.98 and 0.99, respectively (Table S13). The SCT-PS model with clinical variables performed the best on the testing set (AUC=0.99), with sensitivity, specificity, and balanced accuracy of 96%, 94%, and 95%, respectively. The SCT-PS without clinical variables also performed well (AUC=0.98), with sensitivity, specificity, and balanced accuracy of 95%, 93%, and 94%, respectively. Due to a negligible increase in model performance and to maintain model parsimony and transparency, the SCT-PS without clinical variables was considered to be the best model, however, both are presented in the main text (Fig. 4D).

Table S12. Clinical and demographic covariates selected by LASSO.

Sulfonylurea	Biguanide	Any Insulin Use
Thiazolidinedione	Diabetes Medications*	Years since diabetes diagnosis*
Waist size (cm)	Platelet AGI	Anti-depressant medication
Other Drugs	HDL*	BMI
Cardiovascular disease at baseline	AG Inhibitor*	Fibrate*
Herbal Medication*	LDL*	FPG*
Potassium*	Years with dyslipidemia*	

*Includes interaction term with SCT-PS

Table S13. Model performace for predicting C4 membership.

Model	**Variables**	**Sensitivity**	**Specificity**	**Positive Predictive Value (PPV)**	**Negative Predictive Value (NPV)**	**Balanced Accuracy**	**AUC**
GLM	Clinical Variables Only	0.72	0.56	0.41	0.82	0.64	0.67
CT-PS	CT-PS	0.77	0.78	0.60	0.89	0.77	0.82
	CT-PS + Clinical Variables	0.76	0.87	0.71	0.89	0.81	0.88
SCT-PS	SCT-PS	0.95	0.93	0.85	0.98	0.94	0.98
	SCT-PS + Clinical Variables	0.96	0.94	0.87	0.98	0.95	0.99

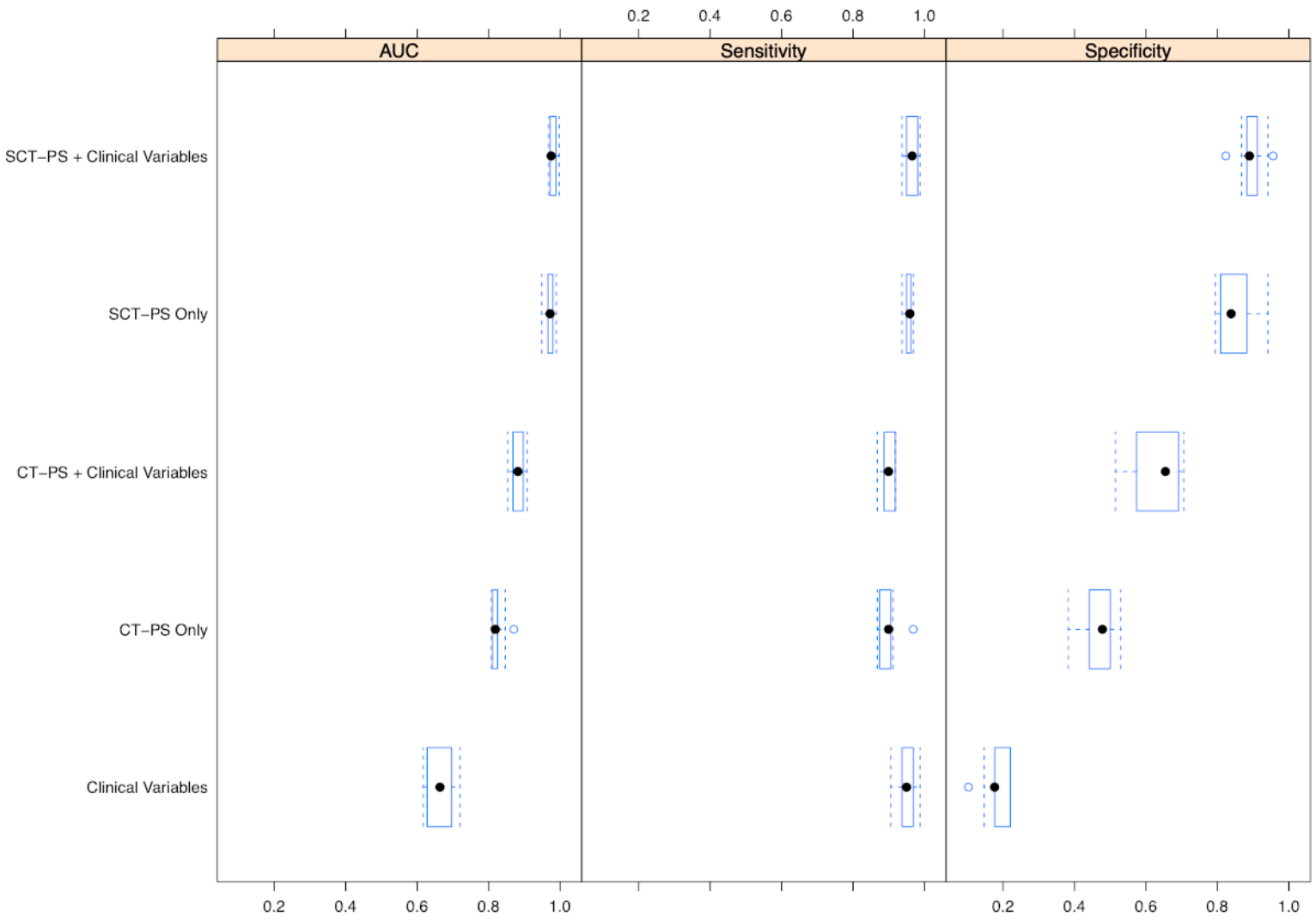

Figure S13. Boxplots of 10-fold cross-validation results.

Assessment of model for clinical group prediction

Propensity Score Matching

The process, descried in supplemental methods, resulted in 2,060 individuals which were then split into a training and test set of 1,368 and 692 indviduals each. A GLM using both the SCT-PS and clinical variables chosen in the full model was trained on the matched training set and then predicted the match test set. The predictions resulted in an AUC of 98%. The similar AUC to the previous testing accuracy suggests that the predictive models are not relying on cohort differences such as age, sex, race, or years since T2D to predict clinical group membership.

Mendelian Randomization

The individual and meta-analyzed results of mendelian randomization, described in supplemental methods, are shown in Figure S14. The intensive treatment arm exhibited the only significant IVW results, suggesting that there is a causal relationship between glycemia reduction and CVD outcomes but only through interaction of SCT-PS and treatment.

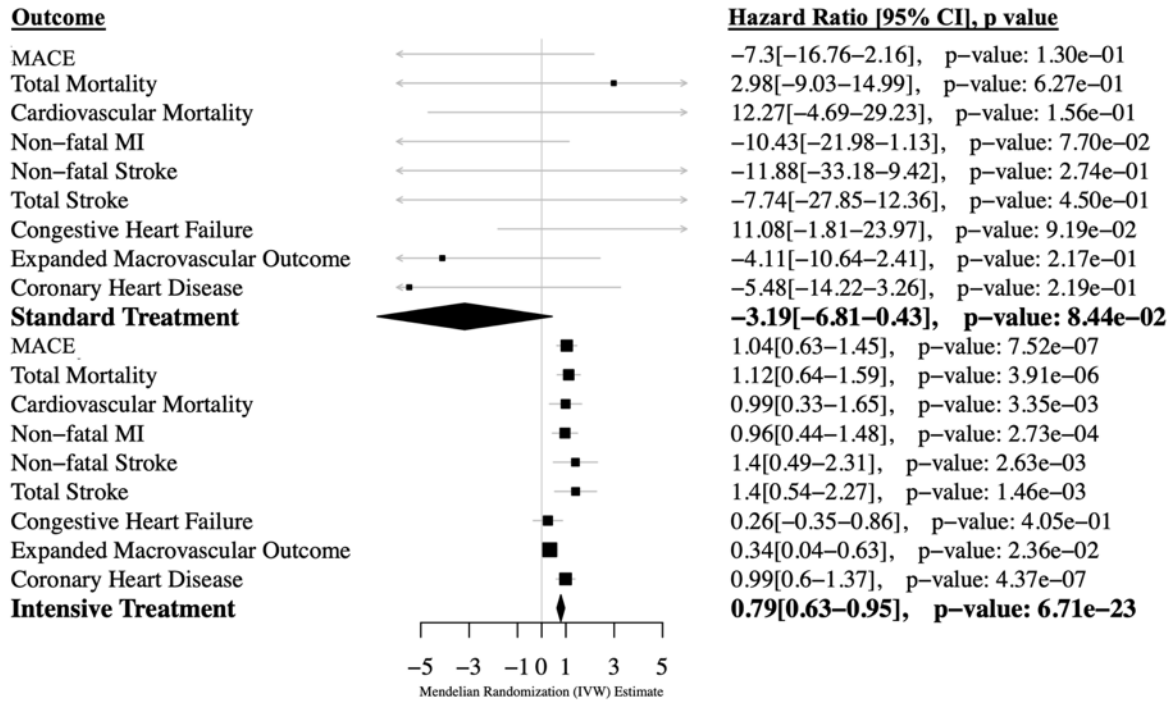

Figure S14. Forest plot showing causal inference of median HbA1c as the exposure variable on CVD risk with SCT-PS as the instrumental variable.

The direction of the IVW estimate is based on the slope of a line fit through the estimate of the SCT-PS association with median HbA1c (x) and the estimate of the SCT-PS associatin with the CVD outcome (y) and through the origin. For the intensive treatment, these estimates for both x and y above are located in the bottom left quadrant and fitting a line through that point and the origin results in a positive slope, and is reflected in the direction of the IVW estimate.

Effect of sample size adjustment on observed risk differences

There was some instablitity noted with smaller sample sizes (n=194 in each group) with the SCT-PS only model (Fig. S13); however, with n=389 in the intensive arm and 778 in the standard arm, 12 out of the 20 (60%) of the iterations were significant (P<.05). Once the sample sizes reached n=389 in the intensive arm and 1167 in the standard arm, 15 out of 20 (75%) were statistically significant (P<.05). Importantly, regardless of the sample sizes, all the effect sizes were consistently in the direction of a reduction in risk with intensive treatment, suggesting that the instances where there was a lack of statistical significance was due to a loss of power from the small sample sizes.

The results for the SCT-PS with clinical features (Fig. S16, were similar to those of the SCT-PS only (Fig. S15). However, the the SCT-PS with clinical variables model failed to reach statistical significance for nearly all iterations, suggesting that it has reduced power compared to the model with SCT-PS alone.

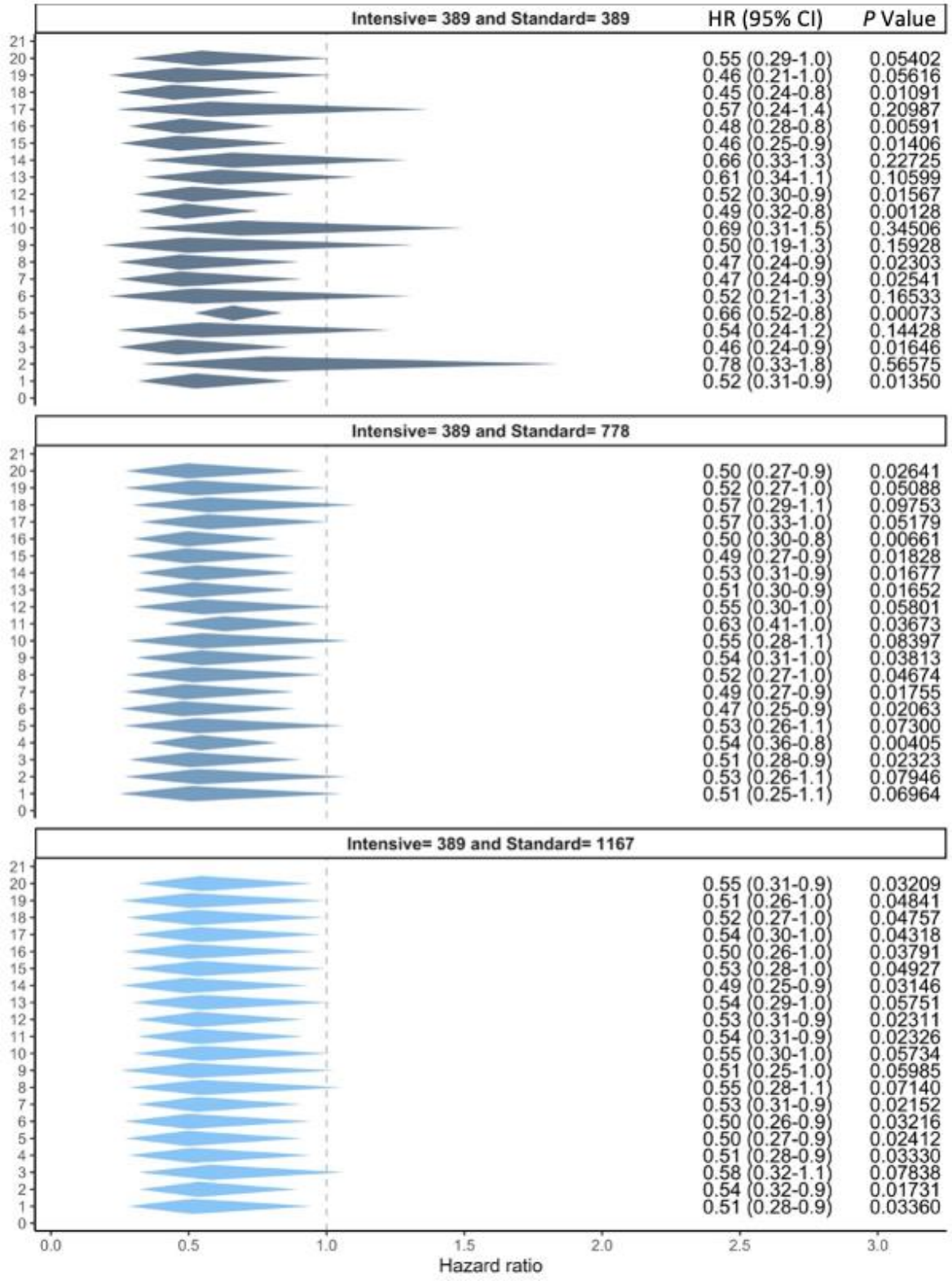

Figure S15. Meta-analyzed risk differences of the SCT-PS model only (no clinical features) between varied sample sizes for predicted intensive and standard groups.

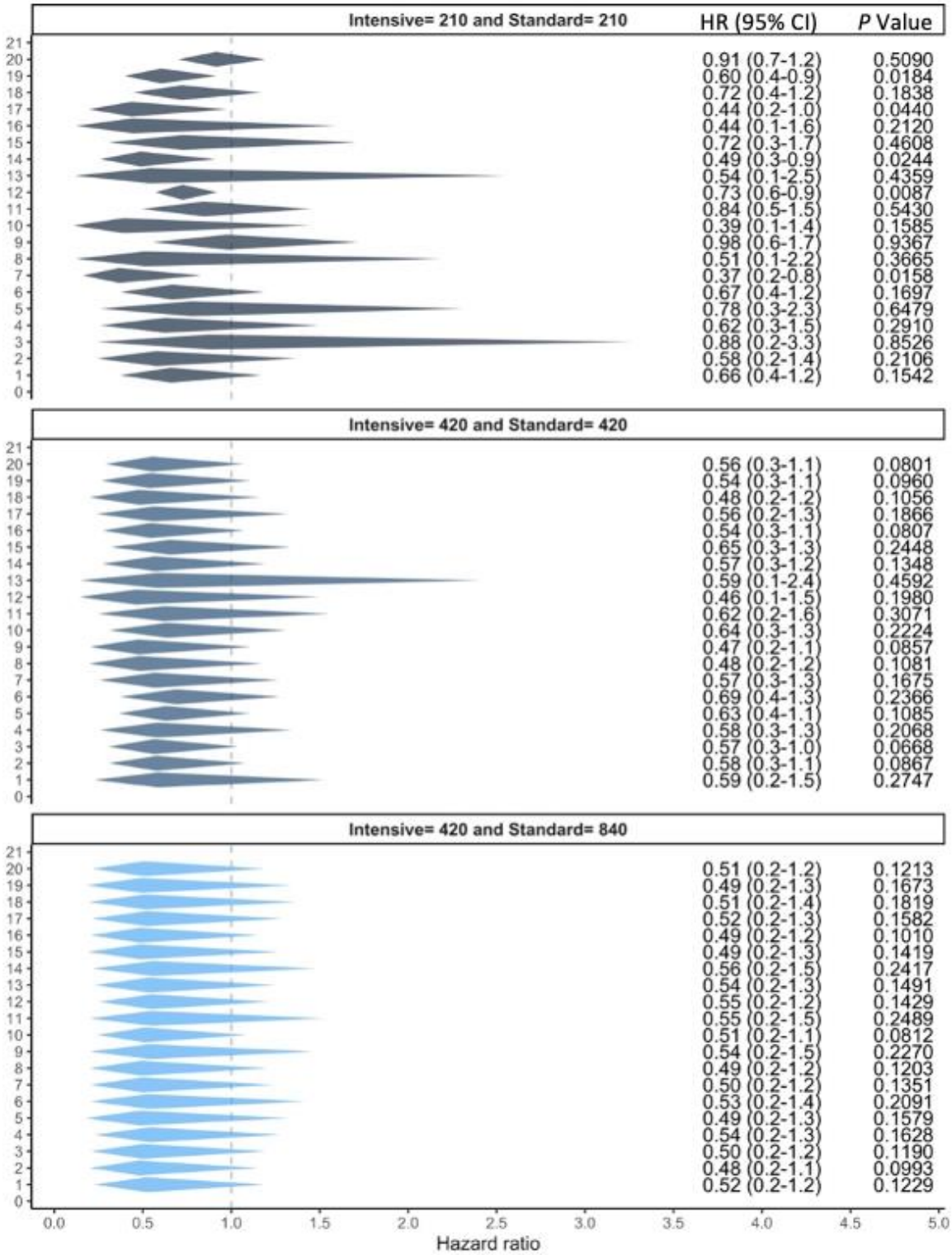

Figure S16. Meta-analyzed risk differences of the SCT-PS model with clinical features between varied sample sizes for predicted intensive and standard groups.

SCT-PS predicted **non-C4** CVD Risk for Intensive versus Standard Treatment

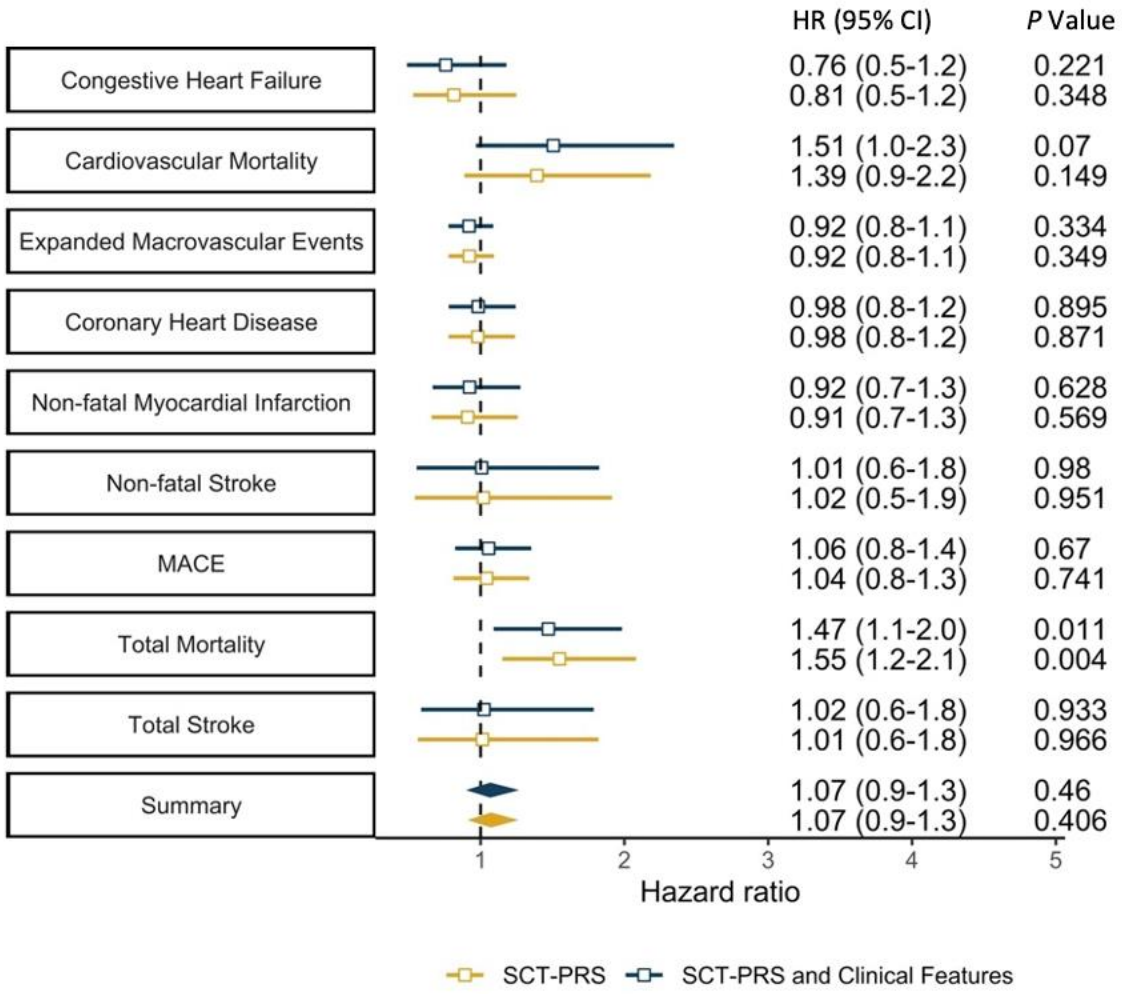

Figure S17. Meta-analyzed risk differences of intensive versus standard treatment of the SCT-PS model for individuals predicted to not be members of C4.

SCT-PS Stratification by Race

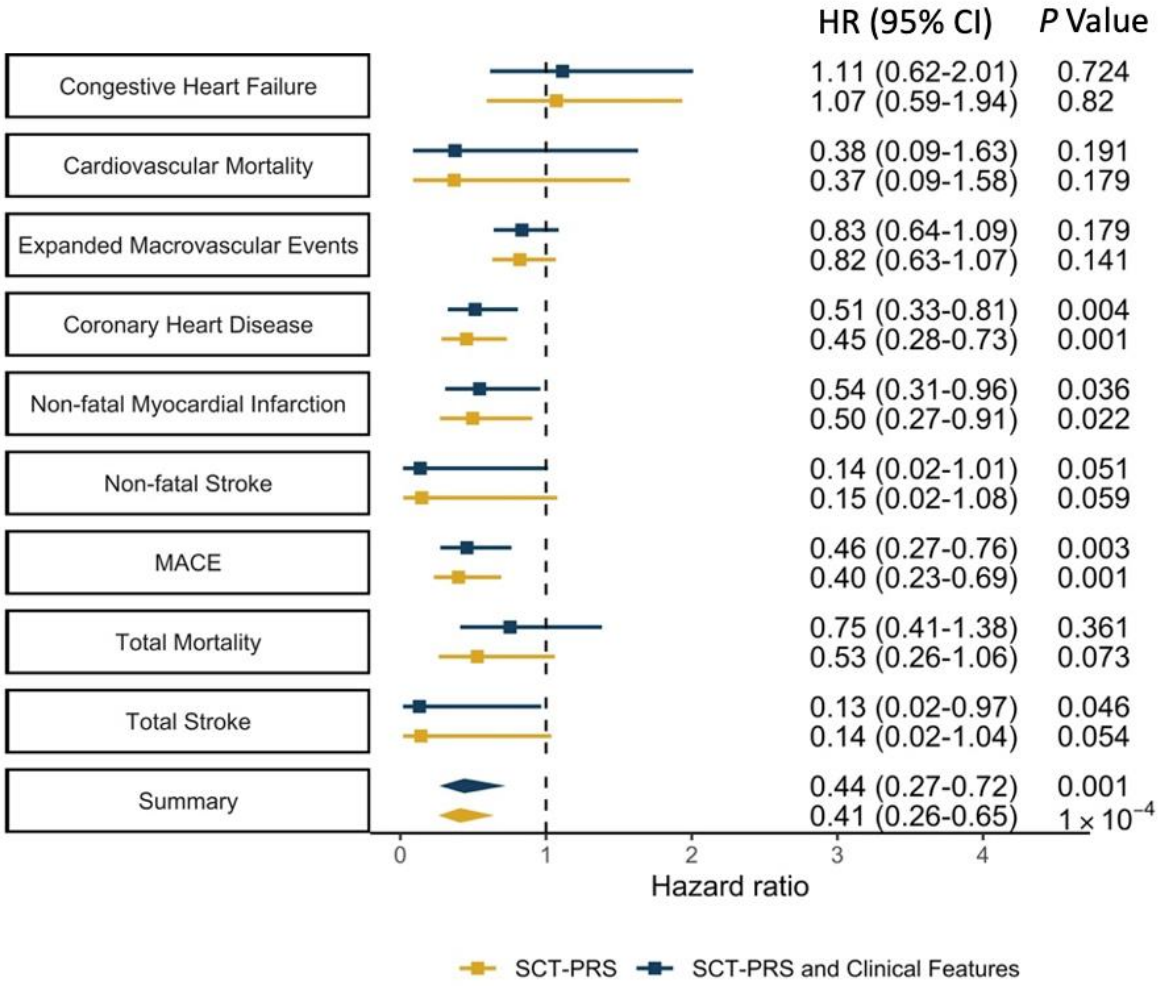

Figure S18. Forest plot of hazard ratios (HR) between of individuals that self-identified as White that were predicted to be in the C4 clinical group based on the SCT-PS that received intensive glycemia treatment compared to those that received standard treatment.

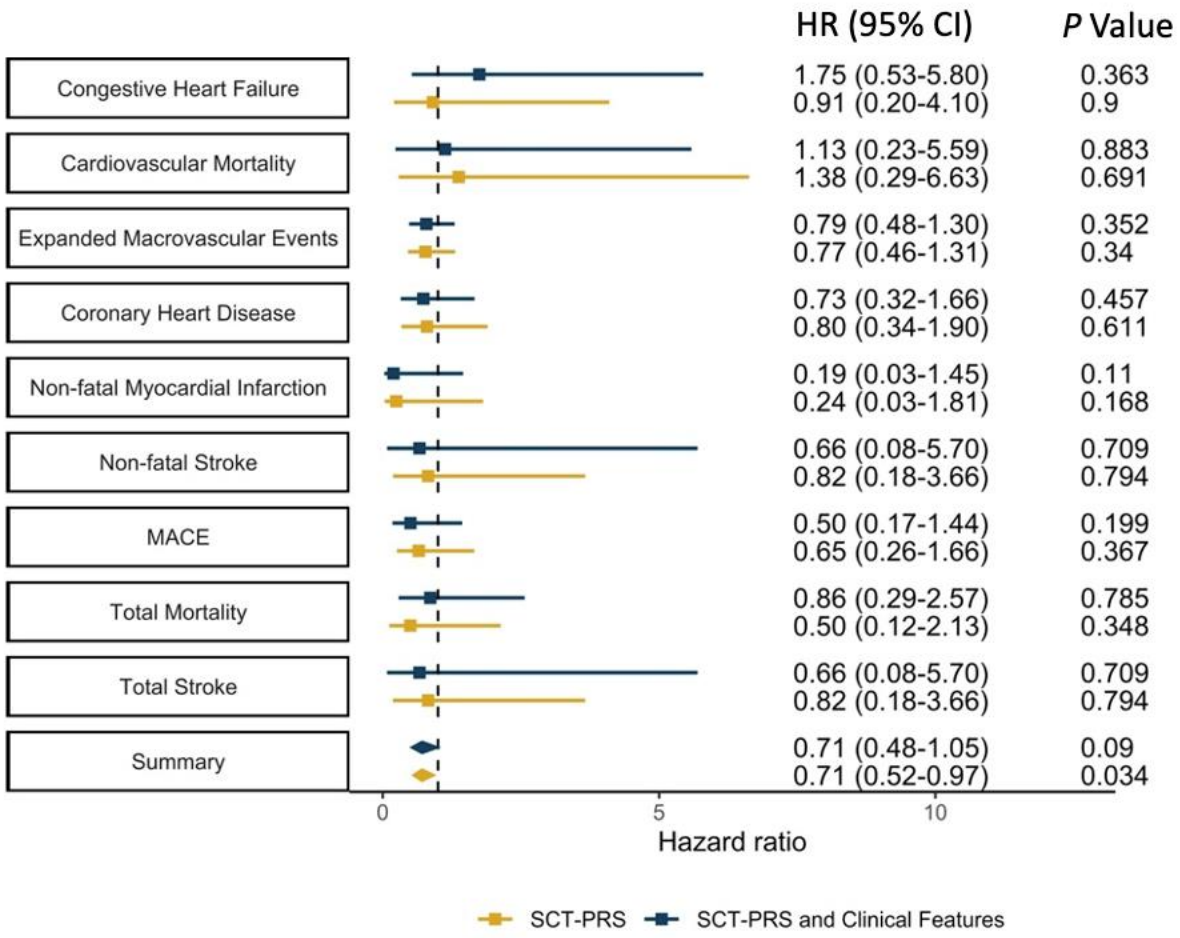

Figure S19. Forest plot of hazard ratios (HR) between of individuals that self-identified as non-White that were predicted to be in the C4 clinical group based on the SCT-PS that received intensive glycemia treatment compared to those that received standard treatment.

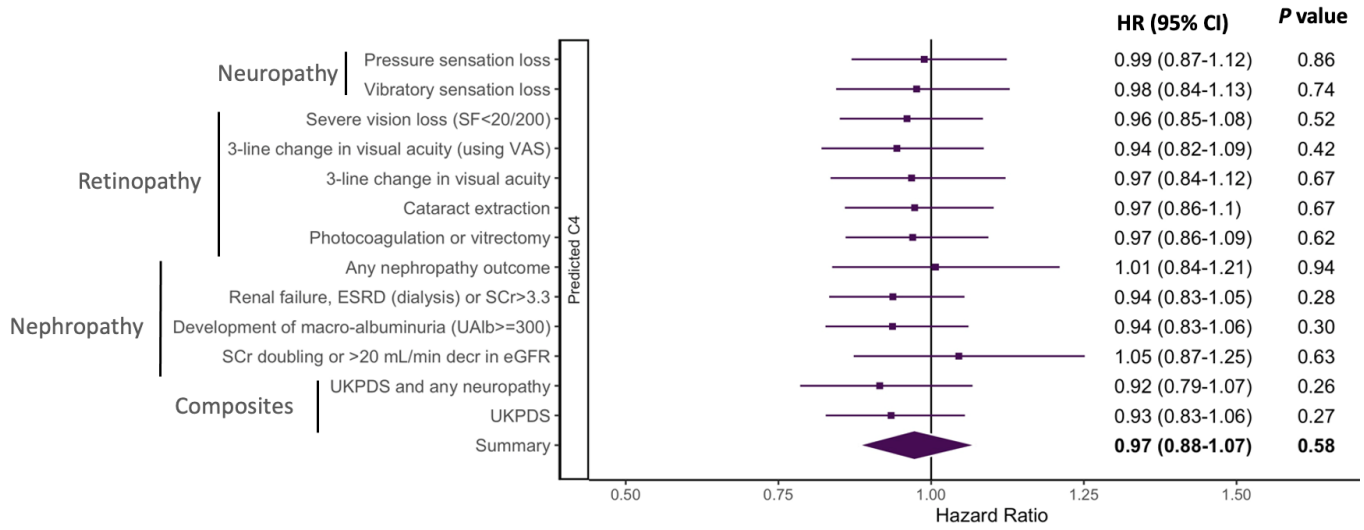

Figure S20. Forest plot of hazard ratios (HR) for microvascular events between predicted C4 in intensive arm and predicted C4 in standard arm.
SCT-PRS was applied to the witheld test set in intensive arm and the whole standard arm. Cox proportional hazards models ascertained risk of individuals outcomes in predicted C4 in intensive arm compared to predicted C4 in standard arm. Summary of risk was calculated using R metafor package while accounting for covariances of outcomes. In the plot, SF, VAS, ESRD, SCr, UAlb, eGFR and UKPDs are abbreviations for Snellen fraction, visual acuity scale, end-stage renal disease, serum creatinine, urine albumin, estimate glomerular filtration rate and UKPDS composite (i.e. retinopathy requiring photocoagulation, vitreous hemorrhage and renal failure), respectively.

Direct Prediction of CVD Outcomes
In order to compare the efficacy of predicting cluster membership as a proxy for risk of an adverse outcome compared to predicting CVD outcomes directly, SCT-PS model with baseline clinical variables and a GLM of only baseline clinical values were assessed to determine if they could be trained to predict MACE and total mortality. The testing accuracy metrics for each model are presented in Table S14.

For MACE, GLMs with only clinical variables displayed similar balanced accuracies to the SCT-PS with clinical variables of 66% and 69%, respectively. The sensitivity and specificity for the SCT-PS and clinical variables was 67% and 70%, respectively, compared to 52% and 79% for the GLM.

For total mortality prediction, GLMs with only clinical variables had a balanced accuracy of 67% compared to 71% for the SCT-PS with clinical variables. The sensitivity and specificity for the SCT-PS and clinical variables was 80% and 61%, respectively, compared to 64% and 71% for the GLM. Overall, although the SCT-PS did reasonably well predicting MACE and total mortality, the predictions for C4 substantially outperformed this suggesting that predicting cluster membership may be more feasible than predicting outcomes directly.

Table S14. Model accuracy for directly predicting MACE and total mortality outcomes.

Outcome	Model	Sensitivity	Specificity	Balanced Accuracy	AUC
MACE	GLM Clinical Variables Only	0.52	0.79	0.66	0.70
	Clinical Variables + SCT-PS	0.67	0.70	0.69	0.73
Total mortality	GLM Clinical Variables Only	0.64	0.71	0.67	0.72
	Clinical Variables + SCT-PS	0.80	0.61	0.71	0.77

Comparison to 2-SNP Genetic Risk Score (GRS) from Shah et al.

The Shah et al. paper focused on White individuales only. Interstingly, in White individuals predicted to benefit using the SCT-PS, SCT-PS with clinical variables, and the 2-SNP GRS there was a significant reduction in risk with intensive glycemia treatment for all models (Fig. S21). The SCT-PS with clinical features had the smallest *P* value across all CVD outcomes [HR=0.37 (0.25-0.56), $P=1.36\text{x}10^{-6}$], followed closely by the SCT-PS only [HR=0.38 (0.26-0.57), $P=2.31\text{x}10^{-6}$] and the 2-SNP GRS displayed an overall reduction [HR=0.61 (0.46-0.79), $P=2.84\text{x}10^{-4}$]. The 95% confidence intervals overlapped across all individual outcomes and meta-analyzed outcomes, indicating that the results were not significantly different from each other at the $P<.05$ level. However, in this analysis, both SCT-PS with and without clinical variables reached statistically significant reduction in risks ($P<.05$) for expanded macrovascular events, non-fatal MI, non-fatal stroke, total, stroke, and total mortality, where the 2-SNP GRS, which was specifically developed for cardiovascular mortality in White subjects, failed to reach significance for these outcomes. In White subjects, both the 2-SNP GRS and SCT-PS with clinical features resulted in a significant reduction in cardiovascular disease mortality, whereas the SCT-PS only model failed to reach significance ($P=.059$). All models resulted in significant reductions of coronary heart disease and MACE in White subjects.

Upon expanding this analysis to all individuals, regardless of race (Fig. S22), we saw a significant improvement of the SCT-PS models over the 2-SNP based on the 95% CI. The SCT-PS with clinical features performed the best on overall risk [HR=0.41 (0.29-0.56), $P=6.54\text{x}10^{-8}$], followed by SCT-PS only [HR=0.46 (0.33-0.64), $P=1.36\text{x}10^{-6}$], and the 2-SNP GRS [HR=0.73 (0.64-0.84), $P=7.26\text{x}10^{-6}$]. Across individual outcome risks, confidence intervals overlapped; however, significant reductions in risk using the SCT-PS were observed for patients that received intensive glycemica treatment of CVD mortality, expanded macrovascular events, non-fatal stroke, total stroke, and total mortality, where the 2-SNP GRS failed to reach significance ($P<.05$) (Fig. S22). All models resulted in a displayed significant reductions in risk for patients receiving intensive glycemia treatment for coronary heart disease, non-fatal MI, and MACE ($P<.05$).

Overall, there appears to be some overlapping potential utility between both of these predictive models, given that they both identified groups that significantly benefitted from intensive glycemia treatment ($P<.05$) (Fig. S21-S22). However, the SCT-PS appears to have more statistical power, especially for outcomes other than cardiovascular mortality and in diverse populations, as demonstrated by the statistically significant reductions in individual CVD outcomes and the SCT-PS approaches outperformed across all CVD outcomes combined when applied to a racially diverse population.

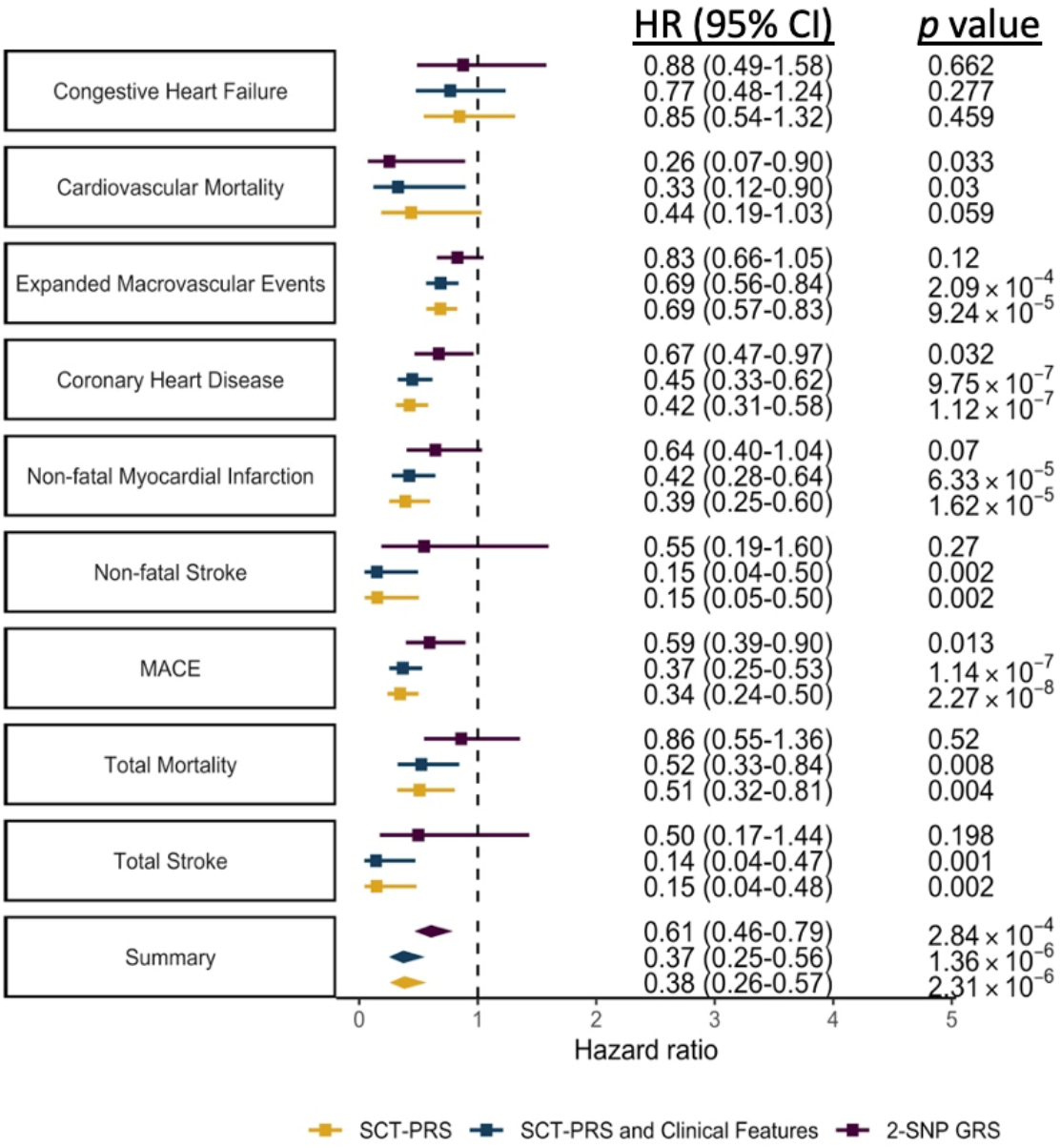

Figure S21. Forest plot of hazard ratios (HR) between of individuals that self-identified as White that were predicted to be in the C4 clinical group based on the SCT-PS that received intensive glycemia treatment compared to those that received standard treatment and those with a 2-SNP GRS of 0, based on Shah et al.

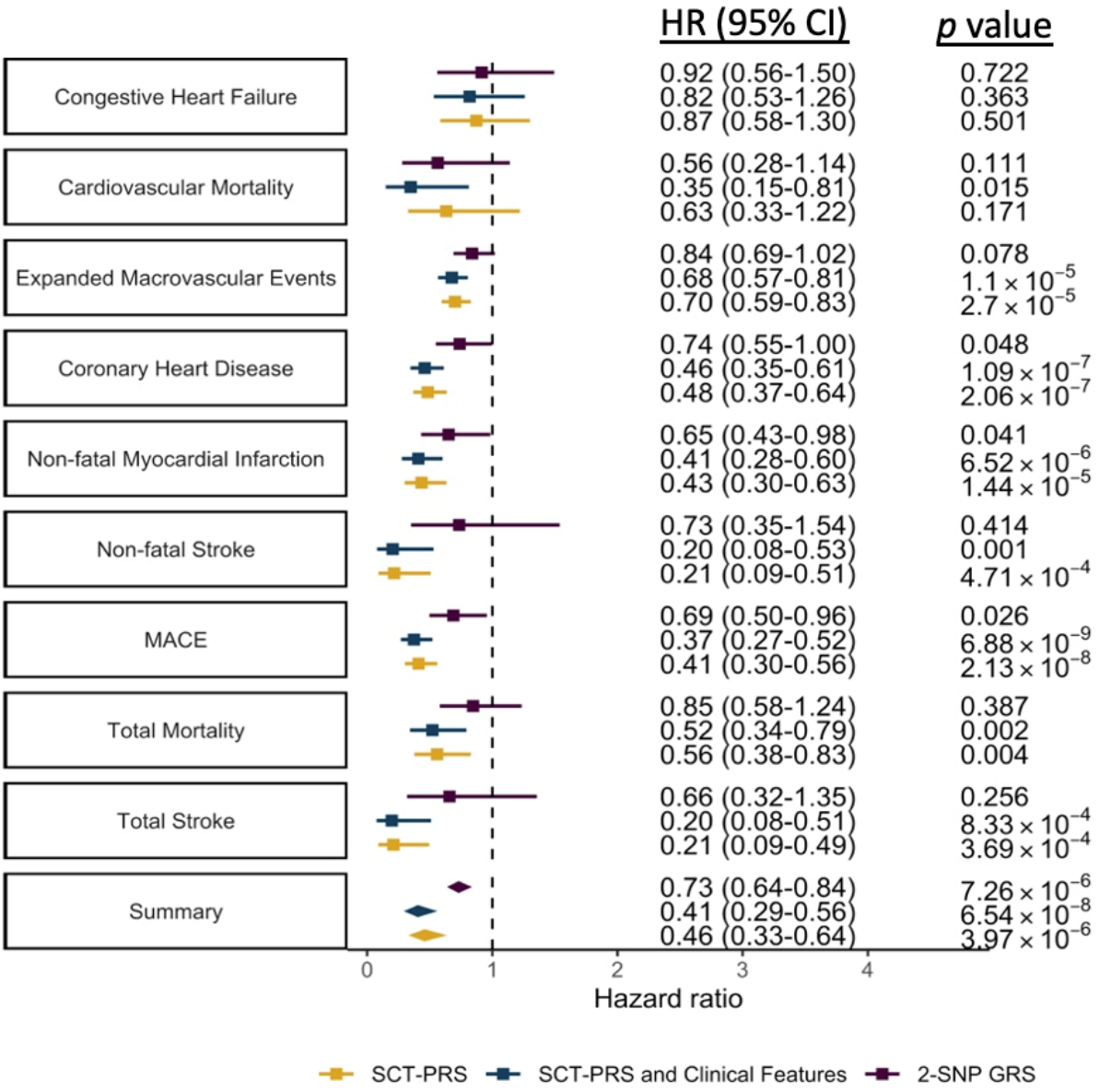

Figure S22. Forest plot of hazard ratios (HR) between of individuals across all races that were predicted to be in the C4 clinical group based on the SCT-PS that received intensive glycemia treatment compared to those that received standard treatment and those with a 2-SNP GRS of 0, based on Shah et al.

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