Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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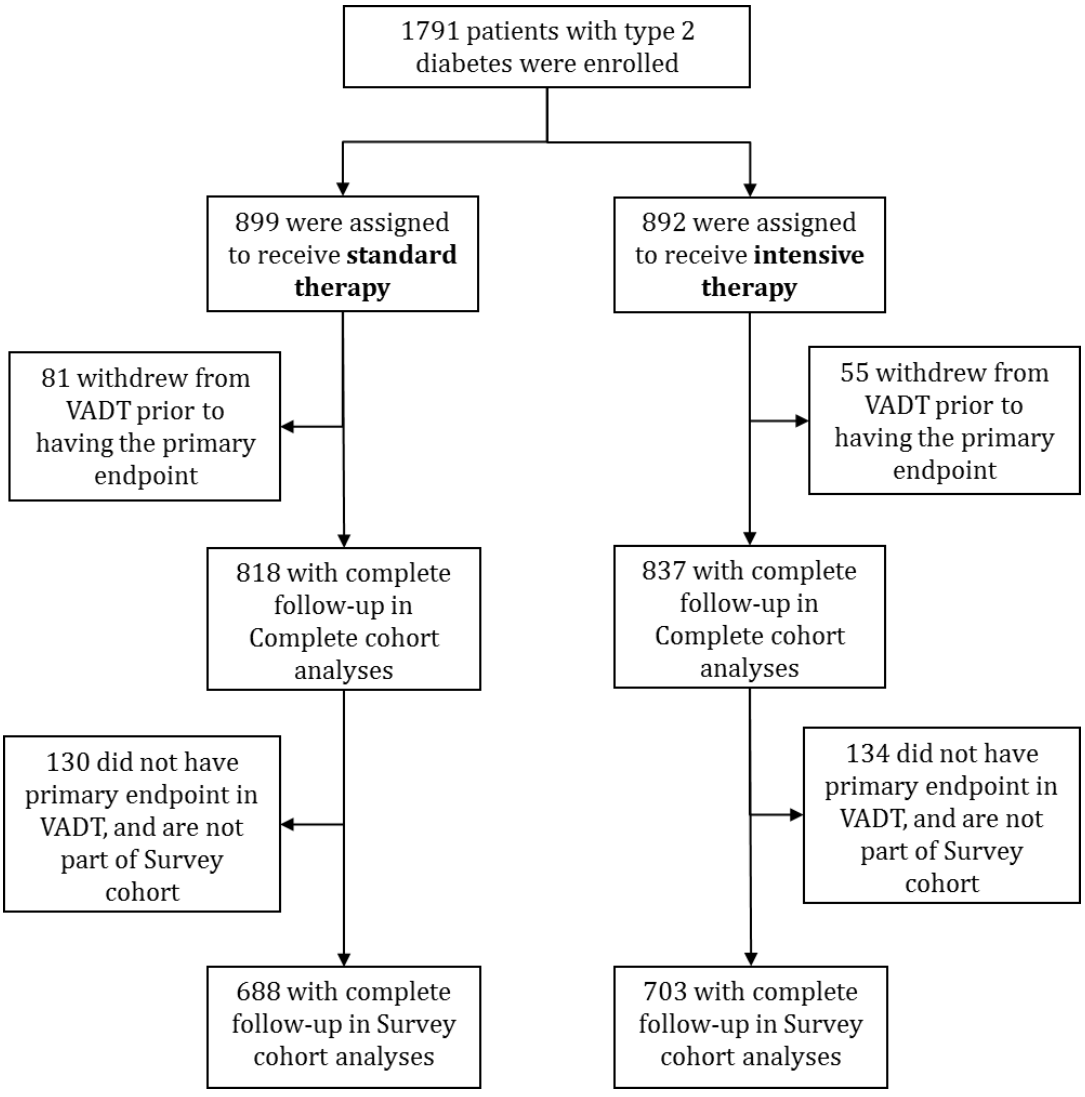
* Participants who left the VADT before its conclusion.

A. Details of Participant Study Flow and Description of Complete Cohort Follow-up

As not all VA Diabetes Trial (VADT) participants were given an opportunity to consent to continued active follow-up, the Ann Arbor VA Health Systems site sought and was granted approval to conduct an analysis of long-term outcomes using registry data for all VADT subjects.[1] The executive committee opted to exclude hard withdrawals from these analyses (those who informed the research team that they no longer wanted to be in the study). Thus, all participants who were alive and enrolled at the conclusion of the VADT (whether or not they participated in further yearly surveys) were followed through a national data registry from VA and CMS (Fig. S1). This larger cohort was called the Complete cohort (described in reference[1]). Some of these patients also provided written informed consent for additional data collection, including yearly surveys and chart reviews; referred to as the Survey cohort. These surveys were used to assess outcomes that were not easily obtained from the data registries, including reports of major cardiovascular events during the prior year, and they were asked to respond to quality of life questions.

The number of patients included in the analyses presented in this paper differs slightly from the number of consented patients described on the ClincialTrials.gov website. The number of patients who consented to participate in follow-up surveys is listed as N=1044 on the website. However, that number includes some patients who withdrew from the original trial and then subsequently consented to participate and receive surveys as part of the follow-up study. The IRB approval in Ann Arbor did not allow us to include data for these patients and thus they were excluded from the analyses presented here. In addition, results of analyses conducted at the Hines center and reported to ClinicalTrials.gov may differ slightly due to different censoring dates. Ann Arbor had approval to use data for patients during the follow-up period, whereas Hines censored some patients when the IRB oversight transitioned from local sites to the Hines IRB.

<u>Figure S1.</u> VADT Enrollment and Follow-up and Follow-up for Primary Outcome. Complete follow-up refers to subjects followed either until an outcome occurred or end of scheduled data collection. Complete and Survey Cohorts were previously described in detail[1] and are characterized within in Supplemental Methods, Section A. This figure was originally published in Hayward RA et al. , follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes.[1]



B. Additional Details on Endpoint Definitions

Events that occurred during the original VADT study period were coded during patient clinic visits and were previously reported in Duckworth et al.[2] We obtained information on diagnoses, procedures, surgeries, and hospitalizations during the follow-up study period from the VA Medical SAS Data Sets, VA/CMS Medicare claims data and the National Death Index (maintained by the CDC), as well as self-report of events in the yearly survey. We obtained information on lab data from the VA Decision Support System.

For patients who were not in the Survey cohort and had not had an event during the original VADT study period, we estimated that we miss only 6% of primary outcomes from the registry data. This estimate is based on the percent of total primary outcomes captured by CMS or NDI and the number of years for which these data sources were not available during our follow-up period.

Table S1. Endpoint Definitions and Coding for Follow-up

Outcome	Data Source	Follow-up	Coding Information
Major CVD Event			
Non-fatal heart attack	Hospital primary discharge diagnosis*		≥1 Inpatient occurrence
	- VA national inpatient registry	15.0 years	
	- CMS national inpatient registry and	13.6 years	
	VA plus adjudication <65 (Survey cohort only)	15.0 years	
Non-fatal stroke	Hospital primary discharge diagnosis*		≥1 Inpatient occurrence
	- VA national inpatient registry	15.0 years	
	- CMS national inpatient registry and	13.6 years	
	VA plus adjudication <65 (Survey cohort only)	15.0 years	
New CHF	Hospital primary discharge diagnosis*		≥1 Inpatient occurrence
	- VA national inpatient registry	15.0 years	for primary discharge or
	- CMS national inpatient registry, or	13.6 years	ejection fraction <40%
	EF < 40% in VA inpatient registry	15.0 years	
Amputation for ischemic diabetic gangrene	If amputation reported on annual survey, charts were obtained and outcome underwent blinded adjudication	15.0 years	≥1 Inpatient or outpatient occurrence
CV death	National Death index (NDI)	13.6 years	Primary cause of death
Secondary Outcomes			
Any Major Diabetes Outcome			
• Primary Outcome	See above	See above	See above
• Non-ischemic amputations	If amputation reported on annual survey, charts were obtained and outcome underwent blinded adjudication	15.0 years	≥1 Inpatient or outpatient occurrence
• ESRD	eGFR < 15	15.0 years	Based on MDRD equation
	- Collected during the original study period		using serum creatinine
	- VA national lab database during VADT-F		
	Dialysis during VADT-F		≥2 Outpatient
	- VA national outpatient registry	15.0 years	occurrences within 1
	- CMS national outpatient registry	13.6 years	year
	Kidney Transplant during VADT-F		≥1 Inpatient or
	- VA national registry	15.0 years	outpatient occurrence
	- CMS national registry	13.6 years	
CVD Death	NDI	13.6 years	Primary cause of death

All-cause Death	VA Vitals Status File	15.0 years	N/A
Hospitalizations	VA national inpatient registry	15.0 years	≥1 Inpatient occurrence
	CMS national inpatient registry	13.6 years	

VADT-F: VA Diabetes Trial Follow-up Study

C. Chart Adjudication

If a participant reported having a heart attack or stroke or amputation in the past year on the survey, they were asked whether they received care for the event within VA or from an outside provider. For subjects under age 65 (for whom CMS data is not available), those reporting an event outside of the VA were asked for written consent to allow review of their hospital records. Medical records were successfully received and reviewed for 15 of 18 (83%) of these reports. In addition, all amputations were reviewed and classified as ischemic gangrene (a macrovascular event) or infection gangrene (a microvascular event).

All medical records meeting the above criteria were reviewed by a physician (RAH) who was blinded to treatment assignment, and a synopsis of the event was created. A blinded 3-person adjudication committee, consisting of two hospitalists and one cardiologist, reviewed this information and either requested more information or classified the event as: an acute heart attack, an acute stroke, new CHF, amputation for ischemic or non-ischemic gangrene, or no study event occurred. Unanimity was achieved in all adjudications.

D. Additional Details on Baseline Participant Characteristics and Medication Use and Risk Factors During the VADT and VADT-F Study Phases

Baseline characteristics for the Complete and Survey cohorts by treatment group are shown in Table S2. There were no differences between treatment groups in either the Complete or Survey cohorts. As noted above, the Complete cohort included all participants who were alive and enrolled at the conclusion of the VADT and had not specifically requested to withdraw from all additional follow-up.

Medication use at the end of the original VADT, the interim analysis, and the final analysis are shown in Table S3. We also provide yearly rates of statin use and hypertension medication use in Tables S4 and S5. We defined medication use as a prescription fill for the medication in the measurement year.

The thiazolidinedione class of medications included Avandia, Pioglitazone, and Rosiglitazone. Oral Sulfonylureas included Amaryl, Glimepiride, Glipizide, Glyburide, Tolazamide. Statins included Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin. Ace/Arbs include Benazepril, Captopril, Enalapril, Fosinopril, Irbesartan, Lisinopril, Losartan, Ramipril, Valsartan. Any HTN Medication included Ace/Arbs, Amiloride, Amlodipine, Atenolol, Bumetanide, Carvedilol, Chlorothiazide, Chlorthalidone, Clonidine, Diltiazem, Doxazosin, Felodipine, Furosemide, Hydralazine, Indapamide, Labetalol, Metolazone, Metoprolol, Minoxidil, Nadolol, Nifedipine, Prazosin, Propranolol, Sotalol, Spironolactone, Tamsulosin, Terazosin, Torsemide, Verapamil.

Table S2. Baseline Characteristics of VADT Complete and Survey Cohorts

Variable	Baseline for Complete Cohort (n=1655)†		Baseline for Survey Cohort (n=1391)†	
	Standard Control (n=818)	Intensive Control (n=837)	Standard Control (n=688)	Intensive Control (n=703)
Age, *in years*	60.5±8.6	60.5±8.8	61.1±8.6	61.1±8.8
Sex*, number (percent).*				
Male	794 (97.1)	814 (97.3)	672 (97.7)	681 (96.9)
Female	24 (2.9)	23 (2.8)	16 (2.3)	22 (3.1)
Years since diagnosis of diabetes	11.5±7.2	11.6±7.9	11.6±7.2	12.0±8.2
Patients with previous cardiovascular event	338 (41.3)	335 (40.0)	297 (43.2)	298 (42.4)
Patients with hypertension*, no.*	593 (72.7)	604 (72.3)	510 (74.2)	504 (71.8)
Race or ethnic group*, no.*				
non-Hispanic white	517 (63.2)	507 (60.6)	446 (64.8)	440 (62.6)
Hispanic white	121 (14.8)	144 (17.2)	100 (14.5)	122 (17.4)
Black	141 (17.2)	141 (16.9)	112 (16.3)	108 (15.4)
Other	39 (4.8)	45 (5.4)	30 (4.4)	33 (4.7)
Tobacco smoking status*, no.*				
Total patients	816 (100)	837 (100)	686 (100)	703 (100)
Current	126 (15.4)	144 (17.2)	100 (14.6)	110 (15.7)
Past	465 (57.0)	468 (55.9)	394 (57.4)	397 (56.5)
Never	225 (27.6)	225 (26.9)	192 (28.0)	196 (27.9)
Weight, *in pounds*	214±36	214±36	214±36	215±35
Body Mass Index	31.1±4.4	31.3±4.4	31.1±4.4	31.3±4.3
Blood pressure, *in mm Hg*				
Systolic	132±17	132±17	132±17	132±16
Diastolic	76±10	76±10	76±10	76±10
Hemoglobin A1c*, %*	9.5±1.6	9.4±1.5	9.4±1.6	9.4±1.4
Cholesterol, *in mg/dl*				
Total	184±54	182±40	183±47	181±40
LDL-C	108±34	107±31	107±33	106±30
HDL-C	36±11	36±10	35±10	36±10
Triglycerides, *mg/dl*	223±365	200±160	219±262	202±158
Median	158	161	160	163
(IQR)	(110-250)	(114 – 230)	(111-260)	(116 – 236)
Estimated GFR‡	82±21	82±23	81±21	81±23
Creatinine, *mg/dl*	1.01±0.22	1.01±0.22	1.02±0.22	1.01±0.22
Ratio of Alb to Creatinine, *mg/gm*	111±346	115±330	121±374	117±331
Estimated 10-y CV risk‡	0.37±0.21	0.36±0.20	0.38±0.21	0.37±0.20

Data are means ± SD, numbers (%) or median (IQR). Data were partially published previously.[1,2]

†Baseline values prior to randomization. The Complete cohort included all participants who were alive and enrolled at the conclusion of the VADT and had not specifically requested to withdraw from all additional follow-up, whereas the Survey cohort reflected the subset who also agreed to further yearly follow-up with

surveys. The n's are for participants who have completed follow-up in the analyses (i.e., followed until the end of May 2017, or had the primary event or died during active follow-up).

‡Estimated GFR is calculated using the Modification of Diet in Renal Disease (MDRD) Study equation. Estimated 10-year cardiovascular (CV) risk is calculated using the UKPDS Risk Engine. Weight = kg x 0.453592; HbA1c (mmol/mol)=10.93(HbA1c %)-23.50); Cholesterol(mmol/L)=x0.02586; Creatinine mmol/L)=x88.4; Triglycerides(mmol/L)=x0.01129.

Table S3. Medication Use at the End of the VADT, and at the Middle and

End of the VADT-F

	End of VADT (2007) N=1519			End of Interim Analysis (2011) N=953			End of Follow-up Study (2017) N=679		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
Insulin									
Standard treatment	503/761	66.1	(62.6, 69.5)	360/469	76.8	(72.7, 80.5)	246/330	74.5	(69.5, 79.2)
Intensive treatment	593/758	78.2	(75.1, 81.1)	385/484	79.5	(75.7, 83.0)	245/349	70.2	(65.1, 74.9)
Metformin									
Standard treatment	369/761	48.5	(44.9, 52.1)	229/469	48.8	(44.2, 53.4)	126/330	38.2	(32.9, 43.7)
Intensive treatment	381/758	50.3	(46.6, 53.9)	235/484	48.6	(44.0, 53.1)	141/349	40.4	(35.2, 45.8)
Thiazolidinediones									
Standard treatment	294/761	38.6	(35.2, 42.2)	28/469	6.0	(4.0, 8.5)	6/330	1.8	(0.7, 3.9)
Intensive treatment	335/758	44.2	(40.6, 47.8)	59/484	12.2	(9.4, 15.4)	8/349	2.3	(1.0, 4.5)
Oral Sulfonylureas									
Standard treatment	312/761	41.0	(37.5, 44.6)	127/469	27.1	(23.1, 31.3)	39/330	11.8	(8.5, 15.8)
Intensive treatment	372/758	49.1	(45.5, 52.7)	116/484	24.0	(20.2, 28.0)	49/349	14.0	(10.6, 18.1)
Acarbose									
Standard treatment	12/761	1.6	(0.8, 2.7)	10/469	2.1	(1.0, 3.9)	6/330	1.8	(0.7, 3.9)
Intensive treatment	64/758	8.4	(6.6, 10.6)	25/484	5.2	(3.4, 7.5)	6/349	1.7	(0.6, 3.7)
Statins									
Standard treatment	629/761	82.7	(79.8, 85.3)	347/469	74.0	(69.8, 77.9)	205/330	62.1	(56.6, 67.4)
Intensive treatment	650/758	85.8	(83.1, 88.2)	381/484	78.7	(74.8, 82.3)	216/349	61.9	(56.6, 67.0)
ACE/ARB									
Standard treatment	640/761	84.1	(81.3, 86.6)	346/469	73.8	(69.5, 77.7)	181/330	54.8	(49.3, 60.3)
Intensive treatment	639/758	84.3	(81.5, 86.8)	350/484	72.3	(68.1, 76.3)	181/349	51.9	(46.5, 57.2)
Any HTN Med									
Standard treatment	699/761	91.9	(89.7, 93.7)	382/469	81.4	(77.6, 84.9)	252/330	76.4	(71.4, 80.8)
Intensive treatment	697/758	92.0	(89.8, 93.8)	414/484	85.5	(82.1, 88.5)	254/349	72.8	(67.8, 77.4)

Note. Medication use is defined as a prescription fill in the measurement year. The number of participants listed includes all patients still alive and enrolled in the study during the time of interest.

ACE inhibitors and angiotensin receptor blockers (ACE/ARB) were also included within any hypertension (HTN) medication.

Table S4. Rate of Statin Use by Year

Year	N*	Total Rate	Standard Treatment	Intensive Treatment
2000	60	63.3	57.6	70.4
2001	812	69.1	68.4	69.8
2002	1502	76.6	76.0	77.3
2003	1720	80.5	79.2	81.8
2004	1664	84.4	84.7	84.0
2005	1617	84.1	83.7	84.5
2006	1560	83.1	82.6	83.7
2007	1519	84.2	82.7	85.8
2008	1033	87.2	85.3	89.0
2009	1022	83.9	82.5	85.1
2010	993	81.9	80.2	83.5
2011	953	76.4	74.0	78.7
2012	922	71.8	70.2	73.3
2013	866	70.7	69.3	71.9
2014	826	71.2	71.2	71.2
2015	774	69.8	67.6	71.8
2016	717	68.5	68.4	68.6
2017	679	62.0	62.1	61.9

*N is the total number of patients eligible to be included in the denominator each year; includes patients still enrolled and alive. The rate of statin use was similar between the standard and intensive treatment groups.

Table S5. Rate of Hypertension Medication Use by Year

		Any HTN Meds			ACE/ARBs		
Year	N	Overall Rate	Standard Treatment	Intensive Treatment	Overall Rate	Standard Treatment	Intensive Treatment
2000	60	83.3	81.8	85.2	71.7	66.7	77.8
2001	812	87.2	86.0	88.4	77.8	77.7	78.0
2002	1502	88.1	87.8	88.5	81.0	80.7	81.3
2003	1720	91.0	91.2	90.8	84.0	84.2	83.7
2004	1664	92.4	92.8	92.0	84.6	85.4	83.8
2005	1617	92.7	92.1	93.3	85.0	84.6	85.5
2006	1560	93.1	93.2	93.1	86.1	86.1	86.1
2007	1519	91.9	91.9	92.0	84.2	84.1	84.3
2008	1033	94.9	93.5	96.2	88.6	87.3	89.8
2009	1022	91.8	89.8	93.7	83.7	82.3	84.9
2010	993	90.1	89.3	90.9	81.5	81.6	81.3
2011	953	83.5	81.4	85.5	73.0	73.8	72.3
2012	922	80.0	78.7	81.4	69.1	70.4	67.8
2013	866	78.9	78.5	79.2	65.7	66.5	64.9
2014	826	79.3	78.1	80.5	65.1	64.0	66.2
2015	774	79.2	78.7	79.7	64.2	63.9	64.5
2016	717	78.7	79.6	77.8	61.2	61.8	60.7
2017	679	74.5	76.4	72.8	53.3	54.8	51.9

*N is the total number of patients eligible to be included in the denominator each year; includes patients still enrolled and alive. The rates of hypertension medication use and ACE/ARB use was similar for the standard and intensive treatment groups.

Figure S2A-F. Risk Factor Measures During the Study Period in the Intensive and Standard Treatment Groups by Year

Changes in median BMI, blood pressure, lipids, by year since the start of the study, starting at year 3 (a point at which all subjects had been enrolled and on protocol for at least 3 months). The BMI averaged 1.3 kg/m^2 (95% CI 1.09, 1.52) higher in the Intensive Treatment Arm, compared to the Standard arm). The error bars (slightly offset for better visibility) represent interquartile ranges. The vertical line represents end of the VADT and beginning of the follow-up study period. Triglyceride values collected during the observational follow-up period (electronic record capture) may include some nonfasting values from both treatment groups. Numbers at risk by year for each risk factor are shown in Table S6. HDL and non-HDL Cholesterol(mmol/L) = x 0.02586; Triglycerides(mmol/L) = x 0.01129.

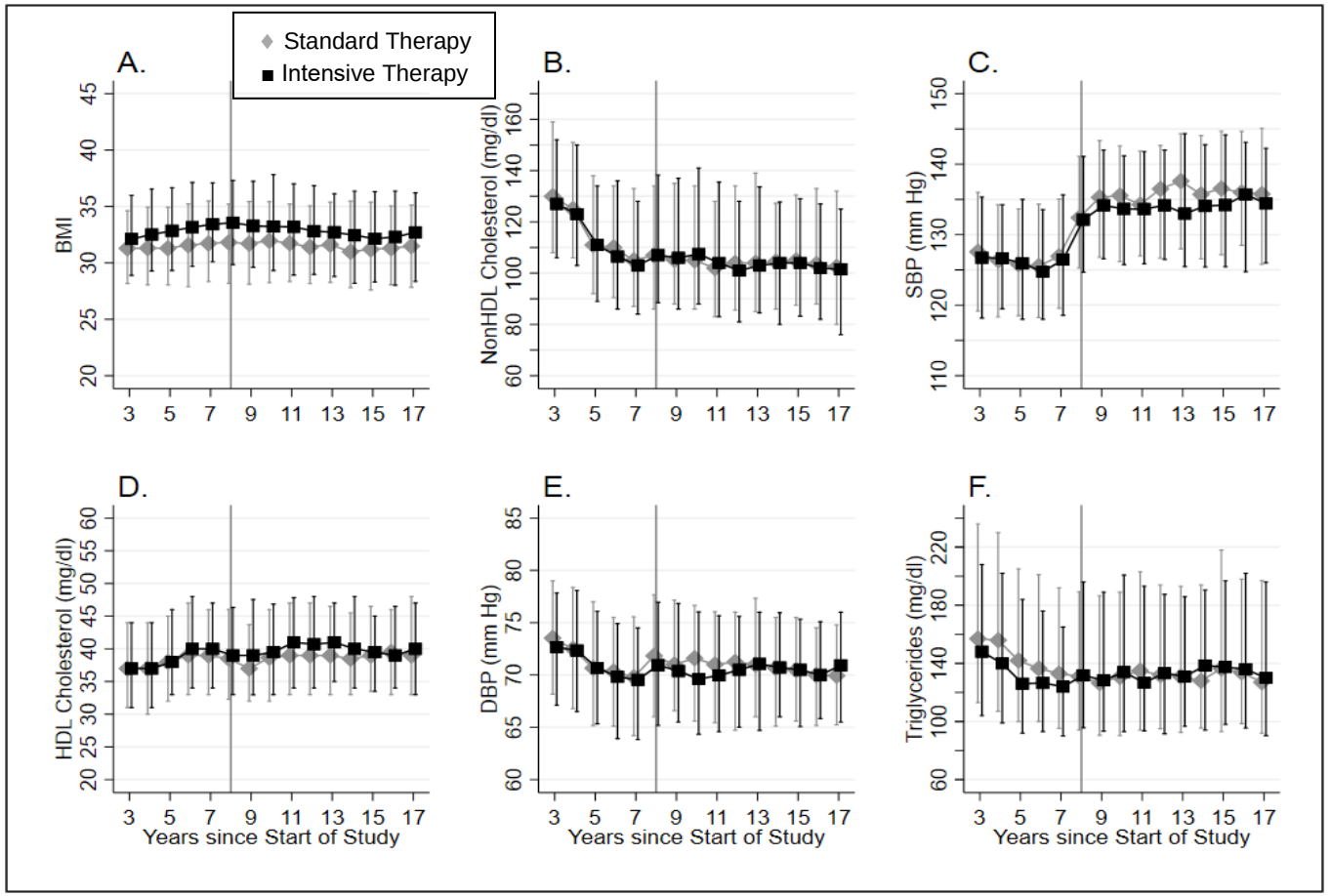


Table S6. Number of Participants Included (in Fig. S2) for each Risk Factor by Study Year

	Years since Start of Study														
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
HbA1c	1,664	1,589	1,512	1,437	1,384	1,329	880	922	815	762	714	630	589	537	412
BP	1,664	1,589	1,514	1,441	1,410	1,360	982	948	848	791	734	644	608	559	478
Lipids	1,500	1,446	1,380	1,310	1,259	1,246	872	870	773	716	668	585	535	480	298
BMI	1,663	1,587	1,511	1,391	1,008	975	892	857	770	711	653	636	604	554	461

F. Additional Outcome Information and Results

In this section we provide additional information on the events included in the primary outcome of any major CVD event and the secondary outcome for any major diabetes event (Table S7 and S8). In addition, we show the time-to-event results for each of the event types (Table S9). The result for prespecified interactions are shown in Table S10.

Table S7. Distribution of Events for the Primary (Composite) Cardiovascular Outcome: Major CVD Events

Outcome	First Event	Total Events
Non-fatal heart attacks	208 (31.5%)	282
Non-fatal strokes	144 (21.8%)	204
New or worsening CHF	221 (33.4%)	306
Amputation for ischemic gangrene*	21 (3.2%)	31
CVD death	67 (10.1%)	194†
Total Events	661	823‡

The First Event represents the number of each event type that was included in the Primary Outcome of Major CVD Events. There were 661 primary outcome events, and 31.5% were non-fatal heart attacks, 21.8% were non-fatal strokes, etc. The Total Events column represents the total number of first events for each event type. For instance, there were a total of 282 first non-fatal heart attacks during follow-up. This number differs from the First Event column because 74 patients had another event that occurred before their first heart attack during follow-up.

*Distinguishing ischemic from infectious gangrene required adjudication and not all recurrent episodes of amputation were adjudicated due to resource prioritization.

†This is the number of CVD deaths in the Survey cohort analysis used for the primary composite outcome; the number of CVD deaths in the Complete cohort analysis for CVD deaths as a secondary outcome is 243.

‡Can include multiple events per subject.

Table S8. Distribution of Events for Any Major Diabetes Event (Composite) Outcome

Outcome	First Event	Total Events
Non-fatal heart attacks	203 (29.1%)	282
Non-fatal strokes	139 (19.9%)	204
New or worsening CHF	212 (30.4%)	306
Amputation for ischemic gangrene*	19 (2.7%)	31
CVD death	66 (9.5%)	194†
Amputation for non-ischemic gangrene*	13 (1.9%)	22
ESRD	45 (6.5%)	86
Total Events	697	931‡

The First Event represents the number of each event type that was included in the Outcome of Any Major Diabetes Events. There were 697 outcome events, and 29.1% were non-fatal heart attacks, 19.9% were non-fatal strokes, etc. The Total Events column represents the total number of first events for each event type. For instance, there were a total of 282 first non-fatal heart attacks during follow-up. This number differs from the First Event column because 79 patients had another event that occurred before their first heart attack during follow-up.

*End stage renal disease (ESRD) (GFR <15 during the original study period; eGFR <15 or dialysis or kidney transplant during the VADT-F).

†This is the number of CVD deaths in the Survey cohort analysis used for the primary composite outcome; the number of CV deaths in the Complete cohort analysis for CVD deaths as a secondary outcome was 243.

‡Can include multiple events per subject.

Table S9. Impact of Intensive Glucose Treatment on Individual Components of Composite Outcomes

Outcome	Standard treatment		Intensive treatment		Hazard ratio (95% CI)
	No. of Events	*Rate per 1000 person-yrs*	*No. of Events*	*Rate per 1000 person-yrs*	
Non-fatal heart attacks	146	20	136	18.1	0.91 (0.72, 1.44)
Non-fatal strokes	102	13.6	102	13.3	0.96 (0.73, 1.27)
New or worsening CHF	153	21.0	153	20.4	0.97 (0.77, 1.21)
Amputation for ischemic gangrene	19	2.4	12	1.5	0.63 (0.31, 1.30)
CVD death	101	11.6	93	10.6	0.91 (0.68, 1.20)
Amputation for non-ischemic gangrene	12	1.53	10	1.26	0.79 (0.34, 1.84)
ESRD	49	6.31	37	4.69	0.73 (0.47, 1.11)

Note. Confidence intervals have not been adjusted for multiple comparisons and inferences drawn from the intervals may not be reproducible. These results are for time to first specific CVD event. End stage renal disease (ESRD) (GFR <15 during the original study period; eGFR <15 or dialysis or kidney transplant during the VADT-F).

Table S10. Examination of Interactions for Primary CVD Outcome or Any Major Diabetes Outcome by UKPDS Risk Score, Prior CVD History, and Duration of Diabetes

	Major CVD Outcome HR (95% CI)	Any Major DM Outcome HR (95% CI)
Treatment	0.86 (0.65, 1.14)	0.83 (0.63, 1.09)
Duration	1.02 (1.01, 1.04)	1.02 (1.01, 1.04)
Treatment X duration*	1.00 (0.98, 1.02)	1.01 (0.99, 1.02)
Treatment	1.03 (0.81, 1.3)	0.98 (0.79, 1.23)
Prior CV Event	3.09 (2.48, 3.85)	2.80 (2.27, 3.46)
Treatment X Prior CV Event*	0.80 (0.59, 1.09)	0.84 (0.63, 1.14)
Treatment	0.91 (0.64, 1.29)	0.91 (0.65, 1.27)
UKPDS	11.18 (6.71, 18.63)	10.43 (6.32, 17.19)
Treatment X UKPDS*	1.10 (0.53, 2.28)	1.06 (0.51, 2.16)

Note. Confidence intervals have not been adjusted for multiple comparisons and inferences drawn from the intervals may not be reproducible.

*No evidence found that treatment effect varied by duration of diabetes, estimated CVD risk (as determined by UKPDS score), or prior CVD history event.

E. Ascertainment of Hospitalizations

Hospitalizations

We used the Medical SAS Datasets (Inpatient, non-VA Inpatient) from the VHA's Corporate Data Warehouse (CDW) and CMS Medicare (MedPar) files to obtain information on inpatient admissions. The non-VA Inpatient files include information on hospitalizations that are paid for / funded by the VA, but provided in non-VA facilities. These sources capture VA and non-VA hospitalizations for patients aged 65 and older; however, we may not capture non-VA admissions paid for by private insurance for patients younger than 65.

We included admissions that occurred after randomization up to date of death, withdrawal date, last visit date, or the end of the follow-up (May 31, 2017). We compared hospitalization rates for the standard and intensive treatment groups based on the time to first hospitalization. We also calculated the number of hospitalizations for each patient and compared groups using a negative binomial model, adjusting for exposure time (time in study).

There were no differences between treatment groups on hospital admissions (see Table S11). Patients in the standard treatment group had an average of 4.4 hospitalizations (SD=5.8, Median=3, IQR=1 – 6, Range=0 – 39) and those in the intensive care group had an average of 4.5 hospitalizations (SD=5.9, Median=3, IQR=1 – 6, Range=0 – 49). The incidence rates were similar between the two groups: 164.7 per 1000 person-years in the standard group and 160.2 per 1000 person-years in the intensive care group. The Hazard Ratio (HR) was 0.98 (95% CI: 0.88, 1.09). The results were similar when comparing the total number of hospitalizations, IRR=1.02 (95% CI: 0.89, 1.17).

Table S11. Impact of Intensive Glucose Treatment on Hospitalizations

Outcome	**Standard treatment**		**Intensive treatment**		
	No. of Events	***Rate***	***No. of events***	***Rate***	***HR (95% CI)***
Hospitalizations*	692	164.7	671	160.2	0.98 (0.88, 1.09)
	Median	***IQR***	***Median***	***IQR***	***IRR †(95% CI)***
Number of Hospitalizations**	3.0	(1 – 6)	3.0	(1 – 6)	1.02 (0.89, 1.17)

*Time to first hospitalization: rate per 1000 person-yrs

†IRR = Incidence Rate Ratio

**Negative Binomial model on total count of hospitalizations, adjusting for exposure time (time in study)

G. Additional Detail on HbA1c Measurement and Models and Examination of Mediation and Legacy Effect by Glycemic Control

We used HbA1c measures collected during clinical visits for the original VADT trial (up to May 31, 2008). We used VHA administrative databases to extract HbA1c measures during the post-trial follow-up period. During the original study, HbA1c was measured at clinical visits every 3 months. If a patient missed a visit, we carried forward the previous HbA1c measure to fill in the missing value. We used the last measure for the reasons outlined below. We used HbA1c measures during the original trial for all patients and during the post-trial follow-up for the patients who consented to additional data collection. We included HbA1c measures up until the first major CVD event (primary outcome), withdrawal date, death date, or until the end of the original trial period for patients who did not consent to additional follow-up and the end of follow-up for the consented patients (December 31, 2015).

During the original trial, patients had between 1 and 31 visits where HbA1c was scheduled to be measured (mean=20.5, SD=7.0, median=23). Patients had missing HbA1c values filled in (i.e., carried forward) for up to 13 visits (mean=1.23, SD=1.78, median=1). This resulted in an average "fill in rate" of 5.8% (SD=8.5%, median=4.0%). Some of the missing values occurred after the primary event and were not included in the analysis. Thus, missing HbA1c values were filled in for up to 13 visits (mean=1.09, SD=1.68, median=0), resulting in an average "fill in rate" of 4.9% (SD=8.1%, median=0%) for values included in the analysis.

We used the last observation carried forward method to fill in missing values due to the low rate of missing. On average, patients had missing values filled in for one visit and 52.8% of patients did not have any missing values. An additional 32.1% of patients had missing HbA1c values filled in for only 1 or 2 visits. In addition, HbA1c is relatively unique in that it reflects glucose control for 3-4 months, so change in quarterly visits are typically relatively modest and thus carrying forward from a prior visit is not clinically inappropriate.

We obtained HbA1c test results from the VHA's Corporate Data Warehouse (CDW) DSS lab files during the post-trial follow-up period. Although the trial ended on May 31, 2008, some patients missed their final study visit during the last six months of the intervention so we included CDW data starting on November 7, 2007 thru December 31, 2015- which helped fill in this six-months gap. During this approximate 8-year period, patients had between 1 and 62 additional HbA1c test results recorded (mean=19.3, SD=10.4, median=19). We used all available HbA1c values as they occurred and did not impute any missing values.

In total, patients had between 1 and 87 HbA1c measures throughout the study period (mean=31.5, SD=16.5, median=30). During the original trial, 98.0% of patients had HbA1c measured at least once a year while they remained in the study. During the post-trial follow-up, 73.5% had HbA1c measured at least once a year while they remained in the study. And 25% had HbA1c measured during most – at least 75% – of their follow-up years. In other words, 98.5% of patients had HbA1c measured during at least 75% of their follow-up years.

We used Cox proportional hazards survival analysis to examine the effects of HbA1c on the primary outcome of major CVD events (see Table 3 in main paper, Tables S13 and S14). Our analysis protocol pre-specified examining a log-linear association between cumulative HbA1c and CVD events in a mediation analysis for the observed treatment effect (e.g., lower CVD risk in the intensive group compared to the Standard group), using similar methods as the DCCT/EDICT (and more recently in the ADVANCE trial group). Unfortunately, the protocol incorrectly (a misstatement) implies that "log of cumulative HbA1c" would be used to assess this log-linear association. Since the Cox model examines a multiplicative effect, cumulative HbA1c, not log of cumulative HbA1c, is the correct way to assess the log-linear effect (as presented in Table 3). We therefore repeated the analyses presented in Table 3 of the main paper using log of cumulative HbA1c, and the degree of attenuation of the Intensive treatment variable (i.e., the evidence for HbA1c mediation) is nearly identical.

Stata version 15.1 was used for all analyses. We assessed violations of the proportional hazards (ph) assumption using two methods. First, we tested if the log relative hazard was time-varying and not time-constant for the covariates included in each model. We used the scaled Schoenfeld residuals on analysis time to test this; significant results suggest that the ph assumption was violated.[3] Second, for HbA1c, we reviewed the plots of the scaled Schoenfeld residuals by analysis time to determine the amount of deviation, if any, from a slope of zero. For treatment group, we reviewed Kaplan-Meier observed survival curves compared to the Cox predicted survival curves and the log-log plots for group, adjusting for HbA1c (where applicable). Closer values for the observed vs. predicted curves indicated that the ph assumption was unlikely to be violated. The log-log plots show the log survival curves for each group versus the log of analysis time. Plots with non-parallel lines suggest that the ph assumption is violated. We determined that a model violated ph assumptions if the test using scaled Schoenfeld residuals was significant and if the Schoenfeld residual plot by time revealed a non-zero slope (for HbA1c) or the log-log plots revealed non-parallel lines (for treatment group).

In Table 3, **Model 1** included the treatment effect only. **Model 2** added baseline HbA1c at the start of the intervention trial. **Model 3** included the treatment effect and HbA1c as a time-varying covariate. In this model, we allowed HbA1c to change during follow-up by including patient HbA1c measures from clinical visits and VHA CDW tables. The basic approach was to split the survival time for each patient based on each new HbA1c measure. Each of these time periods was represented by a separate row in the dataset. For example, a patient with 36 HbA1c measures prior to their outcome event would have 36 rows in the dataset. We then fit the Cox model for time to major CVD outcome event using the HbA1c measures as a time-varying covariate. We adjusted for intra-patient correlation using clustered sandwich estimators to adjust the standard errors for lack of independence.

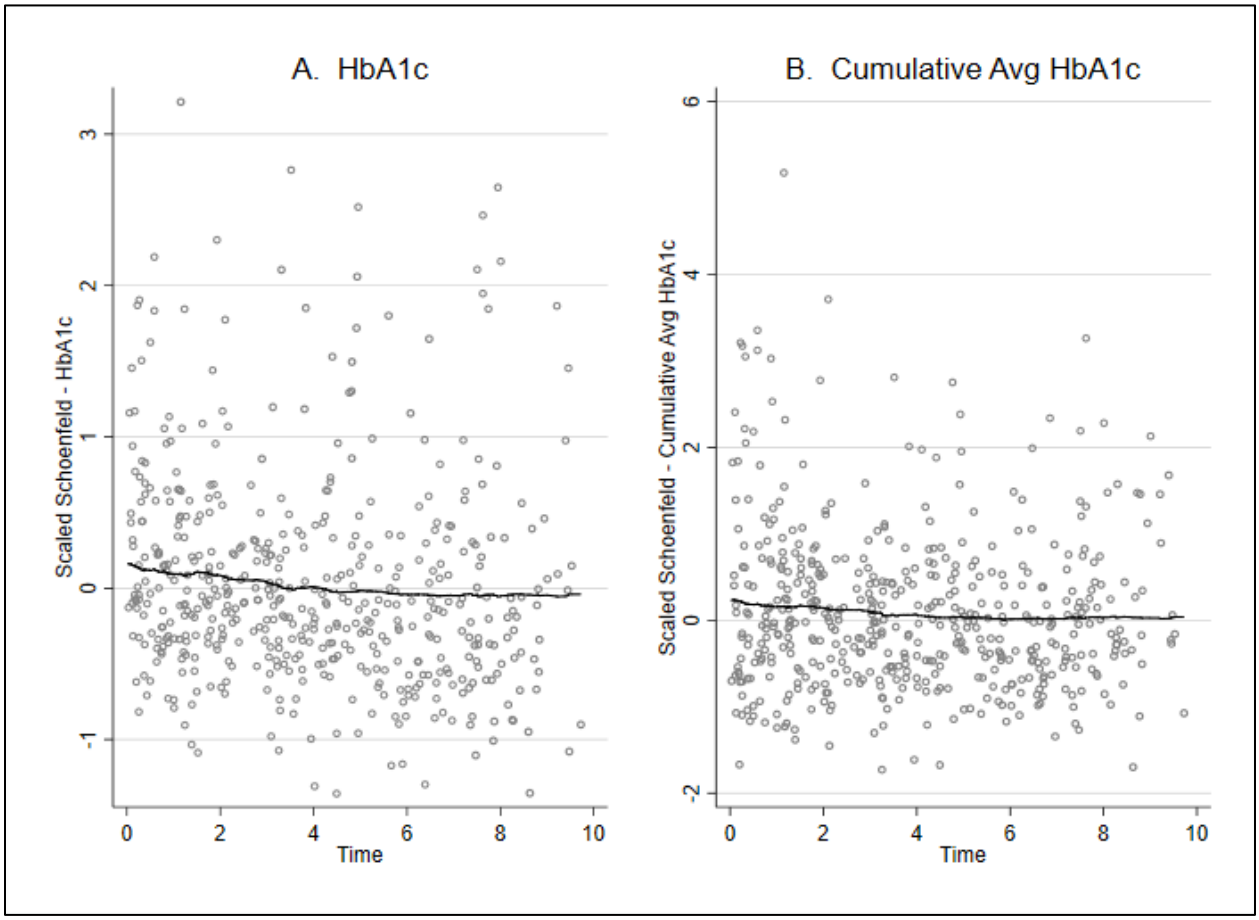
Model 4 included the treatment effect and cumulative average HbA1c as a time-varying covariate. This model was similar to Model 3, but we calculated the average HbA1c for each patient and updated it with

each new HbA1c measure. Table S15 shows a sample of simulated patient records where the cumulative average HbA1c is calculated for two patients over time. As before, we fit the Cox model for time to major CVD outcome event using the cumulative average HbA1c measures as a time-varying covariate and adjusting the standard errors using clustered sandwich estimators.

We fit all four models during two-time periods: 1) Years 0 – 10; and 2) Years 10 – 15. The first time period (Years 0 – 10) reflects the interval of time for which there was glucose separation between the two treatment groups (see Fig. 1). The second time period (Years 10 – 15) reflects the time when HbA1c levels had merged between the two treatment groups and all outcome data (VA, CMS, NDI) are available.

For all four models in the first time period (Years 0 – 10), patients were censored when they had a major CVD event (on or before December 31, 2010); at their last visit date; their death date; date of withdrawal from the study; or at the end of the follow-up period (December 31, 2010). Models 1 & 2 did not violate the ph assumption ($p>0.05$; Schoenfeld residual versus time plot showed a zero-slope for HbA1c; log-log plots did not show non-parallel lines for treatment group). The Log Relative Hazards tests for Models 3 & 4, however, revealed significant results for HbA1c ($p=0.001$ for Model 3; $p=0.041$ for Model 4). The plots for the Schoenfeld residuals versus analysis time showed that the slopes were reasonably close to zero (see Fig. S3 below), thus we concluded that the ph assumption was not violated for these models.

Figure S3. Tests for Proportional Hazards Assumption – Scaled Schoenfeld Residuals versus Analysis Time. Model 3 is shown in Panel A and Model 4 is shown in Panel B.



For the second time period (Years 10-15), we included patients still enrolled in the study as of January 1, 2011 and who had not yet had a major CVD event outcome. We reset time 0 to January 1, 2011 and patients were censored when they had a major CVD event (between January 1, 2011 and December 31, 2015); at their death date; or at the end of the follow-up period (December 31, 2015). This time period excludes 14 patients who did not have an HbA1c measure after 2010 and patients who had an HbA1c measure after 2010 but not before their outcome event. We ran additional analyses to include these patients by carrying forward their last HbA1c measure from the previous time period and the results were similar. All models satisfied the ph assumption.

For patients who withdrew consent during the original intervention trial, we included events that occurred prior to their withdrawal date only. For models using HbA1c measures over time, we included measures that occurred prior to censoring date.

For Models 3 & 4, we also tested whether the use of different time frames for assessing HbA1c results would change the results. In one model, we used the original trial data as described above and then continued to assess HbA1c using three-month intervals during the post-trial follow-up period. We also assessed yearly HbA1c results during the entire study period. Results were similar regardless of the time intervals between HbA1c measures used.

In addition to assessing time-varying HbA1c during these two time periods, we also used the entire study period to assess the impact of cumulative average HbA1c from the beginning of the study (Table S13) and in the most recent 3 years (Table S14) and cumulative average HbA1c calculated. The ph assumption was met for all six of these additional models.

Table S12. Comparison of Events During the VADT and During Observational Follow-up for Primary and Major Secondary Outcomes

Outcome	During the VADT Events per 1000 person-yrs		During VADT follow-up Events per 1000 person-yrs		Hazard Ratio (95% CI)	
	Treatment		Treatment		During VADT	During VADT follow-up
	STD	INT	STD	INT		
Major CVD Event (Primary Outcome)	49.5	41.6	56.2	57.1	0.84 (0.69, 1.03)	1.02 (0.80, 1.29)
Any Major DM Event	51.3	42.8	64.3	63.8	0.83 (0.69, 1.02)	0.99 (0.79, 1.25)
CVD Death	7.4	8.2	19.5	16.7	1.11 (0.71, 1.73)	0.86 (0.64, 1.17)
Any Cause Death	21.3	21.3	50.0	51.1	1.00 (0.77, 1.31)	1.02 (0.86, 1.21)

*Some VADT results above are slightly different from those reported in the original VADT report. This is due to the inclusion of some deaths that occurred in the last 7 months of the VADT that were not yet identified at the time of original publication due to the time lag in national death records. Mortality was determined in the Complete Cohort.

Note. Confidence intervals have not been adjusted for multiple comparisons and inferences drawn from the intervals may not be reproducible.

Table S13. Sensitivity Analysis to Test the Impact of Cumulative Average Glucose Control on the Primary CVD Outcome During the VADT Follow-up Study

	Primary Outcome *N=1791; 661 events* **HR (95% CI)**
HbA1c	
Model 1	
Time-varying cumulative average HbA1c	1.10 (1.03, 1.17)
Model 2	
Intensive Treatment (compared to Standard Treatment)	0.91 (0.78, 1.06)
Model 3	
Intensive Treatment (compared to Standard Treatment)	1.02 (0.86, 1.22)
Time-varying cumulative average HbA1c	1.11 (1.03, 1.19)†

Time varying cumulative average HbA1c reflects running average HbA1c from the beginning of the study. **Model 1** demonstrates that in the full VADT-F the cumulative average HbA1c was associated with an 10% increase in the odds of a major CVD event per 1 point increase in HbA1c, controlling for conventional CVD risk factors. **Model 2** reports the main treatment result of intensive treatment (see **Table 2**) and is repeated here for the reader's convenience. **Model 3** reports a mediation analysis demonstrating that the treatment effect disappears after controlling for cumulative average HbA1c, consistent with degree of HbA1c control being the major causal mechanism for CVD reduction.

Table S14. Sensitivity Analysis to Test the Impact of Recent Glucose Control on the Primary CVD Outcome During the VADT Follow-up Study

	Primary Outcome *N=1791; 661 events* **HR (95% CI)**
HbA1c	
Model 1	
Time-varying cumulative average HbA1c in most recent 3 years	1.08 (1.02, 1.14)
Model 2	
Intensive Treatment (compared to Standard Treatment)	0.91 (0.78, 1.06)
Model 3	
Intensive Treatment (compared to Standard Treatment)	0.97 (0.83, 1.14)
Time-varying cumulative average HbA1c in most recent 3 years	1.08 (1.01, 1.14)†

Time varying cumulative average HbA1c in recent 3 years reflects running average HbA1c from the most recent 3 years. **Model 1** demonstrates that in the full VADT-F the average HbA1c in the most recent 3 years was associated with an 8% increase in the odds of a major CVD event per 1 point increase in HbA1c, controlling for conventional CVD risk factors. **Model 2** reports the main treatment result of intensive treatment (see **Table 2**) and is repeated here for the reader's convenience. **Model 3** reports a mediation analysis demonstrating that the treatment effect shrunk by over half after controlling for recent HbA1c, consistent with degree of HbA1c control being the major causal mechanism for CVD reduction.

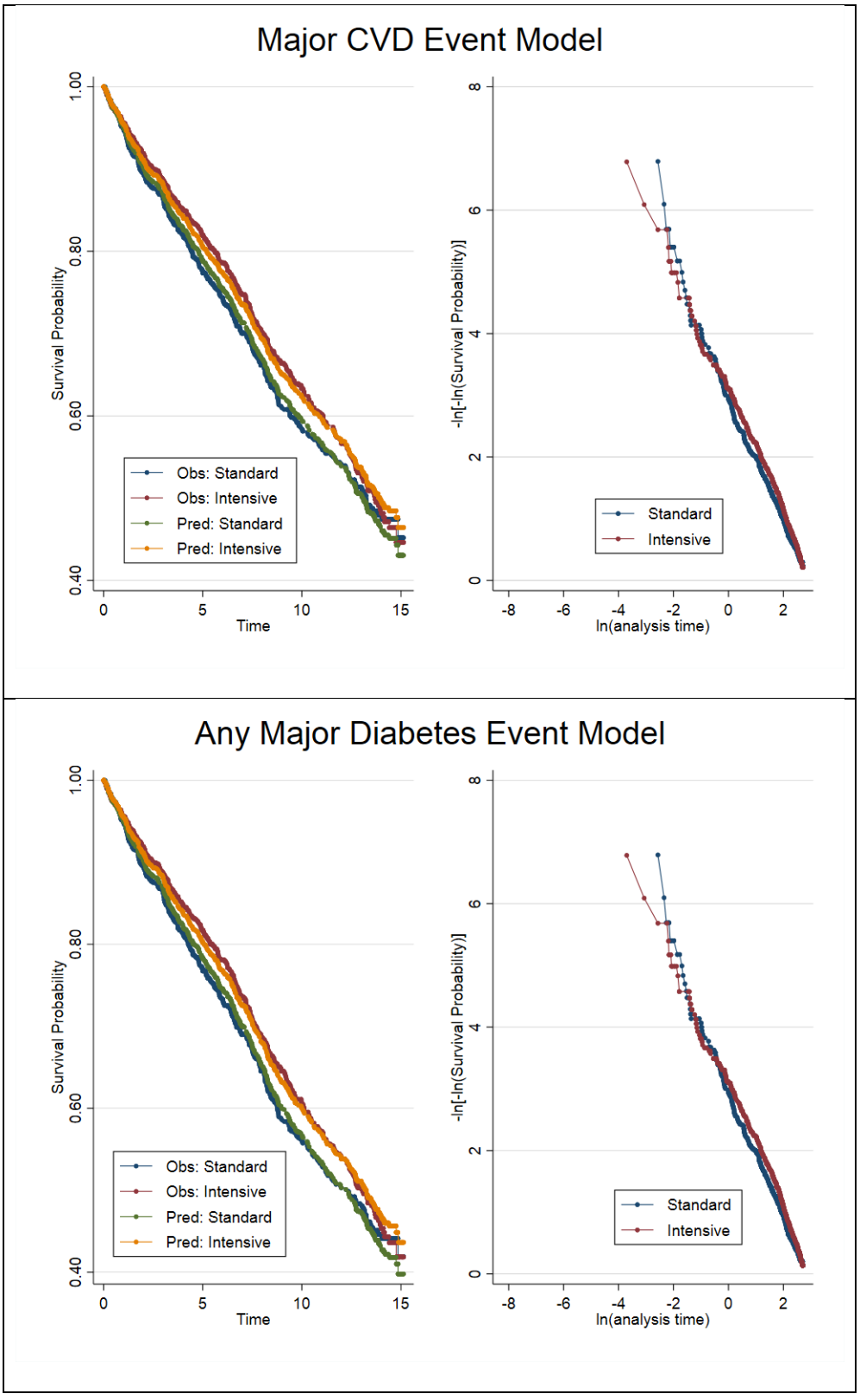
Table S15. Simulated Patient Records for HbA1c Measures Over Time

Patient	HbA1C	Count	Cumulative Average HbA1C
1	9.3	1	9.300
1	8.7	2	9.000
1	8.3	3	8.767
1	8.4	4	8.675
1	8.1	5	8.560
1	7.8	6	8.433
2	10	1	10.000
2	8.7	2	9.350
2	9.2	3	9.300
2	8.5	4	9.100
2	8.9	5	9.060

H. Additional Detail on Model Assumptions

For all Cox models reported in the manuscript, we tested the proportional hazards assumption using the methods outlined in the previous section. The significance test using Schoenfeld residuals revealed a significant result for the major CVD event outcome model (p=0.03). The graphical tests revealed slight violations (see Fig. S4). Similarly, the Schoenfeld residual test revealed significance for the secondary outcome for any major diabetes event (p=0.04). Again, the graphical tests revealed slight violations (see Fig. S4). The tests for the mortality models were not significant (CVD death, p=0.672; all-cause death, p=0.813).

Figure S4. Tests for Proportional Hazards Assumption – Scaled Schoenfeld Residuals versus Analysis Time and Log Log plots. Major CVD Event model is shown in panel 1 and Any Major Diabetes Event model is shown in panel 2.



I. Quality of Life Assessments

Diabetes Quality-of-Life

The Diabetes Quality-of-Life (DQOL) measure[4] was used to assess quality of life during the VADT and was included in the surveys during the follow-up study. The DQOL includes four subscales (Satisfaction, Impact, Worry: Diabetes-Related, Worry: Social/Vocational). We used the Satisfaction and Impact subscales to calculate an overall total DQOL score using the items from the two subscales. Satisfaction is assessed using 15 items and Impact is assessed using 20 items. All 20 Impact items were included during the original VADT, but the follow-up study included 13 of the items. Thus, we used the 13-item scale to assess Impact. The overall total scores were calculated using the method described by Jacobson[5] and range from 0 to 100, with 100 representing greater DQOL.

The total DQOL score was calculated for patients missing < 6 items. We reverse scored all items except Impact item 8, so that higher values were associated with a more positive quality of life. Consistent with Jacobson's method, the items were then summed into a raw score for each scale. Then the patient raw score minus the lowest possible score on each scale is divided by the possible score range (i.e., the highest possible score minus the lowest possible score) and multiplied by 100:

$$Score = \left[\frac{(Raw\ Score - Lowest\ Possible\ Score)}{Score\ Range}\right] * 100$$

This calculation transforms the raw score into a 100-point scale, with a value of 0 representing the lowest possible DQOL score and 100 representing the highest possible DQOL score.

We used the average of the last two available DQOL scores during the post-trial follow-up. A total of N=1033 patients received the DQOL survey during the post-trial follow-up period. Of these patients, 167 did not have a Total DQOL score calculated due to missing values on the individual items comprising the scale. For the 866 patients who had a Total DQOL score, we used an independent sample t-test to compare treatment groups on the total score for DQOL (see Table 2 in main paper; Table S17 below).

Table S16. DQOL Satisfaction and Impact Items

DQOL: Satisfaction Items
1) How satisfied are you with the amount of time it takes to manage your diabetes?
2) How satisfied are you with the amount of time you spend getting checkups?
3) How satisfied are you with the time it takes to determine your sugar levels?
4) How satisfied are you with your current treatment?
5) How satisfied are you with the flexibility you have with your diet?
6) How satisfied are you with the burden your diabetes is placing on your family?
7) How satisfied are you with your knowledge about your diabetes?
8) How satisfied are you with your sleep?
9) How satisfied are you with your social relationships and friendships?
10) How satisfied are you with your sex life?
11) How satisfied are you with your work, school, and household activities?
12) How satisfied are you with the appearance of your body?
13) How satisfied are you with the time you spend exercising?
14) How satisfied are you with your leisure time?
15) How satisfied are you with life in general?
DQOL: Impact Items
1) How often do you feel pain associated with the treatment of your diabetes?
2) How often are you embarrassed by having to deal with your diabetes in public?
3) How often do you have low blood sugar?
4) How often do you feel physically ill?
5) How often does your diabetes interfere with your family life?
6) How often do you have a bad night's sleep?
7) How often do you find your diabetes limiting your social relationships and friendships?
8) How often do you feel good about yourself?
9) How often do you feel restricted by your diet?
10) How often does your diabetes interfere with your sex life?
11) How often does your diabetes keep you from driving a car or using a machine (e.g., a typewriter)?
12) How often does your diabetes interfere with your exercising?
13) How often do you miss work, school, or household duties because of your diabetes?

Table S17. Average DQOL Total Scores for Standard and Intensive Treatment Groups

	Standard Treatment (N=420)		Intensive Treatment (N=446)	
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**
DQOL Total Score	62.19 ± 17.59	(60.51, 63.88)	63.84 ± 17.24	(62.24, 65.45)

Note. The N for each group reflects the number of patients who had DQOL Total Scores calculated during the follow-up period.

J. Supplement References

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