Decadal Trajectories of Glycemic Legacy: A Comprehensive Review of Metabolic Memory and Vascular Outcomes in Diabetes Mellitus

The global burden of diabetes mellitus represents one of the most severe challenges to modern public health, with clinical prevalence estimated at approximately 537 million adults in 2021 and projected to escalate to 783 million by 2045.[1] This spectrum of metabolic disease is fundamentally bifurcated into type 1 diabetes, which is characterized by the autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency, and type 2 diabetes, which accounts for over 90% of cases and involves progressive insulin resistance alongside impaired β-cell secretory capacity.[1] Regardless of the underlying etiology, chronic exposure to a hyperglycemic microenvironment promotes widespread, relentless vascular dysfunction, manifesting as microvascular triopathy—retinopathy, nephropathy, and neuropathy—as well as macrovascular sequelae, including coronary artery disease, myocardial infarction, stroke, and peripheral arterial disease.[1]

Historically, endocrinologists debated whether these devastating long-term complications were strictly dependent on cumulative glycemic exposure or if they represented a parallel, genetically predetermined, or glycemia-independent feature of the disease.[3] This clinical uncertainty was fundamentally resolved by the discovery of "metabolic memory"—frequently referred to as the "glycemic legacy effect" in type 2 diabetes.[2] This phenomenon describes how early, intensive glycemic management confers a long-lasting protective benefit against vascular complications that persists for decades, even after tight glycemic control has relented and intermediate clinical markers like glycated hemoglobin ($\mathrm{HbA_{1c}}$) have converged between treatment cohorts.[4] Conversely, it also implies that an initial period of poorly controlled hyperglycemia programs a trajectory of vascular damage that continues to progress unimpeded despite later pharmaceutical normalization of blood glucose.[2]

Molecular and Epigenetic Engines of Metabolic Memory

The persistence of metabolic memory indicates that transient or prolonged exposure to high glucose initiates enduring pathological alterations in vascular cells that are not immediately corrected by the restoration of normoglycemia.[1] At the cellular level, metabolic memory is driven by a complex interplay of biochemical pathways, oxidative stress, and stable chromatin

remodeling.[2]

Pathway / Driver	Target Cells / Loci	Primary Molecular Mechanism	Pathological Outcome
Histone Methylation (Set7) [7]	Endothelial Cells	Set7 recruitment; elevated $\mathrm{H3K4me1}$ permissive marks at the $\mathrm{NF\text{-}\kappa B\ p65}$ promoter [7]	Sustained inflammation and adhesion molecule transcription [6]
Histone Methylation (Suv39h1) [7]	Vascular Smooth Muscle Cells (VSMCs)	Downregulation of Suv39h1; loss of repressive $\mathrm{H3K9me3}$ chromatin architecture [7]	Persistent activation of pro-inflammatory and atherosclerotic pathways [7]
MicroRNA Dysregulation [7]	VSMCs	Upregulation of $\mathrm{miR\text{-}125b}$ directly targeting and suppressing $\mathrm{Suv39h1}$ translation [7]	De-repression of inflammatory genes and enhanced monocyte-VSMC binding [7]
DNA Methylation (Trained Immunity) [1]	Hematopoietic Stem Cells (HSCs)	Hyperglycemia-induced CpG methylation alterations, specifically at the TXNIP locus [4]	Differentiation into pre-programmed, hyper-inflammatory myeloid lineages [1]
Pro-Fibrotic Signaling [9]	Glomerular and Tubular Cells	Persistent activation of $\mathrm{TGF\text{-}\beta}$ signaling pathways	Relentless extracellular matrix deposition and progressive diabetic

		driving EMT and EndMT [9]	kidney disease [9]
Cellular Senescence (SASP) [8]	Endothelial Cells, Macrophages	Mitochondrial dysfunction and ROS generation triggering permanent cell-cycle arrest [8]	Chronic release of pro-inflammatory cytokines, chemokines, and growth factors [8]

Biochemical Flux and Superoxide Accumulation

The initiation of metabolic memory begins with the intracellular accumulation of glucose, which drives mitochondrial overproduction of reactive oxygen species (ROS).[2] This state of chronic oxidative stress shunts glucose metabolites into four classical pathogenic pathways: the polyol pathway, the hexosamine pathway, protein kinase C (PKC) activation, and the accelerated formation of advanced glycation end-products (AGEs).[2] AGEs accumulate on long-lived extracellular matrix proteins, causing permanent structural stiffness and functional damage to the vascular basement membrane.[5]

Crucially, cellular superoxide levels remain elevated and peroxynitrite continues to accumulate in the microvasculature even after euglycemia is restored, demonstrating a failure of normal cellular scavenging mechanisms to self-correct.[11] In animal models, the administration of antioxidants or agents that degrade AGEs, such as adding α-lipoic acid during the final phase of glycemic normalization, has shown a proof-of-principle reversal of this ROS-mediated cellular persistence of vascular stress.[11]

Epigenetic Imprinting and Chromatin Remodeling

To explain how these chronic pathological states persist in the absence of ongoing hyperglycemia, research has focused on epigenetic modifications—stable, heritable changes in gene expression that occur without altering the underlying DNA sequence.[2] Prominent among these is chromatin remodeling via histone post-translational modifications.[6]

Exposure of endothelial cells to high glucose for as little as $16\ \mathrm{hours}$ induces a sustained, long-term increase in the expression of the inflammatory $\mathrm{NF\text{-}\kappa B\ p65}$ subunit.[7] This is driven by the recruitment of the histone methyltransferase Set7 to the $\mathrm{p65}$ promoter, resulting in the mono-methylation of histone H3 lysine 4 ($\mathrm{H3K4me1}$), a mark associated with active transcription.[7] This epigenetic alteration is prevented only if mitochondrial electron transport chain components are blocked during the initial hyperglycemic insult.[7]

Concurrently, there is a sustained loss of repressive chromatin mechanisms.[7] Under normal conditions, transcription of inflammatory genes is kept in check by repressive chromatin marks, such as the trimethylation of histone H3 lysine 9 ($\mathrm{H3K9me3}$), mediated by the histone methyltransferase Suv39h1.[7] Under diabetic conditions, however, the expression of Suv39h1 is permanently downregulated, leading to a profound reduction in repressive $\mathrm{H3K9me3}$ marks at inflammatory gene promoters.[7]

This downregulation of Suv39h1 is mediated in part by the persistent upregulation of $\mathrm{miR\text{-}125b}$ in diabetic vascular smooth muscle cells.[7] This microRNA directly targets the $\mathrm{Suv39h1}$ transcript, leading to its degradation.[7] Overexpression of Suv39h1 in diabetic cells partially reverses this pro-inflammatory phenotype, proving the causal role of histone modifications in maintaining metabolic memory.[7]

Trained Immunity and Myeloid Programming

Metabolic memory also operates at the level of hematopoietic progenitor cells in the bone marrow, a phenomenon known as trained immunity.[1] Ancillary epigenetic analyses of blood samples from clinical cohorts have demonstrated that historical glycemic exposure induces stable DNA methylation (DNAme) changes at $186\ \text{cytosine-guanine dinucleotides (CpGs)}$.[4] These methylation marks are highly enriched in transcriptional and enhancer regions of blood cells, hematopoietic stem cells (HSCs), and myeloid lineages, with a particularly strong methylation signature observed at the ***TXNIP*** (thioredoxin-interacting protein) promoter.[4]

Because these epigenetic marks are mitotically stable and inherited through cell division, the bone marrow stem cells are programmed to continuously differentiate into hyper-inflammatory monocytes and macrophages.[1] These pre-programmed immune cells migrate into vascular tissues, where they perpetuate local inflammation, accelerate senescence, and drive atherosclerosis even after systemic glucose levels are therapeutically normalized.[1] Mediation analyses indicate that these coordinated CpG methylation signatures explain 68% to 97% of the association between historical glycemia and the future risk of long-term vascular complications.[4]

Apoptotic and Senescent Feedback Loops

Furthermore, metabolic memory promotes sustained cellular senescence and a pro-apoptotic state in targeted tissues.[8] Hyperglycemia-induced mitochondrial damage and chronic ROS accelerate premature senescence in endothelial cells, VSMCs, and macrophages, transforming them into senescent cells characterized by the senescence-associated secretory phenotype (SASP).[8] The SASP involves the continuous, hyperactive secretion of proinflammatory cytokines (such as tumor necrosis factor-α and interleukins), chemokines, and growth factors,

establishing a self-sustaining feedback loop of chronic tissue injury.[6]
Concurrently, pro-apoptotic pathways are persistently activated.[8] In retinal microvascular cells, high glucose exposure causes a sustained upregulation of apoptosis-associated genes, including the tumor necrosis factor (TNF) receptor and ligand families, as well as pro-apoptotic members of the B-cell lymphoma-2 (Bcl-2) family.[8] These apoptotic programs remain active and continue to drive progressive cell death in the retinal capillaries long after normal systemic glycemic management is achieved.[8]

Decadal Evidence in Type 1 Diabetes: The DCCT/EDIC Landmark

The primary clinical evidence establishing the legacy of early glycemic control in type 1 diabetes originates from the Diabetes Control and Complications Trial (DCCT, 1982–1993) and its long-term observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (1994–present).[3]

The DCCT Active Phase

The DCCT randomized $1,441$ participants with type 1 diabetes, aged 13 to 39 years and free of baseline hypertension, hyperlipidemia, or cardiovascular disease, into two cohorts.[15] The primary prevention cohort consisted of 726 individuals with a short duration of diabetes (1 to 5 years) and zero baseline microvascular complications.[15] The secondary intervention cohort comprised 715 individuals with a longer duration of diabetes (up to 15 years), mild-to-moderate nonproliferative retinopathy, and

a urinary albumin excretion rate of less than $200\ \text{mg}/24\ \text{hours}$.[15]
Participants were randomly assigned to either intensive therapy (aimed at achieving blood glucose and HbA_{1c} levels as close to the nondiabetic range as safely possible, utilizing three or more daily insulin injections or external pump therapy guided by self-monitoring) or conventional therapy (designed to maintain safe, asymptomatic glucose control without specific glycemic targets, using one or two daily insulin injections).[3]
Over a mean active follow-up of $6.5\ \text{years}$, the intensive treatment cohort maintained a median HbA_{1c} of approximately $7.0\%\ (53\ \text{mmol/mol})$, compared to $9.0\%\ (75\ \text{mmol/mol})$ in the conventional cohort.[3] The primary adverse effect of the intensive regimen was a threefold increased risk of severe hypoglycemia; however, this was not associated with any decline in cognitive function or quality of life.[3]
Epidemiological analysis of the DCCT data demonstrated a strong, continuous, exponential relationship between HbA_{1c} levels and microvascular risk, with each 10% decrease in mean HbA_{1c} (for example, from 9.0% to 8.1%, or 8.0% to 7.2%) associated with a 39% reduction in the risk of retinopathy progression.[12] Notably, no glycemic threshold was identified at which the risk of complications was entirely eliminated above the normal physiological range of $\text{HbA}_{1c}\ (4.0\%\ \text{to}\ 6.05\%)$.[12]

DCCT Outcome Measure	Primary Prevention Cohort Risk Reduction	Secondary Intervention Cohort Risk Reduction	Combined Cohort Outcome
Retinopathy Progression	76% risk reduction [12]	54% risk reduction [12]	Entirely explained by the mean HbA_{1c} separation during the trial [4]
Nephropathy Development	50% risk reduction [14]	50% risk reduction [14]	Reduced incidence of micro- and macroalbuminuria [14]
Neuropathy Incidence	60% risk reduction [14]	60% risk reduction [14]	Significant reduction in both sensory

			peripheral and autonomic dysfunction [14]

The EDIC Observational Phase

Upon completion of the DCCT in 1993, the randomized phase was ended.[12] The conventional therapy group was transitioned to intensive therapy, and all participants were returned to their primary care physicians for ongoing management.[4] Over 96% of the surviving cohort ($1,394 \text{ individuals}$) voluntarily enrolled in the long-term observational EDIC study.[15] By EDIC Year 1, the historical HbA_{1c} difference of $2.0 \text{ percentage points}$ converged rapidly to a difference of just 0.4% ($p < 0.001$), and both groups maintained an identical average HbA_{1c} of approximately 8.0% throughout the subsequent decades of follow-up.[4] Despite the complete convergence of glycemic control, the former conventional therapy group continued to experience a significantly higher incidence and accelerated progression of diabetes complications.[4] This divergence in clinical outcomes provided the definitive epidemiological proof of metabolic memory in human cohorts.[4]

Decadal Microvascular and Macrovascular Legacy Outcomes

Over more than 30 years of cumulative follow-up in the DCCT/EDIC cohort, the initial 6.5 years of intensive glycemic control translated into a profound reduction in severe, end-stage clinical outcomes [14]:

- **Retinopathy:** The risk of further clinical retinopathy progression (defined as a $3+ \text{ step}$ progression on the Early Treatment Diabetic Retinopathy Study scale assessed every 4 years in EDIC) remained significantly lower in the former intensive group.[4] Severe ocular complications, such as blindness in at least one eye, vitrectomy, or the need for panretinal photocoagulation, were reduced by 50%.[14]
- **Nephropathy:** The protective legacy of early glycemic control was sustained over decades, with the former intensive cohort experiencing a 59% reduction in the incidence of microalbuminuria and an 84% reduction in macroalbuminuria during EDIC Years 1–8.[14] Crucially, the long-term risk of developing an impaired glomerular filtration rate ($\text{eGFR} < 60 \text{ mL/min/1.73m}^2$) was reduced by 50%, and the risk of developing systemic hypertension was reduced by 20%.[14]

- **Neuropathy:** The incidence and prevalence of both diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) remained significantly lower in the former intensive therapy group through EDIC Year 17, demonstrating that early metabolic control preserves small-fiber and autonomic nerve function.[14]
- **Cardiovascular Disease:** Although macrovascular events were rare during the initial DCCT due to the youth of the cohort, a powerful cardiovascular legacy emerged during long-term EDIC follow-up.[3] Through 2013 (representing a mean of $26\ \text{years}$ of follow-up), the former conventional group experienced $217\ \text{cardiovascular events}$ in $102\ \text{subjects}$, compared to $149\ \text{events}$ in $82\ \text{subjects}$ in the former intensive group.[15] This represents a 30% relative risk reduction in the cumulative incidence of any cardiovascular event (including nonfatal myocardial infarction, stroke, cardiovascular death, confirmed angina, or coronary revascularization; $p =$).[15]
- **MACE Outcomes:** The risk of major adverse cardiovascular events (MACE) was reduced by 32% ($p = 0.07$).[15] A highly significant fivefold risk reduction was noted in the development of congestive heart failure, with only $2\ \text{cases}$ occurring in the former intensive group versus $10\ \text{cases}$ in the conventional group.[15]

Daily hazard and incidence function plots indicate that the day-to-day risk of experiencing a first cardiovascular event in both groups began to merge after approximately $17\ \text{to}\ 20\ \text{years}$ of follow-up, suggesting that the cardiovascular memory effect is not infinite and eventually wanes over decades.[15]

Cumulative Glycemic Exposure versus Trajectory Pattern

The clinical significance of metabolic memory has sparked debate regarding the mathematical and biological modeling of diabetic complications.[18]

The Cumulative Exposure Hypothesis

Miller and Orchard proposed that the long-term complication risks in both the DCCT/EDIC cohort and the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort can be explained mathematically by cumulative glycemic exposure alone, without requiring a biological "memory" concept.[18] They modeled glycemic exposure as "$\text{A}_{1c}\text{-Months}$"—the sum of the incremental HbA_{1c} levels above a normal threshold of 6.1% multiplied by the number of months elapsed between visits.[18]

They demonstrated that complications begin to occur once a threshold of approximately

$900\ \mathrm{A_{1c}\text{-}Months}$ is reached.[20] They argued that the lower rate of complications in the intensive group is simply a reflection of this lower cumulative exposure, and that by EDIC Year 18, annual retinopathy progression rates had equalized, suggesting that any apparent "memory" effect had faded as the total lifetime glycemic exposure increased in both groups.[20]

The Rebuttal: Why Glycemic Trajectory and Order Matter

This linear cumulative model was challenged by the primary DCCT/EDIC investigators, who argued that the clinical and biological trajectory of glucose exposure is fundamentally non-linear, and that the chronological order of glycemic exposure is critical.[18] If the $\mathrm{A_{1c}\text{-}Months}$ model were the sole determinant of vascular risk, then a patient who maintained a stable $\mathrm{HbA_{1c}}$ of 8.0% for $20\ \mathrm{years}$ ($\sim 456\ \mathrm{A_{1c}\text{-}months}$) would have the exact same complication risk as a patient who experienced an $\mathrm{HbA_{1c}}$ of 9.0% for $10\ \mathrm{years}$ followed by 7.0% for $10\ \mathrm{years}$ (also $\sim 456\ \mathrm{A_{1c}\text{-}months}$).[18]

Clinical data from the DCCT/EDIC study clearly demonstrate that this is not the case: an early, prolonged period of poorly controlled hyperglycemia induces irreversible structural, mitochondrial, and epigenetic changes that cannot be fully erased by subsequent glycemic control, leading to a much higher complication rate than a trajectory characterized by early, intensive management.[18]

While a waning of the protective legacy effect—termed "metabolic amnesia"—occurs after approximately $12\ \mathrm{to}\ 15\ \mathrm{years}$ of converged glycemia, the early metabolic trajectory sets a long-term vascular health pathway that remains highly significant for more than three decades.[18]

Glycemic Variability: Short-Term versus Long-Term

Analysis of glycemic fluctuations has revealed a key distinction between short-term (within-day) and long-term (month-to-month) variability.[19] Short-term glucose variability, measured during the DCCT as within-day standard deviation (SD) or the mean amplitude of glycemic excursions (MAGE) based on 7-point blood glucose profiles, did not predict the development of retinopathy or nephropathy by EDIC Year 4 after adjusting for mean blood glucose.[19]

In contrast, long-term glycemic variability—expressed as the standard deviation or coefficient of variation of $\mathrm{HbA_{1c}}$ over months to years—is an independent predictor of complications.[19]

Meta-analyses of patients with type 2 diabetes demonstrate that long-term $\mathrm{HbA_{1c}}$ variability is significantly associated with increased risks of stroke ($\mathrm{HR} = 1.40$, $95\%\ \mathrm{CI:}\ 1.31\ \mathrm{to}\ 1.50$), coronary heart disease and myocardial infarction ($\mathrm{HR} = 1.30$, $95\%\ \mathrm{CI:}\ 1.25\ \mathrm{to}\ 1.36$), peripheral arterial disease ($\mathrm{HR} = 1.32$,

95% CI: 1.13 to 1.56), and all-cause and cardiovascular mortality, independent of the mean $\mathrm{HbA_{1c}}$ level.[21]

This long-term glycemic legacy is also evident in epidemiologic registers.[22] A registry-based study from the Swedish National Diabetes Register (NDR) followed $18,450$ individuals with type 1 diabetes over 10 years.[22] Among those with a diabetes duration of ≥ 50 years ($1,023$ survivors), 44% had macrovascular disease, 52% had microvascular complications, and 31% were completely free of both diagnoses.[22]

The survivors who remained completely free of complications were significantly younger and maintained lower $\mathrm{HbA_{1c}}$, body mass index (BMI), and triglyceride levels.[22] Crucially, the mean $\mathrm{HbA_{1c}}$ level remained a highly significant, independent predictor of macrovascular disease, even after 50 years of diabetes duration, confirming that the impact of glycemic exposure is a lifelong determinant of vascular survival.[22]

Evidence in Type 2 Diabetes: Evolution Across Disease Stages

In type 2 diabetes, the manifestation of a glycemic legacy effect is heavily dependent on the disease stage at which intensive glycemic control is initiated.[17]

Early-Stage Type 2 Diabetes: UKPDS and Steno-2

The United Kingdom Prospective Diabetes Study (UKPDS, 1977–1997) randomized $4,209$ newly diagnosed individuals with type 2 diabetes (median age 53 years) to intensive glycemic control (using insulin or sulfonylureas, with a separate metformin arm for overweight patients) or conventional dietary management.[17]

At the end of the randomized trial, the intensive group achieved a median $\mathrm{HbA_{1c}}$ of 7.0% $(53$ mmol/mol$)$ compared to 7.9% $(63$ mmol/mol$)$ in the conventional group, resulting in a significant 25% relative risk reduction in microvascular complications ($p = 0.0099$) and a 16% reduction in myocardial infarction that approached statistical significance ($p = 0.052$).[17]

During the subsequent observational follow-up, the glycemic differences between the treatment groups disappeared within just one year.[17] Despite this complete convergence, the protective legacy of early intensive control persisted and expanded over decades [17]:

- **Insulin/Sulfonylurea Arm:** At the 10-year post-trial follow-up, the intensive group

maintained a persistent 24% risk reduction in microvascular events ($p = 0.001$), alongside newly emergent, highly significant reductions of 15% in myocardial infarction ($p = 0.01$) and 13% in all-cause mortality ($p = 0.007$).[17]

- **Metformin Arm:** Overweight patients originally randomized to the metformin-intensive group experienced a 39% reduction in myocardial infarction, a 50% reduction in coronary death, and a 41% reduction in stroke over a median active treatment period of 10.7 years.[24] By the 10-year post-trial mark, this cohort maintained an 18% reduction in any diabetes-related endpoint, a 31% reduction in myocardial infarction, and a 20% reduction in all-cause mortality, though the microvascular benefits were not sustained.[23]
- **The 44-Year Follow-Up (UKPDS 91):** Published in *The Lancet* in 2024, the third phase of the UKPDS monitored participants from 2007 to 2021 utilizing National Health Service administrative data, representing $80,724 \text{ person-years}$ of data.[23] This study demonstrated that the legacy effect of early intensive control persists into the third decade after the trial's completion.[23] Compared to conventional therapy, the early intensive insulin/sulfonylurea cohort maintained a 17% reduced risk of myocardial infarction, a 26% reduced risk of microvascular complications, and a 10% reduced risk of all-cause mortality.[23] The metformin cohort maintained a 31% reduced risk of myocardial infarction and a 20% reduced risk of all-cause mortality.[23]

The Steno-2 study provided further evidence for target-driven, intensified multifactorial intervention in 160 patients with type 2 diabetes and microalbuminuria (urinary albumin excretion $30 \text{ to } 300 \text{ mg}/24 \text{ hours}$), targeting glycemia, blood pressure, lipid levels, and lifestyle factors over 7.8 years.[25]

At the end of the randomized phase, all surviving participants were transitioned to intensified therapy, and the study continued observationally for over 21 years.[25]

At 21.2 years of total follow-up, participants originally randomized to the intensive multifactorial group showed a median survival gain of 7.9 years compared to the conventional group ($p = 0.005$).[27] This increase in lifespan was matched by an 8.1 year delay in the time to first cardiovascular event ($p = 0.001$) and a 70% reduction in hospitalization for

congestive heart failure ($p < 0.01$).[25]
The risk of long-term microvascular complications was also profoundly reduced, with significant hazard reductions in retinopathy progression ($\mathrm{HR} =$), autonomic neuropathy ($\mathrm{HR} = 0.59$), and progression to overt nephropathy ($\mathrm{HR} =$).[26]

Established Type 2 Diabetes: VADT, ACCORD, and ADVANCE

In sharp contrast to newly diagnosed cohorts, clinical trials conducted in older patients with long-standing, established type 2 diabetes and high baseline cardiovascular risk—namely the Veterans Affairs Diabetes Trial (VADT), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial—do not support a long-term cardiovascular or mortality legacy effect.[17]

- **VADT:** Followed $1,791 \text{ older veterans}$ (mean diabetes duration 11.5 years) randomized to intensive glycemic control (achieving a mean $\mathrm{HbA_{1c}}$ of 6.9%) or standard control (mean $\mathrm{HbA_{1c}}$ of 8.4%) for 5.6 years.[17] At trial completion, no significant difference was observed in cardiovascular events or mortality.[28] Although an interim analysis at 10 years showed a lower incidence of cardiovascular events in the intensive group, by the 15 year follow-up mark this legacy effect was completely lost.[28] The risk of the primary composite cardiovascular outcome was a non-significant 9% lower in the former intensive group ($47.3 \text{ vs. } 51.8 \text{ events per } 1000 \text{ person-years}$; $\mathrm{HR} =$, $95\% \text{ CI: } 0.78 \text{ to } 1.06$), and there was no difference in cardiovascular or all-cause mortality.[28]
- **ACCORD:** Enrolled $10,251 \text{ older participants}$ with an average diabetes duration of 10 years and high baseline cardiovascular risk, comparing intensive control (targeting an $\mathrm{HbA_{1c}} < 6.0\%$; mean achieved 6.4%) with standard control (mean achieved 7.5%).[17] The trial was stopped early at 3.5 years due to a significant 22% increase in all-cause mortality and a 35% increase in cardiovascular death in the intensive cohort.[24] Post-trial follow-up (ACCORDION) showed no legacy effect on the primary composite cardiovascular outcome, though a sustained protective effect on retinopathy progression was maintained.[17]

- **ADVANCE:** Evaluated $11,140$ older participants (mean diabetes duration 8 years) randomized to intensive glycemic control (target $\mathrm{HbA_{1c}} \leq 6.5\%$; achieved 6.5%) or standard control (achieved 7.3%).[17] The active trial demonstrated significant microvascular benefits, primarily driven by a reduction in nephropathy ($\mathrm{HR} = 0.79$, $p = 0.006$).[17] During the 5.4 year post-trial follow-up (ADVANCE-ON), despite rapid post-trial convergence of $\mathrm{HbA_{1c}}$ levels, a significantly reduced risk of end-stage kidney disease (ESKD) was maintained in the former intensive group ($\mathrm{HR} =$, 95% CI: 0.34 to 0.85, $p = 0.007$).[17]

Longitudinal Trial Matrix and Glycemic Legacy Outcomes

To provide an integrated, structured comparison of these landmark trials across both type 1 and type 2 diabetes, the table below synthesizes the baseline patient characteristics, active glycemic separation metrics, follow-up timelines, and hard clinical outcomes.

Trial & Cohort	Diabetes Type	Cohort Profile at Baseline	Active Phase Separation (HbA1c Int vs. Conv)	Follow-Up Horizon	Decadal Legacy Outcomes (Microvascular)	Decadal Legacy Outcomes (Macrovascular & Survival)
DCCT / EDIC [3]	Type 1	Young, duration $1–15$ year, zero baseline cardiovascular disease [15]	7.0% vs. 9.0% [3]	$30+$ Year [15]	50% fewer laser therapies [14]; 59% less microalbuminuria; 50% reduction in impaired	30% reduction in any cardiovascular event ($p =$) [15]; 32% reduction in MACE [15]

					eGFR [14]	
UKPDS [17]	Type 2	Newly diagnosed, median age $53\ \mathrm{years}$, treatment-naive [17]	7.0% vs. 7.9% [17]	$44\ \mathrm{Years}$ (UKPDS 91) [23]	26% fewer microvascular complications (insulin/sulfonylurea) [23]	17% reduction in myocardial infarction; 10% reduction in all-cause mortality [23]
Steno-2 [25]	Type 2	Older, duration $6\ \mathrm{years}$, baseline microalbuminuria [25]	7.9% vs. 9.0% [17]	$21.2\ \mathrm{Year}$ [27]	Retinopathy progression $\mathrm{HR} =$ [26]; nephropathy progression $\mathrm{HR} =$ [26]	Median survival gain of $7.9\ \mathrm{years}$ [27]; 70% reduction in heart failure hospitalization [25]
ADVANCE / ADVANCE-ON [17]	Type 2	Long-standing duration ($8\ \mathrm{years}$), older age, established risk [17]	6.5% vs. 7.3% [17]	$5.4\ \mathrm{Years}$ post-trial [17]	Sustained 46% risk reduction in ESKD ($\mathrm{HR} =$, $p =$) [17]	No macrovascular or mortality legacy effect [17]

ACCORD / ACCORDION [17]	Type 2	Long-standing duration ($10\ \text{years}$), high cardiovascular risk [17]	6.4% vs. 7.5% [17]	$4.0\ \text{Years}$ post-trial [17]	Sustained reduction in diabetic retinopathy progression [17]	Halted early due to 22% increased all-cause mortality; no macrovascular legacy benefit [17]
VADT [17]	Type 2	Advanced duration ($11.5\ \text{years}$), older veterans [17]	6.9% vs. 8.4% [28]	$15\ \text{Years}$ [28]	No significant microvascular legacy [17]	Cardiovascular benefit observed at $10\ \text{years}$ [28] but completely lost by $15\ \text{years}$ ($\text{HR} =$) [28]

Prognostic Intersections of Neuropathies and Microvascular Severity

Beyond the individual assessment of long-term diabetes complications, recent evidence demonstrates a high degree of prognostic cross-talk between microvascular and neuropathic markers.[31]

Marker / Predictor	Target Endpoint / Event	Prognostic Significance & Hazard Ratios	Clinical Context & Studies
Cardiovascular Autonomic	Rapid Kidney Function Decline	eGFR decline excess rate of	Asymptomatic early CAN predicts future

Neuropathy (CAN) [31]		$1.15\ \mathrm{mL/mir}$ (T1D) [31] and $0.34\ \mathrm{mL/mir}$ (T2D) [31]; odds ratios for rapid decline: 2.11 (T1D) and 1.39 (T2D) [31]	kidney failure in both T1D (PERL) and T2D (ACCORD) [31]
Baseline CAN [31]	Major Kidney Function Loss ($\geq 40\%$ eGFR loss)	$\mathrm{HR} = 2.60$, $p =$ (T1D) [31]; $\mathrm{HR} = 1.54$, $p = 3.8 \times$ (T2D) [31]	Impairment of renal blood flow autoregulation due to systemic autonomic failure [31]
Moderate/Severe Diabetic Retinopathy (DR) [32]	Doubling of Serum Creatinine	$\mathrm{HR} =$, $95\%\ \mathrm{CI}: 1.25$ to $4.$ [32]	Severity of DR reflects widespread, systemic microvascular and endothelial damage [32]
Moderate/Severe DR [32]	Incident Cardiovascular Events	$\mathrm{HR} =$, $95\%\ \mathrm{CI}: 1.49$ to $2.$ [32]	Pathogenesis of retinal, renal, and cardiac lesions shows significant pathobiological overlap [32]

Autonomic Control and Renal Decline

Cardiovascular autonomic neuropathy is a severe, frequently underdiagnosed complication characterized by the impairment of autonomic nervous system control over the cardiovascular system.[31] In its early, asymptomatic stages, CAN presents as decreased heart rate variability; as autonomic dysfunction progresses, patients develop resting tachycardia, orthostatic hypotension, and experience a significantly increased risk of silent myocardial infarction, heart failure, and sudden cardiac death.[31]

Importantly, clinical data from both the Nephropathy in Type 1 Diabetes (PERL) study and the

ACCORD trial demonstrate that CAN is a strong, independent predictor of rapid kidney function decline, defined as an eGFR slope of $\leq -5\ \mathrm{mL/min/1.73m^2/year}$.[31] Participants with baseline CAN experienced an excess eGFR decline of $1.15\ \mathrm{mL/min/1.73m^2/year}$ in PERL and $0.34\ \mathrm{mL/min/1.73m^2/year}$ in ACCORD.[31] This translated to odds ratios for rapid kidney function decline of 2.11 ($p = 6.9 \times 10^{-3}$) in PERL and 1.39 ($p = 1.1 \times 10^{-5}$) in ACCORD, as well as significantly increased risks for experiencing a major $\geq 40\%$ eGFR loss event ($\mathrm{HR} = 2.60$ in PERL; $\mathrm{HR} = 1.54$ in ACCORD).[31]

This relationship remains highly significant after adjusting for baseline GFR and albuminuria, indicating that autonomic cardiovascular dysfunction directly impairs intrarenal hemodynamic regulation, predisposing the kidney to accelerated filtration loss and structural decline.[31]

Retinopathy Severity as a Systemic Vascular Barometer

Similarly, the severity of diabetic retinopathy (DR) has been shown to act as a powerful systemic biomarker for both renal and macrovascular outcomes.[32] In the ACCORD trial, participants stratified at baseline with moderate-to-severe DR exhibited a significantly increased risk of developing renal and cardiovascular complications over $4\ \mathrm{years}$ of follow-up compared to those with no or mild DR.[32]

The hazard ratio for doubling of serum creatinine was 2.31 ($95\%\ \mathrm{CI:}\ 1.25\ \mathrm{to}\ 4.26$), while the hazard ratio for an incident cardiovascular event was 1.98 ($95\%\ \mathrm{CI:}\ 1.49\ \mathrm{to}\ 2.62$).[32]

The relative risk of experiencing a cardiovascular event versus a renal event was highly similar in both the no/mild DR stratum ($\mathrm{RR} = 0.96$) and the moderate/severe DR stratum ($\mathrm{RR} = 0.92$).[32] This closely matched risk suggests a shared pathobiology for microvascular and macrovascular complications, where progressive capillary closure in the retina reflects widespread, systemic endothelial dysfunction that simultaneously drives glomerular sclerosis and coronary atherosclerosis.[32] Notably, while retinopathy is a strong predictor of kidney and cardiovascular outcomes in both type 1 and type 2 diabetes, the correlation between retinopathy and nephropathy is significantly stronger in type 1 diabetes.[32]

Brain and Cognitive Legacy: The MIND Sub-study

To evaluate whether metabolic memory or legacy effects extend to neurodegenerative outcomes, the Memory in Diabetes (MIND) sub-study of the ACCORD trial examined cognitive

decline and brain volume changes in $2,977\ \text{participants}$ with type 2 diabetes.[33] Cognition was assessed using the Digit Symbol Substitution Test (DSST), while brain structure was evaluated using total brain volume (TBV) and abnormal white matter volume (AWM) on magnetic resonance imaging (MRI).[33]

At $40\ \text{months}$ of active intervention, intensive glycemic control ($\text{HbA}_{1c} < 6.0\%$) had no significant effect on DSST scores compared to standard control.[33] However, the intensive group demonstrated a modest but significant preservation of total brain volume, with a higher TBV ($4.6\ \text{cm}^3$, $p < 0.05$) than the standard group.[33]

In contrast, intensive blood pressure control (systolic target $< 120\ \text{mm Hg}$) was associated with a lower TBV at $40\ \text{months}$.[33] Interestingly, participants randomized to the combination of intensive glycemic control and standard antihypertensive therapy experienced 62% less TBV loss compared to the other three treatment arms ($\sim -11.0\ \text{cm}^3$ vs. $-\ 17.8\ \text{cm}^3$, $p < 0.0007$).[33]

The intensive glycemic group also demonstrated a significantly higher volume of abnormal white matter ($1.89\ \text{cm}^3$ vs. $1.71\ \text{cm}^3$, $p = 0.0156$).[33]

During the extended observational follow-up (ACCORDION MIND, assessed at a mean of $80\ \text{months}$—approximately $47\ \text{months}$ after the active intensive glycemic intervention was stopped), the differences in therapeutic targets were not sustained.[33] At this 80-month mark, no significant differences remained in the mean change of DSST scores or total brain volume between the glycemic, blood pressure, or lipid treatment groups.[33]

Ultimately, these findings indicate that while intensive glycemic control may offer transient structural preservation of brain volume, these short-term modifications do not translate into a durable, decadal clinical legacy of cognitive protection.[33]

Methodological Distinctions in Legacy Outcomes: Doubling of Creatinine versus ESKD

The long-term follow-up of large-scale clinical trials has highlighted a major methodological challenge in nephrology: the use of surrogate renal endpoints, such as the doubling of serum creatinine, compared to hard clinical endpoints, such as end-stage kidney disease or the initiation of renal replacement therapy.[34]

The Doubling of Creatinine Paradox in ACCORDION and ADVANCE-ON

In the ACCORDION trial, the composite renal outcome consisted of doubling of serum

creatinine, macroalbuminuria, or ESKD.[34] During a mean follow-up of $7.7\ \text{years}$, the study documented $954\ \text{doublings of serum creatinine}$, $351\ \text{self-reported dialysis events}$, and $1,905\ \text{deaths}$.[34] Intensive glycemic control successfully reduced the risk of the overall composite kidney outcome, driven primarily by a reduction in incident macroalbuminuria, but showed no separate, statistically significant benefit for either the doubling of serum creatinine ($\text{HR} = 1.05$) or incident dialysis ($\text{HR} = 0.84$).[34]

Intriguingly, randomization to intensive blood pressure control or fenofibrates resulted in a significantly increased risk of the composite kidney outcome, driven entirely by doubling of serum creatinine ($\text{HR} = 1.52$ for intensive BP; $\text{HR} = 1.83$ for fenofibrate).[34] These findings raised concerns regarding potential renal harm from intensive blood pressure targets and lipid-lowering therapies in patients with type 2 diabetes at high cardiovascular risk.[34]

The "Closer to the Cliff" Phenomenon

This apparent harm is explained by acute, reversible, non-progressive hemodynamic and metabolic shifts in renal function, combined with methodological differences in trial design.[34] In standard renal trials, a doubling of serum creatinine must be verified by a repeat measurement at least $30\ \text{days}$ later to rule out transient spikes.[34] Because ACCORD was designed primarily as a cardiovascular trial, serum creatinine was measured infrequently and doubling was determined based on single, unconfirmed measurements.[34]

Both intensive blood pressure lowering and fenofibrates produce acute, non-progressive increases in serum creatinine—the former by reducing intraglomerular perfusion pressure, and the latter by competitively inhibiting tubular creatinine secretion.[34] These interventions do not cause structural, progressive kidney damage, as demonstrated by the complete reversibility of creatinine levels during washout periods.[34]

However, because these active therapies cause a small but stable upward shift in baseline creatinine, they place these participants "closer to the cliff" of a doubling event.[34] Consequently, any transient, non-progressive physiological stress (such as mild dehydration or minor intercurrent illness) can easily push these patients over the threshold, resulting in a spurious recording of a "doubling of creatinine" event without reflecting actual progression to chronic kidney failure.[34]

Limitations of Dialysis Self-Reporting

Furthermore, self-reported dialysis events in ACCORDION were often unconfirmed for chronicity and were not officially adjudicated.[34] Notably, 73% of the participants who self-reported requiring dialysis ($257 \text{ out of } 351 \text{ individuals}$) had a final documented serum creatinine level of less than 2.0 mg/dL.[34] This low creatinine level indicates that most of these self-reported dialysis events were transient treatments for acute kidney injury (AKI) rather than chronic, progressive end-stage renal disease.[34]

In contrast, pooled analyses of hard ESKD events from the long-term follow-ups of ADVANCE-ON, ACCORDION, and the Veterans Affairs Diabetes Trial Follow-up (VADT-F) show a significant 25% reduction in the risk of actual ESKD ($\text{HR} = 0.75$, $95\% \text{ CI: } 0.58 \text{ to } 0.97$, $p = 0.03$), with no evidence of statistical heterogeneity between the trials.[34]

This demonstrates that single, unconfirmed measurements of doubling of serum creatinine are an unreliable surrogate for ESKD in trials where the active interventions produce acute hemodynamic or metabolic shifts in renal function.[34]

Synthesis and Clinical Paradigm Shifts

The evolution of metabolic memory from a laboratory observation to a clinical reality has reshaped the therapeutic paradigm for diabetes mellitus, highlighting the critical importance of early, aggressive management.[2]

The Pathophysiological Divergence of Disease Stages

The contrasting long-term outcomes between patients with newly diagnosed diabetes (DCCT and UKPDS) and those with advanced, long-standing disease (ACCORD, ADVANCE, and VADT) point to a fundamental pathophysiological model of vascular damage.[28]

In the early stages of diabetes, the vasculature is typically "pristine," lacking significant chronic

structural remodeling, advanced atherosclerotic plaques, or established cellular senescence.[8] Initiating intensive glycemic control at this stage prevents mitochondrial ROS overproduction, limits the accumulation of stable AGEs, and avoids the establishing of pro-inflammatory and pro-fibrotic epigenetic modifications.[2]

Conversely, in patients with a diabetes duration of $\geq 10 \text{ years}$ and preexisting cardiovascular disease, the vascular tissue has already sustained progressive injury.[28] In these advanced vascular environments, chronic tissue damage, cellular senescence, and stable chromatin modifications have already become self-sustaining.[7]

At this late stage, initiating intensive glycemic control cannot reverse established atherosclerotic lesions, deactivate ongoing pro-fibrotic signaling, or erase existing epigenetic imprints in hematopoietic stem cells.[4] This explains why delayed intensive glycemic control fails to offer a long-term survival or cardiovascular benefit in advanced cohorts, and can even increase mortality risk due to a heightened susceptibility to severe, arrhythmia-inducing hypoglycemia.[24]

Confounding by Modern Cardioprotective Care

The era in which these clinical trials were conducted also introduces historical differences that influence the visibility of a legacy effect.[24] The DCCT and UKPDS were conducted in the 1980s and 1990s, an era before statins, ACE inhibitors, and antiplatelet therapies were standard practice.[24] In the absence of these therapies, the physiological impact of glycemic control on vascular complications was highly visible.[28]

In contrast, trials like VADT, ACCORD, and ADVANCE were conducted in a modern era of comprehensive cardiovascular management.[24] The aggressive use of cardioprotective therapies significantly lowered baseline cardiovascular event rates across both treatment groups.[24] This comprehensive background therapy masked the incremental macrovascular benefits of glucose lowering, reducing the visibility of a glycemic legacy effect on cardiovascular outcomes compared to earlier trials.[28]

Future Therapeutic Outlook: Reversing the Memory

These findings indicate that while intensive glycemic control is vital, glucose lowering alone is insufficient to fully arrest the progression of diabetic complications once metabolic memory has been established.[2] Future therapeutic strategies must aim to "erase" or reverse this cellular memory.[1]

Promising avenues of research include:

- **Epigenetic Erasers:** Developing small-molecule inhibitors of Set7 to block permissive histone methylation, or activators of Suv39h1 to restore repressive chromatin architecture.[7]
- **MicroRNA Modulators:** Utilizing antisense oligonucleotides to target and suppress miR-125b, preventing the degradation of chromatin-repressive proteins.[7]
- **Senolytics:** Developing targeted therapies to eliminate senescent cells, neutralizing the pro-inflammatory SASP feedback loop.[8]

- **AGE-Degrading Agents and Antioxidants:** Utilizing molecules to break established AGE cross-links on extracellular proteins, alongside targeted mitochondrial antioxidants to fully normalize cellular ROS levels.[5]

By combining early, intensive glycemic management with therapies that target the epigenetic, senescent, and biochemical mechanisms of metabolic memory, clinicians may eventually be able to prevent or reverse the long-term vascular complications of diabetes, improving survival and quality of life for patients.[1]

Works cited

1. Epigenetic modifications in metabolic memory: What are the memories, and can we erase them? - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC9359656/
2. Metabolic Memory and Chronic Diabetes Complications: Potential Role for Epigenetic Mechanisms - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC3432745/
3. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC3867999/
4. Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC) - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC8929187/
5. Metabolic Memory: Understanding Its Role in Diabetes and Long-Term Health | SciTechnol, accessed on June 1, 2026, https://www.scitechnol.com/peer-review/metabolic-memory-understanding-its-role-in-diabetes-and-longterm-health-R1IO.php?article_id=27911
6. Epigenetic mechanisms in diabetic complications and metabolic memory - PMC - NIH, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC4324095/
7. Epigenetic Mechanisms - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC6699750/
8. Metabolic memory: mechanisms and diseases - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC10899265/
9. Metabolic Memory-Mediated Epigenetic Regulation of EMT in Diabetic Kidney Disease: Mechanisms and Therapeutic Implications - MDPI, accessed on June 1, 2026, https://www.mdpi.com/1422-0067/27/11/4801
10. Effects of metabolic memory on inflammation and fibrosis associated with diabetic kidney disease: an epigenetic perspective - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC8061201/
11. Clinical review 2: The "metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? - Semantic Scholar, accessed on June 1, 2026, https://www.semanticscholar.org/paper/Clinical-review-2%3A-The-%22metabolic-

memory%22%3A-is-more-Ceriello-Ihnat/d36982a490a707776d05dc928a4a65893b57d5b0
12. Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC2622728/
13. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Summary and Future Directions - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC3867991/
14. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: The “Gift” That Keeps on Giving! - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC5131850/
15. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC4839174/
16. Risk Factors for Diabetic Peripheral Neuropathy and Cardiovascular Autonomic Neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC7171957/
17. The legacy effect in diabetes: are there long-term benefits? - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC9196952/
18. Comment on Miller and Orchard: Understanding Metabolic Memory ..., accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC7306126/
19. Effect of Glucose Variability on the Long-Term Risk of Microvascular Complications in Type 1 Diabetes - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC2752912/
20. Understanding Metabolic Memory: A Tale of Two Studies - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC7034186/
21. Long-term HbA1c variability and macro-/micro-vascular complications in type 2 diabetes mellitus: a meta-analysis update - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC10148792/
22. Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC5516128/
23. Forty-four Years of the UK Prospective Diabetes Study: Legacy ..., accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12140635/
24. Paradigm Shift for the Treatment of Type 2 Diabetes Mellitus in Patients with Cardiovascular Disease: Cardiologist's Perspective, accessed on June 1, 2026, https://www.e-jcpp.org/journal/view.php?number=30
25. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC6061176/
26. Studies that changed clinical practice. Steno-2: Multifactorial intervention in type 2

diabetes and microalbuminuria - DiabetesontheNet, accessed on June 1, 2026, https://diabetesonthenet.com/diabetes-primary-care/studies-changed-clinical-practice-steno-2-multifactorial-intervention-type-2-diabetes-and-microalbuminuria/
27. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC5506099/
28. Lack of Glycemic Legacy Effects in the Veterans Affairs Diabetes ..., accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC7307414/
29. Intensive glycemic control: Implications of the ACCORD, ADVANCE, and VADT trials for family physicians - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC2726096/
30. Healthy lifestyle factors and combined macrovascular and microvascular events in diabetes patients with high cardiovascular risk: results from ADVANCE - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC11823187/
31. Cardiovascular Autonomic Neuropathy and Risk of Kidney Function Decline in Type 1 and Type 2 Diabetes: Findings From the PERL and ACCORD Cohorts - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC11043059/
32. The degree of retinopathy is equally predictive for renal and macrovascular outcomes in the ACCORD Trial - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC4252726/
33. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC5633725/
34. ACCORDION: Ensuring That We Hear the Music Clearly - PMC, accessed on June 1, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC6237047/