Review the evolution and current state of evidence regarding the ”legacy effect” (metabolic memory) in both type 1 and type 2 diabetes, focusing on how early intensive glycemic control impacts long-term microvascular and macrovascular outcomes over decades.

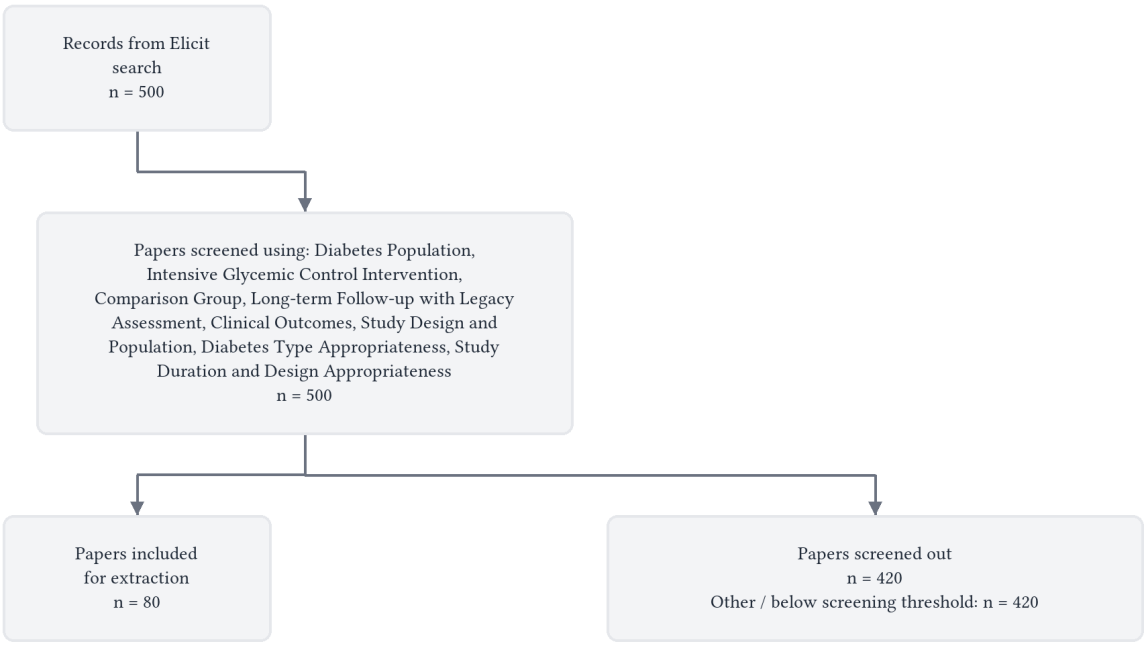
Early intensive glycemic control produces robust and durable reductions in microvascular complications in both type 1 and type 2 diabetes, and generates lasting macrovascular protection in type 1 diabetes and in early-stage type 2 diabetes without established cardiovascular disease, but confers no macrovascular legacy benefit—and may cause harm—when applied late in the disease course to patients with advanced, long-standing diabetes and prior cardiovascular events.

Abstract

The legacy effect—whereby early intensive glycemic control confers long-term protection against diabetic complications beyond the period of active intervention—is strongly and consistently demonstrated for microvascular outcomes in both type 1 and type 2 diabetes, but is conditional and context-dependent for macrovascular outcomes, particularly in type 2 diabetes. In type 1 diabetes, the DCCT/EDIC program established that a 6.5-year intensive treatment phase (median HbA1c 7% versus 9% [1]) in young patients with early-stage disease generated reductions in retinopathy, nephropathy, and neuropathy of 39–76% [2, 3] and cardiovascular event reductions of 42–57% persisting 17–30 years after HbA1c convergence [4, 5] —the clearest demonstration of true metabolic memory independent of ongoing glycemic differences. In type 2 diabetes, intensive control consistently reduces non-fatal myocardial infarction by approximately 10–15% across meta-analyses [6, 7] and produces robust reductions in microalbuminuria and retinopathy progression [8, 9], but does not reduce cardiovascular mortality or all-cause mortality [7, 9]. A macrovascular legacy effect in type 2 diabetes is demonstrable only under specific conditions: early intervention in patients without established cardiovascular disease and with short diabetes duration, as shown by the UKPDS post-trial follow-up [10] and meta-analytic subgroup analyses [11]; it is absent in trials enrolling patients with advanced, long-standing disease and prior cardiovascular events [12, 13].

The heterogeneity of macrovascular legacy effects in type 2 diabetes is explained by several intersecting factors. Disease stage at intervention is paramount: benefits are concentrated in patients with diabetes duration less than 10 years and no prior cardiovascular disease [11, 14], while patients with established vascular disease show no benefit and may face harm from aggressive rapid glycemic reduction, as occurred in ACCORD [15]. Cumulative glycemic exposure—the product of HbA1c separation magnitude and treatment duration—predicts cardiovascular risk reduction [16], such that short trials with modest HbA1c differences generate insufficient cumulative separation to drive durable legacy effects. How intensive control is achieved matters as much as the target: hypoglycemia, which approximately doubles in risk with intensive therapy [8, 9], attenuates or negates cardiovascular benefits, and drugs not inducing hypoglycemia demonstrate superior risk-benefit profiles for both microvascular and macrovascular outcomes [17]. Proposed biological mechanisms—epigenetic modifications, advanced glycation end product accumulation, and mitochondrial oxidative stress [4, 18] —predict the observed pattern of robust legacy effects in early-stage disease and tissues with low cell turnover, and limited reversibility once structural vascular changes are established. Collectively, the evidence supports early, gradual, and hypoglycemia-minimizing intensive glycemic control as the strategy most likely to generate durable legacy benefits, with the window of opportunity for macrovascular protection in type 2 diabetes concentrated in the years immediately following diagnosis.

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "Review the evolution and current state of evidence regarding the "legacy effect" (metabolic memory) in both type 1 and type 2 diabetes, focusing on how early intensive glycemic control impacts long-term microvascular and macrovascular outcomes over decades."

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Diabetes Population**: Does this study involve participants diagnosed with type 1 or type 2 diabetes mellitus according to established diagnostic criteria (ADA, WHO, or equivalent standards)?
- **Intensive Glycemic Control Intervention**: Does this study examine intensive glucose management strategies (such as intensive insulin therapy, tight glycemic targets with HbA1c <7% or equivalent, or comprehensive diabetes management programs aimed at achieving near-normal glycemia)?

- **Comparison Group**: Does this study include a control or comparison group receiving standard, conventional, or less intensive glycemic management?
- **Long-term Follow-up with Legacy Assessment**: Does this study have a minimum 5-year follow-up AND examine outcomes during post-intervention periods or demonstrate persistent benefits/risks after intervention cessation or convergence of glycemic control between groups?
- **Clinical Outcomes**: Does this study report at least one clinical microvascular or macrovascular outcome (diabetic retinopathy, nephropathy, neuropathy, cardiovascular events such as myocardial infarction/stroke/cardiovascular death, peripheral vascular disease, or composite endpoints)?
- **Study Design and Population**: Is this study a randomized controlled trial, prospective cohort study, post-hoc analysis of a major trial, systematic review, or meta-analysis conducted in human participants?
- **Diabetes Type Appropriateness**: Is this study focused on type 1 or type 2 diabetes (rather than exclusively on gestational diabetes)?
- **Study Duration and Design Appropriateness**: Does this study examine interventions for ≥1 year with long-term follow-up AND provide longitudinal outcome data over time (rather than being a short-term intervention study or cross-sectional analysis)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 420

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

  Extract study type and design characteristics relevant to assessing legacy effects in diabetes, including:

- Type of study (RCT with observational follow-up, meta-analysis, cohort study, narrative review, etc.)
- Whether study specifically examined legacy effect/metabolic memory
- Total follow-up duration and structure (intervention period + post-intervention observational period)
- Sample size for type 1 and type 2 diabetes separately

- **Population Characteristics**:

  Extract key population features that affect legacy effect interpretation, including:

- Diabetes type (type 1, type 2, or both)
- Diabetes duration at baseline (early diabetes <5-10 years vs established diabetes)
- Age at intervention start
- Presence of baseline complications or cardiovascular disease
- Any population subgroups analyzed separately for legacy effects

- **Intensive Control Intervention**:

  Extract details about intensive glycemic control interventions relevant to legacy effect assessment, including:

- Definition of 'intensive' vs 'conventional' control used in the study
- HbA1c levels achieved in intensive vs control groups during active intervention period

- Duration of active intensive treatment phase
- Timing of intervention (early in disease course vs later)
- Specific intervention methods (multiple injections, pump therapy, specific medications, etc.)

- **Legacy Effect Evidence**:

  Extract specific evidence for or against metabolic memory/legacy effects, including:

- Whether benefits persisted after intensive control ended or HbA1c levels converged
- Duration of demonstrated legacy effects (how many years post-intervention)
- Magnitude of legacy effects compared to active treatment effects
- Any differences in legacy effects between type 1 vs type 2 diabetes
- Proposed mechanisms or explanations for observed legacy effects

- **Microvascular Outcomes**:

  Extract long-term microvascular complication outcomes from intensive vs conventional glycemic control, including:

- Retinopathy progression, proliferative retinopathy, visual outcomes
- Nephropathy progression, proteinuria, kidney disease endpoints
- Neuropathy development or progression
- Risk reductions (relative risk, hazard ratios, NNT) with confidence intervals
- Whether effects persisted during post-intervention follow-up period
- Separate results for type 1 vs type 2 diabetes when available

- **Macrovascular Outcomes**:

  Extract long-term cardiovascular and macrovascular outcomes from intensive vs conventional glycemic control, including:

- Major adverse cardiovascular events (MACE), cardiovascular death
- Myocardial infarction, stroke, peripheral arterial disease
- All-cause mortality
- Risk reductions (relative risk, hazard ratios, NNT) with confidence intervals
- Whether effects persisted during post-intervention follow-up period
- Differences in legacy effects between type 1 vs type 2 diabetes
- Time to emergence of cardiovascular benefits

- **Temporal Patterns**:

  Extract information about when legacy effects appeared and evolved over time, including:

- Time during active treatment when benefits first emerged
- Time course of benefit persistence after intervention ended
- Any diminishing or strengthening of effects over extended follow-up
- Differences in temporal patterns between microvascular vs macrovascular outcomes
- Changes in evidence or understanding of legacy effects over different time periods or study eras

- **Key Findings**:

  Extract the study's main conclusions about legacy effects and metabolic memory in diabetes, including:

- Primary findings regarding existence and magnitude of legacy effects

- Differences between type 1 vs type 2 diabetes legacy effects
- Clinical implications and recommendations for early intensive control
- Any contradictory findings or limitations in demonstrating legacy effects
- Evolution of understanding compared to earlier research
- Future research needs identified by authors

Results

Characteristics of Included Studies

The 80 sources included in this review span a range of study designs, from landmark primary randomized controlled trials (RCTs) with long-term observational follow-up, to systematic reviews and meta-analyses, to narrative reviews, editorials, and observational cohort studies. Sources address legacy effects in type 1 diabetes (T1DM), type 2 diabetes (T2DM), or both, with varying degrees of directness in examining the metabolic memory hypothesis.

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
D. Nathan, 2013 [1]	Yes	RCT with observational follow-up	T1DM [1]	Yes [1]	~26 years (6.5y DCCT + ~20y EDIC) [1]	1,441 T1DM [1]
Tanika N. Kelly et al., 2009 [19]	No (abstract only)	Meta-analysis of RCTs	T2DM [19]	No [19]	3.4–10.7 years [19]	27,802 T2DM [19]
R. Hayward et al., 2015 [20]	Yes	RCT with observational follow-up	T2DM [20]	Yes [20]	Median 9.8 years [20]	1,791 T2DM [20]
P. Reaven et al., 2019 [12]	No (abstract only)	RCT with observational follow-up	T2DM [12]	Yes [12]	15 years [12]	1,791 T2DM [12]
Gaetano Santulli, 2019 [21]	No (abstract only)	RCT with observational follow-up	T2DM [21]	Yes [21]	Median 13.6y CV events; 15y mortality [21]	1,791 T2DM [21]
W. Aronow, 2019 [22]	No (abstract only)	RCT with observational follow-up	T2DM [22]	Yes [22]	15 years [22]	1,791 T2DM [22]
Legacy effect in diabetes mell [23]	No (abstract only)	Narrative review	T1DM and T2DM [23]	Yes [23]	Decades [23]	Not reported [23]
F. Prattichizzo et al., 2020 [11]	No (abstract only)	Systematic review and meta-analysis	T1DM, pre-diabetes, T2DM [11]	Yes [11]	>10 years post-trial for some RCTs [11]	40,346 [11]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
A. Wright, 2009 [24]	No (abstract only)	Narrative review	T1DM [24]	Yes [24]	10 years [24]	Not reported [24]
A. Wright, 2010 [25]	No (abstract only)	Narrative review	T1DM [25]	Yes [25]	10 years [25]	Not reported [25]
R. Rodríguez-Gutiérrez & V. Montori, 2016 [26]	Yes	Meta-analysis of RCTs and follow-up extensions	T2DM [26]	No [26]	Not specified [26]	Not specified [26]
C. Stettler et al., 2006 [27]	No (abstract only)	Systematic review and meta-analysis	T1DM and T2DM [27]	No [27]	11,293 person-years (T1DM); 43,607 person-years (T2DM) [27]	1,800 T1DM; 4,472 T2DM [27]
R. Pop-Busui et al., 2010 [28]	No (abstract only)	RCT with observational follow-up (DCCT/EDIC)	T1DM [28]	No [28]	Not specified [28]	Not specified [28]
Birgit Fullerton et al., 2014 [3]	No (abstract only)	Systematic review of RCTs	T1DM [3]	No [3]	1–6.5 years [3]	2,230 T1DM [3]
D. Nathan et al., 2013 [4]	Yes	RCT with observational follow-up	T1DM [4]	Yes [4]	Over 30 years [4]	1,441 T1DM [4]
G. Dailey, 2011 [29]	No (abstract only)	Narrative review of trials	T2DM [29]	Yes [29]	13 years (Steno-2); 10 years (UKPDS) [29]	Not specified [29]
M. Lawson et al., 1999 [30]	No (abstract only)	Systematic review and meta-analysis	T1DM [30]	No [30]	>2 years [30]	Not specified [30]
A. Vaag, 2006 [31]	No (abstract only)	RCT (Steno-2)	T2DM [31]	No [31]	7.8 years [31]	160 T2DM [31]
S. Coca et al., 2012 [32]	Yes	Systematic review and meta-analysis	T2DM [32]	No [32]	2–15 years [32]	28,065 T2DM [32]
R. Turner, 1998 [33]	No (abstract only)	RCT (UKPDS)	T2DM [33]	No [33]	Median 11 years [33]	Not specified [33]
M. Monami et al., 2021 [17]	Yes	Meta-analysis of RCTs	T2DM [17]	No [17]	≥2 years [17]	~79,000 T2DM [17]
S. Marso et al., 2010 [6]	No (abstract only)	Meta-analysis	T2DM [6]	No [6]	Mean 5.4 years [6]	27,544 T2DM [6]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
B. Wajchenberg et al., 2008 [34]	No (abstract only)	Narrative review	T1DM [34]	No [34]	Not specified [34]	Not specified [34]
Kelvin Tran & P. Reaven, 2020 [35]	No (abstract only)	Review of RCT with observational follow-up (VADT)	T2DM [35]	Yes [35]	Intervention + 5y + 10y post-trial [35]	Not specified [35]
S. Margolis, 2005 [2]	No (abstract only)	Review/overview	T1DM and T2DM [2]	No [2]	Mean 6.5 years [2]	Not specified [2]
J. Levy, 2001 [36]	No (abstract only)	Clinical trial review (UKPDS)	T2DM [36]	No [36]	Not specified [36]	Not specified [36]
M. Gore & Darren K McGuire, 2009 [37]	No (abstract only)	RCT with observational follow-up (UKPDS)	T2DM [37]	Yes [37]	20 years (10y intervention + 10y follow-up) [37]	4,209 T2DM [37]
Fabian G.S & M. Rizki F, 2025 [38]	No (abstract only)	Systematic review	T1DM and T2DM [38]	Yes [38]	>24 years (T1DM) [38]	80 studies (T1DM + T2DM) [38]
S. Pham et al., 2013 [39]	No (abstract only)	Meta-analysis of RCTs	T2DM [39]	No [39]	Mean ~5 years [39]	28,614 T2DM [39]
B. Braffett et al., 2019 [5]	Yes	RCT with observational follow-up (DCCT/EDIC)	T1DM [5]	Yes [5]	~30 years [5]	1,441 T1DM [5]
I. Dasgupta & Ajay K. Singh, 2017 [40]	No (abstract only)	Meta-analysis of RCTs	T1DM and T2DM [40]	No [40]	Mean 57 months (range 6mo–10y) [40]	1,589 T1DM; 27,654 T2DM [40]
P. Liebson, 2009 [10]	No (abstract only)	RCT with observational follow-up (UKPDS)	T2DM [10]	Yes [10]	4y intervention + 10y follow-up [10]	4,209 T2DM (glucose arm) [10]
E. Zander et al., 2016 [41]	Yes	Review of RCTs with observational follow-up	T1DM and T2DM [41]	Yes [41]	≥10 years [41]	Multiple trials [41]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
D. Matthews, 2020 [15]	Yes	RCT with observational follow-up (ADVANCE/ADVANCE-ON)	T2DM [15]	Yes [15]	~5y intervention + ADVANCE-ON extension [15]	11,140 T2DM [15]
Lorraine Lipscombe, 2009 [42]	No (abstract only)	Meta-analysis	T2DM [42]	No [42]	Mean 5 years [42]	33,040 T2DM [42]
S. Cleland, 2010 [43]	No (abstract only)	Prospective cohort (EURODIAB) and RCT with follow-up (DCCT/EDIC)	T1DM [43]	Yes [43]	6.5y intervention + 17y follow-up [43]	2,787 (EURODIAB); 1,441 (DCCT) [43]
Anna Maria Buehler, 2010 [44]	Yes	Systematic review and meta-analysis	T2DM [44]	No [44]	Not specified [44]	27,814 T2DM [44]
I. R. Unnikrishnan et al., 2011 [45]	No (abstract only)	Narrative review	T2DM [45]	Yes [45]	Not specified [45]	Not specified [45]
B. Hemmingsen et al., 2011 [9]	Yes	Systematic review, meta-analysis, and trial sequential analysis	T2DM [9]	No [9]	3 days–12.5 years [9]	28,614 T2DM [9]
S. Kalra, 2023 [46]	No (abstract only)	RCT with observational follow-up (ADVANCE/ADVANCE-ON)	T2DM [46]	No [46]	Not specified [46]	Not specified [46]
T. Mattila & A. Boer, 2010 [47]	No (abstract only)	Review of RCTs and meta-analyses	T1DM and T2DM [47]	No [47]	Not specified [47]	>30,000 (combined) [47]
Alba E. Morales, 2009 [48]	No (abstract only)	Review of DCCT/EDIC	T1DM [48]	No [48]	>15 years [48]	>1,400 T1DM [48]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
F. Giorgino et al., 2013 [13]	Yes	Narrative review	T2DM [13]	No [13]	ACCORD (~5y), ADVANCE (5y), VADT (~10y) [13]	~23,182 combined T2DM [13]
S. Greenfield et al., 2009 [49]	Yes	Observational longitudinal study	T2DM [49]	No [49]	5 years [49]	2,613 T2DM [49]
H. Itoh et al., 2017 [50]	No (abstract only)	Systematic review of RCTs	T1DM and T2DM [50]	Yes [50]	Not specified [50]	Not specified [50]
R. Roussel et al., 2018 [16]	No (abstract only)	Narrative review/meta-regression	T2DM [16]	No [16]	Not specified [16]	Not specified [16]
I. Tkáč, 2009 [51]	No (abstract only)	Meta-analysis	T2DM [51]	No [51]	Not specified [51]	Not specified [51]
D. Giugliano et al., 2019 [52]	No (abstract only)	Systematic review and meta-analysis	T2DM [52]	No [52]	Not specified [52]	Not specified [52]
J. Davidson, 2004 [53]	Yes	Review of DCCT and UKPDS	T1DM and T2DM [53]	No [53]	6.5y (DCCT); 10y (UKPDS) [53]	3,867 T2DM (UKPDS) [53]
Pankratova Yu et al., 2010 [54]	No (abstract only)	Narrative review	T2DM [54]	No [54]	Not specified [54]	Not specified [54]
J. Buse, 2015 [55]	No (abstract only)	Narrative review	T2DM [55]	No [55]	Not specified [55]	Not specified [55]
P. Kishore et al., 2012 [56]	No (abstract only)	Narrative review	T2DM [56]	No [56]	Not specified [56]	Not specified [56]
V. Miranda et al., 2009 [57]	No (abstract only)	Narrative review	T2DM [57]	Yes (mentions possible legacy effect) [57]	Not specified [57]	Not specified [57]
F. Ismail-Beigi & E. Moghissi, 2008 [14]	No (abstract only)	Narrative review	T2DM [14]	No [14]	Not specified [14]	Not specified [14]
C. Lerch & B. Richter, 2009 [58]	No (abstract only)	Narrative review/editorial	T2DM [58]	No [58]	Not specified [58]	Not specified [58]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
J. P. Lindahl et al., 2014 [59]	No (abstract only)	Narrative review	T1DM [59]	No [59]	Not specified [59]	Not specified [59]
A. Buehler et al., 2013 [7]	No (abstract only)	Systematic review and meta-analysis	T2DM [7]	No [7]	Not specified [7]	27,654 T2DM [7]
S. Virk et al., 2015 [60]	No (abstract only)	Systematic review and meta-analysis	T1DM [60]	No [60]	Not specified [60]	9,302 T1DM [60]
S. Zoungas, 2020 [61]	No (abstract only)	Narrative review	T2DM [61]	No [61]	Not specified [61]	Not specified [61]
R. Aldafas et al., 2023 [8]	Yes	Systematic review and meta-analysis	T2DM [8]	No [8]	4–160 months [8]	34,536 T2DM [8]
Frcp Rury R. Holman, 2002 [62]	No (abstract only)	Review (UKPDS analysis)	T2DM [62]	No [62]	Not specified [62]	Not specified [62]
H. Ping, 2009 [63]	No (abstract only)	Meta-analysis	T2DM [63]	No [63]	Not specified [63]	37,004 T2DM [63]
Vijaykumar Lingegowda, 2011 [64]	No (abstract only)	Meta-analysis (ACP Journal Club summary)	T2DM [64]	No [64]	Not specified [64]	Not specified [64]
Asco et al., 2010 [65]	No (abstract only)	Narrative review	T2DM [65]	No (mentions legacy effect) [65]	Not specified [65]	Not specified [65]
Rachel Folz & N. Laiteerapong, 2021 [18]	Yes	Narrative review	T1DM and T2DM [18]	Yes [18]	Up to 30 years [18]	Multiple trials [18]
V. Montori & Merc Fernández-Balsells, 2009 [66]	No (abstract only)	Narrative review	T2DM [66]	No [66]	Not specified [66]	Not specified [66]
M. Volpe et al., 2011 [67]	No (abstract only)	Narrative review	T2DM [67]	Yes (antihy-pertensive legacy) [67]	Not specified [67]	Not specified [67]
B. Hemmingsen, 2011 [68]	No (abstract only)	Meta-analysis (Cochrane review)	T2DM [68]	No [68]	3 days–12.5 years [68]	~30,000 T2DM [68]
E. Huang et al., 2001 [69]	No (abstract only)	Meta-analysis	T2DM [69]	No [69]	Not specified [69]	Not specified [69]

Study	Full Text Retrieved?	Study Type	Diabetes Type	Specifically Examines Legacy Effect	Total Follow-up Duration	Sample Size
L. Park & D. Wexler, 2010 [70]	Yes	Narrative review	T1DM and T2DM [70]	Yes [70]	21y (UKPDS); 17y (DCCT) [70]	4,620 T2DM (UKPDS); 1,441 T1DM (DCCT) [70]
R. King & P. J. Grant, 2016 [71]	No (abstract only)	Narrative review	T1DM and T2DM [71]	No [71]	Not specified [71]	Not specified [71]
Juliet Meir et al., 2023 [72]	No (abstract only)	Narrative review	T1DM and T2DM [72]	No [72]	Not specified [72]	Not specified [72]
S.G.H.A. Swinnen, 2010 [73]	Yes	Narrative review	T2DM [73]	No [73]	Not specified [73]	Not specified [73]
J. Červený et al., 1998 [74]	Yes	Review of prospective studies	T1DM and T2DM [74]	No [74]	~6 years (DCCT) [74]	1,441 T1DM (DCCT); 110 T2DM (Kumamoto) [74]
T. Crabtree et al., 2022 [75]	Yes	Systematic review and meta-analysis	T2DM (elderly/frail) [75]	No [75]	Not specified [75]	15 clinical studies [75]
J. Kuzhively et al., 2018 [76]	No (abstract only)	Retrospective cohort study	T2DM (advanced nephropathy) [76]	Yes [76]	2 years post-intervention [76]	72 patients [76]
Rim Hasan et al., 2016 [77]	No (abstract only)	Systematic review and meta-analysis	T2DM [77]	No [77]	Not specified [77]	10,897 T2DM [77]
F. Giorgino et al., 2016 [78]	Yes	Narrative review	T2DM [78]	No [78]	ADVANCE (5.4y), VADT (~10y), ACCORD (3.5y active) [78]	Multiple trials [78]
S. Kunutsor et al., 2024 [79]	Yes	Systematic review and meta-analysis of CVOTs	T2DM [79]	No [79]	1.3–5.4 years [79]	169,513 T2DM [79]
L. Mercado-Asis, 2021 [80]	Yes	Retrospective cohort study	T2DM [80]	No [80]	Median 12 years (7–22 years) [80]	76 T2DM [80]

The corpus is dominated by studies focused exclusively on T2DM (approximately 55 of 80 sources), with roughly

15 addressing T1DM alone or T1DM in combination with T2DM. The majority of primary trial evidence for legacy effects derives from a small number of cornerstone studies—the DCCT/EDIC for T1DM [1, 4], and the UKPDS, ACCORD, ADVANCE, and VADT series for T2DM [12, 15, 20, 37] —with the remaining sources largely providing meta-analytic synthesis, narrative review, or commentary on these trials. Most reviews and meta-analyses were available in abstract form only, limiting granular data extraction for some sources. A notable plurality of sources (approximately 35 of 80) specifically engaged with the concept of legacy effects or metabolic memory, while the remainder addressed intensive glycemic control outcomes more broadly. Population characteristics diverge sharply: T1DM studies enrolled younger patients with shorter disease duration (mean age 13–39 years, disease duration 2–15 years at randomization [1, 4]), whereas T2DM trials enrolled middle-aged to older patients (mean ages 54–66 years [70]) with diabetes durations ranging from newly diagnosed (UKPDS [37]) to over 10 years (ACCORD, ADVANCE, VADT [13, 78]).

Microvascular Outcomes of Intensive Glycemic Control

Type 1 Diabetes: Retinopathy, Nephropathy, and Neuropathy

The DCCT/EDIC program provides the most comprehensive and long-term data on microvascular legacy effects in T1DM. During the mean 6.5-year DCCT intervention phase, intensive therapy—targeting HbA1c as close to the nondiabetic range as possible via three or more daily injections or insulin pump therapy—achieved a median HbA1c of 7% versus 9% in the conventional arm [1]. This separation produced striking reductions in all three classical microvascular complications. Retinopathy incidence was reduced by 76% in the primary prevention cohort and progression slowed by 54% in the secondary intervention cohort [20]. Microalbuminuria was reduced by 39% [2], clinical neuropathy by 60% [2], and nephropathy incidence by approximately 35–56% [38].

In the Fullerton et al. 2014 Cochrane review of 12 T1DM RCTs (n=2,230), the development of retinopathy was reduced with a relative risk (RR) of 0.27 (95% CI 0.18–0.42; P<0.00001) and neuropathy was reduced with RR 0.35 (95% CI 0.23–0.53; P<0.00001), both assessed as high quality evidence [3]. Nephropathy incidence showed a moderate-quality RR of 0.56 (95% CI 0.46–0.68; P<0.00001) [3]. Retinopathy progression over at least two years showed RR 0.61 (95% CI 0.49–0.76; P<0.0001) [3]. A systematic review focused on diabetic retinopathy in T1DM by Virk et al. (2015) reported that incident diabetic retinopathy was reduced by intensive versus conventional insulin therapy (RR 0.43; 95% CI 0.23–0.83) and by insulin pump versus multiple daily injections (RR 0.45; 95% CI 0.24–0.83) [60], with the pump benefit independent of HbA1c [60].

The quantitative relationship between HbA1c reduction and microvascular risk is continuous: Nathan et al. (2013) reported that a 10% reduction in mean HbA1c explained 96% of the risk reduction for retinopathy, 98% for nephropathy, and 92% for neuropathy, with every 10% HbA1c reduction associated with approximately 44% lower retinopathy risk, 25% lower microalbuminuria risk, and 30% lower neuropathy risk [4]. Per Davidson (2004), for every 1% decrease in HbA1c, microvascular complications were reduced by 37% (P<0.0001) and amputation or peripheral vascular disease death by 43% (P<0.0001) [53].

Type 2 Diabetes: Retinopathy, Nephropathy, and Neuropathy

Across meta-analyses in T2DM, microvascular benefits are consistently documented but of smaller magnitude than in T1DM. Fabian G.S. & M. Rizki F (2025) report that intensive control in T2DM reduced retinopathy progression by 23–33% and nephropathy by 21–26%, compared to 76% retinopathy reduction and 39–56% nephropathy reduction in

T1DM [38]. The Aldafas et al. (2023) meta-analysis of 19 trials (n=34,536 T2DM) found intensive control reduced microalbuminuria (RR 0.67; 95% CI 0.52–0.85), nephropathy (RR 0.78; 95% CI 0.63–0.97), and retinopathy (RR 0.75; 95% CI 0.63–0.90) [8]. Buehler et al. (2013) found consistent reductions in retinopathy progression (RR 0.80; 95% CI 0.71–0.91), peripheral neuropathy incidence (RR 0.94; 95% CI 0.89–0.99), and nephropathy progression (RR 0.55; 95% CI 0.37–0.80) [7]. The Hemmingsen et al. (2011) systematic review reported a composite microvascular risk reduction (RR 0.88; 95% CI 0.79–0.97; P=0.01) and retinopathy reduction (RR 0.80; 95% CI 0.67–0.94; P=0.009), though trial sequential analysis showed that sufficient evidence had not yet been reached for these estimates [9].

For renal outcomes specifically, the Coca et al. (2012) meta-analysis of 7 T2DM trials (n=28,065) demonstrated that intensive control reduced microalbuminuria (RR 0.86; 95% CI 0.76–0.96) and macroalbuminuria (RR 0.74; 95% CI 0.65–0.85) but did not significantly reduce the doubling of serum creatinine (RR 1.06; 95% CI 0.92–1.22), ESRD (RR 0.69; 95% CI 0.46–1.05), or death from renal disease (RR 0.99; 95% CI 0.55–1.79) [32]. This pattern—robust effects on early surrogate markers but limited evidence for clinically severe renal outcomes—is a recurring finding in T2DM. Monami et al. (2021) similarly found a significant reduction in renal adverse events (Mantel-Haenszel OR 0.73; 95% CI 0.65–0.82) but no significant reduction in ocular adverse events (OR 0.94; 95% CI 0.72–1.22) [17].

The Steno-2 study, a 7.8-year multifactorial intervention in 160 T2DM patients with microalbuminuria, found intensive treatment reduced nephropathy by 61%, retinopathy by 58%, and autonomic neuropathy by 63% relative to conventional care [31] —though these reflect multifactorial (not glucose-only) treatment effects.

Neuropathy: A Notably Inconsistent Endpoint

Across T2DM studies, intensive glycemic control's benefit on neuropathy is less consistent than for retinopathy or nephropathy. Tran & Reaven (2020) note that the VADT did not demonstrate a reduction in neuropathy, though they acknowledge that neuropathy evaluations were less consistent methodologically [35]. Hasan et al. (2016) found that intensive control was associated with a significantly slower decline in sensory vibration threshold (mean difference −8.27; 95% CI −9.75 to −6.79) but no significant effect on other neuropathic change endpoints (RR 0.89; 95% CI 0.75–1.05) or ischemic changes (RR 0.92; 95% CI 0.67–1.26) [77].

Cardiovascular and Macrovascular Outcomes

Meta-analytic Evidence Across T2DM Trials

The macrovascular effects of intensive glycemic control are the most contested area of this literature. Across multiple meta-analyses, a consistent but modest signal for reduction of non-fatal myocardial infarction (MI) emerges in T2DM, without corresponding reductions in cardiovascular mortality or all-cause mortality.

The following table summarizes key cardiovascular outcome estimates from major meta-analyses in T2DM:

Source	Non-fatal MI	Stroke	CV Mortality	All-cause Mortality	Severe Hypoglycemia
Kelly et al., 2009 [19]	Reduced (nonfatal MI) [19]	Uncertain [19]	No reduction [19]	No reduction [19]	Increased [19]

Source	Non-fatal MI	Stroke	CV Mortality	All-cause Mortality	Severe Hypoglycemia
Marso et al., 2010 [6]	IRR 0.86 (95% CI 0.77–0.97; P=0.015) [6]	IRR 1.02 (95% CI 0.88–1.20; P=0.62) [6]	Not significant [6]	IRR 1.01 (95% CI 0.86–1.18; P=0.54) [6]	Not reported [6]
Hemmingsen et al., 2011 [9]	RR 0.85 (95% CI 0.76–0.95; P=0.004) [9]	Not significant [9]	RR 1.11 (95% CI 0.92–1.35) [9]	RR 1.02 (95% CI 0.91–1.13) [9]	RR 2.39 (95% CI 1.71–3.34) [9]
Tkáč, 2009 [51]	OR 0.84 (95% CI 0.75–0.93; P=0.001) [51]	No significant difference [51]	No significant difference [51]	No significant difference [51]	Not reported [51]
Buehler et al., 2013 [7]	RR 0.85 (95% CI 0.76–0.95) [7]	RR 1.02 (95% CI 0.88–1.17) [7]	RR 1.04 (95% CI 0.83–1.29) [7]	RR 1.03 (95% CI 0.90–1.17) [7]	RR 2.39 (95% CI 1.79–3.18) [7]
Monami et al., 2021 [17]	MH-OR 0.90 (95% CI 0.84–0.96) [17]	MH-OR 0.89 (95% CI 0.81–0.98) [17]	MH-OR 0.93 (95% CI 0.85–1.01) [17]	MH-OR 0.95 (95% CI 0.88–1.01) [17]	Increased (hypoglycemia-inducing drugs) [17]
Aldafas et al., 2023 [8]	RR 0.80 (95% CI 0.70–0.91) [8]	Not significant [8]	RR 1.03 (95% CI 0.82–1.30) [8]	No significant reduction (except multifactorial) [8]	RR 2.04 (95% CI 1.34–3.10) [8]
H. Ping, 2009 [63]	Included in CV events: OR 0.91 (95% CI 0.85–0.98; P=0.007) [63]	Not significant [63]	OR 1.03 (95% CI 0.83–1.28; P=0.77) [63]	OR 1.00 (95% CI 0.92–1.08; P=0.98) [63]	OR 2.12 (95% CI 1.24–3.60) [63]
Stettler et al., 2006 [27]	Included in macrovascular composite: IRR 0.38 (T1DM); 0.81 (T2DM) [27]	Reduced in T2DM [27]	Not separately reported [27]	Not separately reported [27]	Not reported [27]
Lipscombe, 2009 [42]	RRR 16% (NNT 131 over 5 years) [42]	RRR 10% (not significant) [42]	Not significant [42]	Not significant [42]	Increased [42]
Huang et al., 2001 [69]	Aggregate cardiac events: RR 0.87 (95% CI 0.74–1.01; not significant) [69]	Not specified [69]	Not specified [69]	Not specified [69]	Not reported [69]

The pattern across these meta-analyses is highly consistent: a 10–15% relative reduction in non-fatal MI, no significant reduction in cardiovascular mortality, and no reduction in all-cause mortality. Severe hypoglycemia risk approximately doubles with intensive control [7–9]. This finding has been replicated in every meta-analysis regard-

less of the specific trials included or methodological approach. Mattila & Boer (2010) summarized this succinctly: intensive control is associated with a 10–15% decrease in nonfatal MI in T2DM but has no effect on stroke, cardiovascular death, or all-cause mortality [47].

Individual Trial Cardiovascular Outcomes: ACCORD, ADVANCE, and VADT

The three large contemporaneous T2DM trials—ACCORD, ADVANCE, and VADT—enrolled patients with established diabetes (mean duration approximately 8–12 years) and high cardiovascular risk, and represent a qualitatively different evidence base than the UKPDS.

ACCORD's intensive arm targeting HbA1c <6.0% was terminated early due to a 22% higher all-cause mortality compared to standard therapy (targeting 7.0–7.9%) [15]. Matthews (2020) emphasizes that the rapid glycemic reduction in ACCORD—from 8.1% to 6.4% within 9 months via multiple agents [15] —contrasted with ADVANCE's gradual reduction from 7.5% to 6.5% over 5 years using gliclazide MR, which achieved a significant 10% reduction in combined macro- and microvascular events [15]. The hypoglycemia rate in ACCORD was approximately six times that in ADVANCE, and weight gain was 3.5 kg in ACCORD's intensive arm versus 0.1 kg in ADVANCE [15]. ADVANCE also showed significantly lower rates of renal complications [15, 46], a finding that subsequently catalyzed interest in renal protection as a key therapeutic target.

The VADT at trial completion (median 5.6 years, median HbA1c 6.9% intensive versus 8.4% standard) showed no significant reduction in major cardiovascular events [21]. At the 9.8-year combined follow-up (Hayward et al. 2015), however, intensive therapy was associated with a significantly lower risk of the primary cardiovascular composite (HR 0.83; 95% CI 0.70–0.99; P=0.04), with an absolute reduction of 8.6 major cardiovascular events per 1,000 person-years [20]. Critically, this benefit was not accompanied by reduced cardiovascular mortality (HR 0.88; 95% CI 0.64–1.20; P=0.42) or all-cause mortality (HR 1.05; 95% CI 0.89–1.25; P=0.54) [20]. By the full 15-year follow-up (Reaven et al. 2019), the risk of major cardiovascular events or death was no longer lower in the intensive group (HR 0.91; 95% CI 0.78–1.06; P=0.23; HR for death 1.02; 95% CI 0.88–1.18) [12]. Importantly, the cardiovascular risk reduction was confined to the extended period in which the HbA1c curves remained separated (HR 0.83; 95% CI 0.70–0.99) but did not continue after equalization of HbA1c levels (HR 1.26; 95% CI 0.90–1.75) [12]. The commentary by Santulli (2019) confirmed that intensive control for 5.6 years did not differ from usual care for major CV events at 13.6-year median follow-up [21].

UKPDS and Its Post-Trial Follow-up: Evidence for Legacy Effect in T2DM

The UKPDS enrolled patients with newly diagnosed T2DM and, following a 10-year active treatment phase achieving median HbA1c 7.0% versus 7.9% [37], demonstrated a borderline 16% reduction in MI risk (P=0.052) and a clear microvascular benefit [37]. Its unique value lies in the 10-year post-trial monitoring phase. Despite complete convergence of HbA1c within the first year after trial end [10], the intensive therapy group retained significant risk reductions over the subsequent decade: a 15% reduction in MI (P=0.01) and a 13% reduction in all-cause mortality (P=0.007) in the sulfonylurea/insulin arm, with similar benefits in the metformin arm [10, 29]. This persistent benefit—emerging only in the post-trial period despite convergence of glycemic control—constitutes the clearest demonstration of a macrovascular legacy effect in T2DM [10, 37]. Unnikrishnan et al. (2011) designated this the "legacy effect," paralleling the "metabolic memory" terminology from DCCT/EDIC [45].

The ADVANCE-ON observational extension similarly showed sustained renal benefits from the ADVANCE gliclazide-based intensive intervention [15, 46], supporting the persistence of nephroprotective effects beyond the active treatment period.

Type 1 Diabetes: Cardiovascular Legacy Effects

The most compelling evidence for cardiovascular legacy effects comes from the DCCT/EDIC program in T1DM. After the mean 6.5-year DCCT intervention, patients were followed in the observational EDIC study where HbA1c levels converged between groups within approximately 1 year [4]. Nevertheless, intensive therapy reduced the risk of any cardiovascular disease event by 42% and the risk of nonfatal MI, stroke, or cardiovascular death by 57–58% over approximately 17 years of combined DCCT/EDIC follow-up [4, 43]. Cleland (2010) noted a hazard ratio for cardiovascular events of 0.70 (95% CI 0.56–0.88) and for any macrovascular event of 0.83 (95% CI 0.73–0.96) [43]. Over 30 years of DCCT/EDIC combined, Braffett et al. (2019) reported approximately 50% reduction in CVD events attributable to the 6.5-year intensive treatment phase [5]. Nathan (2013) reported a 42% reduction in MACE and 58% reduction in fatal/nonfatal MI and stroke, with benefits persisting approximately 18 years after the intensive intervention phase [4].

For macrovascular outcomes, Stettler et al. (2006) found combined incidence rate ratios for any macrovascular event of 0.38 (95% CI 0.26–0.56) in T1DM—markedly larger than the 0.81 (95% CI 0.73–0.91) in T2DM—with T1DM benefits driven primarily by reductions in cardiac and peripheral vascular events [27]. Lawson et al. (1999), in an early meta-analysis of T1DM RCTs, found that intensive insulin therapy decreased the number of macrovascular events (OR 0.55; 95% CI 0.35–0.88; P=0.015), though it had no significant effect on the number of patients developing macrovascular disease (OR 0.72; 95% CI 0.44–1.17) [30].

Thematic Analysis

Theme 1: Disease Stage and Duration at the Time of Intervention

The single most consistent explanatory factor across the literature is the stage of diabetes at which intensive control is initiated. This theme emerges across virtually all studies that examine population characteristics in relation to legacy effects.

In T1DM, the DCCT recruited patients aged 13–39 years with 1–15 years of disease duration and no or minimal complications at baseline [1, 4]. The subsequent metabolic memory effects, persisting for 20–30 years, arose from a population that was early in disease natural history [4, 5]. In T2DM, the contrast between the UKPDS (newly diagnosed patients, mean age ~54 years [70]) and ACCORD/VADT (established disease of 8–12 years, extensive comorbidity and prior CVD in 32–40% [13, 78]) is particularly instructive. The UKPDS demonstrated a post-trial legacy effect in cardiovascular outcomes [10], while neither ACCORD nor VADT demonstrated such a legacy [11, 12]. Ismail-Beigi & Moghissi (2008) articulate this distinction directly: in patients with recently recognized T2DM without prior CVD, glycemic control to near-normal levels appears effective in preventing CVD events and mortality, whereas in established disease with existing CVD, it does not reduce further events or mortality [14].

Prattichizzo et al. (2020), in a meta-analysis of 7 RCTs (n=40,346), found the most pronounced macrovascular protection in patients with diabetes duration less than 10 years (OR 0.73; 95% CI 0.56–0.94; P=0.01) and in those without previous cardiovascular events at baseline (OR 0.64; 95% CI 0.48–0.86; P=0.003), with an even stronger benefit in RCTs with post-trial follow-up greater than 10 years (OR 0.71; 95% CI 0.57–0.88; P=0.002) [11]. Critically, however, no protective legacy effect was observed when examining only events recorded during post-active observational phases (OR 0.99; 95% CI 0.92–1.06; P=0.81) [11], suggesting that in T2DM the macrovascular benefit requires sustained glycemic separation rather than persisting independently.

Folz & Laiteerapong (2021) synthesize this across trial data and observational cohorts, concluding that the glycemic

legacy effect is a long-term benefit conferred to individuals in the early stages of diabetes and that it is muted over time as vasculature changes and complications develop [18]. Santulli (2019) highlights that the VADT-F's failure to demonstrate a legacy effect in advanced T2DM contrasts with UKPDS findings in new-onset disease, and attributes this to the crucial role of early intervention [21].

The Greenfield et al. (2009) observational study (n=2,613 T2DM, 5-year follow-up across 205 Italian practices) provides complementary evidence: tight glycemic control (HbA1c ≤6.5%) was associated with lower cardiovascular event risk in patients with low to moderate comorbidity (HR 0.58; 95% CI 0.41–0.82) but not in those with high comorbidity [49]. This finding directly implicates comorbidity burden—largely a proxy for advanced disease and extensive prior vascular injury—as a modifier of the glycemic benefit.

Theme 2: The Temporal Architecture of Legacy Effects—Microvascular Before Macrovascular

A consistent temporal pattern distinguishes microvascular from macrovascular legacy effects across all diabetes types. Microvascular benefits emerge during active treatment and persist robustly into post-trial follow-up periods [9]. Macrovascular benefits, where present, tend to emerge later and demonstrate a more complex post-trial trajectory.

In T1DM, retinopathy and neuropathy benefits were detectable within the 6.5-year DCCT intervention phase [2], and post-trial persistence of these effects over at least 10 years was documented by Wright (2009, 2010) [24, 25]. Cardiovascular benefits in T1DM, however, only became statistically significant in the EDIC follow-up, approximately 17 years after randomization [4], suggesting a prolonged latency for atherosclerotic plaque consequences to manifest as clinical events.

In T2DM, the Hemmingsen et al. (2011) systematic review noted that microvascular benefits in T2DM take more than five years to emerge [9], and both microvascular and macrovascular effects are more pronounced over extended periods. Kelvin Tran & Reaven (2020) observed that the VADT showed cardiovascular benefit 5 years post-trial (coinciding with continued HbA1c separation of 0.2–0.3 percentage points in the first three post-trial years), which waned by 10 years [35]. This suggests that the intermediate post-trial period, when modest glycemic separation remained, may have been critical to the cardiovascular benefit observed at 10 years but not at 15 years [35].

Itoh et al. (2017), reviewing cardiometabolic memory across 21 positive-memory RCTs spanning diabetes, hypertension, and dyslipidemia, found that transient intensive glucose lowering readily induced memory for suppression of microangiopathies during the active phase, while memory for macroangiopathy suppression tended to appear first in the post-trial observation period [50]. This temporal dissociation—microvascular memory preceding macrovascular memory—is mechanistically plausible given the different pathophysiology of capillary injury (more directly glycemia-mediated) versus atherosclerosis (modulated by multiple intersecting risk factors).

Giorgino et al. (2013) note that in T2DM at least three to five years are usually required before possible differences in nonfatal MI rates become apparent [13], and the UKPDS demonstrated an ever-increasing statistical significance for cardiovascular endpoints over its extended 17-year follow-up period [78].

Theme 3: Mechanisms of Metabolic Memory—Epigenetics, AGEs, and Mitochondrial Dysfunction

Several sources address proposed biological mechanisms for the persistence of metabolic memory beyond the period of active glycemic control. Nathan et al. (2013) identified advanced glycation end products (AGEs) and epigenetic changes due to hyperglycemia as candidate mechanisms [4]. Folz & Laiteerapong (2021) provide the most detailed mechanistic synthesis, identifying epigenetic modifications, intracellular production of superoxide anions, formation

of AGEs, and chronic inflammation as plausible perpetuators of metabolic memory effects [18]. The common denominator across these mechanisms is that prolonged hyperglycemia inscribes lasting molecular changes in vascular and tissue cells that cannot be immediately reversed by normalization of ambient glucose.

For T1DM, the DCCT/EDIC investigators' analyses have shown that the difference in mean HbA1c during the 6.5-year trial accounted for 96% of the retinopathy risk reduction and 98% of the nephropathy risk reduction [4], suggesting that during the active phase, outcomes are almost entirely glycemia-mediated. The subsequent persistence after HbA1c convergence then must reflect these durable molecular changes. Pop-Busui et al. (2010) describe the DCCT/EDIC experience as providing a comprehensive characterization of the natural history of diabetic neuropathy, including insights into how intensive insulin therapy modifies disease progression through mechanisms extending beyond contemporaneous glycemic control [28].

For T2DM, Roussel et al. (2018) approached this mechanistically by examining cumulative glycemic exposure, finding a strikingly strong correlation between the differential glycemic exposure between trial arms (measured as the area between HbA1c curves integrated over time) and cardiovascular risk reduction, and concluding that both a minimum study duration and a minimum HbA1c reduction magnitude are necessary to drive meaningful CVD risk reduction [16]. This dose-response framing for cumulative exposure aligns with the proposed epigenetic models.

The comparative work of King & Grant (2016) emphasizes that hyperglycemia leads to endothelial dysfunction and increased oxidative stress through multiple pathways, culminating in accelerated atherosclerosis [71], while Wajchenberg et al. (2008) highlight that in T1DM there is a synergistic effect of glycemic control and albuminuria on CVD development [34], suggesting that nephroprotection and cardioprotection are mechanistically linked.

Theme 4: Hypoglycemia as an Effect Modifier and Potential Confounder

Every meta-analysis that assessed severe hypoglycemia found a significant increase with intensive control, with risk approximately doubling: RR/OR estimates range from 1.97 to 2.39 across T2DM meta-analyses [7–9, 44]. In T1DM, the DCCT reported a threefold increased risk of hypoglycemia with intensive therapy [1], though without demonstrated decline in cognitive function or quality of life [1].

Hypoglycemia is not merely an adverse effect but a potential mechanism reducing or negating cardiovascular benefits. Tkáč (2009) proposes that any beneficial effect of better glycemic control on atherosclerotic risk may be attenuated by increased hypoglycemia-related mortality in patients with preexisting cardiovascular disease [51]. The ACCORD experience, where intensive therapy was associated with excess mortality, is particularly instructive: the rapid HbA1c reduction to 6.4% generated hypoglycemia rates approximately six times those of ADVANCE [15], and the polypharmacy required (metformin, sulfonylureas, thiazolidinediones, and insulin in combination) introduced both hypoglycemia and weight gain (3.5 kg in the intensive arm [15]) as competing risks.

Monami et al. (2021) specifically stratified by whether glucose-lowering drugs induced hypoglycemia or not, finding that drugs not inducing hypoglycemia were associated with reductions in MACE, renal adverse events, and all-cause mortality, whereas drugs inducing hypoglycemia showed microvascular benefit only for HbA1c ≤48 mmol/mol, with a higher risk of severe hypoglycemia (OR 2.72; 95% CI 1.79–4.13) [17]. This suggests that the net cardiovascular benefit of intensive glycemic control is substantially dependent on how it is achieved, not merely the HbA1c target reached.

In elderly and frail T2DM patients (age ≥60 years), Crabtree et al. (2022) found that intensive glycemic control was associated with reduced microvascular (HR 0.73; 95% CI 0.68–0.79) and macrovascular complications (HR 0.84; 95% CI 0.79–0.89) but also a substantially increased risk of severe hypoglycemia (HR 2.45; 95% CI 2.22–2.72) without a significant all-cause mortality benefit (HR 0.96; 95% CI 0.90–1.03) [75, 75], highlighting the unfavorable benefit-risk

ratio in this population.

Theme 5: Drug Class, Treatment Intensity, and the Legacy Effect

The apparent heterogeneity in legacy effects across T2DM trials is partly attributable to differences in how intensive control was achieved, not simply the degree of HbA1c reduction. The UKPDS metformin substudy showed significant reductions in MI and all-cause mortality in overweight patients despite achieving only intermediate HbA1c reduction (7.4%), a benefit not replicated with sulfonylurea or insulin at lower HbA1c [37], suggesting class-specific effects beyond glycemia per se. Montori & Fernández-Balsells (2009) note that although the UKPDS data link metformin with improved macrovascular outcomes, this was not confirmed in subsequent comparative effectiveness research, and the mechanism remains unknown [66].

The emergence of GLP-1 receptor agonists and SGLT-2 inhibitors has further complicated legacy effect interpretation in T2DM. Giugliano et al. (2019) found that in cardiovascular outcome trials (CVOTs), GLP-1 receptor agonists and SGLT-2 inhibitors were associated with a 14% lower MACE risk in patients with preexisting cardiovascular disease but a nonsignificant 2% higher risk in those without preexisting CVD (P for interaction=0.021) [52] —a pattern opposite to that seen with older intensive glucose control strategies, which show greater benefit in earlier, lower-risk disease. Kunutsor et al. (2024) confirmed that SGLT-2 inhibitors and GLP-1 receptor agonists reduce MACE, cardiovascular death, and kidney-related microvascular outcomes in T2DM CVOTs (n=169,513) [79], with vascular benefits extending beyond glycemic control per se [79]. Santulli (2019) argues that these newer cardioprotective drug classes, none of which were available at the time of UKPDS, must be considered when contextualizing the contemporary relevance of legacy effect research [21].

The ADVANCE experience with gliclazide MR is frequently cited as a model for the type of intensive control likely to generate legacy effects: gradual HbA1c reduction with low hypoglycemia rates [15, 46], sustained renal benefits in the ADVANCE-ON observational extension [15], and an overall risk-benefit profile substantially more favorable than the ACCORD approach [61].

Theme 6: Legacy Effects in Advanced Nephropathy and Specific Microvascular Sub-domains

The concept of legacy effects at advanced disease stages has been directly tested in specialized populations. Kuzhively et al. (2018) conducted a retrospective review of 72 patients who completed the ADN trial (multifactorial intervention in CKD stages 3–4) and found no significant post-intervention effect on ESRD progression overall, with minimal legacy effect observable only in less advanced nephropathy (CKD 3) [76]. This finding aligns with the broader literature's suggestion that once advanced complications are established, glycemic intervention—even multifactorial—has limited capacity to generate lasting benefit.

Coca et al. (2012) similarly found that while intensive control reduces early renal biomarkers (microalbuminuria, macroalbuminuria), clinical endpoints of doubling of serum creatinine, ESRD, and death from renal disease were not significantly reduced over 2–15 years of trial follow-up in T2DM [32]. The cumulative incidence of ESRD (<1.5%) was extremely low compared to albuminuria rates (~23% microalbuminuria), indicating that follow-up durations of current trials may be insufficient to detect hard renal endpoint legacy effects [32]. The Dasgupta & Singh (2017) meta-analysis of 14 trials (n=29,319) specifically addressing kidney outcomes confirmed that intensive versus standard glycemic control did not differ for ESRD (38% relative risk reduction, not statistically significant) or all-cause mortality [40].

For diabetic foot and amputation, Hasan et al. (2016) found a significant 35% reduction in amputation risk (RR 0.65; 95% CI 0.45–0.94; I^2=0%) with intensive control across 9 T2DM RCTs [77], and Aldafas et al. (2023) found major

amputation risk reduced (RR 0.60; 95% CI 0.38–0.96) [8]. Buehler (2010) found a 36% reduction in limb amputation (RR 0.64; 95% CI 0.43–0.96) [44].

Synthesis

The Apparent Contradiction: Strong Legacy Effects in T1DM, Inconsistent Effects in T2DM

The evidence reviewed presents a genuine and important contradiction. For T1DM, the legacy effect is one of the most reproducible and quantitatively large phenomena in clinical diabetes research: a 6.5-year intensive treatment window in young adults without prior vascular disease produced cardiovascular risk reductions of approximately 42–57% persisting over 18–30 years of follow-up after HbA1c convergence [4, 5, 43]. For T2DM, the picture is substantially more heterogeneous: the UKPDS demonstrated clear post-trial macrovascular legacy benefits [10], the VADT showed transient and waning cardiovascular benefits at 10 years that disappeared at 15 years [12], ACCORD showed excess mortality [15], and meta-analyses consistently find non-fatal MI reduction but no survival benefit.

Context and Population Distinctions Explain Much of the Heterogeneity

The most parsimonious explanation for T2DM heterogeneity is that legacy effects are strongly conditioned on disease stage and vascular burden at intervention. Studies finding macrovascular legacy effects—the UKPDS and, conditionally, the VADT at 10 years—enrolled patients with either newly diagnosed T2DM [37] or long diabetes duration but with a meaningful period of continued glycemic separation post-trial [35]. Studies finding no macrovascular legacy effects enrolled patients with established disease of 8–12 years, substantial cardiovascular comorbidity (32–40% with prior CVD [13, 78]), and applied intensive control too late in the atherosclerotic process for molecular "reprogramming" to prevent clinical events.

Prattichizzo et al. (2020) provide direct meta-analytic evidence for this population-context distinction: the cardiovascular benefit of intensive control was OR 0.64 in patients without prior CVD versus essentially null in the overall analysis when post-active phases were examined alone [11]. This suggests the legacy effect is not an intrinsic property of early glycemic normalization but requires: (1) early enough intervention to preempt irreversible vascular injury, (2) sufficient glycemic separation over a meaningful duration, and (3) a vascular bed capable of molecular reprogramming.

Study Quality Hierarchy and the Role of Post-Trial Glycemic Separation

A critical but underappreciated technical factor is whether post-trial glycemic separation was truly absent. In the UKPDS, HbA1c converged within one year after trial end [10], yet benefits persisted and strengthened over 10 years—representing the clearest case for true metabolic memory independent of ongoing glycemic differences. In the VADT, HbA1c declined to a separation of only 0.2–0.3 percentage points within 3 years of trial end [12], a period that overlapped with the 5-year post-trial assessment showing significant benefit [20]. Tran & Reaven (2020) explicitly note that the 5-year post-trial period included 3 additional years of HbA1c separation, suggesting that the "legacy" cardiovascular benefit at 10 years may have reflected ongoing glycemic differences rather than true metabolic memory [35]. By contrast, at 15-year follow-up when any separation had long since disappeared, the cardiovascular benefit was also absent [12]. This distinction—genuine metabolic memory versus prolonged pharmacological effect—is methodologically important and remains incompletely resolved for macrovascular endpoints in T2DM.

The Dose-Response Dimension: Duration × Magnitude of Glycemic Exposure

Roussel et al. (2018) provide a quantitative framework that reconciles many apparent contradictions: examining cumulative glycemic exposure (the integral of the HbA1c difference between arms over trial duration), they find a strong correlation with cardiovascular risk reduction [16]. This implies that short-duration trials with modest HbA1c separation (e.g., ACCORD at 3.5 years with HbA1c 6.4% vs 7.5% [70]) generate insufficient cumulative glycemic separation to drive legacy effects, whereas UKPDS at 10 years (HbA1c 7.0% vs 7.9% [37]) generates a large cumulative differential despite a modest per-year separation. This dose-response model predicts that trials with both longer duration and larger HbA1c separation—like DCCT (6.5 years, 2-percentage-point separation [1])—would generate the largest and most durable legacy effects, which is consistent with the DCCT/EDIC experience.

Mechanistic Models Predict When Legacy Effects Should and Should Not Occur

The epigenetic and AGE-based mechanisms proposed for metabolic memory [4, 18] predict that legacy effects should be strongest in: (1) tissues with low cell turnover where epigenetic marks persist (retina, kidney glomeruli, peripheral nerves), explaining the robust microvascular legacy; (2) patients without pre-existing advanced lesions, because AGE crosslinks and epigenetic reprogramming cannot reverse established fibrosis, atherosclerotic plaque, or glomerulosclerosis; and (3) patients who experienced their critical glycemic exposure early in disease, when vascular beds are most susceptible to reprogramming. This mechanistic model therefore predicts precisely the pattern observed: robust T1DM legacy (young patients, early disease, long post-trial follow-up), robust microvascular legacy in both types, and limited or conditional macrovascular legacy in T2DM dependent on disease stage.

The absence of a legacy effect in the Kuzhively et al. (2018) cohort with advanced diabetic nephropathy (CKD 3–4) [76] and the attenuated effects in elderly T2DM patients [75] are consistent with this framework: at advanced disease stages, structural vascular and renal changes are likely irreversible regardless of glycemic reprogramming.

What Can Be Concluded for Specific Populations and Contexts

Taken together, the evidence supports the following differentiated conclusions. For T1DM, early intensive glycemic control (HbA1c target approximately 7%, initiated within the first 15 years of disease) generates large and durable reductions in all three microvascular complications persisting for at least 20–30 years [4, 5, 24], as well as substantial long-term cardiovascular risk reduction that becomes statistically apparent only after 17+ years [4]. The mechanism is consistent with metabolic memory independent of ongoing glycemic differences. For T2DM, the evidence supports: (a) robust microvascular legacy effects across all stages, though smaller in magnitude than T1DM [18, 38]; (b) macrovascular legacy effects conditional on early intervention in patients without established CVD and with limited vascular burden [11, 14]; (c) no macrovascular legacy in patients with advanced disease, prior CVD, and long disease duration [12, 13]; and (d) net clinical benefit dependent on minimizing hypoglycemia—achievable with drugs not inducing hypoglycemia [17] —and avoiding aggressive rapid glycemic reduction [15]. The legacy effect is substantially stronger and more conclusively demonstrated for microvascular than macrovascular endpoints in both diabetes types, with macrovascular legacy in T2DM remaining a conditional and context-dependent phenomenon rather than a universal property of intensive glycemic control.

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