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The Metabolic Memory Effect in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Long-Term Outcomes Following Early Intensive Glycaemic Control Through May 2026

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ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 June 2026 and was last updated on 3 June 2026.

INTRODUCTION

Review question / Objective Does a durable cardiorenal mortality benefit persist in post-trial follow-up after intensive glycaemic control ends and HbA1c converges, and is the benefit proportional to the depth of HbA1c lowering during the intensive phase?

Rationale This systematic review addresses a critical evidence gap. No comprehensive synthesis with pre-specified interaction analyses currently exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Type 2 diabetes mellitus or impaired glucose tolerance (Da Qing).

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Scopus from January 1, 1977 to May 31, 2026. Manual bibliography searches of UKPDS, ACCORD, ADVANCE, VADT, STENO-2, LOOK AHEAD, Da Qing. Key terms: metabolic memory, legacy effect, post-trial follow-up, UKPDS, ACCORD, ADVANCE, VADT, Da Qing, STENO-2, intensive glycaemic control, type 2 diabetes, long-term mortality.

Participant or population Participants from RCTs of intensive versus conventional glycaemic control in T2DM, followed observationally beyond the trial period during which HbA1c had demonstrably converged between original treatment groups.

Intervention Intensive glycaemic control (any pharmacological strategy achieving HbA1c reduction greater than the comparator arm) during the original trial period.

Comparator Conventional glycaemic control (standard-care comparator arm of the original RCT).

Study designs to be included Post-trial observational follow-up publications from eligible T2DM or IGT intensive glycaemic control RCTs, reporting outcomes during a period in which HbA1c measurements had converged, with minimum 5 years total observation from randomisation.

Eligibility criteria Inclusion: Post-trial follow-up of eligible RCTs; HbA1c convergence documented; reporting at least one of all-cause mortality, CV mortality, MACE, retinopathy, or nephropathy; minimum 5 years total observation.Exclusion: Studies during the active trial period before HbA1c convergence; studies of T1DM; studies without documented HbA1c convergence; follow-up below 5 years.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov, WHO-ICTRP; manual bibliography search of 8 major trial programme chains.

Main outcome(s) All-cause mortality (HR, post-HbA1c-convergence period).

Additional outcome(s) CV mortality; 3-point MACE; retinopathy progression; nephropathy progression. Meta-regression: depth of HbA1c lowering during intensive phase as continuous predictor of legacy mortality HR.

Data management Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

Quality assessment / Risk of bias analysis Newcastle-Ottawa Scale for post-trial observational analyses. RoB 2.0 for any additional prospective arms. GRADE for overall certainty.

Strategy of data synthesis Random-effects DerSimonian-Laird meta-analysis of post-convergence HRs. Meta-regression: depth of HbA1c lowering during intensive phase as continuous moderator. Subgroup analysis: diabetes duration at baseline.

Subgroup analysis T2DM duration below 5 years vs above 10 years at baseline; East Asian vs non-Asian populations; type of intensive treatment; length of original intensive phase (below 5 years vs 5 years or above).

Sensitivity analysis Restriction to trials with minimum 10-year total observation; exclusion of Da Qing (IGT, not T2DM); exclusion of trials with pharmacological convergence post-trial.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Endocrinology and Metabolism; Cardiovascular Epidemiology; Diabetes Pharmacotherapy; Epigenetics.

Keywords metabolic memory; legacy effect; type 2 diabetes; intensive glycaemic control; UKPDS; ACCORD; ADVANCE; post-trial follow-up; cardiovascular mortality; meta-analysis.

Dissemination plans High-impact diabetes or cardiovascular journal; open-access; diabetes guideline committee submission.

Contributions of each author

Author 1 - Abdulrahman Alanazi - As the sole corresponding author and sole affiliated academic, he is responsible for the entirety of the intellectual and scientific work, which would include: Conceptualization and design of the systematic review and meta-analysis. Literature search strategy and execution (PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov through May 31, 2026)
Study selection,.
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Author 2 - Basmah Alanazi - independent literature screening/data verification, clinical input from the health system perspective, and/or manuscript review and approval.
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