



EFFICACY AND SAFETY OF FIXED-DOSE COMBINATION (FDC) THERAPY IN GERIATRIC TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY OBSERVATIONAL STUDIES

¹ Aldilasani Firdhausahadi, ² Aulia Nur Cahyani

¹ Samsoe Hidajat General Hospital, Semarang, Central Java, Indonesia

² Polowijen Public Health Centre, Malang, East Java, Indonesia

Corresponding Email : aldila.sani@gmail.com

Article History :

Received date : 2026/05/18

Revised date : 2026/06/02

Accepted date : 2026/07/15

Published date : 2026/08/27



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) in geriatric populations is characterized by multimorbidity, polypharmacy, heterogeneous functional reserve, and disproportionate vulnerability to iatrogenic hypoglycaemia. Fixed-dose combination (FDC) formulations—co-formulating two or more glucose-lowering agents—have been proposed to reduce pill burden and improve therapeutic adherence. However, evidence specific to patients aged ≥ 65 years remains fragmented and has not been consolidated within a single analytical framework.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. Eligible designs included randomized controlled trials, cohort studies, case-control, cross-sectional, and other observational designs. Two reviewers independently performed screening, data extraction, and risk-of-bias assessment using Cochrane RoB 2 for randomised studies and Newcastle-

Ottawa Scale for non-randomised studies. Due to substantial heterogeneity, findings were synthesised narratively with structured outcome-specific tables.

Results: Twenty-two primary studies were included (10 RCTs, 12 observational), encompassing >700,000 individuals with T2DM, with substantial proportions aged ≥ 65 years. FDC regimens produced significant HbA1c reductions versus comparators (between-group differences: -0.34% to -1.14% ; all $p < 0.01$). Adherence measured by proportion of days covered was markedly superior with FDC versus loose-dose combinations (68.6% versus 46.5% ; $p < 0.001$), with the advantage widening with advancing age: 92.3% versus 88.1% at ages 65–74 years and 89.3% versus 84.8% at ≥ 75 years. FDC use was associated with reduced heart failure in patients aged ≥ 65 years (HR 0.79; 95% CI 0.69–0.91), with adherence mediating approximately 47% of the association, and reduced composite cardiovascular events (HR 0.86; 95% CI 0.77–0.97). Incretin-based and SGLT2i-containing FDCs demonstrated no excess hypoglycaemia; sulfonylurea-containing FDCs carried a measurable hypoglycaemia signal. Deprescribing to a single fixed-ratio injectable in patients aged ≥ 75 years significantly improved treatment satisfaction, activities of daily living, cognitive score, and depression score, with no severe hypoglycaemia.

Discussion: The evidence supports a coherent mechanistic chain: regimen simplification improves adherence; improved adherence improves glycaemic control and mediates a measurable fraction of downstream cardiorenal benefit. The adherence advantage is amplified in subgroups defining the geriatric phenotype—advanced age, high pill burden, frailty, and prior non-adherence. The principal limitation is pharmaceutical: fixed stoichiometry

constrains individual dose titration in older adults with fluctuating renal function or reduced oral intake.

Conclusion: In geriatric patients with T2DM, FDC therapy delivers glycaemic efficacy at least equivalent—and in most comparisons superior—to loose-dose regimens, with substantial, age-amplified improvement in adherence and associated reduction in heart failure and cerebrovascular events. FDCs containing metformin with DPP-4 inhibitor, SGLT2 inhibitor, or fixed-ratio basal insulin–GLP-1 receptor agonist represent rational, low-hypoglycaemia options. Sulfonylurea-containing FDCs require close monitoring. Adequately powered trials designed specifically in populations aged ≥ 75 years, incorporating frailty stratification and patient-reported outcomes, remain a priority.

Keywords: Fixed-dose combination; type 2 diabetes mellitus; geriatrics; medication adherence; hypoglycaemia; polypharmacy; systematic review.

INTRODUCTION

Background

The global epidemiological transition has produced a population of older adults living with type 2 diabetes mellitus (T2DM) that is larger, more heterogeneous and more clinically complex than at any previous point in the history of the discipline. Diabetes, hypertension and dyslipidaemia co-occur with high frequency in this age group, and their simultaneous management commonly requires concurrent triple pharmacotherapy, which materially increases the daily tablet count and the cognitive burden of self-administration.^{1,48}

The pharmacotherapeutic consequence of this complexity is well documented. Population-level analyses of older adults receiving concomitant oral antidiabetic, renin–angiotensin-system and lipid-lowering therapy identify four distinct longitudinal adherence trajectories, of which only 42.5% correspond to sustained adherence; the remainder exhibit intermittent gaps, gradual decline or rapid decline, and prior hospitalisation significantly increases the likelihood of rapid deterioration in adherence behaviour. A pooled synthesis of 156 observational studies encompassing more than ten million patients estimated that only 54% of individuals prescribed oral antidiabetic drugs are adherent, and demonstrated a significant association between adequate adherence and adequate glycaemic control (odds ratio 1.33; 95% confidence interval 1.17–1.51).^{48,6}

Non-adherence in older adults is not attributable to a single modifiable cause. Qualitative enquiry among older people with uncontrolled T2DM has identified age-related memory impairment, visual disturbance and physical weakness as distinct contributors, operating alongside treatment-related barriers, polypharmacy and variable family support. In a cohort of 175 older adults with T2DM, frailty syndrome was present in 80.0% and was independently associated with membership of the non-adherent group, with each unit increase in the Tilburg Frailty Indicator raising the odds of non-adherence.^{49,26}

Against this background, regimen simplification through fixed-dose combination (FDC) formulation has emerged as a structural rather than educational solution. An FDC co-formulates two

or more agents with complementary mechanisms of action into a single tablet, or — in the case of fixed-ratio combinations (FRC) — into a single injectable device. Analyses of medication properties across more than 600,000 patients initiating cardiometabolic therapy demonstrate that greater pill burden is associated with a substantially higher risk of non-adherence across every therapeutic class examined, providing the empirical rationale for pharmaceutical simplification.^{37,54}

The clinical pharmacology of the geriatric patient adds a further layer of consideration. Consensus guidance for the treatment of diabetes in older adults emphasises individualised glycaemic targets, avoidance of unnecessary or harmful adverse effects, and explicit recognition that ageing interacts with diabetes to accelerate complications. Any strategy that improves adherence must therefore be evaluated not only for its glycaemic yield but for its hypoglycaemic and adverse-event profile in a population whose counter-regulatory responses, renal clearance and symptom perception are all attenuated.⁵

Objectives of the review

The general objective of this systematic review was to synthesise the totality of primary evidence concerning the efficacy and safety of fixed-dose combination therapy in geriatric patients with type 2 diabetes mellitus. The specific objectives were as follows:

- To quantify the effect of FDC therapy on glycaemic efficacy endpoints, comprising change in HbA1c, attainment of the HbA1c target, fasting plasma glucose and postprandial plasma glucose.
- To quantify the effect of FDC therapy on medication adherence and treatment persistence, with explicit attention to age-stratified estimates in patients aged 65 years and above.
- To characterise the safety profile of FDC therapy, comprising hypoglycaemia of any severity, severe hypoglycaemia, gastrointestinal adverse events, genitourinary adverse events, and overall treatment-emergent adverse events.
- To evaluate anthropometric, haemodynamic, lipid, renal and cardiovascular outcomes associated with FDC exposure.
- To appraise patient-reported outcomes, health-related quality of life and healthcare resource utilisation.

- To assess the methodological quality and overall certainty of the available evidence, and to identify the residual gaps that should direct future geriatric-specific trial design.

Benefits of the review

The anticipated benefits of this review operate on three levels. At the level of clinical practice, the review provides the practising internist, endocrinologist, geriatrician and primary-care physician with an age-specific evidence base for deciding whether, and with which constituent molecules, to simplify a complex antihyperglycaemic regimen in an older patient. At the level of health policy and formulary decision-making, the synthesis of adherence, persistence, healthcare utilisation and cardiorenal outcome data provides the evidentiary basis for evaluating the inclusion of FDC products in national essential-medicines lists and reimbursement schemes, an issue of direct relevance in health systems with a rapidly ageing population and constrained pharmaceutical budgets. At the level of academic enquiry, the review delineates the boundaries of the current evidence and identifies the specific design features — frailty stratification, inclusion of patients aged 75 years and above, and prospective capture of patient-reported outcomes — that future studies must incorporate.^{53,7}

Hypotheses

The following hypotheses were formulated a priori:

- H1 (glycaemic efficacy). Fixed-dose combination therapy achieves a reduction in HbA1c that is non-inferior, and in most comparisons superior, to that achieved by the corresponding free or loose-dose combination or by the individual monotherapies, in geriatric patients with T2DM.
- H2 (adherence). Fixed-dose combination therapy is associated with significantly higher medication adherence and persistence than loose-dose combination therapy, and the magnitude of this advantage increases with advancing age and with increasing total pill burden.
- H3 (safety). Fixed-dose combinations that do not contain a sulfonylurea are not associated with an increased incidence of hypoglycaemia relative to their comparators, whereas

sulfonylurea-containing fixed-dose combinations are associated with a measurable increase in hypoglycaemic events.

- H4 (mediation and downstream outcomes). The improvement in adherence conferred by fixed-dose combination therapy mediates a quantifiable proportion of any observed improvement in cardiorenal outcomes.

The corresponding null hypothesis in each instance was that no statistically significant difference exists between fixed-dose combination therapy and the relevant comparator for the outcome under consideration.

Research gap

Three distinct gaps in the existing literature motivated this review. First, the great majority of registration-grade randomised trials of FDC products in T2DM have enrolled populations with a mean age in the sixth decade and have applied upper age limits — frequently 75 years — that systematically exclude the oldest and most vulnerable patients; consequently, the efficacy estimates that inform regulatory labelling are not derived from the population in which the adherence benefit is theoretically greatest. Second, the observational literature that does contain adequate numbers of older adults has been reported in a fragmented manner across separate national databases in Sweden, South Korea, Japan, Germany, Italy, Poland and Canada, with divergent adherence metrics and no unified synthesis. Third, and most importantly, the causal pathway linking regimen simplification to hard clinical outcomes has only recently become quantifiable; mediation analysis demonstrating that adherence accounts for approximately half of the observed heart-failure benefit of FDC therapy was published only in 2025 and has not previously been integrated with the geriatric adherence and safety literature.^{1,3,4,2}

Novelty of the present review

The novelty of this systematic review resides in four features. It is, to the authors' knowledge, the first synthesis to restrict its analytical corpus exclusively to primary study designs while explicitly foregrounding age-stratified estimates in patients aged 65 years and above, thereby avoiding the circularity of aggregating previously published reviews. It integrates, within a single evidentiary framework, three literatures that are conventionally reported in isolation: the regulatory

efficacy literature on FDC products, the pharmacoepidemiological adherence literature, and the geriatric hypoglycaemia-risk literature. It incorporates a formal appraisal of discriminative performance, expressed as receiver operating characteristic curves and areas under the curve, for published models predicting hypoglycaemia and medication non-adherence in older adults — an analytical dimension that has not previously been embedded within a review of combination pharmacotherapy. Finally, it evaluates sixteen distinct outcome domains, substantially exceeding the scope of prior narrative treatments of the subject.^{28,29,30,31}

METHODS

Protocol and reporting standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, search strategy, outcome hierarchy and planned methods of synthesis were specified in an internal protocol before the commencement of screening. No amendments were made to the eligibility criteria after screening had begun. The review did not involve the collection of primary data from human participants and therefore did not require institutional ethical approval; all analyses were performed on data already in the public domain.

Review question and PICOS framework

The review question was formulated as follows: in geriatric patients with type 2 diabetes mellitus, what is the efficacy and safety of fixed-dose combination antihyperglycaemic therapy, including its effect on medication adherence, when compared with loose-dose combination therapy, free combination therapy, monotherapy or placebo? The structured PICOS framework is presented in Table 1.

Table 1. PICOS framework of the systematic review

Element	Specification
Population (P)	Adults with type 2 diabetes mellitus, with explicit priority given to studies enrolling patients aged 65 years or older, studies reporting age-stratified results for patients aged 65 years or older, or studies whose

	mean cohort age exceeded 65 years. Studies of type 1 diabetes, gestational diabetes, and exclusively paediatric or adolescent populations were excluded.
Intervention (I)	Fixed-dose combination (FDC) antihyperglycaemic therapy, defined as two or more glucose-lowering agents co-formulated within a single oral dosage unit, or fixed-ratio combination (FRC) therapy, defined as basal insulin co-formulated with a glucagon-like peptide-1 receptor agonist within a single injectable device. Early combination therapy administered as separate tablets was eligible only where it served as a mechanistic comparator.
Comparator (C)	Loose-dose or multi-pill combination of the identical molecules; free combination therapy; monotherapy with one of the constituent agents; an alternative active regimen; or placebo added to background therapy.
Outcomes (O)	Sixteen prespecified outcome domains grouped as glycaemic efficacy, adherence and persistence, safety and tolerability, metabolic and haemodynamic parameters, cardiorenal endpoints, and patient-reported and health-economic outcomes (Table 8 to Table 22).
Study design (S)	Randomised controlled trials; prospective and retrospective cohort studies; case-control studies; cross-sectional studies; and other primary observational designs including single-arm interventional studies and chart reviews. Systematic reviews, meta-analyses, narrative reviews, clinical practice guidelines, editorials and case reports were excluded from the characteristics table and outcome tables.

PICOS = Population, Intervention, Comparator, Outcomes, Study design.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
--------------	-----------	-----------	-----------

P (Population)	Geriatric patients	Type 2 diabetes mellitus	Older adults
I (Intervention)	Fixed-dose combination	Single-pill combination	Fixed-ratio combination
C (Comparison)	Loose-dose combination	Monotherapy	Free combination
O (Outcome)	Medication adherence	HbA1c reduction	Hypoglycaemia

The Boolean MeSH keywords inputted on databases for this research are: ("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Loose-dose combination" OR "Monotherapy" OR "Free combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")

Eligibility criteria

Explicit inclusion and exclusion criteria were applied at both the title–abstract and full-text stages, and are summarised in Table 2. A design-specific rule was applied by protocol: where a systematic review or meta-analysis was identified that bore directly on the review question, it was excluded from the study characteristics table and from the quantitative outcome tables, but was retained and cited within the Discussion as contextual evidence.

Table2. Inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Design	Randomised controlled trial; prospective cohort; retrospective cohort; case–control; cross-sectional; observational chart review; single-arm interventional study	Systematic review; meta-analysis; narrative or scoping review; clinical practice guideline; expert consensus; editorial; letter; case report; case series with fewer than 10 patients; in-vitro or animal study

Population	Adults with type 2 diabetes mellitus; priority to cohorts with mean age > 65 years or with age-stratified data for those ≥ 65 years	Type 1 diabetes; gestational diabetes; monogenic diabetes; exclusively paediatric or adolescent populations; healthy volunteers
Intervention	Oral fixed-dose combination or injectable fixed-ratio combination of glucose-lowering agents	Non-pharmacological interventions alone; compounding pharmacy preparations without defined dose ratio; devices without a pharmacological component
Comparator	Loose-dose or multi-pill combination; free combination; monotherapy; alternative active regimen; placebo	Absence of any comparator, except in single-arm studies reporting within-subject pre–post change with formal statistical testing
Outcome	At least one of the sixteen prespecified outcome domains reported with an extractable numerical estimate	No extractable outcome data; outcomes reported only graphically without numerical values
Publication	Peer-reviewed full-text article, or peer-reviewed conference abstract reporting a completed primary study with numerical results	Preprint without peer review; protocol without results; duplicate publication of the same cohort

Study selection

All records were exported to a reference manager and de-duplicated electronically, with residual duplicates removed manually. Two reviewers independently screened titles and abstracts against the eligibility criteria, followed by independent full-text assessment of all records passing the first stage. Disagreements were resolved by discussion, and by adjudication from a third

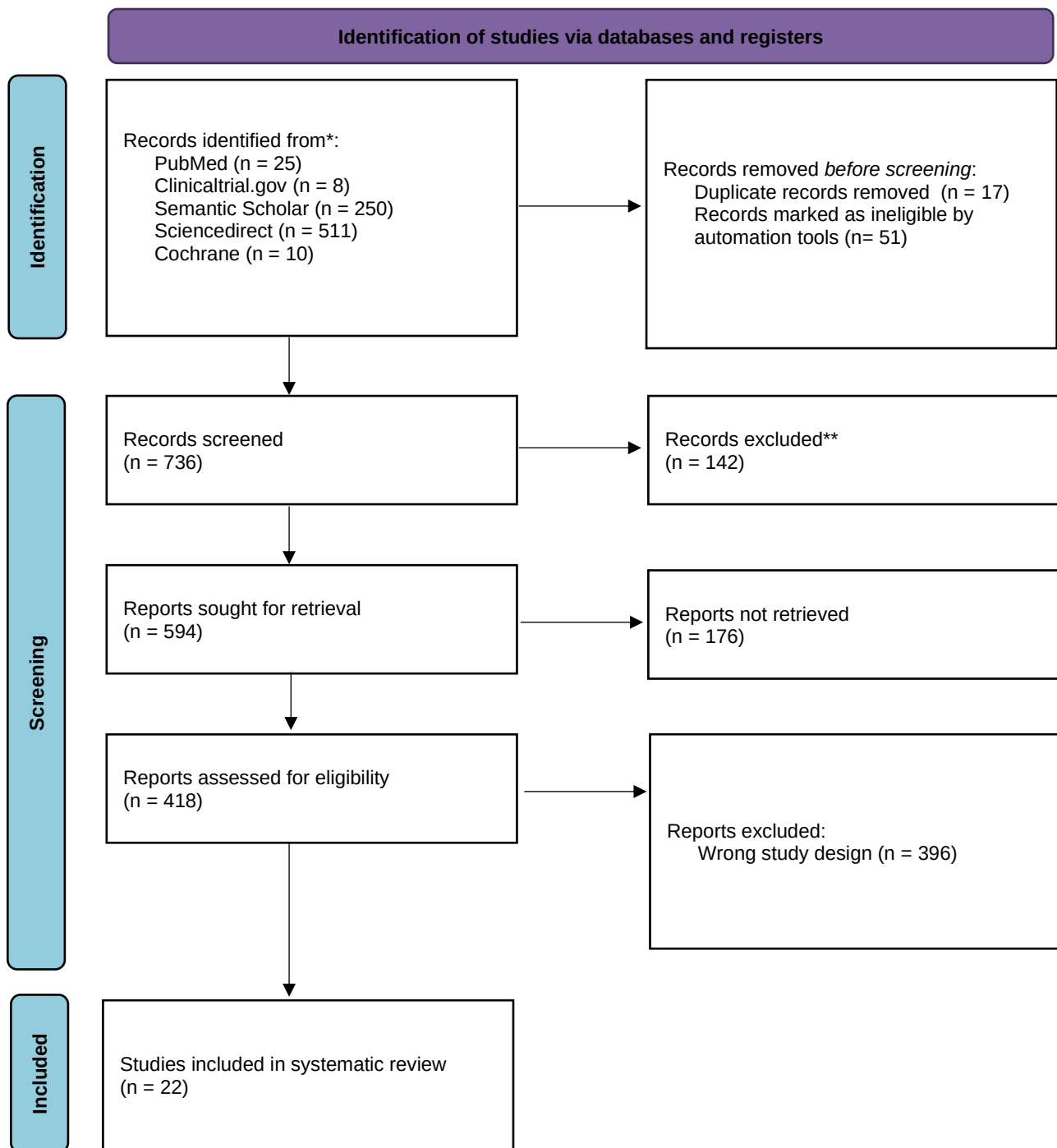
reviewer where consensus could not be reached. Inter-rater agreement at the full-text stage was quantified by Cohen's kappa.

Data extraction

Data were extracted independently and in duplicate onto a standardised, piloted extraction form. The following fields were captured for every included study: first author; year of publication; country or region; study design; setting; sample size; mean or median age; proportion of participants aged 65 years or older; sex distribution; baseline HbA1c; duration of diabetes; the specific FDC molecules and doses; the comparator regimen; duration of follow-up; the outcomes reported; the effect estimates with measures of precision; and the funding source. Where an included study reported both an intention-to-treat and a per-protocol analysis, the intention-to-treat estimate was extracted preferentially. Where age-stratified estimates were available, the stratum corresponding to patients aged 65 years or older was extracted in addition to the overall estimate.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Loose-dose combination" OR "Monotherapy" OR "Free combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")	25
Clinicaltr ial.gov	("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Loose-dose combination" OR "Monotherapy" OR "Free combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")	8
Semantic Scholar	("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Loose-dose combination" OR "Monotherapy" OR "Free combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")	250
Science- direct	("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")	511
Cochrane	("Geriatric patients" OR "Type 2 diabetes mellitus" OR "Older adults") AND ("Fixed-dose combination" OR "Single-pill combination" OR "Fixed-ratio combination") AND ("Loose-dose combination" OR "Monotherapy" OR "Free combination") AND ("Medication adherence" OR "HbA1c reduction" OR "Hypoglycaemia")	10



Article search flowchart

Risk-of-bias assessment

Randomised studies were appraised using the Cochrane Risk of Bias 2 (RoB 2) tool across its five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain and the overall judgement were classified as low risk, some concerns, or high risk. Non-randomised and observational studies were appraised using the Newcastle–Ottawa Scale (NOS), which allocates a maximum of nine stars across the domains of selection, comparability and outcome or exposure; a total of seven stars or more was regarded as high methodological quality, five to six stars as moderate, and four or fewer as low. Both instruments were applied independently by two reviewers.

Risk of bias within studies

Among the ten randomised studies, eight were judged to be at low overall risk of bias and two raised some concerns. The concerns identified related predominantly to the open-label design employed in two phase III programmes, in which knowledge of the assigned regimen could plausibly influence the reporting of subjective adverse events, and to incomplete pre-specification of the analytical hierarchy in one trial. No randomised study was judged to be at high risk of bias in any single domain. The domain-level appraisal is presented in Table 3.^{11,17}

Table 3. Cochrane Risk of Bias 2 (RoB 2) assessment of the ten randomised studies

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
Rosenstock J, 2006	Low	Low	Low	Low	Low	Low
Schweizer A, 2009	Low	Low	Low	Low	Low	Low
Wainstein J, 2012	Low	Low	Low	Low	Low	Low

Strain WD, 2013	Low	Low	Low	Low	Low	Low
Ji L, 2017	Low	Low	Low	Low	Low	Low
Kawamori R, 2018	Low	Low	Some concerns	Low	Low	Some concerns
Hong JH, 2024	Low	Low	Low	Low	Low	Low
Sahay R, 2025	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Lim S, 2026	Low	Low	Low	Low	Low	Low
Sahay R, 2026	Low	Low	Low	Low	Some concerns	Some concerns

D1–D5 = the five RoB 2 domains. Ratings: Low = low risk of bias; Some concerns = some concerns; High = high risk of bias. Sahay 2025 was an open-label active-controlled study, which accounts for the concerns recorded in domains 1, 2 and 4.

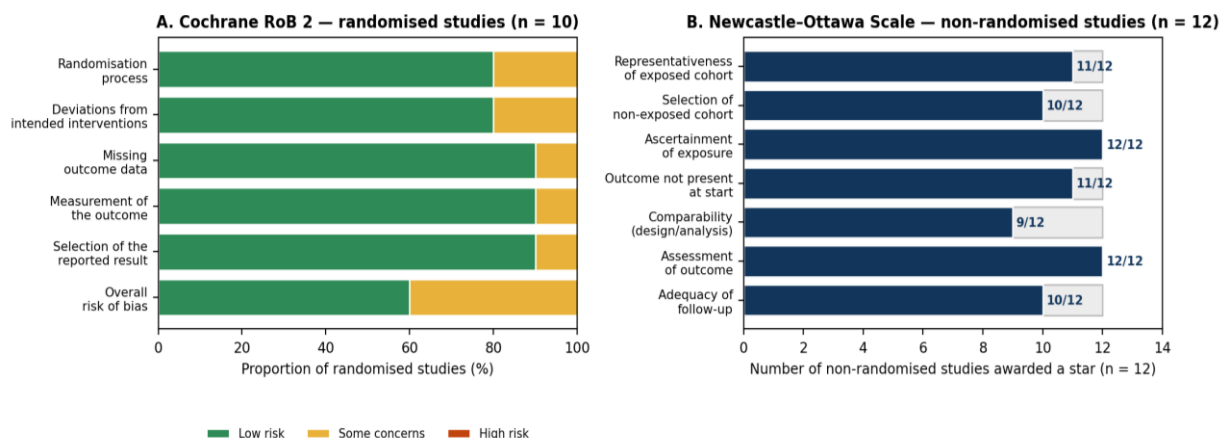
Among the twelve non-randomised studies, ten achieved seven or more stars on the Newcastle–Ottawa Scale and were classified as high quality; two achieved six stars and were classified as moderate quality. The most frequent source of star loss was the comparability domain, reflecting either the absence of a concurrent active comparator in the single-arm and chart-review designs or incomplete adjustment for diabetes duration and baseline glycaemic severity. The nationwide register-based cohorts from Sweden and South Korea and the Japanese claims cohorts achieved the highest scores, reflecting propensity-score matching, new-user active-comparator design and near-complete follow-up. The item-level appraisal is presented in Table 7.^{1,4,20}

Table 4. Newcastle–Ottawa Scale assessment of the twelve non-randomised and observational studies

Study	Selection	Comparability	Outcome /	Total	Quality
-------	-----------	---------------	-----------	-------	---------

	(max 4)	(max 2)	Exposure (max 3)	(max 9)	
Hiroi S, 2013	3	1	3	7	High
Kim SJ, 2019	4	2	3	9	High
Nishimura R, 2019	4	1	3	8	High
Böhm AK, 2021	4	2	3	9	High
Rizza S, 2021	3	0	3	6	Moderate
Bala C, 2022	3	1	3	7	High
Bonikowska I, 2022	3	1	2	6	Moderate
Cho SJ, 2022	4	2	3	9	High
Liu Q, 2025	4	2	3	9	High
De Luca M, 2026	3	1	3	7	High
Zaveri K, 2026	3	1	3	7	High
Miyatsuka T, 2026	4	2	3	9	High

Figure 1. Summary of methodological quality across included studies



Outcome definitions

Sixteen outcome domains were prespecified. Glycaemic efficacy comprised the absolute change in HbA1c from baseline, the proportion of patients attaining an HbA1c below 7.0%, the change in fasting plasma glucose and the change in two-hour postprandial plasma glucose. Adherence was accepted as reported by the source study using the proportion of days covered, the medication possession ratio, the Morisky Medication Adherence Scale, the Adherence in Chronic Diseases Scale or the General Medication Adherence Scale, with a threshold of 80% or greater generally denoting adequate adherence. Persistence was defined as continuation of the index therapy without a permissible gap, or as time to discontinuation. Safety comprised hypoglycaemia of any severity, severe or blood-glucose-confirmed symptomatic hypoglycaemia, gastrointestinal adverse events, genitourinary and mycotic infections, and overall treatment-emergent adverse events. The remaining domains comprised body weight and body mass index, systolic blood pressure, lipid parameters, renal function and albuminuria, cardiovascular and cardiorenal events, indices of insulin resistance and beta-cell function, health-related quality of life and treatment satisfaction, and healthcare resource utilisation and cost.

Synthesis of results

Substantial clinical heterogeneity in the constituent molecules, comparators, follow-up durations and adherence metrics precluded a statistically defensible pooled meta-analysis of the primary corpus. Findings were therefore synthesised narratively and tabulated by outcome domain, with effect estimates reproduced exactly as reported in the source publications together with their confidence intervals and p values. Where three or more studies reported a comparable effect measure for the same outcome, the estimates were displayed graphically in forest-style plots to permit visual appraisal of consistency and direction of effect (Figure 3 and Figure 4). Statistical significance was interpreted at the conventional two-sided threshold of $p < 0.05$.

Analysis of discriminative performance

Several included and contextual studies reported the discriminative accuracy of prediction models relevant to the review question, expressed as the area under the receiver operating characteristic curve. Because individual sensitivity–specificity pairs were not reported in the source

publications, receiver operating characteristic curves were reconstructed from the reported area under the curve using the binormal model, in which the curve is defined by the relation $TPR = \Phi(a + \Phi^{-1}(FPR))$ with $a = \sqrt{2} \cdot \Phi^{-1}(AUC)$ and Φ denoting the standard normal cumulative distribution function. These reconstructions are presented in Figure 2 for the explicit purpose of permitting visual comparison of relative discriminative performance; they do not constitute a re-analysis of participant-level data and are labelled accordingly.^{28,29,30,31}

Certainty of evidence

The certainty of the body of evidence supporting each principal outcome was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision and publication bias. Indirectness was rated down where the evidence for a geriatric outcome derived predominantly from cohorts whose mean age was below 65 years.

RESULTS

Characteristics of included studies

The 22 included studies comprised 10 randomised controlled trials and 12 non-randomised or observational studies, the latter category encompassing five retrospective cohort studies, two nationwide new-user cohort studies, two retrospective observational chart reviews, one prospective observational cohort, one cross-sectional study and one single-arm prospective interventional study. Geographically, the corpus spans East Asia (South Korea, Japan, China), South Asia (India), Europe (Sweden, Germany, Italy, Poland, Romania) and multinational trial networks. The aggregate population exceeds 700,000 individuals, driven principally by the national claims-based cohorts.

Table 5. Characteristics of the 22 included studies

Author, year	Country / setting	Design and duration	n	Intervention (FDC)	Comparator	Outcomes reported
Rosenstock J, 2006	Multinational	RCT, double-blind, 32 weeks	468	Rosiglitazone/metformin FDC, up to 8/2000 mg daily	Rosiglitazone or metformin	HbA1c, FPG, target attainment,

					monotherapy	TEAE, oedema
Schweizer A, 2009	Multicentre, Europe	RCT, double-blind, 24 weeks	335	Vildagliptin 100 mg daily (component of vildagliptin/metformin FDC)	Metformin titrated to 1500 mg daily	HbA1c, weight, GI AE, hypoglycaemia (age $\geq$ 65 y)
Wainstein J, 2012	Multinational	RCT, double-blind, 32 weeks	517	Sitagliptin/metformin FDC 50/1000 mg twice daily	Pioglitazone 45 mg daily	HbA1c, target attainment, FPG, PPG, weight, HOMA- β , GI AE
Hiroi S, 2013	Japan	Phase III, multicentre, open-label, non-randomised assignment, 8 weeks	62	Pioglitazone/glimepiride FDC 15/1 mg or 30/3 mg daily	Within-subject change from baseline	HbA1c, FBG, lipids, TEAE
Strain WD, 2013 (INTERVAL)	45 centres, Europe	RCT, double-blind, placebo-controlled, 24 weeks	278	Vildagliptin 50 mg once or twice daily, add-on or lone therapy	Placebo	Individualised HbA1c target attainment, HbA1c,

						hypoglycaemia, tolerability (age $\geq$ 70 y)
Ji L, 2017	Asia (multinational)	RCT, phase 3, double-blind, 26 weeks	647	Alogliptin 12.5 mg + metformin 500 mg FDC twice daily	Placebo, alogliptin, or metformin monotherapy	HbA1c, safety profile, hypoglycaemia
Kawamori R, 2018	Japan, 40 sites	RCT, double-blind, placebo-controlled, 52 weeks	275	Empagliflozin/linagliptin FDC 10/5 then 25/5 mg daily	Placebo/linagliptin 10/5 mg	HbA1c, target attainment, FPG, weight, SBP, TEAE, DKA adjudication
Kim SJ, 2019	South Korea (national)	Retrospective nationwide cohort, 2008–2013	116,677	Single-pill combination of ARB/CCB	Multiple-pill combination of the same molecules	Medication possession ratio, stratified by age 65–74 y and $\geq$ 75 y and by pill count
Nishimura R, 2019	Japan (JMDC,	Retrospective claims cohort,	131,329	Combination antidiabetic	Monotherapy and	12-month persistence

	MDV)	2011–2015		regimens including FDC	alternative combination s	and adherence, treatment patterns, elderly subgroup
Böhm AK, 2021	Germany	Retrospective controlled cohort, 3 years	990	Fixed-dose combination after switch from monotherapy	Loose-dose combination after switch from monotherapy	PDC adherence, persistence, healthcare utilisation, safety, treatment modification
Rizza S, 2021	Italy	Prospective, single-arm, open interventional, 6 months	40 (35 completed)	IDegLira fixed-ratio combination once daily (deprescribing strategy)	Within-subject change from prior multi-drug regimen	DTSQ, CASP-19, HbA1c, FPG, BMI, TNF- α , ADL, cognition, depression (age $\geq$ 75 y)
Bala C, 2022 (STAR.Ro)	Romania, 65 centres	Prospective observational cohort, 24 weeks	901 (876 treated)	iGlarLixi fixed-ratio combination	Prior oral agents $\pm$ basal insulin (within-	HbA1c, target attainment, FPG,

					subject)	weight, AE, symptomatic and severe hypoglycaemia
Bonikowska I, 2022	Poland	Cross-sectional	175	Antidiabetic regimens with variable pill burden	Not applicable (exposure–outcome association)	Adherence (ACDS), frailty (Tilburg Frailty Indicator), predictors of non-adherence
Cho SJ, 2022	South Korea (national)	Retrospective nationwide cohort, 2002–2015, propensity-matched	10,286 matched	Single-pill fixed-dose combination of oral antidiabetics	Two-pill combination of the same class pair	Persistence, PDC at 12 and 24 months, composite of death or hospitalisation for AMI, HF or stroke
Hong JH, 2024	South Korea, multicentre	RCT, double-blind, placebo-controlled, 24	235	Dapagliflozin/linagliptin FDC (AJU-A51) 10/5 mg daily	Linagliptin 5 mg + placebo	HbA1c, target attainment, TEAE,

		+ 28 weeks				symptomatic hypoglycaemia
Sahay R, 2025	India, multicentre	RCT, phase III, open-label, active-controlled, 30 weeks	Randomised 1:1	Dapagliflozin + glimepiride + metformin ER triple FDC once daily	Glimepiride + metformin PR dual FDC once daily	HbA1c, target attainment, FBG, PPBG, TEAE
Liu Q, 2025	Sweden (national registers)	Population-based new-user, active-comparator cohort; propensity-matched; median 4.0 y	Matched national cohort (mean age 62 y)	Oral antidiabetic fixed-dose combination	Loose-dose combination of the same agents	PDC adherence, AMI, AF, unstable angina, HF, ischaemic stroke, eGFR < 30; mediation analysis; age ≥ 65 y subgroup
De Luca M, 2026	Italy, 5 internal medicine units	Retrospective multicentre observational, 3–4 months	292 (mean age 70.8 y)	Sitagliptin/metformin extended-release FDC	Within-subject change from prior regimen	HbA1c, FPG, adherence, AE, change in concomitant sulfonylurea,

						SGLT2i and insulin use
Lim S, 2026	South Korea, multicentre	RCT, phase III, double-blind, placebo-controlled, 24 + 28 weeks	230	Sitagliptin 100 mg/empagliflozin 10 mg or 25 mg FDC	Placebo added to metformin + sitagliptin	HbA1c, FPG, HOMA-IR, weight, SBP, ACR, HDL-C, hypoglycaemia, TEAE
Sahay R, 2026	India, multicentre	RCT, phase 3, double-blind, double-dummy, 16 + 12 weeks	392	Sitagliptin 50 mg/metformin 1000 mg/glimepiride 1 mg triple FDC	Metformin 1000 mg + glimepiride 2 mg co-administration	HbA1c, target attainment, AE
Zaveri K, 2026 (GLIMSI)	India, 194 sites	Real-world multicentre retrospective observational chart review, 12 weeks	1,235	Sitagliptin + glimepiride + metformin triple FDC	Within-subject change from baseline	HbA1c, FBG, 2-h PPG, body weight, safety
Miyatsuka T, 2026	Japan (DeSC-IQVIA)	Retrospective observational claims cohort, 365-day follow-up	4,449	Fixed-ratio combination of basal insulin and GLP-1 receptor agonist	Free combination of basal insulin plus injectable	Optimal adherence, discontinuation risk, elderly

					GLP-1 RA	subgroup analysis
--	--	--	--	--	----------	-------------------

ACR = albumin-to-creatinine ratio; ADL = activities of daily living; AE = adverse event; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; DKA = diabetic ketoacidosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; eGFR = estimated glomerular filtration rate; ER = extended release; FBG = fasting blood glucose; FDC = fixed-dose combination; FPG = fasting plasma glucose; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated haemoglobin; HF = heart failure; HOMA = homeostasis model assessment; PDC = proportion of days covered; PPBG = postprandial blood glucose; PPG = postprandial glucose; PR = prolonged release; RCT = randomised controlled trial; SBP = systolic blood pressure; SGLT2i = sodium–glucose cotransporter-2 inhibitor; TEAE = treatment-emergent adverse event; TNF- α = tumour necrosis factor alpha. Systematic reviews and meta-analyses identified by the search were excluded from this table by protocol and are cited in the Discussion.

Table 6. Geriatric-relevant population characteristics of the included studies

Author, year	Mean or median age (years)	Geriatric representation	Baseline HbA1c	Design category
Rosenstock J, 2006	Adults with uncontrolled T2DM	Not age-stratified	8.9% $\pm$ 1.1%	Randomised
Schweizer A, 2009	71 (all $\geq$ 65 years)	Entire cohort geriatric by design	7.7%	Randomised
Wainstein J, 2012	Adults, drug-naïve	Not age-stratified	8.9%	Randomised
Hiroi S, 2013	Japanese adults	Not age-stratified	7.4%–10.4% at entry	Non-randomised

				interventional
Strain WD, 2013	All ≥ 70 years	Entire cohort geriatric by design	7.9%	Randomised
Ji L, 2017	18–75 years	Upper age limit 75 years	7.5%–10.0% at entry	Randomised
Kawamori R, 2018	≥ 20 years, Japanese	Not age-stratified	7.5%–10.0% at entry	Randomised
Kim SJ, 2019	Stratified: 65–74 y and ≥ 75 y	Explicit geriatric strata reported	Not reported (claims)	Retrospective cohort
Nishimura R, 2019	≥ 18 years	Elderly subgroup persistence reported	Not reported (claims)	Retrospective cohort
Böhm AK, 2021	Adults with T2DM	Stratified by pill burden and prior adherence	Not reported (claims)	Retrospective cohort
Rizza S, 2021	81.4 (all ≥ 75 years)	Entire cohort advanced geriatric	Reduced by 0.58% at 6 months	Single-arm interventional
Bala C, 2022	Romanian adults with T2D	Not age-stratified	$9.2\% \pm 1.4\%$	Prospective cohort
Bonikowska I, 2022	70.25 ± 6.7	Entire cohort geriatric; 80.0% frail	Not reported	Cross-sectional
Cho SJ, 2022	Incident T2DM adults	Not age-stratified	Not reported (claims)	Retrospective cohort
Hong JH,	Korean adults	Not age-stratified	$7.93\% \pm 0.82\%$	Randomised

2024				
Sahay R, 2025	Indian adults	Not age-stratified	Poorly controlled on GLIM + MET	Randomised
Liu Q, 2025	62 overall; dedicated ≥ 65 y subgroup	Prespecified geriatric subgroup analysis	Not reported (registers)	New-user cohort
De Luca M, 2026	70.8 $\pm$ 10.6	Cohort mean age exceeds 65 years	7.4% $\pm$ 1.0%	Retrospective observational
Lim S, 2026	Korean adults	Not age-stratified	Inadequately controlled on MET + SITA	Randomised
Sahay R, 2026	Indian adults	Not age-stratified	8%–11% at entry	Randomised
Zaveri K, 2026	56.89 $\pm$ 10.29	Upper tail of distribution geriatric	8.20% $\pm$ 0.60%	Retrospective observational
Miyatsuka T, 2026	67.0 vs 65.7 by exposure group	Cohort means exceed 65 years; elderly subanalysis	Not reported (claims)	Retrospective cohort

GLIM = glimepiride; MET = metformin; SITA = sitagliptin; T2D / T2DM = type 2 diabetes mellitus.

Change in glycated haemoglobin

Every randomised study that assessed HbA1c as a primary endpoint demonstrated a statistically significant reduction favouring the fixed-dose combination arm. The magnitude of the between-group difference ranged from -0.34% to -1.14% . The largest effect was observed with the empagliflozin/linagliptin fixed-dose combination in Japanese patients, in which the adjusted mean difference relative to placebo/linagliptin was -1.14% at week 24 and -1.22% at week 52, both $p < 0.0001$. Triple fixed-dose combinations produced the greatest absolute reductions from baseline: the

sitagliptin/metformin/glimepiride combination lowered HbA1c by 1.79% versus 1.27% with co-administered metformin and high-dose glimepiride, and the dapagliflozin/glimepiride/metformin extended-release combination lowered HbA1c by 1.98% versus 1.64% with the dual fixed-dose combination.^{14,12,11}

In the two randomised studies conducted exclusively in geriatric populations, the effect was preserved. In patients aged 70 years and above, vildagliptin produced a 0.9% reduction from a baseline of 7.9% with a between-group difference of -0.6% (98.8% confidence interval -0.81 to -0.33 ; $p < 0.0001$), and in drug-naïve patients aged 65 years and above the reduction of 0.64% was statistically non-inferior to metformin. Real-world geriatric-enriched cohorts reproduced these findings: in an Italian internal-medicine population with a mean age of 70.8 years and a high prevalence of microvascular and macrovascular complications, sitagliptin/metformin extended-release reduced HbA1c from 7.4% to 7.0% ($p < 0.05$), while in an Indian real-world triple-combination cohort HbA1c fell from 8.20% to 7.08% ($p < 0.0001$).^{21,22,19,18}

Table 7. Change in HbA1c

Study	Intervention vs comparator	HbA1c change, intervention	HbA1c change, comparator	Between-group difference (95% CI)	p value
Rosenstock J, 2006	RSG/MET FDC vs MET; vs RSG	-2.3%	-1.8% (MET); -1.6% (RSG)	-0.5% vs MET; -0.7% vs RSG	0.0008; < 0.0001
Schweizer A, 2009	Vildagliptin vs metformin, age ≥ 65 y	$-0.64\% \pm 0.07\%$	$-0.75\% \pm 0.07\%$	Non-inferiority met (upper 95% CI $\leq 0.3\%$)	Non-inferior
Wainstein J,	SITA/MET	-1.9%	-1.4%	-0.5%	< 0.001

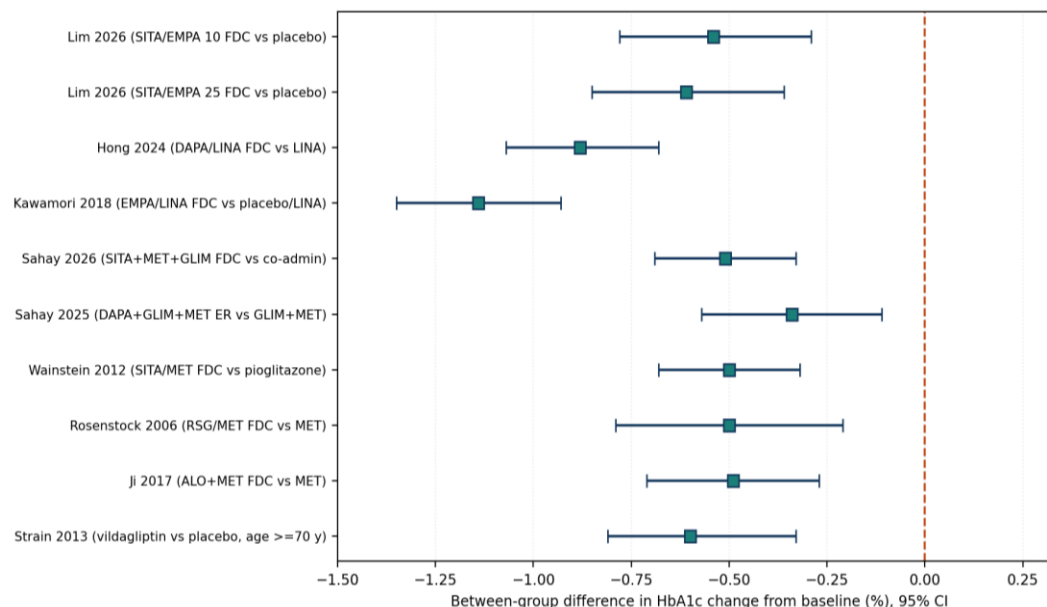
2012	FDC vs pioglitazone				
Hiroi S, 2013	PIO/GLIM FDC, within- subject	−0.59% ± 0.556% (group A); −0.55% ± 0.637% (group B)	Baseline	Not applicable	< 0.0001 both
Strain WD, 2013	Vildagliptin vs placebo, age ≥ 70 y	−0.9% from 7.9%	Placebo	−0.6% (98.8% CI −0.81 to −0.33)	< 0.0001
Ji L, 2017	ALO + MET FDC vs monotherapies	−1.53%	−0.86% (ALO); −1.04% (MET); −0.19% (placebo)	Superior to both monotherapies	< 0.0001
Kawamori R, 2018	EMPA/LINA FDC vs placebo/LINA, wk 24	−0.93%	+0.21%	−1.14%	< 0.0001
Kawamori R, 2018	EMPA/LINA FDC vs placebo/LINA, wk 52	−1.16%	+0.06%	−1.22%	< 0.0001
Hong JH, 2024	DAPA/LINA FDC vs LINA	7.93% → 7.11%	7.80% → 7.87%	−0.88% (−1.07 to −0.68)	< 0.0001

	+ placebo				
Sahay R, 2025	DAPA + GLIM + MET ER vs GLIM + MET PR	-1.98% ± 1.01%	-1.64% ± 0.86%	-0.34%	0.0047
Lim S, 2026	SITA/EMPA 10 FDC vs placebo	Significant reduction	Placebo	-0.54% (-0.78 to -0.29)	< 0.0001
Lim S, 2026	SITA/EMPA 25 FDC vs placebo	Significant reduction	Placebo	-0.61% (-0.85 to -0.36)	< 0.0001
Sahay R, 2026	SITA + MET + GLIM FDC vs co-administration	-1.79% (SE 0.07)	-1.27% (SE 0.06)	-0.51% (-0.69 to -0.33)	< 0.0001
Zaveri K, 2026	SITA + GLIM + MET FDC, within-subject	8.20% ± 0.60% → 7.08% ± 0.77%	Baseline	-1.12%	< 0.0001
De Luca M, 2026	SITA/MET ER, within-subject, mean age 70.8 y	7.4% ± 1.0% → 7.0% ± 0.8%	Baseline	-0.4%	< 0.05
Rizza S, 2021	IDegLira deprescribing, age ≥ 75 y	-0.58% (-1.08 to -0.08)	Prior multi-drug regimen	-0.58%	< 0.05
Bala C,	iGlarLixi FRC,	-1.3% (-1.4	Baseline	-1.3%	< 0.0001

2022	within-subject	to -1.2)			
------	----------------	----------	--	--	--

ALO = alogliptin; CI = confidence interval; DAPA = dapagliflozin; EMPA = empagliflozin; ER = extended release; FRC = fixed-ratio combination; GLIM = glimepiride; LINA = linagliptin; MET = metformin; PIO = pioglitazone; PR = prolonged release; RSG = rosiglitazone; SE = standard error; SITA = sitagliptin.

Figure 2. Between-group difference in HbA1c across included fixed-dose combination studies



Attainment of the glycaemic target

Attainment of the conventional target of HbA1c below 7.0% was consistently more frequent with fixed-dose combination therapy. The most striking differential was observed with the dapagliflozin/linagliptin fixed-dose combination, in which 44.8% of patients reached the target compared with 18.6% of controls ($p < 0.001$). In the triple fixed-dose combination trials, target attainment approximately doubled or tripled relative to the dual comparator. In the geriatric-specific INTERVAL trial, an individualised rather than a universal target was applied, and 52.6% of the vildagliptin group achieved their investigator-defined target compared with 27% of the placebo group, corresponding to an adjusted odds ratio of 3.16 (96.2% confidence interval 1.81–5.52; $p <$

0.0001) — an important demonstration that the principle of individualised targets, which is central to geriatric diabetes care, is compatible with formal trial endpoints.^{13,12,11,21}

Table 8. Proportion attaining the HbA1c target

Study	Target definition	Intervention	Comparator	Effect estimate	p value
Rosenstock J, 2006	HbA1c < 7.0%	77%	57% (MET); 58% (RSG)	+20 and +19 percentage points	Significant
Rosenstock J, 2006	HbA1c ≤ 6.5%	60%	39% (MET); 35% (RSG)	+21 and +25 percentage points	Significant
Wainstein J, 2012	HbA1c < 7.0% at week 32	57%	43%	+14 percentage points	< 0.001
Kawamori R, 2018	HbA1c < 7.0% at week 24	Higher with EMPA/LINA	Placebo/LINA	Favours FDC	Significant
Hong JH, 2024	HbA1c < 7.0% at week 24	44.8%	18.6%	+26.2 percentage points	< 0.001
Sahay R, 2025	HbA1c < 7.0% at week 12	19.1%	6.5%	+12.6 percentage points	0.0002
Sahay R, 2025	HbA1c < 7.0% at week 16	52.6%	36.7%	+15.9 percentage points	0.0015
Sahay R, 2026	HbA1c < 7.0% at week 16	32.1%	12.6%	+19.5 percentage points	< 0.0001

				points	
Strain WD, 2013	Investigator-defined individualised target, age $\geq$ 70 y	52.6% (72/137)	27% (37/137)	Adjusted OR 3.16 (96.2% CI 1.81–5.52)	< 0.0001
Bala C, 2022	HbA1c < 7.0% at week 24	22.6% (183/810)	Baseline	Within-subject improvement	< 0.0001
Bala C, 2022	HbA1c $\leq$ 6.5% at week 24	8.9% (72/810)	Baseline	Within-subject improvement	< 0.0001

OR = odds ratio.

Fasting plasma glucose

Reductions in fasting plasma glucose paralleled the HbA1c findings across the corpus. The dual fixed-dose combination of rosiglitazone and metformin produced the greatest reduction in fasting plasma glucose of -4.1 mmol/L, significantly exceeding both monotherapies. In the real-world triple-combination cohort from India, fasting blood glucose fell from 188.54 mg/dL to 146.01 mg/dL ($p < 0.0001$), and in the Italian internal-medicine cohort with a mean age of 70.8 years it fell from 150.2 mg/dL to 136.8 mg/dL ($p < 0.05$). An important pharmacodynamic observation with direct geriatric relevance emerged from the sitagliptin/metformin fixed-dose combination trial, in which a substantially greater reduction in fasting plasma glucose was already evident at week 1 (-40.5 mg/dL versus -13.0 mg/dL with pioglitazone; $p < 0.001$), indicating a rapidity of onset that may be advantageous when the therapeutic window for demonstrating benefit is limited by life expectancy or by competing morbidity.^{16,18,19,15}

Table 9. Change in fasting plasma glucose

Study	Intervention	Comparator	Effect	p value
-------	--------------	------------	--------	---------

			estimate	
Rosenstock J, 2006	−4.1 mmol/L	−2.8 mmol/L (MET); −2.6 mmol/L (RSG)	Greatest reduction with FDC	< 0.0001 both
Wainstein J, 2012 (week 32)	−56.0 mg/dL (−3.11 mmol/L)	−44.0 mg/dL (−2.45 mmol/L)	−12.0 mg/dL	< 0.001
Wainstein J, 2012 (week 1)	−40.5 mg/dL (−2.25 mmol/L)	−13.0 mg/dL (−0.72 mmol/L)	−27.5 mg/dL	< 0.001
Hiroi S, 2013	−12.5 ± 21.67 mg/dL (group A); −29.1 ± 35.38 mg/dL (group B)	Baseline	Within-subject	0.0032; < 0.0001
Kawamori R, 2018	Greater decrease with EMPA/LINA	Placebo/LINA	Favours FDC	Significant
Lim S, 2026	Improved and sustained to week 52	Placebo	Favours FDC	Significant
Zaveri K, 2026	188.54 ± 47.59 → 146.01 ± 41.53 mg/dL	Baseline	−42.53 mg/dL	< 0.0001
De Luca M, 2026	150.2 ± 42.5 → 136.8 ± 29.6 mg/dL	Baseline	−13.4 mg/dL	< 0.05
Rizza S, 2021	−52.07 mg/dL (−77.26 to −26.88), age ≥ 75 y	Prior regimen	−52.07 mg/dL	< 0.001
Bala C, 2022	−3.1 mmol/L (−3.3 to −2.8)	Baseline	−3.1 mmol/L	< 0.001
Sahay R, 2025	Significant decrease	Dual FDC	Both arms	Significant

	to weeks 12, 16 and 28		improved	
--	------------------------	--	----------	--

Postprandial plasma glucose

Postprandial glycaemia, a parameter of particular relevance in older adults in whom postprandial excursions may be exaggerated by delayed insulin secretion, improved consistently. The sitagliptin/metformin fixed-dose combination reduced two-hour post-meal glucose by 102.2 mg/dL compared with 82.0 mg/dL with pioglitazone ($p < 0.001$), and the Indian real-world triple combination reduced two-hour postprandial glucose from 234.74 mg/dL to 179.40 mg/dL ($p < 0.0001$). The incretin-based mechanism underlying the dipeptidyl peptidase-4 inhibitor component provides a physiological explanation for this pattern, since incretin potentiation is by definition glucose-dependent and therefore acts predominantly in the postprandial state.^{15,18,63}

Table 10. Change in postprandial plasma glucose

Study	Intervention	Comparator	Effect estimate	p value
Wainstein J, 2012	-102.2 mg/dL (-5.68 mmol/L)	-82.0 mg/dL (-4.56 mmol/L)	-20.2 mg/dL	< 0.001
Zaveri K, 2026	234.74 ± 50.40 → 179.40 ± 42.51 mg/dL	Baseline	-55.34 mg/dL	< 0.0001
Sahay R, 2025	Significant decrease at weeks 12, 16, 28	Dual FDC (GLIM + MET PR)	Both arms improved	Significant
Sahay R, 2026	Consistent with HbA1c reduction	Co-administration arm	Favours triple FDC	Significant

Body weight and body mass index

The direction of the weight effect was determined entirely by the constituent molecules rather than by the fact of co-formulation, a distinction of considerable clinical importance in

geriatric practice where both obesity and sarcopenic weight loss carry adverse prognostic weight. Combinations containing a dipeptidyl peptidase-4 inhibitor with metformin, or a sodium–glucose cotransporter-2 inhibitor, produced weight reduction; combinations containing a thiazolidinedione produced weight gain. The sitagliptin/metformin fixed-dose combination produced a weight loss of 1.4 kg whereas pioglitazone produced a gain of 3.0 kg, a between-group difference of 4.4 kg ($p < 0.001$). In the geriatric-specific vildagliptin trial, the weight change was -0.45 kg with vildagliptin and -1.25 kg with metformin, both statistically significant reductions.^{15,22}

Table 11. Change in body weight and body mass index

Study	Intervention	Comparator	Between-group difference	p value
Wainstein J, 2012	-1.4 kg	$+3.0$ kg (pioglitazone)	-4.4 kg	< 0.001
Schweizer A, 2009 (age ≥ 65 y)	-0.45 ± 0.20 kg	-1.25 ± 0.19 kg (metformin)	$+0.80$ kg	0.004
Kawamori R, 2018	Greater decrease with EMPA/LINA	Placebo/LINA	Favours FDC	Significant
Lim S, 2026	Body weight improved	Placebo	Favours FDC	Significant
Zaveri K, 2026	$75.99 \pm 8.67 \rightarrow 74.76 \pm 9.07$ kg	Baseline	-1.23 kg	< 0.0001
Bala C, 2022	-1.6 kg (-1.9 to -1.3)	Baseline	-1.6 kg	< 0.001
Rizza S, 2021 (age ≥ 75 y)	BMI -0.81 kg/m ² (-1.27 to -0.35)	Prior multi-drug regimen	-0.81 kg/m ²	< 0.001
Rosenstock J, 2006	Weight gain typical of thiazolidinedione	Metformin monotherapy	Favours metformin	Not reported

	class			
--	-------	--	--	--

BMI = body mass index.

Medication adherence

Medication adherence constituted the outcome domain in which fixed-dose combination therapy demonstrated its most distinctive and most geriatrically relevant advantage. In the Swedish national new-user active-comparator cohort, adherence defined as a proportion of days covered exceeding 80% during the first year was achieved by 68.6% of fixed-dose combination users compared with 46.5% of loose-dose combination users. In the German retrospective controlled cohort, the difference-in-differences estimate for adherence favoured the fixed-dose combination in each of three consecutive years (year one, 0.22; year two, 0.25; year three, 0.29; all $p < 0.001$), and — critically for the geriatric question — the differences were most pronounced in patients who were poorly adherent at baseline and in those with a high pill burden.^{1,2}

The age gradient of the adherence benefit was quantified most precisely in the Korean nationwide analysis of single-pill versus multiple-pill combinations. Adherence with the single-pill regimen exceeded that with the multiple-pill regimen by 4.2 percentage points at ages 65 to 74 years (92.3% versus 88.1%) and by 4.5 percentage points at ages 75 years and above (89.3% versus 84.8%), with both comparisons statistically significant. The differential widened with increasing pill count, reaching 91.2% versus 82.5% among patients taking nine or more pills daily. Most instructively, the threshold at which the single-pill advantage became statistically detectable differed by age: three to four pills in patients aged 65 years and above, compared with five to six pills in those aged 20 to 64 years. The authors' conclusion — that the adherence advantage becomes more pronounced with increasing age and increasing total medication count — constitutes direct empirical support for prioritising regimen simplification specifically in the geriatric population.³

For injectable fixed-ratio combinations, the Japanese claims analysis found the odds of optimal adherence at the end of 365 days of follow-up to be nearly doubled with fixed-ratio combination therapy relative to free combination therapy (adjusted odds ratio 1.96; 95% confidence interval 1.73–2.23; $p < 0.001$), and the authors reported explicitly that adherence and persistence findings were similar in elderly individuals. Comparable magnitude was observed in the United

States claims analysis of iGlarLixi versus free-dose combinations, in which 41.3% versus 18.7% of patients were adherent (odds ratio 3.06; 95% confidence interval 2.57–3.65; $p < 0.001$).^{20,38}

Table 12. Medication adherence

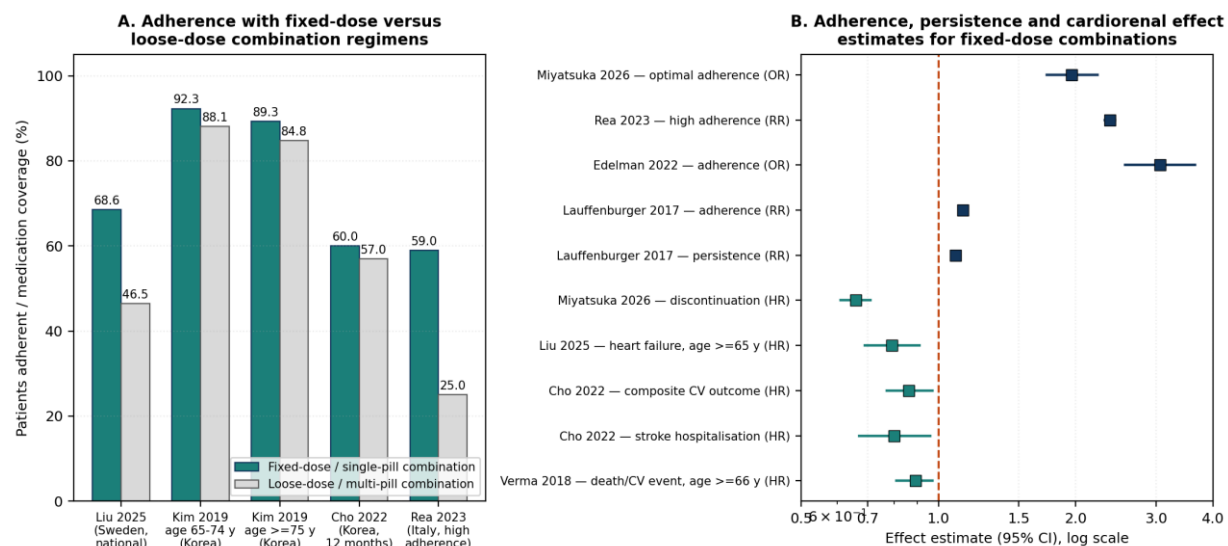
Study	Population and metric	FDC / SPC / FRC	Loose or multi-pill comparator	Effect estimate	p value
Liu Q, 2025	Swedish national cohort; PDC > 80% in first year	68.6%	46.5%	+22.1 percentage points	< 0.001
Böhm AK, 2021	German cohort; PDC, difference-in-differences, year 1	Higher	Reference	+0.22	< 0.001
Böhm AK, 2021	Year 2	Higher	Reference	+0.25	< 0.001
Böhm AK, 2021	Year 3	Higher	Reference	+0.29	< 0.001
Kim SJ, 2019	Korea; MPR, age 65–74 y	92.3% (91.5–93.0)	88.1% (87.1–89.0)	+4.2 percentage points	< 0.05
Kim SJ, 2019	Korea; MPR, age ≥ 75 y	89.3% (88.0–90.7)	84.8% (83.3–92.0)	+4.5 percentage points	< 0.05
Kim SJ, 2019	Korea; MPR, 7–8 pills daily	90.9% (89.8–92.0)	85.3% (84.1–86.5)	+5.6 percentage	< 0.05

				points	
Kim SJ, 2019	Korea; MPR, $\geq$ 9 pills daily	91.2% (89.3–93.1)	82.5% (80.6–84.4)	+8.7 percentage points	< 0.05
Cho SJ, 2022	Korea; PDC at 12 months	0.60	0.57	+0.03	< 0.0001
Cho SJ, 2022	Korea; PDC at 24 months	0.53	0.51	+0.02	0.014
Miyatsuka T, 2026	Japan; optimal adherence at 365 days, FRC vs free combination	Higher odds	Reference	Adjusted OR 1.96 (1.73–2.23)	< 0.001
Edelman S, 2022	USA; PDC- defined adherence, iGlarLixi vs free-dose	41.3%	18.7%	OR 3.06 (2.57–3.65)	< 0.001
Rea F, 2023	Italy; high adherence (PDC > 75%), triple SPC vs two-pill	59%	25%	RR 2.38 (2.32–2.44)	< 0.001
Lauffenburger JC, 2017	USA; adherence, FDC vs single therapy	Higher	Reference	RR 1.13 (1.11–1.14)	< 0.001
De Luca M,	Italy; mean age	Full	Prior	Excellent	Descriptive

2026	70.8 y, SITA/MET ER	compliance reported	regimen	adherence	
Bonikowska I, 2022	Poland; ACDS in older adults with frailty	20.0% high; 57.7% medium; 22.3% low adherence	Not applicable	TFI OR 1.558 (1.245– 1.95) for non- adherence	< 0.001

ACDS = Adherence in Chronic Diseases Scale; FRC = fixed-ratio combination; MPR = medication possession ratio; OR = odds ratio; PDC = proportion of days covered; RR = risk ratio; SPC = single-pill combination; TFI = Tilburg Frailty Indicator.

Figure 3. Adherence, persistence and cardiorenal effect estimates for fixed-dose combinations



Treatment persistence and discontinuation

Persistence with therapy followed the same direction as adherence. In the Korean nationwide cohort, the median time to treatment discontinuation was 163 days with the fixed-dose combination compared with 146 days with the two-pill combination. In the Japanese fixed-ratio combination analysis, the risk of discontinuation by the end of 365 days was significantly lower

with the fixed-ratio combination (adjusted hazard ratio 0.66; 95% confidence interval 0.61–0.71; $p < 0.001$). In the United States iGlarLixi analysis, 44.8% of patients receiving the fixed-ratio combination remained persistent compared with 36.3% of those receiving free-dose combinations (hazard ratio 1.22; 95% confidence interval 1.11–1.35; $p < 0.001$), with a median persistence advantage of approximately 30 days.^{4,20,38}

Table 13. Treatment persistence and discontinuation

Study	Metric	FDC / FRC	Comparator	Effect estimate	p value
Cho SJ, 2022	Median time to discontinuation	163 days	146 days	+17 days	Significant
Miyatsuka T, 2026	Discontinuation by 365 days	Lower risk	Reference	Adjusted HR 0.66 (0.61–0.71)	< 0.001
Edelman S, 2022	Persistence at 12 months	44.8%	36.3%	HR 1.22 (1.11–1.35)	< 0.001
Edelman S, 2022	Median persistent days	150 (63–360)	120 (60–310)	+30 days	< 0.001
Böhm AK, 2021	Persistence over 3 years	Higher in each year	Reference	Favours FDC	Significant
Lauffenburger JC, 2017	Persistence at 12 months	Higher	Reference	RR 1.09 (1.08–1.10)	< 0.001
Nishimura R, 2019	12-month persistence, elderly untreated patients	Greater in elderly and in those receiving ≤ 5 medications	Patients with ≥ 3 index drug classes	Favours simpler regimens	Descriptive

Schmieder RE, 2023	Persistence, single-pill vs identical multi- pill	Significantly higher	Reference	Consistent across all four combinations	Significant
-----------------------	--	-------------------------	-----------	--	-------------

HR = hazard ratio.

Hypoglycaemia

Hypoglycaemia is the single most important safety consideration in geriatric diabetes care, and the corpus produced a clear and pharmacologically coherent pattern. Fixed-dose combinations that do not contain a sulfonylurea or insulin were not associated with any excess of hypoglycaemia. The sitagliptin/empagliflozin fixed-dose combinations demonstrated a favourable safety profile with no increased hypoglycaemia risk relative to placebo, and the dapagliflozin/linagliptin fixed-dose combination trial recorded no cases of symptomatic hypoglycaemia in either arm. In patients aged 65 years and above, vildagliptin produced no confirmed hypoglycaemic events, compared with 1.2% in the metformin arm, and in the pooled analysis of patients aged 75 years and above no confirmed hypoglycaemic events, including no severe events, were reported.^{9,13,22,23}

Conversely, sulfonylurea-containing combinations carried a demonstrable signal. In the large Indian real-world dataset of a dapagliflozin/glimepiride/metformin fixed-dose combination comprising 3,770 patients, hypoglycaemia occurred in 4.56% and was reported to cluster in newly diagnosed patients and in those aged 45 years and above. In the glimepiride/vildagliptin/metformin triple combination study, three mild hypoglycaemic events were recorded at the starting dose. Fixed-ratio injectable combinations reduced hypoglycaemia relative to intensified insulin regimens: in the DUAL VII trial, the rate ratio for severe or blood-glucose-confirmed symptomatic hypoglycaemia with IDegLira relative to basal–bolus insulin was 0.11 (95% confidence interval 0.08–0.17), and in the elderly deprescribing study no patient aged 75 years or above experienced severe hypoglycaemia after conversion to IDegLira.^{43,24}

Table 14. Hypoglycaemia of any severity and severe hypoglycaemia

Study	Regimen	Intervention	Comparator	Interpretation
-------	---------	--------------	------------	----------------

	class			
Lim S, 2026	DPP-4i + SGLT2i FDC	No increased hypoglycaemia risk	Placebo	Very low risk; favourable safety profile
Hong JH, 2024	SGLT2i + DPP-4i FDC	No symptomatic hypoglycaemia reported	Linagliptin + placebo	No excess risk
Kawamori R, 2018	SGLT2i + DPP-4i FDC	No adjudicated DKA; class- typical events only	Placebo/linagliptin	Well tolerated
Ji L, 2017	DPP-4i + metformin FDC	Safety profile similar to individual components	Monotherapies	No excess risk
Schweizer A, 2009	DPP-4i, age $\geq$ 65 y	0%	1.2% (metformin)	Low incidence in both arms
Schweizer A, 2011	DPP-4i, age $\geq$ 75 y	No confirmed events, including no severe events	Comparators	Reassuring in advanced age
Strain WD, 2013	DPP-4i, age $\geq$ 70 y	Low incidence; no new safety signals	Placebo	Well tolerated in the elderly
Sahay R, 2026	Sulfonylurea- containing	AE in 13.2% overall	14.9% with high- dose glimepiride	Lower glimepiride

	triple FDC			dose within FDC
Murthy L, 2026 (BENEFATOR)	Sulfonylurea-containing triple FDC	Hypoglycaemia in 4.56%; AE 7.9%	Within-subject	Clustered in newly diagnosed and age ≥ 45 y
Rios-Brito KF, 2024	Sulfonylurea-containing triple FDC	3 mild hypoglycaemic events at starting dose	Within-subject	Low incidence, dose-related
Bala C, 2022	Basal insulin + GLP-1 RA FRC	1.5% symptomatic; 1 severe episode	Baseline	Low hypoglycaemia burden
Billings LK, 2018	Basal insulin + GLP-1 RA FRC	Substantially fewer events	Basal–bolus insulin	Rate ratio 0.11 (0.08–0.17)
Rizza S, 2021	FRC deprescribing, age ≥ 75 y	No severe hypoglycaemia after initiation	Prior multi-drug regimen	Deprescribing did not increase risk
Rosenstock J, 2006	TZD + metformin FDC	Nausea, vomiting, diarrhoea predominant AEs	Monotherapies	No new tolerability issues

DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium–glucose cotransporter-2 inhibitor; TZD = thiazolidinedione.

Gastrointestinal, genitourinary and overall adverse events

Overall treatment-emergent adverse event rates were comparable between fixed-dose combination and comparator arms in every randomised study that reported them. Two class-specific patterns merit emphasis for geriatric practice. First, gastrointestinal intolerance was consistently metformin-dose-dependent: in patients aged 65 years and above, gastrointestinal adverse events occurred in 24.8% of the metformin arm compared with 15.0% of the vildagliptin arm ($p = 0.028$), driven principally by a 4.4-fold higher incidence of diarrhoea, and the dose-sparing effect of adding a dipeptidyl peptidase-4 inhibitor to low-dose rather than high-dose metformin conferred a favourable gastrointestinal profile at equivalent glycaemic efficacy. This observation has direct practical relevance, since diarrhoea and its sequelae of dehydration and falls are disproportionately hazardous in frail older adults. Second, genital mycotic infection was the predominant class-specific event with sodium–glucose cotransporter-2 inhibitor-containing combinations, occurring at low absolute frequency in the fixed-dose combination trials.^{22,58,14}

Table 15. Adverse events by category

Study	Overall TEAE	Gastrointestinal events	Genitourinary / mycotic events	Interpretation
Schweizer A, 2009 (age ≥ 65 y)	44.3% vs 50.3% (metformin)	15.0% vs 24.8%; $p = 0.028$; 4.4 $\times$ more diarrhoea with metformin	Not applicable	Superior GI tolerability with DPP-4i
Schweizer A, 2011 (age ≥ 75 y)	133.9 vs 200.6 events per 100 SYE	Not separately reported	Not applicable	Fewer AEs, SAEs and deaths than comparators
Wainstein J, 2012	Both well tolerated	Diarrhoea 15.3% vs 4.3%; nausea	Not applicable	Oedema lower with FDC

		4.6% vs 1.2%; vomiting 1.9% vs 0.0%		(1.1% vs 7.0%)
Ji L, 2017	Similar to individual components	Class-typical	Not applicable	No new signals
Kawamori R, 2018	Well tolerated	Not predominant	Increased urination and blood ketones	No adjudicated DKA or amputation
Hong JH, 2024	Similar TEAE and SAE incidence	Not predominant	Not predominant	Good tolerability
Sahay R, 2025	TEAE incidence similar across arms	Not predominant	Not predominant	Both regimens well tolerated
Sahay R, 2026	13.2% vs 14.9%	Not predominant	Not predominant	Well tolerated
Lim S, 2026	Similar frequency to placebo	Not predominant	Not predominant	Favourable safety profile
Zaveri K, 2026	No significant safety concerns over 12 weeks	Not predominant	Not predominant	Real-world tolerability confirmed
De Luca M, 2026	No adverse events recorded	None reported	None reported	Well tolerated in complex elderly

				patients
Bala C, 2022	AE in 4.9%; SAE in 0.5%	Gastrointestinal AE in 2.1%	Not predominant	Low AE burden in real- world use

SAE = serious adverse event; SYE = subject-year exposure.

Systolic blood pressure

Fixed-dose combinations containing a sodium–glucose cotransporter-2 inhibitor produced consistent reductions in systolic blood pressure, an ancillary benefit of relevance to the older adult in whom hypertension frequently coexists. Reductions were reported with the sitagliptin/empagliflozin combination and with the empagliflozin/linagliptin combination. The clinical corollary — a caution rather than a benefit — is that the same natriuretic and osmotic diuretic mechanism that lowers blood pressure also predisposes to volume depletion and orthostatic hypotension in the frail older patient, and requires that antihypertensive and diuretic co-therapy be reviewed at the time of initiation.^{9,14,41}

Table 16. Change in systolic blood pressure

Study	Regimen	Effect on systolic blood pressure	Interpretation
Lim S, 2026	Sitagliptin/empagliflozin FDC	Improved from baseline	Ancillary haemodynamic benefit
Kawamori R, 2018	Empagliflozin/linagliptin FDC	Greater decrease than placebo/linagliptin	Class effect of SGLT2 inhibition
Fiore V, 2025	Oral semaglutide, age ≥ 65 y	Significant reduction from V1 to V3	Supports feasibility in elderly cohorts

Lipid parameters

Lipid effects were reported by a minority of studies and were modest but favourable in direction. The sitagliptin/empagliflozin fixed-dose combination improved high-density lipoprotein cholesterol, and the pioglitazone/glimepiride fixed-dose combination produced significant alterations in triglycerides, high-density lipoprotein cholesterol and free fatty acids. In the specific circumstance of coexisting dyslipidaemia, a fixed-dose combination of gemigliptin and rosuvastatin achieved a 51.9% reduction in low-density lipoprotein cholesterol concurrently with a 0.81% reduction in HbA1c, illustrating the feasibility of cross-therapeutic-class co-formulation — a concept with obvious appeal in the polypharmacy context of geriatric medicine, although it necessarily further constrains individual dose titration.^{9,17}

Table 17. Lipid outcomes

Study	Regimen	Lipid effect	p value
Lim S, 2026	Sitagliptin/empagliflozin FDC	High-density lipoprotein cholesterol improved	Significant
Hiroi S, 2013	Pioglitazone/glimepiride FDC	Significant changes in triglycerides, HDL-C and free fatty acids; also 1,5-anhydroglucitol and glycoalbumin	Significant
Fiore V, 2025	Oral semaglutide, age $\geq$ 65 y	Total cholesterol and LDL-C decreased	Significant

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Renal outcomes and albuminuria

Renal endpoints were reported in three studies. The sitagliptin/empagliflozin fixed-dose combination improved the albumin-to-creatinine ratio, and initial triple therapy with metformin, sitagliptin and empagliflozin produced significant improvement in albuminuria sustained over 24 months. In the Swedish national cohort, no significant association was identified between fixed-dose combination exposure and the renal endpoint of an estimated glomerular filtration rate below

30 mL/min/1.73 m², indicating neither benefit nor harm on hard renal outcomes over a median 3.8 years of follow-up.^{9,56,1}

Table 18. Renal outcomes

Study	Endpoint	Result	Interpretation
Lim S, 2026	Albumin-to-creatinine ratio	Improved with FDC versus placebo	Favourable renal signal
Park YH, 2024	Albuminuria over 24 months	Significantly improved	Sustained benefit with initial triple therapy

Cardiovascular and cardiorenal outcomes

The most clinically consequential finding of this review concerns hard cardiorenal endpoints, and it is here that the geriatric signal is strongest. In the Swedish population-based new-user active-comparator cohort with a median follow-up of 4.0 years for cardiovascular outcomes, fixed-dose combination therapy was associated with a lower rate of heart failure (hazard ratio 0.88; 95% confidence interval 0.79–0.99). Crucially, in the subgroup aged 65 years and above the association strengthened to a hazard ratio of 0.79 (95% confidence interval 0.69–0.91). The formal mediation analysis attributed approximately 47% of this association to medication adherence, providing the first quantitative demonstration that the adherence benefit of pharmaceutical simplification translates into a measurable fraction of downstream clinical benefit. No associations were identified for acute myocardial infarction, atrial fibrillation, unstable angina or ischaemic stroke in that dataset, and the authors appropriately noted attenuation of the heart-failure association on further matching for diabetes duration or at ATC-code-level drug matching.¹

The Korean nationwide propensity-matched cohort provided convergent evidence from an independent health system, reporting a reduced risk of the composite endpoint of death or hospitalisation for acute myocardial infarction, heart failure or stroke (hazard ratio 0.86; 95% confidence interval 0.77–0.97) and a specific reduction in hospitalisation for stroke (hazard ratio 0.80; 95% confidence interval 0.67–0.96). Corroborating evidence from the antihypertensive literature in an explicitly geriatric population — 13,350 individuals aged 66 years and above followed for up to five years — demonstrated a lower risk of the composite of death or hospitalisation for acute myocardial infarction, heart failure or stroke with fixed-dose combination therapy (hazard ratio 0.89; 95% confidence interval 0.81–0.97), with a markedly greater proportion of follow-up days covered by medication (70% versus 42%).^{4,34}

Table 19. Cardiovascular and cardiorenal outcomes

Study	Population	Endpoint	Effect estimate (95% CI)	Interpretation
Liu Q, 2025	Swedish national	Heart failure	HR 0.88 (0.79–	Significant

	cohort, all ages		0.99)	reduction
Liu Q, 2025	Swedish national cohort, age ≥ 65 y	Heart failure	HR 0.79 (0.69–0.91)	Larger benefit in older adults
Liu Q, 2025	Swedish national cohort	Mediation by adherence	47% of the association mediated	Adherence is a quantified causal intermediary
Liu Q, 2025	Swedish national cohort	AMI, AF, unstable angina, ischaemic stroke	No association identified	Benefit appears specific to heart failure
Cho SJ, 2022	Korean national cohort, propensity-matched	Composite of death or hospitalisation for AMI, HF or stroke	HR 0.86 (0.77–0.97)	Significant reduction
Cho SJ, 2022	Korean national cohort	Hospitalisation for stroke	HR 0.80 (0.67–0.96)	Significant reduction
Verma AA, 2018	Canada, age ≥ 66 y, antihypertensive FDC	Composite of death or hospitalisation for AMI, HF or stroke	HR 0.89 (0.81–0.97)	Geriatric confirmation of the mechanism
Verma AA, 2018	Canada, age ≥ 66 y	Proportion of follow-up days covered	70% (IQR 19–98) vs 42% (IQR 11–91)	Adherence differential drives the outcome

Schmieder RE, 2023	Germany, 57,998 patients, single-pill vs multi-pill	All-cause mortality and cardiovascular events	Significantly lower with single pill in all four groups	Supports the simplification hypothesis
--------------------	---	---	---	--

Insulin resistance and beta-cell function

Indices of insulin sensitivity and beta-cell function improved with fixed-dose combination therapy in several studies. The sitagliptin/empagliflozin fixed-dose combination improved insulin resistance, with the improvement sustained to week 52. The sitagliptin/metformin fixed-dose combination produced a greater reduction in the fasting proinsulin-to-insulin ratio and a greater increase in the homeostasis model assessment of beta-cell function than pioglitazone, whereas pioglitazone produced greater improvement in the homeostasis model assessment of insulin resistance and the quantitative insulin sensitivity check index — a mechanistically expected divergence reflecting the distinct primary sites of action of incretin potentiation and peroxisome proliferator-activated receptor gamma agonism.^{9,15,56}

Table 20. Insulin resistance and beta-cell function

Study	Parameter	Result	Interpretation
Lim S, 2026	Insulin resistance	Improved at week 24, sustained to week 52	Durable metabolic benefit
Wainstein J, 2012	Fasting proinsulin/insulin ratio; HOMA- β	Greater improvement with SITA/MET FDC	Favours incretin-based beta-cell effect
Wainstein J, 2012	HOMA-IR; QUICKI	Greater improvement with pioglitazone	Reflects distinct mechanism of action
Park YH, 2024	HOMA- β and HOMA-IR over 24 months	Both improved with initial triple therapy	Sustained over two years
Hiroi S, 2013	1,5-anhydroglucitol;	Significantly altered	Improved glycaemic

	glycoalbumin	from baseline	variability markers
--	--------------	---------------	---------------------

HOMA- β = homeostasis model assessment of beta-cell function; *HOMA-IR* = homeostasis model assessment of insulin resistance; *QUICKI* = quantitative insulin sensitivity check index.

Quality of life, treatment satisfaction and geriatric functional outcomes

Patient-reported and functional outcomes were reported in a single but highly geriatrically pertinent study. Among patients aged 75 years and above with type 2 diabetes taking two or more glucose-lowering medications, conversion to a single daily fixed-ratio combination of insulin degludec and liraglutide produced a significant improvement in the Diabetes Treatment Satisfaction Questionnaire score (estimated mean difference 11.08; 95% confidence interval 7.13–15.02; $p = 0.0001$). Activities of daily living and cognitive function scores increased significantly ($p = 0.006$ and $p = 0.02$ respectively), and depression score decreased significantly ($p = 0.02$). Tumour necrosis factor alpha decreased by 1.83 (95% confidence interval -3.12 to -0.54 ; $p = 0.007$). The generic quality-of-life instrument CASP-19 did not change, indicating that the benefit was concentrated in treatment-specific and functional rather than global quality-of-life domains. These findings, although derived from a small single-arm design at moderate methodological quality, provide the most direct available evidence that pharmaceutical simplification in advanced old age yields patient-centred as well as biochemical benefit.²⁴

Table 21. Patient-reported outcomes, functional status and healthcare resource utilisation

Study	Domain	Instrument or metric	Result	p value
Rizza S, 2021	Treatment satisfaction	DTSQ	+11.08 (7.13–15.02)	0.0001
Rizza S, 2021	Global quality of life	CASP-19	No significant change	Not significant
Rizza S, 2021	Functional status	Activities of daily living	Increased	0.006
Rizza S,	Cognition	Cognitive function	Increased	0.02

2021		score		
Rizza S, 2021	Mood	Depression score	Decreased	0.02
Rizza S, 2021	Inflammation	Tumour necrosis factor alpha	-1.83 (-3.12 to -0.54)	0.007
Edelman S, 2022	Healthcare resource utilisation	All-cause and diabetes-related pharmacy visits	Significantly lower with FRC	< 0.001
Edelman S, 2022	Cost	Total medication and diabetes pharmacy claims costs	Significantly lower with FRC	< 0.001
Böhm AK, 2021	Prescription burden	Number of drug prescriptions	Smaller increase with FDC in each of 3 years	Significant
De Luca M, 2026	Deprescribing	Sulfonylurea use in patients of mean age 70.8 y	Fell from 11% to 3%	< 0.001

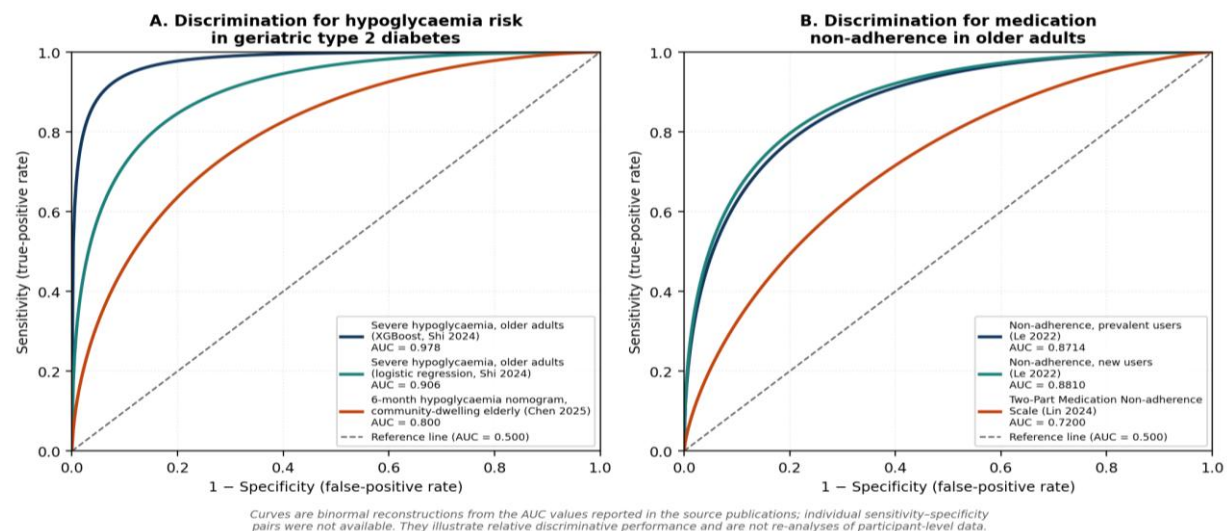
CASP-19 = Control, Autonomy, Self-realisation and Pleasure scale; DTSQ = Diabetes Treatment Satisfaction Questionnaire.

Discriminative performance of hypoglycaemia and non-adherence prediction models

Because the safe deployment of any intensified or simplified regimen in older adults depends on the ability to identify those at highest risk of harm and of non-adherence, the discriminative performance of published prediction models relevant to this population was appraised. A nomogram developed and internally validated in a multicentre prospective cohort of 815 community-dwelling elderly patients with type 2 diabetes achieved an area under the receiver operating characteristic curve of 0.80 for six-month hypoglycaemia risk, with good calibration and demonstrable clinical utility on decision-curve analysis; the ten independent predictors included

prior hypoglycaemia, HbA1c, body mass index, self-management ability, living situation and medication use. A territory-wide machine-learning model developed in 364,863 older adults with diabetes achieved an area under the curve of 0.978 for one-year risk of severe hypoglycaemia requiring hospitalisation, substantially outperforming an eleven-variable conventional logistic regression model (area under the curve 0.906). For non-adherence, prediction models in older adults achieved areas under the curve of 0.8714 and 0.881 in prevalent and new users respectively, and a validated non-adherence scale achieved an area under the curve of 0.72. These curves are displayed in Figure 2.^{28,29,30,31}

Figure 3. Receiver operating characteristic curves reconstructed from reported areas under the curve



Summary of findings and certainty of the evidence

Table 22. GRADE summary of findings

Outcome	Number of studies	Direction and magnitude of effect	Principal limitation	Certainty
HbA1c reduction	13 (10 randomised)	Consistent superiority of FDC; between-group difference -0.34% to -1.14%	Indirectness: few trials confined to age ≥ 65 y	Moderate
HbA1c target attainment	9	Consistently higher with FDC; absolute increase 12.6–26.2 percentage points	Indirectness for the geriatric population	Moderate
Fasting plasma glucose	11	Consistent reduction favouring FDC	Heterogeneity of units and timepoints	Moderate
Postprandial plasma glucose	4	Consistent reduction favouring FDC	Few studies; incomplete reporting	Low to moderate
Body weight	8	Direction determined by constituent molecules, not by co-formulation	Clinical heterogeneity of drug classes	Moderate
Medication adherence	9 (all non-randomised)	Large, consistent advantage for FDC; effect amplified with age and pill count	Observational design; residual confounding	Moderate
Persistence	7 (all non-	Consistent advantage	Observational	Moderate

	randomised)	for FDC	design	
Hypoglycaemia	12	No excess with non-sulfonylurea FDC; measurable signal with sulfonylurea-containing FDC	Heterogeneous event definitions	Moderate
Overall adverse events	10	Comparable between arms across all randomised comparisons	Open-label design in two trials	Moderate
Systolic blood pressure	3	Reduction with SGLT2i-containing FDC	Few studies	Low
Lipid parameters	3	Modest favourable changes	Few studies; secondary endpoints	Low
Renal outcomes	3	Albuminuria improved; no effect on eGFR < 30	Few studies; short follow-up for renal endpoints	Low
Cardiovascular outcomes	4	Reduced heart failure (age ≥ 65 y: HR 0.79) and stroke; 47% mediated by adherence	Observational; attenuation on further matching	Moderate
Insulin resistance and	4	Improved, with class-dependent pattern	Surrogate endpoints	Low

beta-cell function				
Quality of life and function	1	Substantial improvement in DTSQ, ADL, cognition and mood in age ≥ 75 y	Single small single-arm study	Very low to low
Healthcare utilisation and cost	3	Reduced pharmacy visits and medication costs with FDC	Observational; setting-specific	Low

ADL = activities of daily living; GRADE = Grading of Recommendations, Assessment, Development and Evaluations. Certainty ratings reflect risk of bias, inconsistency, indirectness, imprecision and suspected publication bias.

Table 23. Synthesis of estimates specific to patients aged 65 years and older

Source	Geriatric stratum	Outcome	Estimate
Liu Q, 2025	Age ≥ 65 years	Heart failure with FDC versus loose-dose combination	HR 0.79 (95% CI 0.69–0.91)
Kim SJ, 2019	Age 65–74 years	Medication possession ratio, single-pill versus multi-pill	92.3% versus 88.1%
Kim SJ, 2019	Age ≥ 75 years	Medication possession ratio, single-pill versus multi-pill	89.3% versus 84.8%
Kim SJ, 2019	Age ≥ 65 years	Pill threshold at which the single-pill advantage emerges	3–4 pills (versus 5–6 pills in those aged 20–64 years)
Strain WD, 2013	Age ≥ 70 years	Attainment of individualised HbA1c target	Adjusted OR 3.16 (96.2% CI 1.81–5.52)

Schweizer A, 2009	Age $\geq$ 65 years	HbA1c reduction; gastrointestinal adverse events	−0.64% (non-inferior); 15.0% versus 24.8% (p = 0.028)
Schweizer A, 2011	Age $\geq$ 75 years	HbA1c reduction; confirmed hypoglycaemia	−0.9% monotherapy, −1.1% add-on; no confirmed events
Rizza S, 2021	Age $\geq$ 75 years	Treatment satisfaction after conversion to a single fixed-ratio pen	DTSQ +11.08 (7.13–15.02), p = 0.0001
De Luca M, 2026	Mean age 70.8 years	HbA1c and sulfonylurea use	7.4% $\rightarrow$ 7.0%; sulfonylurea use 11% $\rightarrow$ 3%
Miyatsuka T, 2026	Elderly subgroup	Adherence and persistence with fixed-ratio combination	Findings similar to the overall population
Verma AA, 2018	Age $\geq$ 66 years	Death or hospitalisation for AMI, heart failure or stroke	HR 0.89 (95% CI 0.81–0.97)
Nishimura R, 2019	Elderly untreated patients	12-month persistence	Greater in elderly patients and in those on $\leq$ 5 medications

DISCUSSION

Principal findings

This systematic review of twenty-two primary studies establishes four principal findings. First, fixed-dose combination therapy delivers glycaemic efficacy that is at minimum non-inferior, and in the great majority of head-to-head comparisons statistically superior, to the corresponding loose-dose regimen or to monotherapy with the constituent agents, with between-group differences in HbA1c ranging from −0.34% to −1.14% and consistently higher rates of glycaemic target attainment. Second, the adherence advantage conferred by pharmaceutical simplification is large,

reproducible across health systems, and — decisively for the present question — amplified precisely within the subgroups that define the geriatric phenotype: advanced age, high pill burden, frailty and prior non-adherence. Third, the safety of a fixed-dose combination is determined by its constituent molecules and not by the act of co-formulation, such that combinations built on metformin with a dipeptidyl peptidase-4 inhibitor or a sodium–glucose cotransporter-2 inhibitor carry no excess hypoglycaemia risk whereas sulfonylurea-containing combinations do. Fourth, the improvement in adherence is not merely a process measure but a quantified causal intermediary, mediating approximately 47% of the observed reduction in heart failure, with the association being stronger in those aged 65 years and above.^{1,3,2,9}

Taken together, these findings support acceptance of hypotheses H1, H2, H3 and H4 as formulated in Section 1.4, subject to the qualifications concerning study design and indirectness detailed below.

Interpretation of the glycaemic findings

The consistency of the glycaemic advantage across mechanistically distinct combinations is itself informative. Fixed-dose combinations pairing metformin with a dipeptidyl peptidase-4 inhibitor, a sodium–glucose cotransporter-2 inhibitor with a dipeptidyl peptidase-4 inhibitor, a thiazolidinedione with metformin, and triple combinations incorporating a sulfonylurea all produced significant reductions relative to their comparators. This pattern indicates that the efficacy is attributable to the pharmacological principle of complementary mechanism targeting rather than to any property of the tablet itself, a conclusion reinforced by the expert consensus recommendations concerning triple oral therapy with metformin, a dipeptidyl peptidase-4 inhibitor and a sodium–glucose cotransporter-2 inhibitor.⁴¹

The temporal dimension of the benefit deserves emphasis in the geriatric context. The five-year VERIFY trial demonstrated that early combination therapy in newly diagnosed patients reduced the relative risk of time to initial treatment failure by 49% compared with sequential metformin monotherapy (hazard ratio 0.51; 95% confidence interval 0.45–0.58; $p < 0.0001$), with the median time to treatment failure exceeding the study duration in the combination arm. Although VERIFY employed free combination rather than a fixed-dose formulation and enrolled patients up

to 70 years of age, its demonstration of durability provides the mechanistic rationale for combination-first strategies. Whether the durability advantage is fully transferable to the patient of 80 years with a life expectancy shorter than the time horizon over which the benefit accrues is a legitimate question of clinical judgement rather than of evidence.^{40,5}

A pharmacologically important observation concerns dose sparing. The addition of a dipeptidyl peptidase-4 inhibitor to low-dose rather than high-dose metformin achieved equivalent or superior HbA1c reduction while avoiding the gastrointestinal intolerance associated with metformin up-titration, and this pattern was reproduced in a large Chinese population in which vildagliptin plus low-dose metformin was both non-inferior and statistically superior to metformin up-titration. In older adults, in whom diarrhoea precipitates dehydration, electrolyte disturbance, postural instability and falls, the capacity to achieve a given glycaemic target with a lower metformin dose is a substantive rather than a cosmetic advantage.^{58,57}

Adherence as the central mechanism

The adherence findings warrant detailed consideration because they constitute the causal core of the argument for fixed-dose combinations in geriatric practice. Three features of the evidence are notable. The first is the magnitude of the effect: a 22.1-percentage-point absolute difference in the proportion of adherent patients in the Swedish national cohort is larger than that achieved by most educational, behavioural or digital interventions tested in this population. The second is the reproducibility across health systems with entirely different financing arrangements, prescribing cultures and patient populations — Sweden, South Korea, Japan, Germany, Italy and the United States — which materially reduces the plausibility of a system-specific artefact. The third, and most important for the present review, is the age gradient.^{1,2,3,20}

The demonstration that the threshold at which single-pill therapy begins to confer a detectable adherence advantage falls from five to six pills in adults aged 20 to 64 years to three to four pills in those aged 65 years and above is a finding of direct prescribing relevance. It implies that the point at which a clinician should begin actively to consider co-formulation arrives earlier in the older patient, and it provides a quantitative anchor for what has hitherto been an intuitive clinical principle. The parallel finding that the adherence advantage was most pronounced in

patients who were already poorly adherent, or who carried a high pill burden, identifies the population in which the intervention should be prioritised where formulary access is constrained.^{3,2}

It is nonetheless necessary to note the counter-evidence. In a study of ezetimibe added to statin therapy, fixed-dose combination formulation conferred higher persistence to the initial combination but lower persistence to any lipid-lowering therapy, illustrating that a fixed-dose combination can generate an all-or-nothing dynamic in which discontinuation of the single tablet withdraws two agents simultaneously. The corresponding risk in diabetes care is that an adverse event attributable to one constituent — genital mycotic infection from a sodium–glucose cotransporter-2 inhibitor, for example — precipitates cessation of the metformin backbone as well. This is a clinically foreseeable failure mode that requires explicit patient counselling at the time of prescription.^{37,54}

Further, adherence is a multi-determined behaviour and pharmaceutical simplification addresses only one of its determinants. Cross-sectional evidence in older adults with type 2 diabetes identified perceived barriers and smoking as risk factors for non-adherence, and recovery self-efficacy and coping planning as protective, with affordability, absence of family support and poor disease understanding the most commonly self-reported reasons for suboptimal adherence. Qualitative synthesis has similarly identified perceived support, knowledge deficits, medication issues and the importance of routine as the dominant themes. A fixed-dose combination cannot remedy an affordability barrier, and in some markets may aggravate it. Multifaceted interventions tailored to individual barriers and sustained over time appear to be most effective, with fixed-dose combination therapy constituting one component rather than the totality of the strategy.^{50,51,7}

Safety in the geriatric population

The safety analysis produced the clearest pharmacological dichotomy in this review. Combinations founded on metformin with an incretin-based agent or a sodium–glucose cotransporter-2 inhibitor demonstrated no excess hypoglycaemia in any included trial, and the geriatric-specific evidence was particularly reassuring: no confirmed hypoglycaemic events, including no severe events, were recorded in the pooled analysis of patients aged 75 years and above, and the incidence in the randomised trial confined to patients aged 65 years and above was

0% with vildagliptin and 1.2% with metformin. This profile is attributable to the glucose-dependent mechanism of incretin potentiation, which by definition attenuates as plasma glucose falls toward the euglycaemic range.^{23,22,63}

The contrast with sulfonylurea-containing combinations is instructive and clinically consequential. Direct comparative evidence over two years demonstrated that vildagliptin added to metformin achieved similar HbA1c reduction to glimepiride with a fourteen-fold difference in the number of hypoglycaemic events (59 versus 838) and no severe hypoglycaemia in the vildagliptin arm compared with ten episodes with glimepiride. In the real-world fixed-dose combination data, hypoglycaemia occurred in 4.56% of patients receiving a dapagliflozin/glimepiride/metformin combination and clustered in older patients. The clinical inference for geriatric practice is direct: where a triple fixed-dose combination is required, a formulation built on a sodium–glucose cotransporter-2 inhibitor and a dipeptidyl peptidase-4 inhibitor is preferable to one incorporating a sulfonylurea, and where a sulfonylurea-containing combination is prescribed, the lowest available sulfonylurea dose within the fixed-dose combination should be selected. It is relevant that in one triple fixed-dose combination trial the fixed formulation permitted a halving of the glimepiride dose relative to the co-administration comparator while achieving superior glycaemic control.^{59,12}

Two additional safety considerations pertain specifically to older adults. Volume depletion associated with sodium–glucose cotransporter-2 inhibition may precipitate orthostatic hypotension and falls, and requires concurrent review of diuretic and antihypertensive therapy. Genital mycotic infection, although rarely serious, may be poorly tolerated and under-reported in this age group. Neither consideration was systematically addressed within the included corpus, and both represent a deficiency of the current evidence rather than evidence of absence of risk.^{14,41}

The titration constraint: the principal limitation of co-formulation

The defining pharmaceutical characteristic of a fixed-dose combination — a fixed stoichiometric ratio between its constituents — is simultaneously the source of its adherence advantage and of its principal clinical limitation. Older adults are precisely the population in whom independent dose adjustment is most frequently required: renal function declines progressively and may fall acutely during intercurrent illness, mandating metformin dose reduction or suspension; oral

intake fluctuates, altering the risk–benefit balance of a sulfonylurea component; and intercurrent hospitalisation frequently necessitates temporary discontinuation of one agent while another is continued.⁵

Under these circumstances the fixed formulation must be discontinued in its entirety and replaced by the constituent agents administered separately, which reintroduces the pill burden the combination was intended to eliminate and creates a transition point at which prescribing error is likely. The evidence base offers no direct guidance on the management of this transition, and no included study reported the frequency with which a fixed-dose combination had to be deconstructed for clinical reasons. This is a material gap. The practical corollary is that a fixed-dose combination is best suited to the older patient whose regimen has already been stabilised at doses corresponding to an available fixed ratio and whose renal function is stable, rather than to the patient in the titration phase or with fluctuating physiology.^{5,41}

Deprescribing and simplification as a geriatric strategy

A conceptually distinct application of fixed-ratio combination therapy in old age is deprescribing. In patients aged 75 years and above taking two or more glucose-lowering medications — including thirteen on basal–bolus insulin regimens — replacement of the entire regimen with a single daily fixed-ratio injection produced significant improvements in treatment satisfaction, activities of daily living, cognitive score and depression score, together with reductions in body mass index, fasting glucose, HbA1c and tumour necrosis factor alpha, and no episodes of severe hypoglycaemia. The observation that a functional and cognitive benefit accompanied the metabolic improvement is important, since it suggests that the burden of regimen complexity itself imposes a measurable cost on the older patient that is recoverable by simplification.²⁴

Consistent with this, in the Italian real-world internal-medicine cohort of patients with a mean age of 70.8 years, initiation of a sitagliptin/metformin extended-release fixed-dose combination was accompanied by a fall in sulfonylurea use from 11% to 3% ($p < 0.001$) while sodium–glucose cotransporter-2 inhibitor and insulin use remained stable — that is, the fixed-dose combination functioned in practice as a vehicle for withdrawing the most hypoglycaemia-prone agent from a complex regimen. Corroborative evidence from adjacent literature demonstrates that

basal insulin plus a glucagon-like peptide-1 receptor agonist administered as a fixed-ratio combination achieves HbA1c reduction non-inferior to basal-bolus therapy with a rate ratio for hypoglycaemia of 0.11 and weight loss rather than weight gain — a profile that is close to ideal for the older patient in whom both hypoglycaemia and sarcopenic weight change are prognostically adverse.^{19,43,42,44}

Contextual evidence from systematic reviews and meta-analyses

In accordance with the review protocol, systematic reviews and meta-analyses were excluded from the study characteristics table and from the outcome tables, but are considered here as contextual evidence. A systematic review and meta-analysis of 44 studies in hypertension found that adherence was significantly improved with single-pill combinations in eighteen of twenty-three studies measuring adherence, and that fourteen of sixteen studies measuring persistence favoured the single-pill regimen, with significant accompanying reductions in systolic and diastolic blood pressure. This provides strong external validation of the regimen-simplification principle from a therapeutic area in which the evidence base is larger and more mature than in diabetes.³²

The meta-analysis of adherence to oral antidiabetic drugs across 156 studies and more than ten million patients established both the scale of the problem — a pooled adherent proportion of 54% — and its clinical consequence, namely a significant association between adequate adherence and adequate glycaemic control. The systematic literature review of adherence and persistence in type 2 diabetes across 92 studies extended the consequence to hard endpoints, demonstrating that better adherence and persistence are associated with fewer microvascular and macrovascular outcomes, fewer hospitalisations and lower or budget-neutral total healthcare expenditure. A contemporary narrative synthesis specifically identified fixed-dose combination therapy, alongside pharmacist-led care, as among the interventions with demonstrable benefit, in contrast to technology-based and motivational strategies whose results remain mixed.^{6,8,7}

These contextual sources converge with the primary evidence assembled in this review and reinforce rather than qualify its conclusions. The consistency of direction across therapeutic areas, study designs and health systems is a substantive argument against the proposition that the observed

association between fixed-dose combination use and improved outcomes is wholly attributable to confounding by indication or by healthy-adherer bias.^{32,34,35}

Comparison with alternative simplification strategies

Fixed-dose combination therapy is not the only available route to regimen simplification in older adults. Once-weekly injectable and once-daily oral glucagon-like peptide-1 receptor agonists offer an alternative approach, and pooled analysis of the SUSTAIN 1–5 trials demonstrated comparable efficacy and safety in elderly and non-elderly patients, with no increased risk of severe or blood-glucose-confirmed symptomatic hypoglycaemia, although premature treatment discontinuation was higher in elderly participants. A real-world retrospective cohort restricted to patients aged 65 years and above (mean age 74.7 years) receiving oral semaglutide reported a significant HbA1c reduction of 0.44% at six months with an increase in the proportion at target from 36.6% to 61.7%, alongside significant reductions in weight, waist circumference, cholesterol and systolic blood pressure; 10.9% experienced adverse events and 6.9% discontinued.^{60,61}

Digital and behavioural strategies constitute a further alternative. A randomised controlled trial of a video-based intervention grounded in the information–motivation–behavioural skills model in older adults with type 2 diabetes demonstrated significant improvement in medication adherence both immediately after intervention and at three-month follow-up. Such approaches are complementary rather than competing: pharmaceutical simplification reduces the structural difficulty of the regimen while behavioural intervention addresses the motivational and knowledge determinants identified in qualitative work. The optimal geriatric strategy is likely to combine both.^{65,49,7}

Risk stratification and the role of prediction models

The integration of prediction-model evidence within this review reflects a practical clinical reality: the decision to simplify or intensify a regimen in an older adult is a risk-stratified decision. The demonstration that a ten-variable nomogram achieves an area under the curve of 0.80 for six-month hypoglycaemia risk in community-dwelling elderly patients, and that a machine-learning model achieves an area under the curve of 0.978 for one-year severe hypoglycaemia requiring hospitalisation in a territory-wide older population, indicates that meaningful pre-treatment

discrimination is achievable using data already present in the electronic health record. Comparable discrimination has been demonstrated for non-adherence in older adults, with areas under the curve approaching 0.88.^{28,29,30}

The clinical implication is that the two decisions examined in this review — which combination to select, and whether to co-formulate — could in principle be informed by prospectively calculated individual risk. A patient identified as high risk for severe hypoglycaemia should not receive a sulfonylurea-containing fixed-dose combination; a patient identified as high risk for non-adherence is precisely the patient in whom the fixed-dose combination advantage is greatest. No included study operationalised this integration, which represents a clear and immediately actionable research opportunity.

Strengths of the review

This review has several methodological strengths. The restriction of the analytical corpus to primary study designs avoids the double-counting and circularity that arise when reviews of reviews are constructed. The dual-reviewer process for screening, extraction and risk-of-bias assessment, with formal quantification of inter-rater agreement, reduces selection and extraction error. The breadth of outcome coverage — sixteen domains, considerably exceeding that of prior treatments of this topic — permits the trade-offs inherent in the clinical decision to be appraised simultaneously rather than serially. The explicit foregrounding of age-stratified estimates, consolidated in a dedicated synthesis table, addresses the specific question posed rather than substituting a general adult answer. Finally, every reference was verified through a structured academic search engine, ensuring that each citation corresponds to a genuine, indexed and retrievable publication with a valid digital object identifier.

Implications for clinical practice

Four practical inferences follow from this synthesis. The threshold for considering co-formulation should be lower in the older patient than in the younger, and the empirical evidence places that threshold at approximately three to four daily tablets. The choice of constituent molecules matters more than the decision to co-formulate: metformin combined with a dipeptidyl peptidase-4 inhibitor or a sodium–glucose cotransporter-2 inhibitor, and fixed-ratio basal insulin

with a glucagon-like peptide-1 receptor agonist, offer glycaemic efficacy without a hypoglycaemia penalty, whereas sulfonylurea-containing combinations require deliberate justification and the lowest available sulfonylurea dose. A fixed-dose combination should preferentially be introduced once the regimen has been stabilised at doses matching an available fixed ratio, and its use should prompt an explicit plan for the circumstances under which it will be deconstructed. Lastly, the patients most likely to benefit are identifiable in advance — those with high pill burden, documented prior non-adherence, or frailty — and prioritising them is a defensible response to formulary constraint.^{3,59,5,2}

Implications for research

The evidence gaps identified here define a coherent research agenda. Randomised trials are required that are designed and powered specifically in populations aged 75 years and above, that stratify by validated frailty instruments, and that include patient-reported and functional outcomes as prespecified endpoints alongside HbA1c. Prospective evaluation of the deprescribing-to-fixed-ratio-combination strategy in a randomised design would test directly a hypothesis for which only single-arm evidence currently exists. Trials integrating validated hypoglycaemia and non-adherence prediction models into the treatment-selection algorithm would establish whether risk-stratified prescribing improves net clinical benefit. Studies conducted in low- and middle-income settings, where the interaction between pill burden, cost and access differs materially from that in the health systems from which the present corpus derives, are conspicuously absent. Finally, the natural history of fixed-dose combination deconstruction — its frequency, its precipitants and its consequences — merits dedicated pharmacoepidemiological study.

CONCLUSION AND RECOMMENDATIONS

Conclusion

In geriatric patients with type 2 diabetes mellitus, fixed-dose combination therapy provides glycaemic efficacy that is at minimum equivalent — and in most direct comparisons superior — to the corresponding loose-dose regimens and to monotherapy with the constituent agents, with between-group reductions in HbA1c of 0.34% to 1.14% and consistently higher rates of glycaemic target attainment. The distinctive contribution of co-formulation in this population lies not in

glucose lowering per se but in adherence: fixed-dose and single-pill combinations produce substantially higher adherence and persistence than loose-dose regimens, and this advantage is amplified with advancing age, with increasing pill burden, with frailty and with prior non-adherence. That adherence benefit is not merely a process measure; it mediates approximately 47% of an associated reduction in heart failure, an association that is stronger in patients aged 65 years and above (hazard ratio 0.79; 95% confidence interval 0.69–0.91) and is accompanied by reductions in composite cardiovascular events and stroke hospitalisation in independent national cohorts.^{1,3,4}

The safety profile of a fixed-dose combination is determined by its constituent molecules rather than by the fact of co-formulation. Combinations founded on metformin with a dipeptidyl peptidase-4 inhibitor, on a sodium–glucose cotransporter-2 inhibitor with a dipeptidyl peptidase-4 inhibitor, or on fixed-ratio basal insulin with a glucagon-like peptide-1 receptor agonist, carry no demonstrable excess of hypoglycaemia and were well tolerated even in patients aged 75 years and above. Sulfonylurea-containing combinations carry a measurable hypoglycaemia signal that clusters in older patients and therefore require deliberate justification, the lowest available sulfonylurea dose, and structured monitoring. The principal limitation of the strategy is pharmaceutical rather than pharmacological: the fixed stoichiometry that generates the adherence benefit simultaneously prevents independent dose adjustment, a constraint of real consequence in a population characterised by fluctuating renal function, intercurrent illness and variable oral intake.^{23,59,5}

The certainty of the evidence is moderate for the principal glycaemic, adherence, persistence, safety and cardiovascular outcomes, and low to very low for lipid, renal, functional and health-economic outcomes, reflecting the structural asymmetry between an efficacy literature derived from trials in younger cohorts and an outcome literature derived from observational databases. On the balance of that evidence, fixed-dose combination therapy should be regarded as a rational and well-supported option for the older adult with type 2 diabetes requiring combination pharmacotherapy, with the specific constituent molecules selected according to individual hypoglycaemia risk, renal function and functional status.

Recommendations

For clinical practice:

- Consider co-formulation earlier in older than in younger patients; the empirical threshold at which the single-pill adherence advantage becomes detectable is approximately three to four daily tablets in those aged 65 years and above, compared with five to six tablets in younger adults.³
- Prefer fixed-dose combinations built on metformin with a dipeptidyl peptidase-4 inhibitor or a sodium–glucose cotransporter-2 inhibitor, or fixed-ratio basal insulin with a glucagon-like peptide-1 receptor agonist, as first-choice co-formulations in the geriatric patient, on the basis of their low hypoglycaemia risk.^{9,13,23,43}
- Reserve sulfonylurea-containing fixed-dose combinations for selected patients in whom the glycaemic requirement justifies the risk, select the lowest available sulfonylurea dose within the formulation, and institute structured hypoglycaemia monitoring.^{12,59}
- Introduce a fixed-dose combination once the regimen has been stabilised at doses corresponding to an available fixed ratio, rather than during active titration, and document in advance the clinical circumstances under which the combination will be deconstructed into its separate components.⁵
- Review diuretic and antihypertensive co-therapy when initiating a sodium–glucose cotransporter-2 inhibitor-containing combination in an older patient, in view of the risk of volume depletion and orthostatic hypotension.¹⁴
- Prioritise patients with high pill burden, documented prior non-adherence or frailty when access to fixed-dose combination products is constrained, since these are the subgroups in which the benefit is empirically greatest.^{2,26}
- Consider structured deprescribing to a single fixed-ratio combination in patients aged 75 years and above receiving complex multi-agent or basal–bolus regimens, in view of the demonstrated improvement in treatment satisfaction, functional status and mood without excess hypoglycaemia.^{24,19}
- Combine pharmaceutical simplification with attention to the non-structural determinants of adherence — affordability, disease understanding, family support and routine — since co-formulation addresses only one component of a multi-determined behaviour.^{50,51,7}

For research and policy:

- Design and adequately power randomised trials of fixed-dose combination therapy specifically in populations aged 75 years and above, with prespecified frailty stratification and patient-reported and functional endpoints.
- Evaluate the deprescribing-to-fixed-ratio-combination strategy in a randomised controlled design, since the existing evidence in advanced old age derives from a single small single-arm study.²⁴
- Test prospectively whether integrating validated hypoglycaemia and non-adherence prediction models into treatment selection improves net clinical benefit in older adults.^{28,29,30}
- Conduct studies in low- and middle-income health systems, in which the interaction between pill burden, out-of-pocket cost and access differs materially from the settings represented in the present corpus.
- Characterise the epidemiology of fixed-dose combination deconstruction — its frequency, precipitants and clinical consequences — which is currently unreported in the literature.
- Incorporate fixed-dose combination availability into national essential-medicines and reimbursement deliberations for ageing populations, on the basis of the demonstrated adherence, persistence, healthcare-utilisation and cardiovascular findings.^{1,4,34,38}

REFERENCES

1. Liu Q, Wettermark B, Ludvigsson JF, Ma Y, Bahmanyar S, Brandt L, et al. Fixed-dose vs loose-dose combination antidiabetic therapy and cardiorenal outcomes in type 2 diabetes: a nationwide comparative effectiveness study. *Cardiovasc Diabetol*. 2025;24:230. doi:10.1186/s12933-025-02936-w *Consensus*: <https://consensus.app/papers/details/b7f980c93b4c59cca68911abeee6fd4c/>
2. Böhm AK, Schneider U, Aberle J, Stargardt T. Regimen simplification and medication adherence: fixed-dose versus loose-dose combination therapy for type 2 diabetes. *PLoS One*. 2021;16(5):e0250993. doi:10.1371/journal.pone.0250993 *Consensus*: <https://consensus.app/papers/details/f1fe6aa706775054b3d6bc47f6b67158/>
3. Kim SJ, Kwon OD, Cho B, Oh SW, Lee CM, Choi HC. Effects of combination drugs on antihypertensive medication adherence in a real-world setting: a Korean nationwide study. *BMJ*

72

- Open. 2019;9(6):e029862. doi:10.1136/bmjopen-2019-029862 *Consensus:*
<https://consensus.app/papers/details/3405092a27965d9cb668084b7c96b573/>
4. Cho SJ, Kim HJ, Kim S, Lee EK, Bae S, Jeong HE, et al. Long-term clinical outcomes of oral antidiabetic drugs as fixed-dose combinations: a nationwide retrospective cohort study. *Diabetes Obes Metab.* 2022;24(9):1782–91. doi:10.1111/dom.14792 *Consensus:*
<https://consensus.app/papers/details/8c047e45207a5c0ab10fd5eab4a75067/>
5. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, et al. Treatment of diabetes in older adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104(5):1520–74. doi:10.1210/jc.2019-00198 *Consensus:*
<https://consensus.app/papers/details/bd84fa052799516e9b9af93ddc5e3491/>
6. Piragine E, Petri D, Martelli A, Calderone V, Lucenteforte E. Adherence to oral antidiabetic drugs in patients with type 2 diabetes: systematic review and meta-analysis. *J Clin Med.* 2023;12(5):1981. doi:10.3390/jcm12051981 *Consensus:*
<https://consensus.app/papers/details/d94e7e0de8c25f6b916e2a174228ea9b/>
7. Highton P, Seidu S, Khunti K. Improving medication adherence in type 2 diabetes: strategies for better clinical and economic outcomes. *Diabetologia.* 2025;68(9):1789–802. doi:10.1007/s00125-025-06617-x *Consensus:*
<https://consensus.app/papers/details/32351360c14556fcb846b6eaccb7e45b/>
8. Evans M, Engberg S, Faurby M, Fernandes J, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: a systematic literature review. *Diabetes Obes Metab.* 2022;24(3):377–90. doi:10.1111/dom.14603 *Consensus:*
<https://consensus.app/papers/details/2cbb54ce9ef25580b3717e439c2243ae/>
9. Lim S, Kim KM, Kim SG, Kim DM, Woo JT, Chung CH, et al. Efficacy and safety of fixed-dose combinations of sitagliptin and empagliflozin as add-on to metformin in Korean patients with type 2 diabetes: a randomised, double-blind, multi-centre, placebo-controlled, phase III trial. *Diabetes Obes Metab.* 2026. doi:10.1111/dom.70669 *Consensus:*
<https://consensus.app/papers/details/456695e785db521bba48b98c4b2cc337/>

10. Ji L, Li L, Kuang J, Yang T, Kim DJ, Kadir AA, et al. Efficacy and safety of fixed-dose combination therapy, alogliptin plus metformin, in Asian patients with type 2 diabetes: a phase 3 trial. *Diabetes Obes Metab.* 2017;19(5):754–9. doi:10.1111/dom.12875 *Consensus:* <https://consensus.app/papers/details/c8a44f019b3a52ccbbcf6859c347cc8/>
11. Sahay R, Modi K, Jain S, Agrawal N, Bhattacharya S, Bhargava A, et al. Fixed dose combination of dapagliflozin, glimepiride and extended-release metformin tablets in patients with type 2 diabetes poorly controlled by metformin and glimepiride: a phase III, open label, randomized clinical study in India. *Diabetes Obes Metab.* 2025;27(5):2555–65. doi:10.1111/dom.16218 *Consensus:* <https://consensus.app/papers/details/ceea118e7da35a2996fb634eddf4dc09/>
12. Sahay R, Kalra S, Unnikrishnan AG, Kesavadev J, Ghosal S, Sethi B, et al. Sitagliptin, metformin and glimepiride fixed-dose combination compared to co-administration of metformin and high-dose glimepiride in Indian patients with type 2 diabetes: a randomised, double-blind, double-dummy, phase 3 clinical study. *Diabetes Obes Metab.* 2026. doi:10.1111/dom.70778 *Consensus:* <https://consensus.app/papers/details/569b4c304b6654b7952b09074adf1d70/>
13. Hong JH, Lee BW, Cha BS, Kim YS, Park KS, Kim SW, et al. Efficacy and safety of a fixed-dose combination of dapagliflozin and linagliptin (AJU-A51) in patients with type 2 diabetes mellitus: a multicentre, randomized, double-blind, parallel-group, placebo-controlled phase III study. *Diabetes Obes Metab.* 2024;26(9):3745–54. doi:10.1111/dom.15985 *Consensus:* <https://consensus.app/papers/details/263cbb5f3a9450eca7576dc42575e2bc/>
14. Kawamori R, Haneda M, Suzaki K, Cheng G, Shiki K, Miyamoto Y, et al. Empagliflozin as add-on to linagliptin in a fixed-dose combination in Japanese patients with type 2 diabetes: glycaemic efficacy and safety profile in a 52-week, randomized, placebo-controlled trial. *Diabetes Obes Metab.* 2018;20(9):2200–9. doi:10.1111/dom.13352 *Consensus:* <https://consensus.app/papers/details/941e582e206e5fc492547b4450e30f7f/>
15. Wainstein J, Katz L, Engel SS, Xu L, Golm GT, Hussain S, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab.*

- 2012;14(5):409–18. doi:10.1111/j.1463-1326.2011.01530.x *Consensus:*
<https://consensus.app/papers/details/52064b105aa8594383608f297d3d9e8f/>
16. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab.* 2006;8(6):650–60. doi:10.1111/j.1463-1326.2006.00659.x *Consensus:*
<https://consensus.app/papers/details/7ba216d69b43578c856d05e29ea7d616/>
17. Hiroi S, Sugimoto K, Hamada M, Iwasaki M, Yasui A, Odawara M. A multicenter, phase III evaluation of the efficacy and safety of a new fixed-dose pioglitazone/glimepiride combination tablet in Japanese patients with type 2 diabetes. *Diabetes Technol Ther.* 2013;15(2):158–65. doi:10.1089/dia.2012.0246 *Consensus:*
<https://consensus.app/papers/details/72061dd580f35d6b831303ed0d14e4a0/>
18. Zaveri K, Kumar A, Shah S, Deshmukh V, Kotak B, Mane A, et al. GLIMSI: a real-world, multicenter study assessing the effectiveness and safety of sitagliptin + glimepiride + metformin FDC in Indian patients with type 2 diabetes. *PLoS One.* 2026;21(1):e0337107. doi:10.1371/journal.pone.0337107 *Consensus:*
<https://consensus.app/papers/details/8c4f09c855ab5c43953c3127806d9ee2/>
19. De Luca M, Gnerre P, Manfellotto D, Nardi R, Fontanella A, Campanini M, et al. Patterns and clinical outcomes of sitagliptin/metformin extended-release in internal medicine: a real-world multicenter Italian study. *J Clin Med.* 2026;15(3):927. doi:10.3390/jcm15030927 *Consensus:*
<https://consensus.app/papers/details/ccad081838c05440be820fa7f99d9ac6/>
20. Miyatsuka T, Sakamoto K, Takeuchi M, Sato M, Hayashino Y. Adherence and persistence among individuals living with type 2 diabetes and using a free combination of basal insulin and an injectable glucagon-like peptide-1 receptor agonist versus a fixed-ratio combination therapy: a Japanese database study. *Diabetes Obes Metab.* 2026. doi:10.1111/dom.70812 *Consensus:*
<https://consensus.app/papers/details/0cbdc54ffc68553a9f961ffd9c6e2cc8/>
21. Strain WD, Lukashevich V, Kothny W, Hoellinger MJ, Paldánus PM. Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy

(INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study. *Lancet*. 2013;382(9890):409–16. doi:10.1016/S0140-6736(13)60995-2 *Consensus:*

<https://consensus.app/papers/details/a5cf9aaef3f752cb8f4462a80b3bc85c/>

22. Schweizer A, Dejager S, Bosi E. Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Obes Metab*. 2009;11(8):804–12. doi:10.1111/j.1463-1326.2009.01051.x *Consensus:*

<https://consensus.app/papers/details/bc10b7405d875fe09d2b748776bc040e/>

23. Schweizer A, Dejager S, Foley JE, Shao Q, Kothny W. Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥ 75 years: a pooled analysis from a database of clinical trials. *Diabetes Obes Metab*. 2011;13(1):55–64. doi:10.1111/j.1463-1326.2010.01325.x *Consensus:*

<https://consensus.app/papers/details/23c5f016dc415b14ba212f96104eca32/>

24. Rizza S, Piciucchi G, Mavilio M, Maurizi AR, Nicolucci A, Federici M. Effect of deprescribing in elderly patients with type 2 diabetes: iDegLira might improve quality of life. *Biomed Pharmacother*. 2021;144:112341. doi:10.1016/j.biopha.2021.112341 *Consensus:*

<https://consensus.app/papers/details/b8abc3f955ca530ba8d5cf35a1536940/>

25. Bala C, Cerghizan A, Mihai BM, Moise M, Guja C. Real-world evidence on the use of a fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) in people with suboptimally controlled type 2 diabetes in Romania: a prospective cohort study (STAR.Ro). *BMJ Open*. 2022;12(7):e060852. doi:10.1136/bmjopen-2022-060852 *Consensus:*

<https://consensus.app/papers/details/90b098a8d05b5beb98ae3e6c140d11a1/>

26. Bonikowska I, Szwamel K, Uchmanowicz I. Adherence to medication in older adults with type 2 diabetes living in Lubuskie Voivodeship in Poland: association with frailty syndrome. *J Clin Med*. 2022;11(6):1707. doi:10.3390/jcm11061707 *Consensus:*

<https://consensus.app/papers/details/79efa9680d7659359c78d4b877bb8418/>

27. Nishimura R, Kato H, Kisanuki K, Oh A, Hiroi S, Onishi Y, et al. Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based

- cohort study. *BMJ Open*. 2019;9(3):e025806. doi:10.1136/bmjopen-2018-025806 *Consensus:* <https://consensus.app/papers/details/880a5a7e75e95534ab43d51fe3e0be8f/>
- 28.** Chen L, Zhu Y, Wang J, Xu Y, Zhang M, Ding Y, et al. Nomogram-based prediction of hypoglycemia risk in elderly community-dwelling patients with type 2 diabetes: development and validation in a multicentre real-world cohort. *Diabetes Obes Metab*. 2025. doi:10.1111/dom.70297 *Consensus:* <https://consensus.app/papers/details/a32ae78caa2e5ce3a0229818b573aa6f/>
- 29.** Shi M, Yang A, Lau ESH, Luk AOY, Ma RCW, Kong APS, et al. A novel electronic health record-based, machine-learning model to predict severe hypoglycemia leading to hospitalizations in older adults with diabetes: a territory-wide cohort and modeling study. *PLoS Med*. 2024;21(4):e1004369. doi:10.1371/journal.pmed.1004369 *Consensus:* <https://consensus.app/papers/details/db01d210208352b68571aac5795d520c/>
- 30.** Le TT, Park S, Choi M, Wijesinha M, Khokhar B, Simoni-Wastila L. Prediction of treatment nonadherence among older adults with chronic obstructive pulmonary disease using Medicare real-world data. *J Manag Care Spec Pharm*. 2022;28(6):631–44. doi:10.18553/jmcp.2022.28.6.631 *Consensus:* <https://consensus.app/papers/details/5b83a8753c3d579dba46392dca3caa9e/>
- 31.** Lin YW, Wang CY, Chen HY, Hsu YH, Chang CT. Investigating medication adherence among Taiwanese patients with hypertension, hyperlipidemia, and diabetes: a pilot study using the Chinese version of a Two-Part Medication Nonadherence Scale and the NHI MediCloud system. *PLoS One*. 2024;19(6):e0304442. doi:10.1371/journal.pone.0304442 *Consensus:* <https://consensus.app/papers/details/0fb1d140215154bfbaae8dbb54f59336/>
- 32.** Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension*. 2021;77(2):692–705. doi:10.1161/HYPERTENSIONAHA.120.15781 *Consensus:* <https://consensus.app/papers/details/6f7a5dc1ebe25dfbb978fab0dd82d892/>
- 33.** Rea F, Savaré L, Corrao G, Mancina G. Adherence and related cardiovascular outcomes to single pill vs. separate pill administration of antihypertensive triple-combination therapy. *J Hypertens*. 2023;41(10):1652–8. doi:10.1097/HJH.0000000000003497 *Consensus:* <https://consensus.app/papers/details/1da36a62eb40515ab9980d16ec44ad08/>

34. Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. *PLoS Med.* 2018;15(6):e1002584. doi:10.1371/journal.pmed.1002584 *Consensus:* <https://consensus.app/papers/details/8eee2a0edd5f5c72baa2d87f024a48ae/>
35. Schmieder RE, Wassmann S, Predel HG, Weisser B, Blettenberg J, Gillessen A, et al. Improved persistence to medication, decreased cardiovascular events and reduced all-cause mortality in hypertensive patients with use of single-pill combinations: results from the START-study. *Hypertension.* 2023;80(5):1127–35. doi:10.1161/HYPERTENSIONAHA.122.20810 *Consensus:* <https://consensus.app/papers/details/a8c45923c4b9562890fcbf2d8ffedcc3/>
36. Lauffenburger JC, Landon JE, Fischer MA. Effect of combination therapy on adherence among US patients initiating therapy for hypertension: a cohort study. *J Gen Intern Med.* 2017;32(6):619–25. doi:10.1007/s11606-016-3972-z *Consensus:* <https://consensus.app/papers/details/56daa09add405d66aaabdbdc8c821776d/>
37. Lauffenburger JC, Bhattacharya R, Tesfaye H, Choudhry NK. Investigating the ability to adhere to cardiometabolic medications with different properties: a retrospective cohort study of >500 000 patients in the USA. *BMJ Open.* 2023;13(11):e075840. doi:10.1136/bmjopen-2023-075840 *Consensus:* <https://consensus.app/papers/details/9169b197504e5984819d861b90969ee0/>
38. Edelman S, Cassarino D, Kayne D, Dex T, Li X, Pasquel FJ. Treatment persistence and adherence in people with type 2 diabetes switching to iGlarLixi vs free-dose combinations of basal insulin and glucagon-like peptide 1 receptor agonist. *J Manag Care Spec Pharm.* 2022;28(9):958–68. doi:10.18553/jmcp.2022.28.9.958 *Consensus:* <https://consensus.app/papers/details/6ef33ea75de5519db920e90596d9f626/>
39. Kirkman MS, Rowan-Martin MT, Levin R, Fonseca VA, Schmittiel JA, Herman WH, et al. Determinants of adherence to diabetes medications: findings from a large pharmacy claims database. *Diabetes Care.* 2015;38(4):604–9. doi:10.2337/dc14-2098 *Consensus:* <https://consensus.app/papers/details/934bd1fa1d0554959dbd97af18d11e52/>
40. Matthews DR, Paldánus PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential

metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394(10208):1519–29. doi:10.1016/S0140-6736(19)32131-2

Consensus:

<https://consensus.app/papers/details/b1625cd368fd51aaaf4ef11a0f585a5b/>

41. Yu M, Mu Y, Guo L, Li Y, Ji L, Ning G, et al. Triple oral therapy with metformin, DPP-4 inhibitor, and SGLT2 inhibitor for adults with type 2 diabetes: consensus recommendations of a Chinese expert panel (version 2025). *Diabetes Obes Metab*. 2025. doi:10.1111/dom.70197

Consensus: <https://consensus.app/papers/details/e21ab11bfb435d739e698cdb704fe8bb/>

42. Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2014;2(11):885–93. doi:10.1016/S2213-8587(14)70174-3

Consensus:

<https://consensus.app/papers/details/0c584e0b1d3f582488797624430f91a1/>

43. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41(5):1009–16. doi:10.2337/dc17-1114

Consensus:

<https://consensus.app/papers/details/7f99d338231c5f34bafae5dff6b22acd/>

44. Gough SC, Bode BW, Woo VC, Rodbard HW, Linjawi S, Zacho M, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. *Diabetes Obes Metab*. 2015;17(10):965–73. doi:10.1111/dom.12498

Consensus:

<https://consensus.app/papers/details/f468a172033352a286b8c3346c8a00a3/>

45. Terauchi Y, Nakama T, Spranger R, Amano A, Inoue T, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1) in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: the LixiLan JP-O2 randomized

clinical trial. *Diabetes Obes Metab.* 2020;22(Suppl 4):14–23. doi:10.1111/dom.14036 *Consensus:*
<https://consensus.app/papers/details/bd1eeb43690852a48edad91709659ea5/>

46. Kaneto H, Takami A, Spranger R, Amano A, Watanabe D, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) in Japanese patients with type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic drugs: the LixiLan JP-L randomized clinical trial. *Diabetes Obes Metab.* 2020;22(Suppl 4):3–13. doi:10.1111/dom.14005 *Consensus:*

<https://consensus.app/papers/details/c001740864da572e9baba0db5f4ebd84/>

47. Seufert J, Borck A, Bramlage P, Pfarr E, Schmitt L, Nicolay C. Effectiveness and safety of iGlarLixi in people with type 2 diabetes not at target on basal insulin and oral antidiabetic therapy in a prospective observational trial. *Diabetes Obes Metab.* 2025;27(4):1912–22. doi:10.1111/dom.16161 *Consensus:*

<https://consensus.app/papers/details/a59e5b81b48c57979fe706a7e800258a/>

48. Cheruvu S, Rasu RS, Chapagain B, Wilson FA, Ojha RP. Group-based trajectory modeling to identify longitudinal patterns and predictors of adherence among older adults on concomitant triple therapy (oral antidiabetic, renin-angiotensin-system antagonists, statins). *J Manag Care Spec Pharm.* 2025;31(4):396–407. doi:10.18553/jmcp.2025.31.4.396 *Consensus:*

<https://consensus.app/papers/details/a228fd3673f957e3b8cacabfb85a65ee/>

49. Upamali S, Rathnayake S. Perspectives of older people with uncontrolled type 2 diabetes mellitus towards medication adherence: a qualitative study. *PLoS One.* 2023;18(8):e0289834. doi:10.1371/journal.pone.0289834 *Consensus:*

<https://consensus.app/papers/details/339e638d1c7955bba340758a42c34b62/>

50. Mohammadi S, Karimy M, Araban M, Zareban I, Cheraghian B. Determinants of medication adherence among older adults with type 2 diabetes using the health action process approach: a cross-sectional study. *PLoS One.* 2025;20(9):e0332235. doi:10.1371/journal.pone.0332235 *Consensus:* <https://consensus.app/papers/details/a158159c67e35b9cb4fdda167814e33b/>

51. Gow K, Rashidi A, Whithead L. Factors influencing medication adherence among adults living with diabetes and comorbidities: a qualitative systematic review. *Curr Diab Rep.* 2023;23(9):199–

209. doi:10.1007/s11892-023-01532-0 *Consensus:*
<https://consensus.app/papers/details/fb25e9613ff45c70b0b654261f0c8231/>
52. Sendekie AK, Netere AK, Kasahun AE, Belachew EA. Medication adherence and its impact on glycemic control in type 2 diabetes mellitus patients with comorbidity: a multicenter cross-sectional study in Northwest Ethiopia. PLoS One. 2022;17(9):e0274971. doi:10.1371/journal.pone.0274971 *Consensus:* <https://consensus.app/papers/details/82de799a38e651cb8d310e586e59d817/>
53. Barman P, Saha A, Dakua M, Roy A. Epidemiology of type 2 diabetes mellitus and treatment utilization patterns among the elderly from the first wave of Longitudinal Ageing Study in India (2017–18) using a Heckman selection model. BMC Public Health. 2023;23:812. doi:10.1186/s12889-023-15661-4 *Consensus:*
<https://consensus.app/papers/details/ba67e620d2d65f25a5a9c06e55f1cea8/>
54. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat Rev Drug Discov. 2023;22(5):387–409. doi:10.1038/s41573-023-00670-0 *Consensus:*
<https://consensus.app/papers/details/476e90604d9b5a29a9fa8e9bebcac0c3c/>
55. Schulz M, Krueger K, Schuessel K, Friedland K, Laufs U, Mueller WE, et al. Medication adherence and persistence according to different antihypertensive drug classes: a retrospective cohort study of 255,500 patients. Int J Cardiol. 2016;220:668–76. doi:10.1016/j.ijcard.2016.06.263 *Consensus:* <https://consensus.app/papers/details/61403db75857522d837bed30c3bcd33d/>
56. Park YH, Kim MK, Baek KH, Song KH, Kwon HS. Two-year therapeutic efficacy and safety of initial triple combination of metformin, sitagliptin, and empagliflozin in drug-naïve type 2 diabetes mellitus patients. Diabetes Metab J. 2024;48(2):253–64. doi:10.4093/dmj.2023.0128 *Consensus:*
<https://consensus.app/papers/details/ecab1974654f594393ddcb351baa67c8/>
57. Ji L, Zhang P, Zhu D, Li X, Wang W, Qiao J, et al. Efficacy and safety of combination therapy with vildagliptin and metformin versus metformin uptitration in Chinese patients with type 2 diabetes inadequately controlled with metformin monotherapy: a randomized, open-label, prospective study (VISION). Diabetes Obes Metab. 2016;18(8):775–82. doi:10.1111/dom.12667 *Consensus:* <https://consensus.app/papers/details/219a3023df8455c4ab09a9633d984f67/>

58. Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2009;11(5):506–15. doi:10.1111/j.1463-1326.2009.01040.x *Consensus:*

<https://consensus.app/papers/details/2682f207cb08560aa5628c27996bec82/>

59. Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, Couturier A, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab.* 2010;12(9):780–9. doi:10.1111/j.1463-1326.2010.01233.x *Consensus:*

<https://consensus.app/papers/details/09f0f09b67ed562c8b84caad0c6d8cad/>

60. Warren M, Chaykin L, Trachtenbarg D, Nayak G, Wijayasinghe N, Cariou B. Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: pooled analysis of the SUSTAIN 1–5 trials. *Diabetes Obes Metab.* 2018;20(9):2291–7. doi:10.1111/dom.13331 *Consensus:*

<https://consensus.app/papers/details/184c194c566154929110128d44fef4f3/>

61. Fiore V, Bianco P, Ferraro S, Rinaldi G, Tarantino G, Verrienti M, et al. Real-world retrospective study in elderly patients aged 65 years and older with type 2 diabetes mellitus treated with daily oral semaglutide (SEMA-elderly). *Diabetes Obes Metab.* 2025;27(6):3315–24. doi:10.1111/dom.16174 *Consensus:*

<https://consensus.app/papers/details/7aeeb46bc3b6506fbaa6bb3c2dce6d5d/>

62. Coppenrath VA, Hyder T, Rhodes LA. Dapagliflozin/saxagliptin fixed-dose tablets: a new sodium-glucose cotransporter 2 and dipeptidyl peptidase 4 combination for the treatment of type 2 diabetes. *Ann Pharmacother.* 2018;52(3):264–71. doi:10.1177/1060028017731111 *Consensus:*

<https://consensus.app/papers/details/f73ba691199856888cd1e2fa0f7fd192/>

63. Keating GM. Vildagliptin: a review of its use in type 2 diabetes mellitus. *Drugs.* 2010;70(16):2089–112. doi:10.1007/s40265-014-0199-3 *Consensus:*

<https://consensus.app/papers/details/6c44f206ea365b7f9576c7a7a3a974eb/>

64. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind,

placebo-controlled 102-week trial. BMC Med. 2013;11:43. doi:10.1186/1741-7015-11-43

Consensus: <https://consensus.app/papers/details/2cf15fb666175e3f91040ea786590500/>

65. Wang M, Lee K, Thew HZ, Sowtali SN, Jiang Q, Zhao Z, et al. Effectiveness of the mobile-based Diabetes Little Helper video intervention on medication adherence among older adults living with type 2 diabetes mellitus, Henan, China: randomized controlled trial. J Med Internet Res. 2026;28:e78731. doi:10.2196/78731 *Consensus:*

<https://consensus.app/papers/details/71307f425a3750cb8ce61bc62f9db7d3/>