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BEYOND METFORMIN: A DECADAL REVIEW OF EMERGING ORAL HYPOGLYCAEMICS AND THEIR REAL-WORLD IMPACT ON GLYCEMIC CONTROL

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ABSTRACT

Background: The landscape of oral hypoglycemic agents (OHAs) for type 2 diabetes mellitus (T2DM) has transformed dramatically over the past two decades. Beyond metformin, newer classes—notably sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and more recently oral glucagon-like peptide-1 receptor agonists (GLP-1 RAs)—offer distinct advantages but also unique risks. **Objective**: This review synthesises evidence from the last 20 years to evaluate the impact of trending OHAs on glycaemic control, body weight, cardiovascular outcomes, and adverse events, with a focus on real-world applicability. **Methods**: A structured PubMed search (2004–2024) was conducted for randomised controlled trials, meta-analyses, and retrospective observational studies. Inclusion criteria: adult T2DM patients, use of SGLT2 inhibitors, DPP-4 inhibitors, or oral GLP-1 RAs, with outcomes including HbA1c, major adverse cardiovascular events (MACE), or hospitalisation for heart failure. Exclusion criteria: animal studies, paediatric populations, and non-English articles. **Results**: Forty-three articles met inclusion criteria. SGLT2 inhibitors consistently reduced MACE (HR 0.86, 95% CI 0.80–0.92) and heart failure hospitalisations. DPP-4 inhibitors showed neutral cardiovascular effects but favourable safety. Oral semaglutide achieved HbA1c reductions of -1.2% to -1.6% with weight loss of 3–5 kg, albeit higher gastrointestinal side effects. **Conclusion**: Newer OHAs have moved beyond glucose lowering to target organ protection. Individualisation based on cardiovascular, renal, and weight profiles is now mandatory. Clinicians must navigate trade-offs between efficacy and tolerability.

KEYWORDS: Type 2 diabetes mellitus, SGLT2 inhibitors, DPP-4 inhibitors, oral semaglutide, cardiovascular outcomes, glycaemic control, real-world evidence.

AIM

This review aims to critically evaluate the clinical impact of currently trending oral hypoglycemic medications—specifically SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin), DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin), and the first oral GLP-1 receptor agonist (semaglutide)—in the management of type 2 diabetes mellitus over the past two decades. Unlike earlier narrative reviews that focused solely on HbA1c reduction, we aim to synthesise evidence on patient-important outcomes: major adverse cardiovascular events, heart failure hospitalisations, chronic kidney disease progression, body weight changes, and gastrointestinal tolerability. Additionally,

we seek to highlight the shift from a "glucocentric" to an "organ-protective" prescribing paradigm. By including both landmark randomised controlled trials and real-world retrospective analyses, we intend to provide a balanced, clinically actionable overview for endocrinologists, primary care physicians, and formulary decision-makers. Ultimately, this review will identify evidence gaps, particularly regarding long-term adherence and safety in multimorbid elderly patients.

INTRODUCTION

For nearly a century, the pharmacological management of type 2 diabetes mellitus (T2DM) revolved around a single metric: lowering blood glucose. Metformin, introduced in the 1950s, remained the unchallenged first-line therapy due to its efficacy, safety profile, and low cost. However, the past twenty years have witnessed a seismic shift. The discovery that diabetes is not merely a metabolic disorder but a complex cardiovascular and renal disease has reshaped treatment guidelines worldwide.[1,2] Today, the choice of an oral hypoglycemic agent (OHA) is no longer determined solely by its ability to reduce HbA1c but by its impact on hard clinical endpoints—death, myocardial infarction, stroke, heart failure, and kidney failure.[3]

The turning point arrived with regulatory mandates from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2008, requiring cardiovascular outcome trials (CVOTs) for all new diabetes drugs.[4] This seemingly bureaucratic requirement unexpectedly revolutionised the field. Between 2015 and 2020, a series of landmark CVOTs—EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58—demonstrated that two classes of OHAs, SGLT2 inhibitors and GLP-1 receptor agonists, reduced major adverse cardiovascular events (MACE) and hospitalisation for heart failure, even in patients without established cardiovascular disease.[1,5,6] For the first time, diabetes medications were shown to save lives beyond glucose control.[2]

SGLT2 inhibitors work by blocking glucose reabsorption in the proximal renal tubule, inducing glucosuria.[7] This unique mechanism lowers HbA1c without stimulating insulin secretion, thereby avoiding hypoglycaemia.[8] More intriguingly, their cardiovascular benefits appear mediated through haemodynamic and metabolic pathways—reducing preload, afterload, and improving cardiac energetics—rather than through glycaemia alone.[9] Concurrently, DPP-4 inhibitors, which prolong the action of endogenous incretins, offered a different value proposition: near-neutral weight effect, very low hypoglycaemia risk, and excellent tolerability.[10] However, CVOTs for DPP-4 inhibitors (SAVOR-TIMI 53, EXAMINE, TECOS) found cardiovascular neutrality, not superiority.[11-13]

More recently, the development of an oral formulation of semaglutide, a GLP-1 receptor agonist previously only available as an injection, has broken another barrier.[14] The PIONEER trial programme demonstrated that oral semaglutide achieves HbA1c reductions comparable to injectable GLP-1 RAs, with additional benefits in weight loss and systolic blood pressure reduction.[15,16] Yet, gastrointestinal adverse events—nausea, vomiting, diarrhoea—remain a significant barrier to adherence.[17]

Despite these advances, real-world evidence reveals persistent gaps. Many eligible patients do not receive SGLT2 inhibitors or GLP-1 RAs due to cost, fear of side effects (genital mycotic infections for SGLT2 inhibitors, gastrointestinal distress for GLP-1 RAs), or clinician inertia.[18,19] Furthermore, elderly patients with frailty or chronic kidney disease are often excluded from trials, leaving uncertainty about risk-benefit ratios in these vulnerable populations.[20] This review, therefore, not only summarises efficacy data but also critically examines the translation of trial findings into everyday clinical practice.

Methods: Search Strategy and Data Sources

A systematic literature search was conducted on PubMed, MEDLINE, and Cochrane Library databases for articles published between January 2004 and December 2024. The search strategy combined MeSH terms and free-text keywords: ("SGLT2 inhibitor" OR "empagliflozin" OR "dapagliflozin" OR "canagliflozin") AND ("DPP-4 inhibitor" OR "sitagliptin" OR "linagliptin" OR "saxagliptin") AND ("oral semaglutide" OR "GLP-1 receptor agonist oral") AND ("type 2 diabetes" OR "T2DM") AND ("cardiovascular outcomes" OR "heart failure" OR "HbA1c" OR "adverse events"). Additional hand-searching of reference lists of included articles and relevant reviews was performed.

Study Selection – Inclusion and Exclusion Criteria

Inclusion criteria

- Randomised controlled trials (RCTs), post-hoc analyses, meta-analyses, and retrospective observational studies.
- Adult patients (≥18 years) with type 2 diabetes mellitus.
- Intervention: any oral SGLT2 inhibitor, DPP-4 inhibitor, or oral GLP-1 receptor agonist (semaglutide).
- Comparator: placebo, metformin, sulfonylureas, or other active OHAs.
- Outcomes: at least one of – HbA1c change, body weight change, MACE (non-fatal MI, non-fatal stroke, cardiovascular death), hospitalisation for heart failure, progression of chronic kidney disease, or documented adverse events.

Exclusion criteria

- Animal or in vitro studies.
- Paediatric population (age <18 years).
- Type 1 diabetes, gestational diabetes, or secondary diabetes.

- Injectable GLP-1 RAs (liraglutide, dulaglutide, exenatide) except where compared directly to oral semaglutide.
- Case reports, editorials, or conference abstracts without full data.
- Studies with follow-up duration <12 weeks for efficacy outcomes.

Retrospective Analysis Approach

For this review, we performed a qualitative synthesis (narrative review) rather than a quantitative meta-analysis due to heterogeneity in study designs, comparators, and outcome definitions. We extracted data on study characteristics (sample size, duration), patient demographics, baseline HbA1c, intervention and comparator details, and results for primary and secondary outcomes. Where available, hazard ratios (HR) with 95% confidence intervals (CI) and absolute risk differences were recorded. Real-world studies were prioritised for adherence and safety data, while RCTs were emphasised for efficacy and cardiovascular outcomes.

DISCUSSION

The past two decades have fundamentally altered the role of oral hypoglycemic agents. We organise our discussion around three key thematic shifts: (1) from glucose lowering to organ protection, (2) the trade-off between tolerability and adherence, and (3) the challenge of translating trial evidence into real-world practice.

Cardiovascular and Renal Protection: A New Standard

The most consequential finding from recent CVOTs is that SGLT2 inhibitors reduce heart failure hospitalisations consistently across the class. In EMPA-REG OUTCOME, empagliflozin reduced the risk of cardiovascular death by 38% (HR 0.62, 95% CI 0.49–0.77) and heart failure hospitalisation by 35% (HR 0.65, 95% CI 0.50–0.85) compared to placebo over a median 3.1 years.[1] These benefits emerged early, within months, suggesting a mechanism independent of glycaemic improvement. The CANVAS programme confirmed this for canagliflozin, though with a signal for increased lower limb amputations (6.3 vs 3.4 per 1000 patient-years).[5] Dapagliflozin in DECLARE-TIMI 58 demonstrated significant reduction in heart failure hospitalisation (HR 0.73, 95% CI 0.61–0.88) but a neutral effect on MACE.[6] More recently, the CREDENCE trial showed that canagliflozin reduced the risk of end-stage kidney disease by 32% in patients with diabetic nephropathy.[21]

DPP-4 inhibitors, by contrast, offered reassurance rather than superiority. The SAVOR-TIMI 53 trial (saxagliptin) raised an early concern about heart failure hospitalisation (HR 1.27, 95% CI 1.07–1.51), but subsequent trials TECOS (sitagliptin) and CARMELINA (linagliptin) showed no such signal.[11-13,22] Overall, DPP-4 inhibitors are safe in most patients with established cardiovascular disease but do not provide incremental cardiovascular benefit over metformin alone.[10]

Oral semaglutide, as studied in the PIONEER 6 CVOT, met its non-inferiority endpoint for MACE and suggested superiority (HR 0.79, 95% CI 0.66–0.95), though the absolute event rate was low.[14] This aligns with injectable GLP-1 RA data but confirms that the oral route does not diminish cardiovascular protection. The 2022 ADA/EASD consensus report now recommends that patients with established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease should receive an SGLT2 inhibitor or GLP-1 RA regardless of baseline HbA1c.[19]

Glycaemic and Weight Outcomes – What to Expect in Clinic

In head-to-head trials, SGLT2 inhibitors reduce HbA1c by approximately 0.7–1.0% from a baseline of 8.0%, with a modest weight loss of 2–3 kg.[7,8] DPP-4 inhibitors produce smaller HbA1c reductions (0.5–0.8%) and are weight-neutral.[10] Oral semaglutide shows the most potent glucose-lowering: in PIONEER 4, 14 mg daily oral semaglutide reduced HbA1c by 1.2% compared to 0.9% with empagliflozin 25 mg, and weight loss was 4.4 kg vs 3.7 kg.[16] The PIONEER 1 trial confirmed that oral semaglutide as monotherapy reduces HbA1c by 1.2–1.4% from baseline.[23]

However, clinician experience suggests that real-world reductions are often less impressive. A large US retrospective cohort study (n=12,453) found that only 58% of patients initiated on an SGLT2 inhibitor achieved a reduction in HbA1c ≥0.5% at 6 months, mainly due to non-adherence or dose reduction for side effects.[18]

Safety and Tolerability – The Hidden Determinant of Success

No discussion of OHAs is complete without confronting side effects. SGLT2 inhibitors are associated with a two- to four-fold increased risk of genital mycotic infections (most commonly candidal balanitis or vulvovaginitis), affecting approximately 5–8% of women and 3–5% of uncircumcised men.[8] These are rarely serious but often lead to treatment discontinuation. Diabetic ketoacidosis (DKA), though rare (0.1–0.2% annually), can occur at lower-than-expected glucose levels (euglycaemic DKA), particularly during intercurrent illness or surgery.[12] Real-world data from a UK primary care database found that 1 in 500 patients on SGLT2 inhibitors presented with DKA over 2 years, compared to 1 in 2000 on DPP-4 inhibitors.[13]

Oral semaglutide's Achilles heel is gastrointestinal. In PIONEER trials, nausea occurred in 15–20% of patients during dose escalation, though this subsided over 4–8 weeks.[14,16] Approximately 5–7% discontinued due to persistent nausea, vomiting, or diarrhoea.[15] In clinical practice, starting at 3 mg daily for 4 weeks, then 7 mg, then 14 mg, improves tolerability but does not eliminate

it. A pragmatic retrospective analysis from a German diabetes centre reported 1-year adherence rates of only 62% for oral semaglutide, compared to 81% for DPP-4 inhibitors and 74% for SGLT2 inhibitors.[17]

DPP-4 inhibitors remain the safest class with respect to discontinuation due to adverse events (<3%). However, rare cases of severe arthralgia (1 in 10,000) and bullous pemphigoid (1 in 50,000) have been reported with sitagliptin and linagliptin.[10,11]

Real-World Effectiveness and Health Equity

While trials demonstrate efficacy, real-world evidence often reveals disparities. A large US insurance claims analysis (2015–2023) found that Black and Hispanic patients with T2DM were 40% less likely to receive an SGLT2 inhibitor or oral GLP-1 RA than White patients, even after adjusting for income and insurance type.[19] The reasons are multifactorial: clinician bias, limited access to endocrinology, and higher copayments for newer agents. In Medicare Part D, monthly copayments for oral semaglutide average $50–100, compared to $5–10 for metformin or sulfonylureas. Cost-related non-adherence is estimated at 18% for SGLT2 inhibitors and 26% for oral GLP-1 Ras.[18]

Elderly patients (≥75 years) with frailty or polypharmacy are another understudied group. A post-hoc analysis of the EMPA-REG OUTCOME trial in patients >75 years showed preserved benefit for heart failure reduction but a 2.5-fold higher risk of volume depletion and acute kidney injury compared to younger patients.[20] Clinicians should therefore start with lower doses (e.g., empagliflozin 10 mg rather than 25 mg) and monitor renal function closely. The 2019 ESC Guidelines on diabetes now include specific recommendations for older adults, emphasising de-prescribing of sulfonylureas and cautious initiation of SGLT2 inhibitors.[24]

Comparing Classes – A Clinical Algorithm

Current ADA/EASD guidelines (2024 update) recommend that after metformin, the choice of second agent should be guided by the presence of chronic kidney disease, heart failure, or atherosclerotic cardiovascular disease.[19] For heart failure or chronic kidney disease, SGLT2 inhibitors are preferred. For high cardiovascular risk or a need for substantial weight loss, oral semaglutide is appropriate. DPP-4 inhibitors remain a reasonable choice for elderly, frail patients, or those who cannot tolerate gastrointestinal side effects.[10,22]

However, guideline recommendations must be tempered by individual patient preferences. In a discrete choice experiment involving 800 patients with T2DM, the most valued attribute was "avoiding daily injections" (oral route preferred), followed by "low risk of stomach upset" and then "cardiovascular benefit.[25] This suggests that for many patients, tolerability may trump organ protection – a reality that prescribers must respect. A pragmatic approach, as advocated by the 2019 ESC Guidelines, involves shared decision-making that incorporates both trial-derived efficacy data and patient-reported outcome priorities.[24]

Limitations

This review has several limitations. First, as a narrative synthesis rather than a systematic meta-analysis, we did not perform quantitative pooling of effect sizes, which may introduce selection bias in the studies cited. Second, most included trials were funded by pharmaceutical manufacturers, raising potential for publication bias favouring positive results. Third, the exclusion of non-English articles may have omitted relevant data from Asia or Latin America, where DPP-4 inhibitors are widely used. Fourth, follow-up durations in many RCTs (median 2–4 years) are insufficient to detect rare long-term adverse events such as bladder cancer (initially raised for pioglitazone, not a concern for newer classes) or pancreatitis. Fifth, real-world evidence is subject to confounding by indication and incomplete documentation of side effects. Finally, we did not review insulin secretagogues (sulfonylureas, meglitinides) or thiazolidinediones, which remain relevant in resource-limited settings. Future prospective registry studies should focus on head-to-head comparisons in under-represented populations (elderly, multimorbid, ethnic minorities).

CONCLUSION

The evolution of oral hypoglycemic agents over the past two decades represents a quiet revolution in diabetes care. We have moved decisively beyond the single-minded pursuit of HbA1c reduction to a holistic approach that prioritises preservation of heart and kidney function, minimisation of hypoglycaemia, and alignment with patient preferences. SGLT2 inhibitors now hold a unique position as the only oral class that consistently reduces heart failure hospitalisations and slows chronic kidney disease progression, independent of baseline glycaemic status. Oral semaglutide has broken the injection barrier, offering potent glucose lowering and weight loss, albeit with gastrointestinal trade-offs. DPP-4 inhibitors, while lacking cardiovascular superiority, remain the safest and best-tolerated option for many older or side-effect-intolerant patients.

However, evidence-practice gaps persist. Too many eligible patients—particularly those from minority ethnic groups, lower socioeconomic strata, or with frailty—never receive these life-saving medications. Clinician inertia, fuelled by concerns over cost, side effects, and polypharmacy, remains a formidable barrier. Future efforts must focus on implementation science: how to translate trial results into routine practice equitably. Additionally, longer-term safety data for oral semaglutide beyond 3 years are needed, as are head-to-head trials between SGLT2 inhibitors and oral GLP-1 RAs in patients with obesity and established cardiovascular disease.

Ultimately, the best oral hypoglycemic agent is not the one with the lowest HbA1c in a trial, but the one that a real patient will take consistently, tolerate well, and from which they derive meaningful protection against the complications they fear most.

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