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Research Article

Impact of an Algorithm-Based Combination Therapy on Glycemic Control in Newly Diagnosed Type 2 Diabetes Mellitus: A Retrospective Observational Study

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ABSTRACT
Background: Early, individualized pharmacotherapy is increasingly advocated to achieve prompt glycemic control and preserve ß-cell function in type 2 diabetes mellitus (T2DM) . Real-world evidence on structured, algorithm-driven combination regimens at diagnosis remains limited.
Methods: We reviewed computerized outpatient records (January–October 2021) of adults with newly diagnosed T2DM attending a specialty clinic. Patients were stratified by baseline glycated hemoglobin (HbA1c) into Group 1 (7–9%), Group 2 (9–11%), and Group 3 (> 11%). A proprietary software generated treatment lines (triple, quadruple, or quintuple oral combinations) according to fasting/post-prandial glucose–derived estimated HbA1c. Weight and glycemic indices were recorded at baseline, 3 and 6 months. The primary outcome was change in HbA1c.
Results: Of 890 screened patients, 343 met inclusion criteria. Baseline mean ± SD HbA1c was 7.22 ± 0.54%, 9.09 ± 0.61%, and 12.92 ± 2.54% in Groups 1–3, respectively. HbA1c fell significantly at 3 months (–16.9%, –30.1%, –52.2%; $p < 0.01$) and was sustained at 6 months (Figure 1). Mean fasting and post-prandial glucose declined by 14–57% and 27–61%, respectively (Tables 2–3). Body weight remained neutral in Groups 1–2 but increased modestly in Group 3 (+5.4%, $p = 0.016$). Medication burden decreased over time: in Group 3 the proportion receiving quintuple therapy fell from 100% to 0.5%, while triple or dual therapy rose to 80.6% by month 6 (Figure 2). No severe hypoglycemia or ketoacidosis was reported.
Conclusion: An algorithm-based strategy delivering intensive, baseline HbA1c-matched oral combinations achieved rapid, durable glycemic control with progressive treatment de-escalation in newly diagnosed T2DM. Pragmatic digital algorithms may complement current guidelines by operationalizing early combination therapy.

Keywords: Type 2 Diabetes, Early Combination Therapy, Algorithm, Hba1c, SGLT2 Inhibitor, DPP-4 Inhibitor, Retrospective Study.

INTRODUCTION

Timely attainment of glycemic targets at the onset of type 2 diabetes is pivotal to delaying micro- and macrovascular complications [1]. Conventional stepwise intensification, often anchored to metformin monotherapy, may expose patients to prolonged periods of hyperglycemia – the so-called "metabolic memory" [2]. Mounting evidence advocates earlier combination therapy to circumvent therapeutic inertia, preserve β-cell reserve, and extend glycemic durability [3]. The landmark VERIFY trial demonstrated that initiating vildagliptin plus metformin halved glycemic failure over five years compared with metformin alone [4]. Likewise, real-world data show that sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl-peptidase-4 (DPP-4) inhibitors used upfront confer greater HbA1c reductions and cardiometabolic benefits versus delayed introduction [5,6]. Clinical algorithms distil guideline recommendations into point-of-care decisions, potentially standardising therapy while accommodating patient heterogeneity [7]. Digital algorithms incorporating fasting and post-prandial glucose to estimate HbA1c can dynamically match drug potency to glycemic burden, but empirical validation is sparse. Few studies have explored multi-drug regimens that escalate above triple therapy at diagnosis, despite guideline latitude for such an approach when baseline HbA1c exceeds 9–10% [1]. We therefore examined a real-world cohort managed with an in-house software that automatically allocates triple, quadruple or quintuple oral combinations according to calculated HbA1c tiers in newly diagnosed T2DM. We hypothesised that this algorithm-based intensification would lead to substantial HbA1c reductions within six months,

with the possibility of dose de-escalation as glycemia normalises. The present study addresses three knowledge gaps: (i) the effectiveness of extreme combination therapy (≥4 agents) at presentation; (ii) its safety and weight impact; and (iii) whether structured tapering is feasible without glycemic rebound. Our findings may inform guideline discussions on incorporating pragmatic, data-driven algorithms into routine diabetes care [8]

MATERIALS AND METHODS

Study Design and Population

This retrospective observational study analysed electronic outpatient records from a tertiary diabetes clinic in western India. Eligible patients were adults (30–80 years) with newly diagnosed T2DM between 1 January and 31 October 2021 who had complete baseline and follow-up data at 3 and 6 months. Exclusion criteria were hospitalization for hyperglycemic emergencies, type 1 diabetes, estimated glomerular filtration rate < 45 mL/min/1.73 m², chronic liver disease, pregnancy, or concurrent enrolment in interventional trials.

Treatment Algorithm

A proprietary software integrated fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) to derive estimated HbA1c using the validated Nathan regression equation. Patients were stratified into three HbA1c tiers triggering preset oral drug combinations:

- Group 1 (7–9%): metformin + pioglitazone + dapagliflozin
- Group 2 (9–11%): metformin + pioglitazone + dapagliflozin + teneligliptin
- Group 3 (> 11%): metformin + pioglitazone + dapagliflozin + teneligliptin + gliclazide

Dose adjustments followed standard prescribing information. Tapering to fewer agents was algorithmically suggested once FBS ≤ 110 mg/dL and PPBS ≤ 140 mg/dL on two consecutive visits.

Data Collection

Demographics, anthropometry, FBS, PPBS, and laboratory HbA1c were extracted at baseline, 3 months, and 6 months. Adverse events were recorded passively. The study adhered to the Declaration of Helsinki and was approved by the institutional ethics committee (reference IEC-/2022-/DM-/04); individual consent was waived for de-identified data.

Statistical Analysis

Continuous variables are presented as mean ± SD or median (IQR) as appropriate; categorical data as frequencies (%). Paired t-tests compared within-group changes; ANOVA evaluated between-group differences. A two-tailed $p \leq 0.05$ denoted significance. Analyses were performed using SPSS v17.

RESULTS

Patient Characteristics

A total of 343 patients met inclusion criteria: 74 (21.6%) in Group 1, 81 (23.6%) in Group 2, and 220 (64.1%) in Group 3 (Table 1). Mean age was 49.8 ± 10.3 years and 56% were male. Baseline BMI averaged 75–77 kg across groups with no significant inter-group difference.

Glycemic Outcomes

Marked HbA1c reductions were observed in all groups by month 3, with stabilization or further improvement by month 6 (Figure 1, Table 2). Group 3, despite the highest baseline HbA1c (12.92 ± 2.54%), achieved a mean 6-month HbA1c of 6.24 ± 1.61% (–6.68 percentage points, $p < 0.001$). FBS and PPBS followed similar trajectories, with relative declines proportional to baseline dysglycemia (Table 3).

Weight and Safety

Weight remained stable in Groups 1–2 but increased by 4 kg in Group 3 (Table 4). No cases of severe hypoglycemia or diabetic ketoacidosis were reported. Two patients discontinued pioglitazone due to edema.

De-Escalation of Therapy

By month 6, 66.2% of Group 3 had been tapered to triple therapy, and 14.4% to dual therapy (Figure 2). Comparable step-downs occurred in Groups 1–2, with > 85% maintained on ≤ dual therapy without loss of glycemic control.

Table 1. Baseline Characteristics by Hba1c Stratum

Variable	Group 1 (7–9%, n=74)	Group 2 (9–11%, n=81)	Group 3 (> 11%, n=220)
Age (years)	48.9 ± 9.8	50.5 ± 10.9	49.7 ± 10.2
Male sex, %	55	58	56

Weight (kg)	77.7 ± 14.7	70.9 ± 22.3	75.5 ± 17.9
FBS (mg/dL)	135 ± 20	154 ± 47	265 ± 69
PPBS (mg/dL)	186 ± 27	268 ± 31	377 ± 96
HbA1c (%)	7.22 ± 0.54	9.09 ± 0.61	12.92 ± 2.54

Table 2. Mean Hba1c Over 6 Months

Time-point	Group 1	Group 2	Group 3
Baseline	7.22 ± 0.54	9.09 ± 0.61	12.92 ± 2.54
3 months	6.00 ± 1.45	6.35 ± 1.07	6.17 ± 1.38
6 months	5.46 ± 0.93	6.45 ± 0.83	6.24 ± 1.61
ΔBaseline–6 mo	–1.76 (24%)	–2.64 (29%)	–6.68 (52%)

Table 3. Change in Fasting and Post-Prandial Glucose

Metric	Group 1	Group 2	Group 3
FBS Baseline (mg/dL)	134.98 ± 20.24	154.46 ± 46.70	264.74 ± 69.22
FBS 6 mo	102.04 ± 21.78	115.80 ± 21.53	113.80 ± 35.76
PPBS Baseline	186.13 ± 27.29	267.94 ± 30.57	377.06 ± 96.28
PPBS 6 mo	117.94 ± 32.00	161.14 ± 33.08	150.32 ± 60.17

Table 4. Body-Weight Trajectory

Time-point	Group 1 (kg)	Group 2 (kg)	Group 3 (kg)
Baseline	77.74 ± 14.73	70.95 ± 22.27	75.45 ± 17.89
3 months	74.55 ± 14.41	67.63 ± 16.46	76.06 ± 18.73
6 months	72.10 ± 11.57	70.70 ± 6.38	79.51 ± 19.50

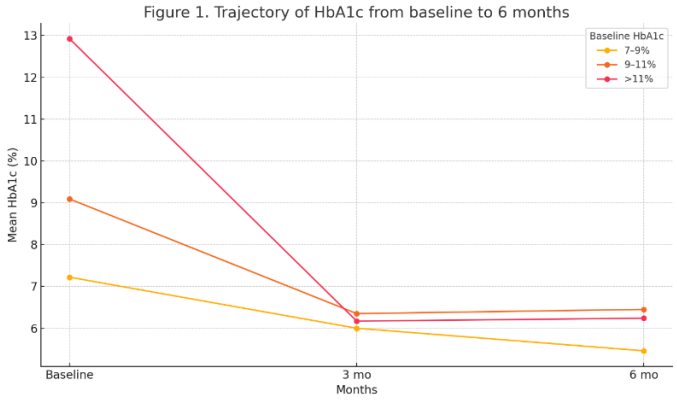

Figure 1. Trajectory of Hba1c from Baseline to 6 Months

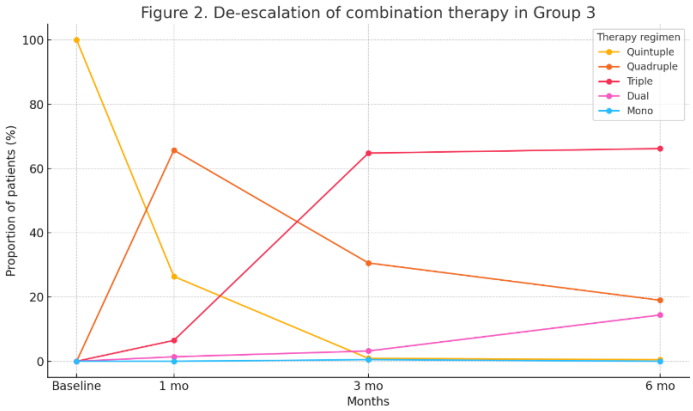

Figure 2. De-Escalation of Combination Therapy in Group 3

DISCUSSION

This real-world analysis demonstrates that an algorithm-driven, intensively titrated oral combination strategy can normalise glycemia within three months of T2DM diagnosis, even when baseline HbA1c exceeds 11%. The magnitude of HbA1c reduction in Group 3 (–6.7 percentage points) parallels the early insulinization protocols reported by Weng et al. [9] and exceeds the 1.5–2.0% average decline observed with standard dual therapy [1]. Our findings corroborate the VERIFY trial in affirming the superiority of early combination therapy for glycemic durability [4]; however, we extend this concept by incorporating SGLT2 and DPP-4 inhibitors and scaling drug number to baseline HbA1c.

Algorithmic de-escalation yielded a two-thirds shift from quintuple to triple or dual therapy within six months, echoing treat-to-target paradigms that advocate medication simplification once euglycemia is achieved [10]. Importantly, weight neutrality was maintained except for a modest gain in the highest-risk group, plausibly attributable to pioglitazone-induced fluid retention [11]. The inclusion of dapagliflozin may have mitigated weight gain and provided cardiorenal protection, aligning with evidence that SGLT2 inhibitors reduce heart failure and renal events irrespective of baseline HbA1c [12].

Concerns regarding hypoglycemia with sulfonylurea-containing regimens were unfounded in our cohort, likely owing to algorithm-mediated dose tapering and the insulin-independent glucose lowering of adjunct agents [13]. The absence of eGFR < 45 mL/min/1.73 m² minimised SGLT2-related ketoacidosis risk [14].

Strengths of our study include a sizeable sample of very-high HbA1c patients, pragmatic algorithm application, and objective laboratory endpoints. Limitations encompass its retrospective design, lack of a sequential-add-on comparator, and single-centre Indian setting which may limit generalisability. We did not capture lifestyle adherence or continuous glucose monitoring metrics, and longer follow-up is needed to assess durability beyond six months.

Current ADA Standards recommend considering initial combination therapy when HbA1c is ≥ 9% and insulin when ≥ 10% or if catabolic features are present [1]. Our results suggest that carefully selected, multi-drug oral regimens might obviate the need for insulin in a substantial subset, provided close follow-up and algorithmic tapering are feasible. Prospective trials comparing algorithm-guided combination therapy with conventional stepwise intensification are warranted.

CONCLUSION

In a real-world cohort of newly diagnosed T2DM, a digital algorithm assigning triple-to-quintuple oral combinations achieved rapid, clinically meaningful HbA1c reductions that were maintained at six months while allowing systematic de-escalation of therapy. The strategy was safe and weight-neutral in most patients. Algorithm-based, patient-tailored intensification may represent a pragmatic bridge between guideline recommendations and day-to-day practice, meriting validation in prospective multicentre studies.

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