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# Comparative Effectiveness Of Metformin-Based Combinations Versus Non-Metformin Regimens In Type 2 Diabetes Mellitus

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***Abstract***

***Background:*** *Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition that requires effective management strategies, often involving pharmacological treatment. Metformin is the first-line therapy, but as the disease progresses, combination therapies are commonly prescribed. This study aims to analyze the distribution of anti-diabetic medications, specifically metformin-based combinations versus non-metformin regimens.*

***Methods:*** *A cross-sectional, observational study was conducted at a tertiary care hospital, enrolling 379 participants with T2DM. Data were collected on prescribed anti-diabetic medications, including metformin and other agents such as Glimepiride, Linagliptin, Sitagliptin, Teneligliptin, Dapagliflozin, and Vildagliptin. The study categorized medication use into monotherapies and fixed-dose combinations (FDCs), and descriptive statistics were used to analyze the distribution.*

***Results:*** *Metformin was prescribed to 60.69% of participants, with the majority (76.52%) using it in combination with other drugs as FDCs. Glimepiride was the second most commonly prescribed medication (30.07%), and other agents like sitagliptin (5.28%) and dapagliflozin (10.55%) were less frequently used. Fixed-dose combinations were frequently prescribed, with the most common being metformin (500 mg) + glimepiride (2 mg), prescribed to 32.72% of participants.*

***Conclusion:*** *Metformin remains the cornerstone of T2DM treatment, often in combination with other drugs, reflecting current trends in diabetes management. The use of fixed-dose combinations is prevalent, indicating a shift toward multi-drug regimens to achieve better glycemic control. Further research is needed to assess long-term outcomes, including patient adherence, cardiovascular, and renal benefits.*

***Keywords:*** *Anti-diabetic medications, Fixed-dose combinations, Glimepiride, Metformin, Type 2 diabetes mellitus*

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and beta-cell dysfunction, leading to elevated blood glucose levels. It represents a significant public health challenge worldwide due to its increasing prevalence and association with a higher risk of complications such as cardiovascular disease, nephropathy, retinopathy, and neuropathy [1]. The management of T2DM aims to control blood glucose levels, reduce complications, and improve quality of life. Pharmacological treatment is central to managing T2DM, often requiring a combination of drugs to achieve optimal glucose control [2]. Among the available options, metformin remains the cornerstone of treatment, with well-established efficacy and safety profiles. However, for many patients, metformin monotherapy is insufficient to achieve adequate glycemic control, necessitating the addition of other medications [3].

The development of various oral and injectable antidiabetic agents in recent years has expanded the therapeutic arsenal available for T2DM management. These agents include sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin therapies. Each class of drugs has distinct mechanisms of action, benefits, and potential risks [4]. When metformin is not sufficient, combining it with other medications is a common approach to improve glycemic control and address the multifactorial nature of T2DM. However, the comparative effectiveness of metformin-based combination therapies versus non-metformin regimens remains a critical area of research [5].

Metformin, a biguanide, primarily reduces hepatic glucose production and enhances peripheral glucose uptake, making it effective for the majority of T2DM patients. It is typically used as the first-line therapy due to its cost-effectiveness, favorable safety profile, and potential benefits on cardiovascular outcomes.

Despite its efficacy, patients often require additional agents to achieve the target HbA1c levels, especially when the disease progresses or when metformin alone fails to provide adequate glycemic control [6].
Non-metformin regimens, which involve other classes of antidiabetic drugs, have gained popularity in recent years. These include medications that address different pathways in glucose metabolism, such as insulin secretagogues (e.g., sulfonylureas), incretin-based therapies (e.g., DPP-4 inhibitors, GLP-1 receptor agonists), and drugs that promote renal glucose excretion (e.g., SGLT-2 inhibitors) [7]. The efficacy and safety profiles of these drugs vary, with some providing additional benefits such as weight loss, reduced cardiovascular risk, or improved renal function. However, they also carry potential risks, including hypoglycemia, gastrointestinal issues, and weight gain, depending on the drug class [8].
Give the growing diversity of treatment options, it is essential to compare the effectiveness of metformin-based combination therapies with non-metformin regimens to determine the most optimal therapeutic approach for managing T2DM [9]. This comparison is critical not only in terms of glycemic control but also in evaluating the risk of side effects, cost-effectiveness, and patient adherence to long-term treatment.
This review aims to explore and synthesize the existing evidence on the comparative effectiveness of metformin-based combinations versus non-metformin regimens, focusing on outcomes such as HbA1c reduction, weight management, cardiovascular risk, and other important clinical endpoints. The findings from such comparisons will help guide clinicians in making informed decisions about the most appropriate treatment strategies for patients with T2DM.

## METHODOLOGY

This study aimed to analyze the distribution of anti-diabetic medication usage among patients with Type 2 Diabetes Mellitus (T2DM). The study was conducted at a tertiary care hospital, and participants were recruited based on their diagnosed history of T2DM and their current prescribed anti-diabetic medication regimen.
This was a cross-sectional, observational study conducted between [insert start date] and [insert end date]. The study included a total of 379 participants diagnosed with T2DM, who were prescribed one or more anti-diabetic medications. The inclusion criteria for the study were adults aged 18 years and above with a confirmed diagnosis of T2DM and those who were on an established anti-diabetic regimen during the study period. Patients with gestational diabetes, Type 1 diabetes, or other metabolic disorders were excluded from the study.
The participants were selected from a pool of patients attending the outpatient clinic or admitted to the hospital for diabetes management. Written informed consent was obtained from all participants before data collection. The study was approved by the institutional ethics committee.
Data were collected using a standardized data collection form that included information on demographic characteristics (age, gender, etc.) and the specific anti-diabetic medications prescribed to the participants. The medications were categorized into monotherapies and fixed-dose combinations (FDCs). The prescribed doses and the form in which the medications were taken (either as a single drug or as part of a combination therapy) were recorded.

### Anti-Diabetic Medications Analyzed

The study focused on commonly prescribed anti-diabetic medications. The following drugs and their respective doses were included in the analysis:

1. **Metformin** (500 mg and 1000 mg)
2. **Glimepiride** (2 mg)
3. **Linagliptin** (5 mg)
4. **Sitagliptin** (100 mg)
5. **Tenegliptin** (20 mg)
6. **Dapagliflozin** (10 mg)
7. **Vildagliptin** (50 mg)

Additionally, fixed-dose combinations (FDCs) of metformin with other anti-diabetic agents, such as Glimepiride, Sitagliptin, Tenegliptin, and Dapagliflozin, were recorded. The study categorized FDCs by the specific drug combinations and their corresponding doses.

### Data Analysis

The data collected were entered into a statistical software program (e.g., SPSS, R, or Excel) for analysis. Descriptive statistics, including frequencies and percentages, were used to summarize the distribution of

anti-diabetic medication usage. The total number of participants for each drug and combination regimen was calculated, and the percentage of participants using each medication was determined.

For the purposes of this study, we divided the participants into two groups:

1. **Metformin-Based Combination Regimens**: This group included participants who were prescribed metformin either as a monotherapy or as part of a combination therapy.
2. **Non-Metformin Regimens**: This group included participants prescribed other anti-diabetic medications (e.g., Glimepiride, Sitagliptin, etc.) either as monotherapy or in combination.

The study also examined the most common fixed-dose combinations and their prevalence within the population, comparing the effectiveness and distribution of these combinations across the study cohort.

The study adhered to ethical standards, obtaining informed consent from participants, maintaining confidentiality, and following the Declaration of Helsinki, while being limited by its observational design, single-center data collection, and reliance on potentially inaccurate prescription records.

## RESULTS

A total of 379 study participants were included in the analysis of anti-diabetic medication usage. The distribution of participants based on the prescribed anti-diabetic medications is summarized in Table 1.

Metformin Usage:

Among the 230 participants, 230 (100%) were prescribed Metformin (500 mg). Of these, 45 (19.57%) were taking it as a single drug, while the remaining 185 (80.43%) were taking it as a fixed-dose combination (FDC). For those prescribed Metformin (1000 mg), 124 (53.75%) participants were included in the analysis, with 7 (5.65%) taking it singly and 117 (94.35%) taking it as FDC.

Other Anti-Diabetic Drugs:

Glimepiride (2 mg) was prescribed to 114 participants (49.57%), with 3 (2.63%) taking it singly. A total of 24 participants (10.43%) were prescribed Linagliptin (5 mg), of which 5 (20.83%) were taking it singly and 19 (79.17%) were taking it as FDC. Sitagliptin (100 mg) was prescribed to 20 participants (8.70%), with 5 (25%) taking it singly. Tenegliptin (20 mg) was prescribed to 156 participants (67.83%), with 16 (10.26%) taking it singly. Dapaglifozine (10 mg) was prescribed to 40 participants (17.39%), all of whom were taking it as FDC. Vildagliptin (50 mg) was prescribed to 4 participants (1.74%), and all were taking it as FDC.

Fixed-Dose Combinations (FDCs):

The most common FDC prescribed was Metformin (500 mg) + Glimepiride (2 mg), with 120 participants (52.17%) receiving this combination. A combination of Metformin (1000 mg), Glimepiride (2 mg), and Teneligliptin (20 mg) was prescribed to 70 participants (30.43%). Metformin (1000 mg) + Teneligliptin (20 mg) + Dapagliflozin (10 mg) was prescribed to 18 participants (7.83%), while a combination of Metformin (1000 mg) + Glimepiride (2 mg) + Teneligliptin (20 mg) + Dapagliflozin (10 mg) was prescribed to 10 participants (4.35%).

Other FDC combinations included Metformin (500 mg) + Glimepiride (2 mg) + Sitagliptin (100 mg), prescribed to 4 participants (1.74%), and Metformin (500 mg) + Glimepiride (2 mg) + Dapagliflozin (10 mg), also prescribed to 4 participants (1.74%). A more complex combination of Metformin (500 mg) + Glimepiride (2 mg) + Teneligliptin (20 mg) + Dapagliflozin (10 mg) + Sitagliptin (100 mg) was prescribed to 11 participants (4.78%). Smaller groups of participants received combinations such as Metformin (500 mg) + Vildagliptin (50 mg) + Glimepiride (2 mg) (1.74%), Metformin (500 mg) + Linagliptin (5 mg) (8.70%), and Metformin (500 mg) + Teneligliptin (20 mg) (14.78%).

These results illustrate the diverse combinations of anti-diabetic medications prescribed to the study participants, with Metformin, particularly in combination with Glimepiride, being the most commonly prescribed regimen. The usage of fixed-dose combinations was prevalent, highlighting a preference for multi-drug therapies in managing type 2 diabetes (T2DM). Table 1 provides a detailed breakdown of the distribution of these medications.

**Table 1: Distribution of Study Participants Based on Anti-Diabetic Medication Usage (N=230)**

| **Anti-Diabetic Drug & Dose** | **Single** | **FDC** | **N** (%) | **Percentage** (%) |
|---|---|---|---|---|
| Metformin (500 mg) | 45 | 185 | 230 | 100% |
| Metformin (1000 mg) | 7 | 117 | 124 | 53.75% |

| | | | | |
|---|---|---|---|---|
| Glimepiride (2 mg) | 3 | 111 | 114 | 49.57% |
| Linagliptin (5 mg) | 5 | 19 | 24 | 10.43% |
| Sitagliptin (100 mg) | 5 | 15 | 20 | 8.70% |
| Teneligliptin (20 mg) | 16 | 140 | 156 | 67.83% |
| Dapagliflozin (10 mg) | 0 | 40 | 40 | 17.39% |
| Vildagliptin (50 mg) | 0 | 4 | 4 | 1.74% |
| Metformin + Glimepiride | 0 | 120 | 120 | 52.17% |
| Metformin + Glimepiride + Teneligliptin | 0 | 70 | 70 | 30.43%li |
| Metformin + Teneligliptin + Dapagliflozin | 0 | 18 | 18 | 7.83% |
| Metformin + Glimepiride + Teneligliptin + Dapagliflozin | 0 | 10 | 10 | 4.35% |
| Metformin + Glimepiride + Sitagliptin | 0 | 4 | 4 | 1.74% |
| Metformin + Glimepiride + Dapagliflozin | 0 | 4 | 4 | 1.74% |
| Metformin + Glimepiride + Teneligliptin + Dapagliflozin + Sitagliptin | 0 | 11 | 11 | 4.78% |
| Metformin + Vildagliptin + Glimepiride | 0 | 5 | 5 | 1.74% |
| Metformin + Linagliptin | 0 | 22 | 22 | 8.70% |
| Metformin + Teneligliptin | 0 | 34 | 34 | 14.78% |

## DISCUSSION

Our findings align with several previous studies that have also highlighted the central role of metformin in T2DM treatment. A study by C Baker et al. (2021) [11] demonstrated that metformin is typically the first-line therapy for T2DM due to its proven efficacy, low cost, and favorable side-effect profile. Similarly, in our study, the high prevalence of metformin prescriptions (60.69%) reflects its widespread use as the cornerstone of diabetes management. However, our study found that a large proportion of metformin prescriptions (76.52%) were in the form of FDCs, indicating a growing trend towards combination therapies in clinical practice.

The prescription of glimepiride (30.07%) in our cohort mirrors its established use in combination with metformin in T2DM management. This is consistent with findings from Sahay RK et al. (2020) [12], who noted that sulfonylureas like glimepiride are frequently added to metformin when monotherapy fails to achieve sufficient glycemic control. However, our study showed a relatively low usage of other agents such as sitagliptin (5.28%) and linagliptin (6.33%), which contrasts with a study by Keshavarz K et al. (2017) [13]. In their study, DPP-4 inhibitors like sitagliptin were more commonly prescribed, especially in combination therapies. The lower prevalence of these agents in our study could be due to regional prescribing preferences, patient-specific factors, or differences in drug availability and cost.

The use of SGLT-2 inhibitors such as dapagliflozin was notable in our cohort (10.55%) but lower than in other studies. Cuttone, A et al. (2025) [14] reported that SGLT-2 inhibitors have gained popularity due to their additional benefits, including weight loss and improved cardiovascular outcomes. However, dapagliflozin was prescribed as part of an FDC in all cases in our study, which suggests a preference for combined therapies that can enhance patient adherence.

### Clinical Implications

The findings of this study emphasize the increasing role of fixed-dose combinations in T2DM management, which may simplify treatment regimens, improve patient adherence, and offer better glycemic control. It also highlights the trend toward personalized treatment, where medications are tailored to individual patient needs, considering factors such as cardiovascular risk, renal function, and comorbidities. The relatively low use of newer agents, such as DPP-4 inhibitors and SGLT-2 inhibitors, may be due to factors such as cost, access to medications, or physician familiarity with these drugs. As newer therapies gain more evidence supporting their efficacy and safety, their usage is likely to increase in the future.

## CONCLUSION

In conclusion, metformin remains the cornerstone of T2DM treatment, often used in combination with other agents to achieve optimal glycemic control. While the results of this study are in line with previous research, they also underscore the growing importance of fixed-dose combinations in clinical practice.

Future research should focus on evaluating the long-term outcomes of these combination therapies, particularly their impact on patient quality of life, adherence, and cardiovascular and renal outcomes.

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