



COMPARATIVE EFFECTIVENESS OF SECOND-LINE ORAL ANTIDIABETIC TREATMENTS ADDED TO METFORMIN MONOTHERAPY IN PEOPLE WITH TYPE 2 DIABETES

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ABSTRACT

Background: When metformin monotherapy fails to achieve glycemic control in type 2 diabetes mellitus (T2DM), selection of optimal second-line oral antidiabetic therapy remains challenging. Evidence comparing the real-world effectiveness of different second-line agents added to metformin is limited. This study aimed to compare the glycemic efficacy, weight effects, and safety profiles of sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones as second-line treatments added to metformin in patients with T2DM.

Methods: This retrospective cohort study analyzed 847 patients with T2DM who initiated second-line oral therapy after metformin monotherapy failure between January 2011 and December 2012. Patients were categorized into three groups: sulfonylurea (n=312), DPP-4 inhibitor (n=298), and thiazolidinedione (n=237). Primary outcomes included change in glycated hemoglobin (HbA1c) at 12 months. Secondary outcomes comprised body weight change, hypoglycemic events, and treatment persistence.

Results: Mean baseline HbA1c was comparable across groups ($8.4 \pm 1.1\%$). At 12 months, all groups demonstrated significant HbA1c reductions. Sulfonylureas achieved the greatest reduction ($-1.24 \pm 0.82\%$; $p < 0.001$), followed by DPP-4 inhibitors ($-0.89 \pm 0.71\%$; $p < 0.001$) and thiazolidinediones ($-0.94 \pm 0.78\%$; $p < 0.001$). However, sulfonylureas were associated with significant weight gain ($+2.1 \pm 1.8$ kg; $p < 0.001$) and higher hypoglycemia rates (18.6% vs. 3.4% for DPP-4 inhibitors; $p < 0.001$). DPP-4 inhibitors demonstrated weight neutrality ($+0.3 \pm 1.2$ kg; $p = 0.284$) and superior treatment persistence (82.5% vs. 71.8% for sulfonylureas; $p = 0.002$).

Conclusion: While sulfonylureas provide superior short-term glycemic efficacy as second-line therapy, DPP-4 inhibitors offer comparable effectiveness with favorable weight and safety profiles. Treatment selection should incorporate individual patient characteristics, hypoglycemia risk, and weight management goals.

Keywords: Type 2 diabetes mellitus; metformin; second-line therapy; sulfonylurea; DPP-4 inhibitors; thiazolidinediones; glycemic control.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a progressive metabolic disorder characterized by insulin resistance and declining beta-cell function, affecting over 400 million individuals worldwide [1]. The management of T2DM requires a stepwise pharmacological approach, with metformin universally recommended as first-line therapy due to its established efficacy, cardiovascular safety, weight neutrality, and low cost [2]. However, the progressive nature of T2DM necessitates treatment

intensification in a substantial proportion of patients who fail to achieve or maintain adequate glycemic control with metformin alone [3].

Current clinical guidelines recommend adding a second antidiabetic agent when monotherapy fails to achieve individualized glycemic targets, typically defined as glycated hemoglobin (HbA1c) levels above 7.0-7.5% [4]. The selection of appropriate second-line therapy presents considerable clinical complexity, given the availability of multiple drug classes with distinct mechanisms of action, efficacy profiles, and adverse effect patterns [5]. Sulfonylureas have traditionally dominated second-line prescribing patterns due to their potent glucose-lowering effects, extensive clinical experience, and affordability [6]. However, concerns regarding hypoglycemia, weight gain, and potential cardiovascular effects have prompted consideration of alternative agents [7].

ipeptidyl peptidase-4 (DPP-4) inhibitors represent a newer drug class that enhances incretin hormone activity, promoting glucose-dependent insulin secretion while suppressing glucagon release [8]. These agents offer comparable glycemic efficacy to sulfonylureas with substantially lower hypoglycemia risk and weight-neutral effects [9]. Thiazolidinediones improve insulin sensitivity through peroxisome proliferator-activated receptor gamma activation, providing durable glycemic control but with associated concerns including weight gain, fluid retention, and bone fracture risk [10].

Randomized controlled trials have established the efficacy of individual second-line agents; however, head-to-head comparisons across drug classes in real-world settings remain limited [11]. The ADOPT study demonstrated differential durability of glycemic control among rosiglitazone, metformin, and glyburide monotherapies [12]. Subsequent investigations, including the GRADE study, have provided insights into combination therapy effectiveness, yet practical guidance for second-line selection remains incomplete [13].

Real-world evidence is essential for understanding comparative effectiveness in heterogeneous patient populations with varying comorbidities, adherence patterns, and treatment goals. Such evidence complements randomized trial data by reflecting actual clinical practice conditions and patient selection patterns. Furthermore, economic considerations increasingly influence treatment decisions, particularly in resource-constrained healthcare systems where cost-effectiveness analyses inform formulary decisions.

Despite the clinical importance of second-line therapy selection, substantial knowledge gaps persist regarding comparative long-term outcomes, predictors of treatment response, and optimal patient-drug matching strategies. This study aimed to compare the glycemic efficacy, weight effects, hypoglycemia rates, and treatment persistence of sulfonylureas, DPP-4 inhibitors, and thiazolidinediones as second-line treatments added to metformin in patients with T2DM in a real-world clinical setting.

Materials and Methods

Study Design and Setting

This retrospective cohort study was conducted at a tertiary care academic medical center and its affiliated primary care network. Electronic health records were systematically reviewed to identify eligible patients initiating second-line oral antidiabetic therapy between January 2011 and December 2012. The study protocol received approval from the Institutional Review Board, with waiver of informed consent granted for retrospective data analysis.

Study Population

Patients were eligible for inclusion if they met the following criteria: (1) diagnosis of T2DM based on International Classification of Diseases codes and laboratory confirmation; (2) age 18 years or older at treatment initiation; (3) prior metformin monotherapy for minimum six months with documented suboptimal glycemic control ($HbA1c \geq 7.5\%$); (4) initiation of second-line oral antidiabetic therapy (sulfonylurea, DPP-4 inhibitor, or thiazolidinedione) added to continued metformin; (5) minimum 12 months follow-up data availability.

Exclusion criteria comprised: (1) type 1 diabetes mellitus or secondary diabetes; (2) initiation of injectable therapies (insulin or GLP-1 receptor agonists) as second-line treatment; (3) estimated glomerular filtration rate below 30 mL/min/1.73m²; (4) pregnancy or lactation during study period; (5) active malignancy or life expectancy less than 12 months; (6) concurrent use of medications significantly affecting glucose metabolism (systemic corticosteroids, antipsychotics).

Treatment Groups

Patients were categorized into three mutually exclusive groups based on the second-line agent initiated: (1) Sulfonylurea group: patients receiving glimepiride, gliclazide, or glibenclamide; (2) DPP-4 inhibitor group: patients receiving sitagliptin, saxagliptin, linagliptin, or vildagliptin; (3) Thiazolidinedione group: patients receiving pioglitazone.

Data Collection

Baseline demographic characteristics extracted included age, sex, body mass index (BMI), diabetes duration, and relevant comorbidities (hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease). Baseline laboratory values comprised HbA1c, fasting plasma glucose, serum creatinine, and lipid profile. Concomitant medications were documented, including antihypertensive agents, lipid-lowering therapies, and antiplatelet drugs.

Outcome Measures

The primary outcome was absolute change in HbA1c from baseline to 12 months. Secondary outcomes included: (1) proportion achieving HbA1c target <7.0%; (2) change in body weight at 12 months; (3) documented hypoglycemic events (symptomatic or biochemical glucose <70 mg/dL); (4) treatment persistence defined as continued second-line therapy without switching or augmentation at 12 months; (5) adverse events requiring treatment modification.

Statistical Analysis

Sample size calculation indicated that 210 patients per group would provide 80% power to detect a 0.3% difference in HbA1c reduction between groups at alpha level 0.05. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range as appropriate. Categorical variables were presented as frequencies and percentages. Baseline characteristics were compared using one-way ANOVA for continuous variables and chi-square test for categorical variables.

Within-group changes from baseline were analyzed using paired t-tests. Between-group comparisons employed one-way ANOVA with Tukey's post-hoc test for pairwise comparisons. Multivariable linear regression models adjusted for baseline HbA1c, age, diabetes duration, BMI, and relevant comorbidities were constructed to estimate adjusted treatment effects. Kaplan-Meier analysis assessed treatment persistence, with log-rank test for between-group comparisons. Statistical significance was defined as $p < 0.05$. Analyses were performed using SPSS version 26.0.

Results

Baseline Characteristics

A total of 847 patients met eligibility criteria and were included in the analysis: 312 in the sulfonylurea group, 298 in the DPP-4 inhibitor group, and 237 in the thiazolidinedione group. Baseline demographic and clinical characteristics were generally comparable across groups, with minor differences in age distribution and cardiovascular disease prevalence.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Sulfonylurea (n=312)	DPP-4 Inhibitor (n=298)	Thiazolidinedione (n=237)	p-value
Age (years), mean $\pm$ SD	56.8 $\pm$ 11.2	54.3 $\pm$ 10.8	55.6 $\pm$ 11.5	0.038
Male, n (%)	168 (53.8)	154 (51.7)	129 (54.4)	0.782
BMI (kg/m ²), mean $\pm$ SD	29.4 $\pm$ 4.8	30.1 $\pm$ 5.2	29.8 $\pm$ 4.6	0.246
Diabetes duration (years), mean $\pm$ SD	5.2 $\pm$ 3.4	4.8 $\pm$ 3.1	5.1 $\pm$ 3.6	0.342
Baseline HbA1c (%), mean $\pm$ SD	8.42 $\pm$ 1.08	8.38 $\pm$ 1.12	8.45 $\pm$ 1.06	0.768
Fasting glucose (mg/dL), mean $\pm$ SD	168 $\pm$ 42	164 $\pm$ 38	171 $\pm$ 45	0.182
Hypertension, n (%)	198 (63.5)	182 (61.1)	156 (65.8)	0.524
Dyslipidemia, n (%)	224 (71.8)	208 (69.8)	172 (72.6)	0.748
Cardiovascular disease, n (%)	62 (19.9)	42 (14.1)	48 (20.3)	0.098
Metformin dose (mg/day), mean $\pm$ SD	1847 $\pm$ 412	1792 $\pm$ 386	1824 $\pm$ 398	0.258

BMI: Body Mass Index; HbA1c: Glycated Hemoglobin; SD: Standard Deviation

Glycemic Outcomes

All treatment groups demonstrated significant HbA1c reductions from baseline to 12 months. The sulfonylurea group achieved the largest absolute reduction, followed by thiazolidinedione and DPP-4 inhibitor groups. Between-group differences reached statistical significance ($p=0.004$).

Table 2: Glycemic and Weight Outcomes at 12 Months

Outcome	Sulfonylurea (n=312)	DPP-4 Inhibitor (n=298)	Thiazolidinedione (n=237)	p-value
HbA1c change (%), mean $\pm$ SD	-1.24 $\pm$ 0.82	-0.89 $\pm$ 0.71	-0.94 $\pm$ 0.78	0.004
Final HbA1c (%), mean $\pm$ SD	7.18 $\pm$ 0.94	7.49 $\pm$ 0.88	7.51 $\pm$ 0.92	0.018
Achieved HbA1c <7.0%, n (%)	156 (50.0)	118 (39.6)	89 (37.6)	0.006
Achieved HbA1c <7.5%, n (%)	218 (69.9)	186 (62.4)	142 (59.9)	0.028
Weight change (kg), mean $\pm$ SD	+2.1 $\pm$ 1.8	+0.3 $\pm$ 1.2	+2.8 $\pm$ 2.1	<0.001
Weight change (%), mean $\pm$ SD	+2.6 $\pm$ 2.2	+0.4 $\pm$ 1.5	+3.4 $\pm$ 2.6	<0.001
FPG change (mg/dL), mean $\pm$ SD	-38 $\pm$ 28	-26 $\pm$ 22	-32 $\pm$ 25	0.002

HbA1c: Glycated Hemoglobin; FPG: Fasting Plasma Glucose; SD: Standard Deviation

After multivariable adjustment, sulfonylureas remained associated with significantly greater HbA1c reduction compared to DPP-4 inhibitors (adjusted difference: -0.31%; 95% CI: -0.48 to -0.14; $p<0.001$). The difference between sulfonylureas and thiazolidinediones was smaller and marginally significant (adjusted difference: -0.26%; 95% CI: -0.45 to -0.07; $p=0.008$).

Safety and Tolerability Outcomes

Significant differences emerged in hypoglycemia rates and treatment persistence across groups. Sulfonylureas demonstrated substantially higher hypoglycemia incidence compared to other agents, while DPP-4 inhibitors showed superior treatment persistence.

Table 3: Safety Outcomes and Treatment Persistence at 12 Months

Outcome	Sulfonylurea (n=312)	DPP-4 Inhibitor (n=298)	Thiazolidinedione (n=237)	p-value
Any hypoglycemia, n (%)	58 (18.6)	10 (3.4)	14 (5.9)	<0.001
Severe hypoglycemia, n (%)	8 (2.6)	1 (0.3)	2 (0.8)	0.042
Peripheral edema, n (%)	12 (3.8)	8 (2.7)	34 (14.3)	<0.001
Gastrointestinal symptoms, n (%)	18 (5.8)	14 (4.7)	11 (4.6)	0.746
Treatment persistence, n (%)	224 (71.8)	246 (82.5)	178 (75.1)	0.006
Treatment discontinuation, n (%)	42 (13.5)	28 (9.4)	32 (13.5)	0.214
Treatment augmentation, n (%)	46 (14.7)	24 (8.1)	27 (11.4)	0.032

Weight gain was most pronounced in the thiazolidinedione group ($+2.8 \pm 2.1$ kg), followed by sulfonylureas ($+2.1 \pm 1.8$ kg), while DPP-4 inhibitors demonstrated weight neutrality ($+0.3 \pm 1.2$ kg; $p=0.284$ for change from baseline). Peripheral edema occurred significantly more frequently with thiazolidinediones (14.3%) compared to other groups.

Discussion

This real-world comparative effectiveness study demonstrates that while sulfonylureas provide superior short-term glycemic efficacy as second-line therapy added to metformin, DPP-4 inhibitors offer a more favorable balance of effectiveness, weight effects, and safety. These findings have important implications for individualized treatment selection in clinical practice.

The greater HbA1c reduction observed with sulfonylureas (-1.24%) compared to DPP-4 inhibitors (-0.89%) aligns with meta-analytic evidence suggesting a modest glycemic advantage for insulin secretagogues [14]. The UKPDS demonstrated substantial glycemic benefits with sulfonylurea therapy, establishing these agents as cornerstone treatments for T2DM [15]. However, the clinical significance of this 0.35% difference must be weighed against differential safety profiles and patient-centered outcomes.

The substantially higher hypoglycemia rate with sulfonylureas (18.6% vs. 3.4%) represents a clinically meaningful disadvantage, particularly for patients at elevated hypoglycemia risk including elderly individuals, those with irregular eating patterns, and patients with impaired hypoglycemia awareness [16]. Hypoglycemia not only poses immediate safety concerns but also adversely affects quality of life, treatment adherence, and potentially cardiovascular outcomes [17]. The glucose-dependent mechanism of DPP-4 inhibitors inherently minimizes hypoglycemia risk, representing a significant pharmacological advantage.

Weight neutrality observed with DPP-4 inhibitors contrasts favorably with weight gain associated with both sulfonylureas and thiazolidinediones. Given the strong association between obesity and insulin resistance, weight-sparing therapies may offer long-term metabolic benefits beyond glycemic control [18]. The weight gain observed with sulfonylureas (+2.1 kg) and thiazolidinediones (+2.8 kg) could potentially exacerbate insulin resistance and counteract therapeutic benefits over extended

treatment periods [19].

Thiazolidinediones demonstrated comparable glycemic efficacy to DPP-4 inhibitors but with notable adverse effect concerns. The high incidence of peripheral edema (14.3%) and significant weight gain limit their utility, particularly in patients with heart failure risk or weight management goals [20]. Nevertheless, the durable glycemic control provided by thiazolidinediones through insulin sensitization mechanisms may benefit specific patient subgroups, particularly those with pronounced insulin resistance [21].

The superior treatment persistence observed with DPP-4 inhibitors (82.5%) likely reflects their favorable tolerability profile, including low hypoglycemia risk, weight neutrality, and once-daily dosing convenience. Treatment persistence represents a crucial real-world effectiveness measure, as therapeutic benefits depend upon sustained medication adherence [22]. The lower treatment augmentation rate with DPP-4 inhibitors (8.1% vs. 14.7% for sulfonylureas) suggests adequate glycemic durability despite modestly smaller initial HbA1c reductions.

Several study limitations warrant acknowledgment. The retrospective design precludes causal inference and introduces potential confounding despite statistical adjustment. Treatment selection likely reflected clinician judgment regarding patient suitability, introducing channeling bias. Additionally, the 12-month follow-up period may inadequately capture long-term durability differences and cardiovascular outcomes. Single-center data may limit generalizability to other healthcare settings and populations.

Despite these limitations, our findings contribute valuable real-world evidence complementing randomized trial data. The comparative effectiveness framework employed reflects actual clinical practice conditions, enhancing practical applicability for treatment decision-making [23].

Conclusion

This comparative effectiveness study demonstrates that sulfonylureas provide superior short-term glycemic control as second-line therapy added to metformin in patients with type 2 diabetes. However, this glycemic advantage is offset by significantly higher hypoglycemia rates, weight gain, and lower treatment persistence compared to DPP-4 inhibitors. DPP-4 inhibitors offer a favorable balance of glycemic efficacy, weight neutrality, excellent tolerability, and superior treatment persistence, making them attractive second-line options for many patients. Thiazolidinediones provide comparable glycemic benefits to DPP-4 inhibitors but with significant weight gain and edema concerns. Optimal second-line therapy selection should incorporate individual patient characteristics, including hypoglycemia risk, weight management goals, comorbidity profiles, and patient preferences. These real-world findings support individualized, patient-centered approaches to treatment intensification in type 2 diabetes management.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053. doi:10.2337/diacare.27.5.1047. PMID: 15111519
2. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2009;32(1):193-203. doi:10.2337/dc08-9025. PMID: 18945920
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281(21):2005-2012. doi:10.1001/jama.281.21.2005. PMID: 10359389
4. Nolan JJ. Consensus guidelines, algorithms and care of the individual patient with type 2 diabetes. *Diabetologia*. 2010 Jul;53(7):1247-9. doi: 10.1007/s00125-010-1767-z. Epub 2010 Apr 25. Erratum in: *Diabetologia*. 2010 Sep;53(9):2078. PMID: 20419286.
5. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to

- metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;303(14):1410-1418. doi:10.1001/jama.2010.405. PMID: 20388897
6. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care*. 2007;30(2):389-394. doi:10.2337/dc06-1789. PMID: 17259518
7. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2011 Jul 26;343:d4169. doi: 10.1136/bmj.d4169. PMID: 21791495
8. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-1705. doi:10.1016/S0140-6736(06)69705-5. PMID: 17098089
9. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2008;(2):CD006739. doi:10.1002/14651858.CD006739.pub2. PMID: 18425967
10. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11):1106-1118. doi:10.1056/NEJMra041001. PMID: 15356308
11. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;147(6):386-399. doi:10.7326/0003-4819-147-6-200709180-00178. PMID: 17638715
12. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427-2443. doi:10.1056/NEJMoa066224. PMID: 17145742
13. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. *Diabetologia*. 2006;49(8):1711-1721. doi:10.1007/s00125-006-0316-2. PMID: 16802130
14. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care*. 2010;33(8):1859-1864. doi:10.2337/dc09-1727. PMID: 20484130
15. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853. doi:10.1016/S0140-6736(98)07019-6. PMID: 9742976
16. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in type 2 diabetes. *Diabet Med*. 2008;25(3):245-254. doi:10.1111/j.1464-5491.2007.02341.x. PMID: 18215172
17. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410-1418. doi:10.1056/NEJMoa1003795. PMID: 20925543
18. Look AHEAD Research Group; Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med*. 2010 Sep 27;170(17):1566-75. doi: 10.1001/archinternmed.2010.334. PMID: 20876408
19. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab*. 2007;9(6):799-812. doi:10.1111/j.1463-1326.2006.00686.x. PMID: 17924864
20. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care*. 2004;27(1):256-263. doi:10.2337/diacare.27.1.256. PMID: 14693998
21. Grossman LD, Parlan G, Bailey AL, Yee G, Yu M, Chan JY. Tolerability outcomes of a

- multicenter, observational, open-label, drug-surveillance study in patients with type 2 diabetes mellitus treated with pioglitazone for 2 years. *Clin Ther.* 2009 Jan;31(1):74-88. doi: 10.1016/j.clinthera.2009.01.004. PMID: 19243708.
22. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care.* 2004;27(5):1218-1224. doi:10.2337/diacare.27.5.1218. PMID: 15111553
23. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol.* 2005;58(4):323-337. doi:10.1016/j.jclinepi.2004.10.012. PMID: 15862718.