


BRIEF REPORT

Glycemic Improvement with a Fixed-dose combination of DPP-4 inhibitor + metformin in patients with Type 2 diabetes (GIFT study)

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This study investigates changes in A1C following a switch from dual therapy of metformin and DPP-4 inhibitor to a fixed-dose combination (FDC) of metformin + DPP-4 inhibitor following the introduction of the FDC in the provincial formulary. The LMC Diabetes Registry was queried retrospectively for patients with type 2 diabetes, aged between 18 and 80 years with at least one A1C recorded prior and ≥ 3 months post-switch. Five hundred and sixty-eight subjects with mean age 64 ± 12 years and mean A1C $7.7\% \pm 1.2\%$ met study criteria. Overall, A1C was 0.3% lower post-switch to FDC ($P < .01$). In stratified analysis, subjects with baseline A1C between 7% and 10% had 0.4% lower A1C ($P < .01$), with 31% of these subjects reaching target A1C $\leq 7\%$, post-switch. A1C reduction was greater among patients with a higher baseline pill burden: 0.4% among those using ≥ 10 pills/day vs. 0.1% for those with < 10 pills/day ($P = .02$). In this real-world study, switching to FDC of metformin + DPP-4 inhibitor was associated with a significant improvement in A1C. Switching to FDC, especially in patients with high pill burden, can improve A1C goal achievement in clinical practice.

KEYWORDS

adherence, DPP-4 inhibitor, fixed-dose combination, type 2 diabetes

1 | INTRODUCTION

Non-adherence to medication is a continuing clinical challenge in chronic disease therapy, including type 2 diabetes (T2D),¹ possibly leading to adverse consequences.² Pill burden is thought to be a primary contributor to non-adherence to medications in patients with T2D.³ Published studies suggest that fixed-dose combinations (FDCs) of oral antihyperglycaemic agents (AHA) may improve adherence rates (by reducing pill burden, regimen complexity and costs) compared to co-administered medications from 2 different classes.^{4,5} In addition, a limited number of published studies, utilizing older therapies, suggest an improvement in glycaemic control in favour of FDC.⁵⁻⁹

Dipeptidyl peptidase-4 (DPP-4) inhibitors are increasingly popular as the second-choice medication after metformin monotherapy fails to achieve glycaemic control targets. The greater glycaemic efficacy of the combination of DPP-4 inhibitor and metformin has been

shown in prior reports¹⁰⁻¹³ and can be explained by their complementary mechanisms of action. DPP-4 inhibitors are well tolerated, associated with reduced frequency of hypoglycaemia compared to sulfonylurea and have a lower rate of therapy discontinuation among patients with T2D in primary care practices.¹⁴

The potential value of an FDC of metformin and DPP-4 inhibitors vs separate prescriptions of these medications has not been thoroughly investigated. Only 1 published study to date has evaluated adherence and glycaemic outcomes of an FDC of metformin with a DPP-4 inhibitor medication.¹⁵ Although there were differences with respect to treatment compliance between the fixed-dose and free-dose combinations in this study, these did not result in a reduction in glycosylated haemoglobin (A1C).

After the provincial formulary coverage included the first FDC of DPP-4 inhibitor + metformin in Ontario, starting in February 2012, a majority of patients have been switched to that product. Therefore, the Glycemic Improvement with a Fixed-dose combination of DPP-4

inhibitor + metformin in patients with Type 2 diabetes (GIFT) study was conceptualized to characterize the changes in glycaemic control parameters among patients with T2D in a real-world setting, following a switch from co-administered dual therapy (CDT) with metformin and a DPP-4 inhibitor to an FDC of metformin + DPP-4 inhibitor.

2 | METHODS

2.1 | Study criteria and data collection

Data were retrieved for subjects who had previously consented to be included in the LMC Registry (from seven LMC Diabetes & Endocrinology sites in Ontario, Canada) and who met the study inclusion criteria of 18 to 80 years of age with T2D. Other inclusion criteria were: (1) a prior combination regimen of metformin and DPP-4 inhibitor (linagliptin, saxagliptin or sitagliptin) separately, with a subsequent documented switch to an FDC of DPP-4 inhibitor + metformin (linagliptin/metformin, saxagliptin/metformin or sitagliptin/metformin) within a 38-month period between February 1, 2012 and March 31, 2015; (2) at least 1 traceable A1C value prior to and following FDC medication switch (≥ 3 months but within 1 year post switch date); (3) at least 1 visit with an LMC physician following the FDC switch. Exclusion criteria included estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m², discontinuation of FDC of DPP-4 inhibitor + metformin within 3 months of the switch, or enrolment in any investigational study. All patient confidentiality principles of the Personal Health Information Protection Act were followed. The Research Ethics Review Board, IRB Services, approved the study.

2.2 | Data timepoints

The primary outcome variable of A1C was collected within 1 year prior and 1 year post FDC switch. Baseline time-point refers to the last observation of the variable before the date when the switch was made to an FDC of metformin + DPP-4 inhibitor. Follow-up time point refers to the last observation of the variable greater than 2 months post switch and was obtained before March 31, 2016. Additional variables collected at baseline and follow-up include laboratory results, weight, body mass index (BMI), waist circumference, and systolic (SBP) and diastolic blood pressure (DBP). Missing laboratory results were retrieved from the Ontario Lab Information System (OLIS). Additional medication-related data collections were made for metformin dose, type of DPP-4 inhibitor and dose (including sitagliptin, saxagliptin or linagliptin), and all other classes of prescribed AHAs. A determination of total daily pill burden, that is, the total number of

all prescription pills/day/patient (for all medical conditions) was also made.

2.3 | Statistical analysis

Baseline characteristics were summarized as mean (standard deviation) for continuous variables and count (percentage) for categorical variables. The primary outcome of change of A1C level from baseline to follow-up was tested by the paired t-test. The proportion of patients who achieved the target A1C level ($\leq 7\%$) prior to and post medication switch were compared, along with the following stratifications for sensitivity analysis: oral AHAs alone or not; insulin use or not; change in metformin dose or not; sitagliptin use or not. Exploratory analyses of A1C were performed on the following stratifications of subjects: A1C between 7% and 10% (inclusive); pill burden, ie, pill counts ≥ 10 vs < 10 pills per day; age ≥ 65 vs < 65 years; diabetes duration ≥ 10 vs < 10 years; South Asian vs Caucasian vs other ethnicities. The McNemar test was used for comparing subgroups prior to and post medication switch. Secondary outcomes also included fasting blood glucose, weight, BMI, waist circumference, SBP and DBP, tested by the paired t-test.

No formal sample size calculation was performed. Since the statistical analyses are exploratory in nature, no adjustment for the overall type I error rate was implemented. A nominal significance level of 5% was used to help interpret the results. All analyses were performed in SPSS 19.0 and SAS 9.2.

3 | RESULTS

The GIFT study enrolment criteria were met for 568 patients (Table S1 shows baseline characteristics). Mean A1C was 7.7% (± 1.2) at baseline, with 36% of the subjects having an A1C level $\leq 7\%$ prior to the switch. The average age of the cohort was 63.6 (± 11.6) years, 56% being male, with an average diabetes duration of 12.7 (± 7.8) years. Subjects were primarily of South Asian (41%) or Caucasian (37%) ethnic origin. Additional AHAs were used by 71% of subjects; 40% of patients were also using insulin.

Among the full GIFT cohort of 568 subjects, mean A1C was reduced by 0.3% (standard deviation [SD] 1.1%) ($P < .01$) at follow-up (Table 1), and an additional 8% of subjects reached target A1C levels $\leq 7\%$ ($P = .01$). For the subgroup of subjects with uncontrolled baseline A1C (7%–10%), A1C was reduced by 0.4% (SD, 1.1%) ($P < .01$), and 31% of subjects reached target A1C $\leq 7\%$ post FDC switch ($P < .01$).

TABLE 1 Change in A1C: Fixed-dose combination (FDC) vs co-administered dual therapy (CDT) of metformin + DPP-4 inhibitor

		CDT metformin + DPP-4 inhibitor	FDC metformin + DPP-4 inhibitor	P value
Full cohort ($n = 568$)	A1C	7.7%	7.4%	$< .01$
	Proportion achieving target A1C $\leq 7\%$	36%	44%	.01
Uncontrolled – baseline A1C between 7% and 10% ($n = 328$)	A1C	8.0%	7.6%	$< .01$
	Proportion achieving target A1C $\leq 7\%$	0%	31%	$< .01$

Similar statistically significant A1C reductions were observed post FDC switch in 3 pre-specified, stratified sensitivity analyses: subjects using oral AHAs alone with no insulin use; subjects with no change in metformin dose; subjects using sitagliptin (as the most commonly used DPP-4 inhibitor in the cohort) prescribed as CDT with metformin, who were then switched to FDC of sitagliptin + metformin (with metformin dosage unchanged). There were no significant weight or blood pressure changes noted in the full cohort nor in the pre-specified stratified analyses.

A1C reduction was 0.4% (SD, 0.8%) for the high pill burden stratification (baseline pill count ≥ 10 /day) vs 0.1% (SD, 1.1%) for subjects with < 10 pills/day ($P = .02$). A1C improvement post switch was observed regardless of ethnicity. Stratified analyses of age and diabetes duration led to a statistically significant A1C improvement in subjects ≥ 65 years of age (-0.4% , $P < .01$) and in subjects with diabetes duration ≥ 10 years (-0.3% , $P < .01$) (Figure 1).

4 | DISCUSSION

This retrospective, real-world study shows improvement in glycaemic control following a switch from co-administered dual therapy with metformin and a DPP-4 inhibitor to a fixed-dose combination of metformin + DPP-4 inhibitor. The clinical significance of this degree of A1C reduction is illustrated by its consistency in the pre-specified stratified analysis results. In addition, 31% of subjects with uncontrolled A1C (7%-10%) at baseline achieved a target A1C level of $\leq 7\%$ post FDC switch.

GIFT is the first published study, to our knowledge, to systematically analyse and observe glycaemic improvement with the use of an FDC combining newer AHAs. One prior study, analysing the efficacy of FDC with metformin and vildagliptin, did not find differences in glycaemic control.¹⁵ Although adherence was not directly measured in our retrospective study, we believe that the particular A1C benefit seen in subjects with a higher baseline pill burden (pill count ≥ 10 /day) supports the hypothesis that improved adherence post switch is the most likely explanation for the observed improvement in glycaemic control. Pill burden as an independent contributor to non-adherence in T2D has been well documented.^{3,16} Additional contributing benefits of FDC-related improved adherence in the GIFT study may include better tolerability (less GI adverse effects) of the FDC form of metformin rather than the generic form^{17,18} and the reduced dispensing costs of a combination prescription as opposed to separate pills.

Overall, our results align with other published reports in T2D and provide new insights into the importance of pill-count reduction as a means of improving adherence and metabolic target achievement.⁴⁻⁹ The GIFT study results may have potentially important practical clinical implications. An improvement in A1C in the range of 0.3% to 0.4% by combining medicines into FDCs could obviate the need to add medications in certain cases, by helping target A1C achievement. Finally, it should be acknowledged that, in addition to perceived pill burden, non-adherence to therapy is a multi-factorial and complex problem that includes other barriers, for example, perceived adverse effects,¹⁹ dosing frequency and regimen complexity,^{3,20} and memory issues, especially among the elderly. With concerted efforts targeting all these barriers, improvement in adherence could potentially lead to

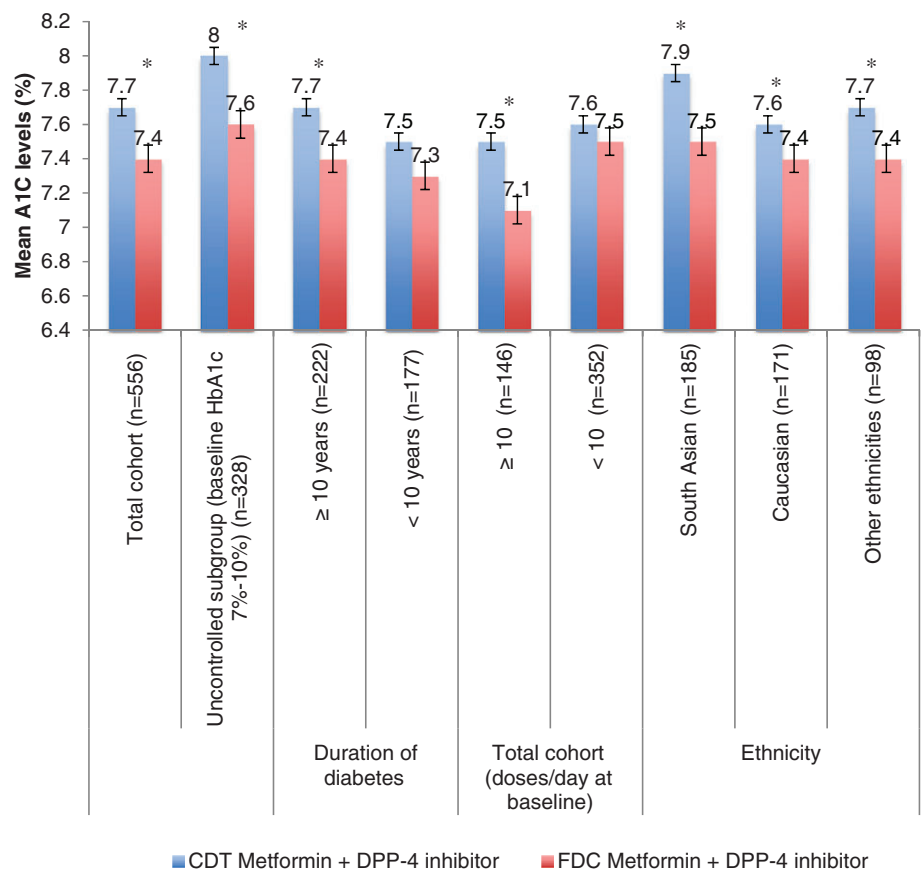


FIGURE 1 Change in A1C levels from CDT metformin + DPP-4 inhibitor to FDC metformin + DPP-4 inhibitor.

* indicates $P < .05$.

reduced emergency room visits and hospitalizations, as well as probable mortality benefits.²¹

Strengths of the GIFT study include thorough data collection within the LMC patient registry and the access to OLIS for missing laboratory values. On the other hand, our study has several possible limitations. The retrospective design of the study with before-and-after within-group comparisons could be considered a shortcoming. However, for adherence research, a retrospective analysis has potential advantages compared to a prospective study design; retrospective adherence and subsequent glycaemic measurements may be less prone to biases that may arise from study participation, close subject monitoring or exclusion of less adherent subjects in a prospective study.²² In addition, the potential for selection bias in the GIFT study is limited because the majority of patients in Ontario were switched to FDC following drug formulary coverage, starting in February 2012. Finally, there exists the possibility that changes to other AHAs could have influenced the results in this real-world study. Nonetheless, the results of a series of sensitivity analyses were consistent and there were no observed changes in weight or blood pressure over the study period. Both of these findings add validity to the study results.

In conclusion, intensification of oral anti-hyperglycaemic therapy with an FDC of DPP-4 inhibitor and metformin, rather than adding the DPP-4 inhibitor as a separate pill, may yield better glycaemic control in real-world use and should be considered as a standard of care for clinical practice.

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Conflict of interest

H. B. reports research support or personal fees from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Pfizer, Takeda and Valeant, outside the submitted work. C. Y. is a current employee of Genentech in Oncology Biostatistics, Genentech, South San Francisco, California, but was not an employee of Genentech at the time the analyses were conducted. C. Y. has no other conflicts of interest to declare. R. A. reports personal fees from Novo Nordisk, Janssen, Sanofi, Bristol-Myers Squibb, AstraZeneca, Takeda, Becton Dickinson, Eli Lilly, Medtronic and Amgen, and research support from Merck, Boehringer-Ingelheim, Regeneron, Abbott, Quintiles, ICON, GlaxoSmithKline and Medpace, outside the submitted work. No relevant conflicts of interest exist for E. J., K. V. and E. S.

Author contributions

H. S. B., C. Y., K. V., E. S. and R. A. designed the study, planned the analysis and implemented the study. E. J., K. V. and E. S. performed electronic registry data queries and cleaned the data generated. H. S. B., C. Y. and R. A. interpreted the data. H. S. B. and E. J. wrote the first draft of the manuscript. C. Y. performed the statistical analyses. All authors critically revised the manuscript for important intellectual content and approved the final manuscript. H. S. B. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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