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ORIGINAL RESEARCH

Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs

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Background: In patients with type 2 diabetes mellitus, basal-bolus strategies can improve treatment by offering dosing flexibility, and improved satisfaction, adherence, and clinical outcomes. The purpose of this study was to compare real-world outcomes between US patients initiating analog insulin therapy with insulin glargine and those initiating with a premixed analog insulin (PMX).

Methods: This was a retrospective study of data from patients (≥18 years) with type 2 diabetes mellitus in the IMPACT® database who initiated insulin treatment with insulin glargine (GLA) or a PMX. Clinical and economic outcomes were measured over one year, including persistence and adherence, consumption of insulin, glycemic outcomes, incident hypoglycemia, and health care resource utilization and cost.

Results: Data from 2,502 patients were included in the analyses (n = 834 for PMX, n = 1,668 for GLA). Compared with PMX, persistence was higher and consumption of insulin was lower for GLA (both $P < 0.0001$). Adherence, glycemic outcomes, and hypoglycemia-related events were similar between groups, as were health care utilization and total health care costs. Diabetes-related drug and supply costs were lower for GLA than for PMX ($P < 0.0001$ and $P = 0.046$, respectively).

Conclusion: In US patients with type 2 diabetes mellitus, initiating insulin with once-daily GLA, rather than a PMX, is associated with increased treatment persistence and similar clinical and hypoglycemic outcomes, but lower diabetes pharmacy and supply costs. GLA may be a more flexible option than PMX. However, these results also show suboptimal glycemic control in the real-world setting despite change in treatment regimens and call for optimization in management of patients with type 2 diabetes mellitus.

Keywords: type 2 diabetes mellitus, insulin glargine, rapid acting insulin, premixed insulin, clinical outcomes, treatment persistence

Introduction

Oral antidiabetic drugs and lifestyle interventions are initially recommended for the management of most patients with type 2 diabetes mellitus (T2DM),[1] but since T2DM is a progressive disease, these interventions often fail over time.[2,3] Current guidelines for the management of T2DM recommend initiating insulin if noninsulin therapy at maximal tolerated doses does not achieve or maintain glycemic control over 3–6 months.[1,4] Typically, patients will initiate analog insulin therapy with a single daily injection of basal analog insulin,[1,5] such as a regular human insulin, the intermediate-acting neutral protamine Hagedorn insulin, or the long-acting analog insulin glargine

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(GLA) or detemir. To target meal-related glucose excursions, prandial insulin (eg, rapid-acting GLA or aspart) may also be added to the regimen. Such a "basal-bolus" therapeutic regimen may be the most appropriate strategy when basal analog insulin alone is no longer sufficient to reach the glycated hemoglobin (A_{1c}) target.[5,6] In these cases, rapid-acting insulin can be added to the basal analog insulin, providing physical, psychologic, and treatment satisfaction benefits to patients.[7] A simplified, stepwise approach of one or two preprandial injections before the meals of greatest glycemic impact can be used, as well as a traditional three preprandial injections approach.[8] Alternatively, patients may initiate insulin treatment with (or switch to) premixed analog insulins (PMX; a fixed combination of intermediate-acting insulin with regular insulin or a rapid-acting insulin).[9,10]

Although basal-bolus treatment is more complicated for patients than PMX treatment, it allows for more flexibility, especially with irregular mealtimes; however, PMX regimens generally result in larger decreases in A_{1c} levels. Of note, dose flexibility has been shown to be an important attribute of injectable treatments for T2DM from the patient perspective,[11] which can contribute to increased patient satisfaction with therapy.[12] Furthermore, lower treatment satisfaction is associated with poor adherence to medication;[13] greater satisfaction with treatment is related to better clinical outcomes.[14,15] In addition, GLA and detemir are associated with smaller increases in weight and a reduced incidence of hypoglycemia compared with, for example, neutral protamine Hagedorn insulin.[1]

A previously published randomized clinical trial showed that GLA-based basal-bolus treatment is as effective as PMX treatment,[16] and that GLA-based basal-bolus treatment causes less hypoglycemia than PMX. Patient-reported outcomes are also more positive for GLA-based basal-bolus treatment when compared with PMX treatment.[17] However, few studies have compared real-world outcomes following initiation of basal only or basal-bolus therapy versus PMX; such information would assist with treatment decisions and help optimize the management of patients with T2DM.

The purpose of this study was to compare real-world outcomes between US patients with T2DM requiring analog insulin therapy initiating with GLA, with or without a rapid-acting insulin, and those initiating with a PMX.

Materials and methods

Patients

This was a retrospective study of data from IMPACT®, a US, nationally managed care database that comprises about 50 US health care plans and contains medical claims, pharmacy claims, eligibility data, and laboratory results for 107 million patients, of whom 73% had pharmacy benefits and 18% had laboratory results.

Data from adult US patients (≥18 years) diagnosed with T2DM, defined as having at least one inpatient visit or at least two physician visits (≥30 days apart) with a primary or secondary diagnosis of T2DM (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 250.x0 or 250.x2), were identified for inclusion in the analysis. Patients were required to have continuous health plan coverage of both medical and pharmacy benefits for ≥6 months before (baseline period) and at least one year after (follow-up period) initiation of GLA or PMX (the index date), and must have at least one A_{1c} test result at both baseline and at the end of the one-year follow-up period. Patients using only oral antidiabetic drugs or glucagon-like peptide-1 in the baseline period were eligible for inclusion, while patients were excluded if they had used any type of insulin, including a PMX, in the baseline period. Using an intent-to-treat approach, patients were assigned to treatment cohorts according to the type of insulin with which they initiated treatment, ie, GLA or PMX. Within the GLA cohort, patients could initiate rapid-acting insulin any time between 30 days prior to and 360 days after insulin glargine initiation (also known as a basal-bolus/plus treatment regimen) or stay only on GLA, also known as a basal-only treatment regimen.

Outcomes

Clinical and economic outcomes were measured over a one-year follow-up period, including persistence and adherence, consumption of insulin, glycemic outcomes, hypoglycemia event, and health care resource utilization and cost. Treatment persistence was defined as a patient remaining on the study drug during the follow-up period, without discontinuation or switching after initiation.[18–22] Study medication was considered discontinued if the prescription was not refilled within the expected time of medication coverage (the 90th percentile of the time, stratified by the metric quantity supplied, between first and second fills among patients with at least one refill). Patients who restarted their initial medication after a period without it during follow-up were considered nonpersistent. Sensitivity analyses were also conducted using 75th and 95th percentiles of the time, so that for patients in the GLA group, the treatment persistence was based on GLA use; since rapid-acting insulin could be added anytime during the follow-up period, treatment persistence with rapid-acting insulin was

not measured. For patients in the PMX group, the treatment persistence was based on PMX use; patients could switch between different types of PMX (aspart or lispro) during the follow-up period, but would still be considered as persistent users of PMX. Treatment adherence was measured by both traditional medication possession ratio (MPR) and adjusted MPR; the traditional MPR does not take into account the difference in package sizes between insulin medications, and the adjusted MPR addresses this limitation by using the total number of days of drug supply during the follow-up period divided by the total number of days in the follow-up period, multiplied by the average days between prescription refills divided by average days of drug supply for patients.[23] The daily average consumption of insulin was calculated as the total number of units dispensed before the last refill of study drug divided by the total number of days between initiation and last refill during the follow-up period.

With regards to glycemic control outcomes, A_{1c} level was analyzed as the follow-up value, change from baseline, and percentage of patients meeting target A_{1c} (<7.0%). Hypoglycemia was also reported as a health care encounter (outpatient, inpatient, or emergency room visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia (ICD-9 code 250.8, diabetes with other specified manifestations; 251.0, hypoglycemic coma; 251.1, other specified hypoglycemia; or 251.2, hypoglycemia, unspecified).[24] The setting of the hypoglycemic event (outpatient, emergency room, or hospital) was used as proxy for severity of the event.

In addition, for economic outcomes, health care resource utilization was determined using outpatient visits, emergency room, visits, inpatient admissions, inpatient length of stay (days), endocrinologist visits, and diabetes-related health care resource utilization using claims with a primary or secondary diagnosis of diabetes (ICD-9-CM code 250.xx). Health care costs were also computed as plan-paid amounts of adjudicated claims, and diabetes-related health care costs included costs from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM code 250.xx), antidiabetic medications, and glucose meters and test strips.

Statistical analyses

Selection bias is inherent in real-world retrospective studies, because patients prescribed one treatment often differ systematically from patients prescribed a comparison treatment. The analysis was conducted using an intent-to-treat approach. Propensity score matching at a 1:2 ratio was used to match patients in the PMX cohort with those in the GLA cohort to adjust appropriately for a lack of randomization between the cohorts by removing observed differences in baseline demographic and clinical characteristics.[25] Each patient is assigned a propensity score, which is a fitted value of the probability of being a member of the overall cohort. To match patients from the two cohorts, a 1:2 nearest neighbor greedy match between glargine and premix initiators was performed using the propensity score for each patient. A patient from one cohort could only be matched to a patient from the other cohort if their propensity scores were very similar (±0.01 units apart); patients who could not be matched were dropped from the analysis. A propensity score weighted generalized linear model was used as the main multivariate analysis method; age, baseline A_{1c}, copay, initial year, region, health plan, diabetes education, baseline comorbidities, diabetes medication, health care utilizations, and costs were controlled in the model.

Among matched patients, baseline characteristics, clinical outcomes, and economic parameters were summarized and compared, with *P*-values provided by Student's *t*-test or χ^2 test as appropriate. Kaplan–Meier curves were used to examine time to treatment discontinuation between both cohorts and time to add rapid-acting insulin in the GLA cohort. For the health care resource utilization and health care costs analysis, raw data are compared; regression modeling was not used in this study, thus transformation was not needed.

Results

Patient characteristics

Data from a total of 2,502 matched patients were included in the analyses (834 in the PMX cohort and 1,668 in the GLA cohort). All baseline demographic and clinical characteristics, health care utilizations, and health care costs were balanced after propensity score matching (Table 1). Overall, 47.6% of patients were women, the mean age was 55.8 years, the mean baseline A_{1c} was 9.6%, and the mean number of oral antidiabetic drugs at baseline was 2.1.

Treatment persistence and adherence

Patients in the GLA cohort were more treatment-persistent with initiated insulin than those in the PMX cohort (55.9% versus 45.4%, $P < 0.0001$, Figure 1). These results remained consistent in the sensitivity analyses using the 75th percentile of the time (75th percentile, 28.1% versus 23.4%, $P = 0.0125$). On average, patients in the GLA cohort remained on treatment for 26 days longer than those in the PMX cohort (280 days versus 254 days, $P < 0.0001$), and the Kaplan–Meier survival curve shows that patients in the PMX cohort

Table 1 Clinical and economic characteristics at baseline

Characteristics	PMX (n = 834)	GLA (n = 1,668)	*P*-value
Age in years, mean (SD)	55.93 (11.13)	55.63 (11.57)	0.5298
Male, n (%)	439 (52.64)	870 (52.16)	0.8209
Region, n (%)			
North East	315 (37.77)	608 (36.45)	0.5192
South	387 (46.40)	774 (46.40)	1.0000
Mid West	32 (3.84)	69 (4.14)	0.7195
West	86 (10.31)	196 (11.75)	0.2833
Unknown	14 (1.68)	21 (1.26)	0.3995
A_{1c}, %, mean (SD)	9.55 (2.17)	9.56 (2.20)	0.9304
Charlson comorbidity index, mean (SD)	0.69 (1.26)	0.70 (1.29)	0.8343
Comorbidity, n (%)			
Hypertension	560 (67.15)	1,063 (63.73)	0.0914
Hyperlipidemia	509 (61.03)	1,043 (62.53)	0.4665
Myocardial infarction	15 (1.80)	29 (1.74)	0.9144
Congestive heart failure	64 (7.67)	153 (9.17)	0.2092
Peripheral vascular disease	57 (6.83)	108 (6.47)	0.7325
Renal disease	48 (5.76)	78 (4.68)	0.2446
Retinopathy	120 (14.39)	238 (14.27)	0.9356
Neuropathy	107 (12.83)	210 (12.59)	0.8650
Nephropathy	57 (6.83)	121 (7.25)	0.7003
Chronic pulmonary disease	94 (11.27)	176 (10.55)	0.5846
Cancer	44 (5.28)	103 (6.18)	0.3672
OADs, n (SD)	2.12 (0.86)	2.14 (0.84)	0.6389
Medication, n (%)			
Metformin	642 (76.98)	1,265 (75.84)	0.5281
SUs	599 (71.82)	1,230 (73.74)	0.3077
DPP-4	73 (8.75)	144 (8.63)	0.9200
GLP-1	71 (8.51)	119 (7.13)	0.2197
TZDs	380 (45.56)	746 (44.72)	0.6908
Meglitinides	57 (6.83)	142 (8.51)	0.1435
Alpha-glucosidase	16 (1.92)	35 (2.10)	0.7641
Baseline hypoglycemia, n (%)			
Any hypoglycemia	38 (4.56)	64 (3.84)	0.3910
Any inpatient/ER-related hypoglycemia	15 (1.80)	31 (1.86)	0.9162
Health care utilization, n (%)			
Any hospitalization	109 (13.07)	220 (13.19)	0.9333
Any diabetes-related hospitalization	94 (11.27)	189 (11.33)	0.9644
Health care cost in $, mean (SD)			
Total cost	8,310 (14,996)	8,058 (14,668)	0.6872
Total diabetes-related cost	2,739 (5,480)	2,747 (5,505)	0.9714

Notes: The following variables were used in the propensity score matching analysis: age; A_{1c} %; comorbidity (hyperlipidemia, myocardial infarction, retinopathy, neuropathy, nephropathy); medication (metformin, DPP-4 inhibitors, statins, calcium channel blockers); baseline all-cause health care utilization (any hospitalization, number of hospitalization days, number of office visits, number of endocrinologist visits); baseline diabetes-related health care utilization (any hospitalization, number of hospitalization days, number of emergency department visits, any office visits, number of office visits); baseline all-cause health care costs (total costs, inpatient costs); baseline diabetes-related health care costs (total costs, inpatient costs, prescription costs); copay ($0–$15, $16–$30); initial year (2001, 2002, 2006, 2007, 2008, 2009); health plan type (point-of-service, others); geographic region (North East, Mid West, unknown); diabetes education.

Abbreviations: A_{1c}, glycated hemoglobin; DPP-4, dipeptidyl peptidase-4; ER, emergency room; GLA, insulin glargine; GLP-1, glucagon-like peptide 1; PMX, premixed analog insulin; SU, sulfonylurea; TZD, thiazolidinedione; OAD, oral antidiabetic drugs; SD, standard deviation.

discontinued treatment more quickly than those in the GLA cohort (Figure 2B).

Adherence rates were similar between the two cohorts (adjusted MPR 0.66 versus 0.64, $P = 0.19$ for GLA and PMX, respectively, Figure 1). By the end of one-year follow-up, 8.5% of patients in the GLA cohort had switched to a PMX; however, of patients in the PMX cohort, 10.9% received GLA and 12.5% received a rapid-acting insulin.

During one-year follow-up in the GLA cohort, 21.7% (n = 363) of patients added a rapid-acting insulin. At baseline, these patients had significantly higher levels of illness than those who stayed on GLA only (baseline Charlson comorbidity index, 0.85 versus 0.66, $P = 0.01$; hospitalization,

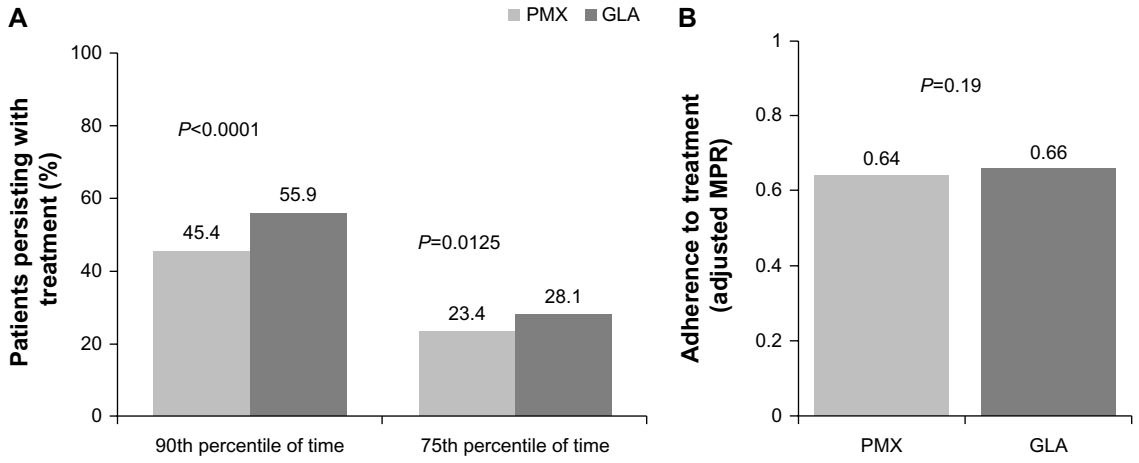

Figure 1 Treatment persistence (**A**) and adherence (**B**) in the PMX and GLA cohorts.
Abbreviations: GLA, insulin glargine; PMX, premixed analog insulin; MPR, medication possession ratio.

21.7% versus 10.8%, $P < 0.001$). The average time for adding rapid-acting insulin was 95.54 ± 111.64 days (median 42 days, Figure 2A).The percentage of patients in the GLA cohort using a rapid-acting insulin was similar for each quarter of the follow-up period, with 13.0%, 11.9%, 12.8%, and 13.0% filling a prescription for a rapid-acting insulin in quarters one, two, three, and four, respectively.

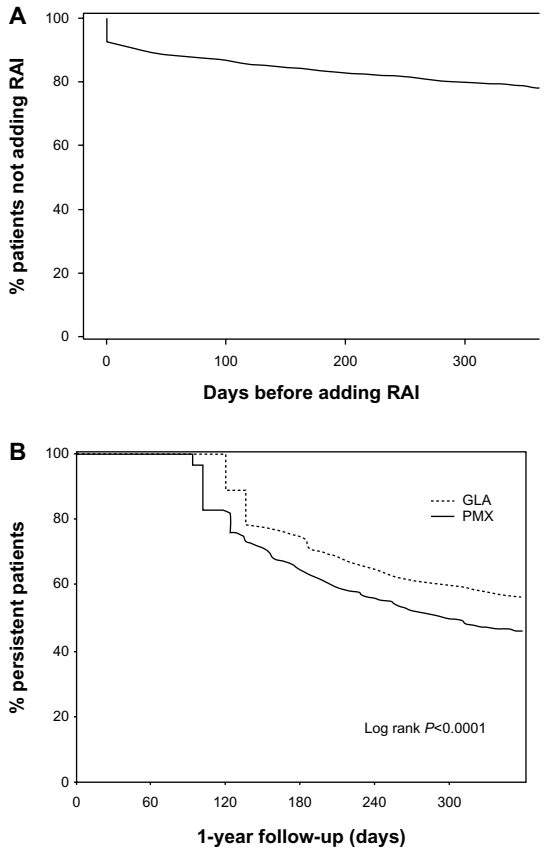

Figure 2 Kaplan–Meier curves for the time to adding RAI (**A**) and for time to treatment discontinuation (**B**).
Abbreviations: GLA, insulin glargine; RAI, rapid-acting insulin; PMX, premixed analog insulin.

Clinical outcomes

At the end of one-year follow-up, the reduction from baseline A_{1c} level was similar between the GLA and PMX cohorts (−1.26 versus −1.23%, $P = 0.784$), and only 25% patients achieved the goal of glycemic control (A_{1c} <7.0%) at the end of follow-up (GLA 25.2% versus PMX 24.7%, $P = 0.769$, Figure 3A). However, there was a significant difference in the insulin doses between the groups, with the daily average consumption for patients in the GLA cohort being 29.0 U/day (30 U/day of rapid-acting insulin if added) and 43.9 U/day for patients in the PMX cohort ($P < 0.0001$, Figure 3B).

Hypoglycemia-related outcomes were also similar between the GLA and PMX cohorts. The respective hypoglycemia outcomes for the GLA and PMX cohorts were: 7.67% versus 8.75% for prevalence of any hypoglycemia ($P = 0.3492$); 2.82% versus 3.84% for prevalence of inpatient/emergency room-related hypoglycemia ($P = 0.1693$); 2.54 versus 0.75 events per patient year for incidence of any hypoglycemia ($P = 0.2472$); and 0.24 versus 0.32 events per patient year for incidence of inpatient/emergency room-related hypoglycemia ($P = 0.2190$, Figure 4A and B).

Health care utilization and cost outcomes

At one year of follow-up, health care utilization outcomes were similar for the GLA and PMX cohorts, except for the number of endocrinology visits, which was higher for PMX than for GLA (1.97 versus 1.68, $P = 0.01$). Although mean

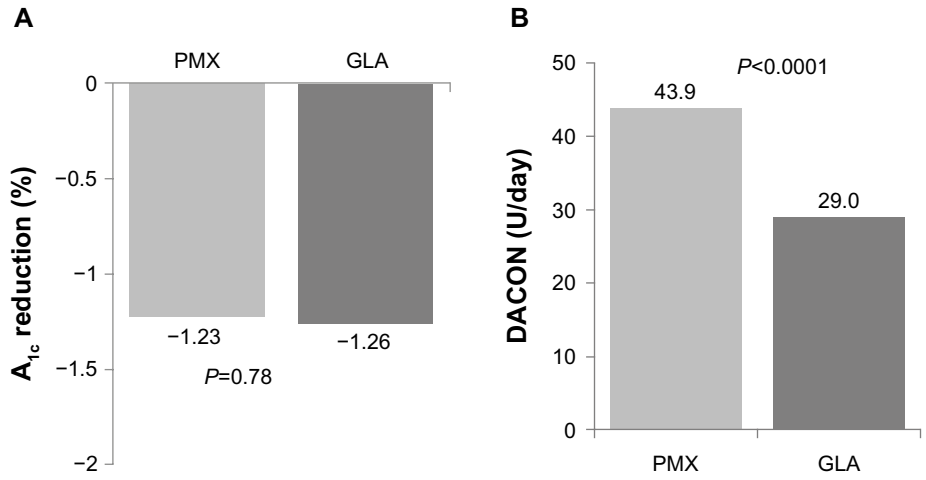

Figure 3 A_{1c} reduction (**A**) and DACON (**B**) at the end of one-year follow-up.
Abbreviations: A_{1c}, glycated hemoglobin; DACON, daily average consumption; GLA, insulin glargine; PMX, premixed analog insulin.

total health care costs were similar between the GLA and PMX cohorts over one year ($18,108 versus $17,754, $P = 0.735$), diabetes drug costs were significantly lower in the GLA than in the PMX cohorts ($2,041 versus $2,416, $P < 0.0001$, Figure 5). In addition, diabetes supply costs were lower in the GLA than in the PMX cohorts at one year ($357 versus $391, $P = 0.046$, Figure 5).

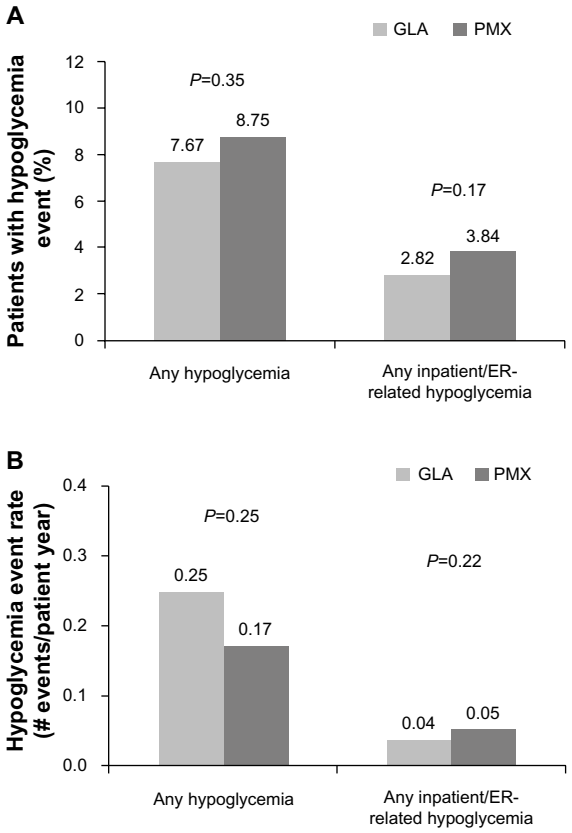

Figure 4 Hypoglycemia incidence (**A**) and prevalence (**B**) at the end of one-year follow-up.
Abbreviations: ER, emergency room; GLA, insulin glargine; PMX, premixed analog insulin.

Discussion

In this real-world study, patients with T2DM who initiated insulin treatment with once-daily GLA-based regimens were more persistent with their therapy than those who initiated with a PMX, while showing a similar A_{1c} reduction. Previous studies have found that, when compared with basal insulin alone, premixed insulin formulations lower A_{1c} levels to a greater extent but at the same time result in slightly more hypoglycemic events[9,26,27] and more weight gain.[9,26–28] Similarly, others have reported fewer hypoglycemic events with GLA in a basal-bolus regimen than with PMX.[16,29–31] In this study, there were no statistically significant differences in the rates of hypoglycemia between the GLA and PMX cohorts. The data also indicate that the glycemic control achieved by patients in this study, in general, was not good, with average A_{1c} levels of 8.3% at the end of follow-up and a responder rate of approximately 25% only. Better outcomes for both GLA and insulin detemir are usually reported from clinical trials.[32] This suggests that, in the real-world setting, patients might not be titrating appropriately, whether on GLA or PMX, and may explain the unexpected similarity in rates of hypoglycemia.

The American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) guidelines recommend that when initiating insulin therapy, either basal insulin (with or without rapid-acting insulin) or premixed insulin, both the patient's A_{1c} levels and willingness to take more than one injection per day should be considered.[4] The ADA/EASD guidelines acknowledge the inability to

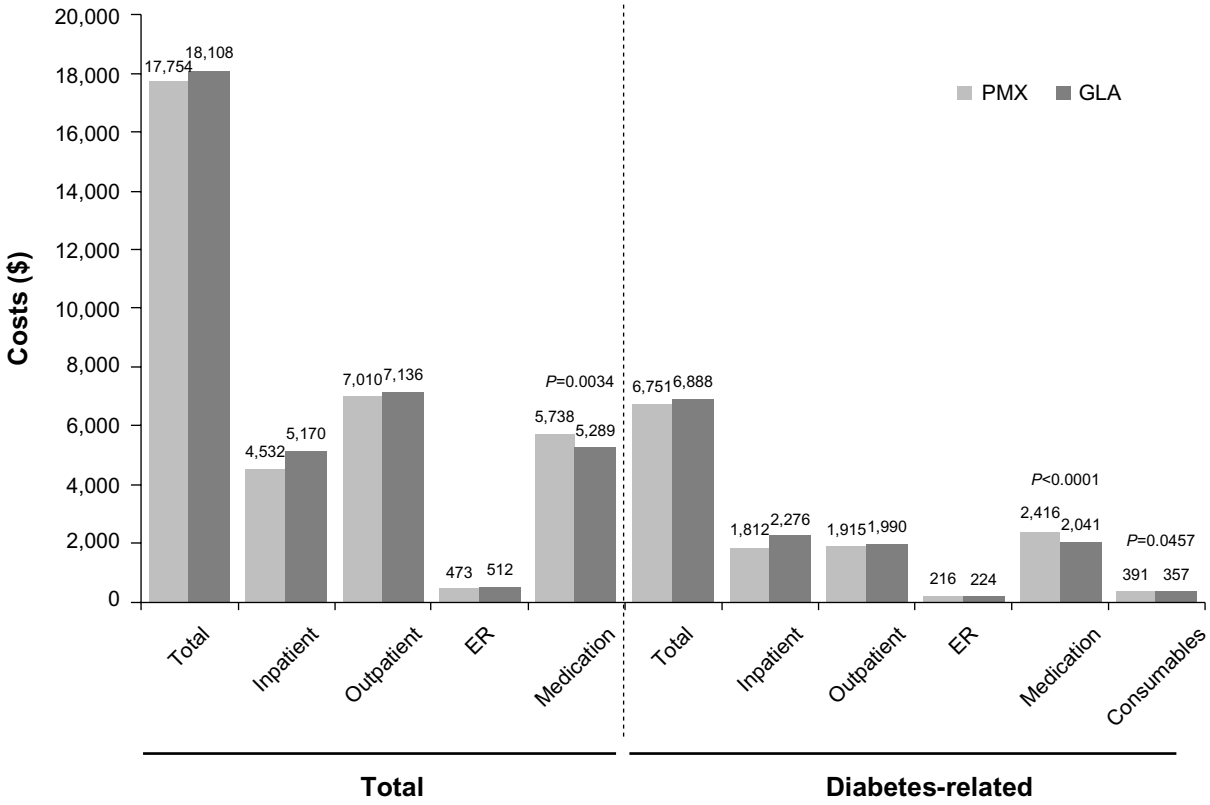

Figure 5 Health care cost outcomes at one-year follow-up.
Abbreviations: ER, emergency room; GLA, insulin glargine; PMX, premixed analog insulin.

titrate the shorter-acting separately from the longer-acting component of premixed insulins as a disadvantage of these formulations. Nonetheless, the inflexible but relatively simple insulin regimen may be appropriate for those patients who have a regular lifestyle and eating habits.[4]

In this study, most patients in the GLA cohort stayed on the GLA-only regimen during the one-year follow-up, and thus better maintained a once-daily treatment regimen compared with the twice-daily regimen required with a PMX. This is important, since patients prefer, or are more satisfied with, analog insulin therapy that requires fewer injections,[33,34,35] and insulin omission has been related to the need for more daily injections.[36] The use of GLA plus a rapid-acting insulin has been reported to result in better patient satisfaction than PMX.[17] Furthermore, a basal-insulin-based therapeutic strategy allows more flexibility than use of a PMX. In this study, patients in the GLA cohort could start with once-daily GLA injections, and then add additional injections of a rapid-acting insulin as necessary. In fact, the data show that those patients in the GLA cohort who added rapid-acting insulin were already sicker at baseline. In contrast, those who were treated with PMX had to follow a daily regimen of two injections. This might explain the high rate of switching to a GLA-based treatment regimen in the PMX group.

Despite better treatment persistence and lower diabetes drug and supply costs, the GLA group had total health care costs similar to those in the PMX group. This could be contributed to the fact that the GLA group itself was a heterogeneous group, consisting of patients being treated with either basal-only and basal-bolus/plus regimens, the latter of whom were sicker at baseline and could therefore have incurred a higher follow-up cost. A recent Canadian study reported that self-measured blood glucose testing among insulin users constitutes a significant proportion of diabetes-related pharmacy costs. The annual number of self-measured blood glucose tests was lower among premixed insulin users compared with users of basal insulin with or without bolus insulin. Premix users had lower annual pharmacy costs than basal and basal-bolus insulin users. The proportional costs for insulin therapy as a part of total pharmacy costs were highest for basal-bolus users (54%) and lowest for basal-only users (43%). Similarly, the annual costs associated with self-measured blood glucose testing accounted for a smaller proportion of total pharmacy costs among basal insulin users (38%) compared with basal-bolus and premix users (both about 41%).[37]

This study has a number of limitations. Firstly, the length of follow-up was only one year and may not have been long enough to detect the long-term clinical and economic benefits of the better treatment persistence associated with the GLA cohort. Secondly, it is a retrospective observational analysis of claims data which may be subject to selection bias and confounding. The presence of a claim for a filled prescription does not indicate whether the medication was actually consumed, or that it was taken as prescribed, and the presence of a diagnosis code on a medical claim may be incorrectly coded or included as rule-out criteria rather than actual disease. In addition, patients switching study drug during the follow-up period in each cohort could result in bias in the adjusted results. Further, dosing information was estimated based on filled pharmacy claims which could introduce a bias to the results based on the frequency and dose of treatment differences. The number of rapid-acting insulin injections is also not known in the real-world setting of this study. Finally, the analyses were based on data from a managed care population and patients with missing baseline or outcomes data were excluded from the study, and may not be representative of other populations or generalizable to all patients with T2DM.

Conclusion

This real-world study shows that for US patients with T2DM failing oral antidiabetic drugs, initiating insulin with a once-daily GLA-based regimen, instead of a PMX, is associated with increased treatment persistence and similar clinical and hypoglycemic events outcomes, but lower diabetes pharmacy and supply costs. Most patients initiating with GLA stayed on the GLA-only regimen during one-year follow-up; those who added a rapid-acting insulin were already more severely ill at baseline. Thus, GLA may be a more flexible treatment option than PMX and result in better treatment persistence. However, in both cohorts, only one of five patients were able to achieve the goal for glycemic control of $A_{1c} < 7.0\%$ by the end of follow-up. This suggested suboptimal titration by the patients and/or their physicians in the real-world setting, and calls for optimal management of patients with T2DM.

Disclosure

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