

Analysis of a Delivery Device Conversion for Insulin Aspart: Potential Clinical Impact in Veterans

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IN BRIEF Insulin therapies using a wide variety of delivery devices are available to accommodate individual patients' needs. In this study of veterans with diabetes, converting from insulin aspart delivered with vials and syringes to insulin aspart delivered via a pen device resulted in no significant change in A1C. Although insulin pen delivery devices offer benefits, providers should thoroughly consider all potential reasons for uncontrolled diabetes before modifying a patient's insulin delivery method.

Long-term studies in the management of diabetes, including the U.K. Prospective Diabetes Study and the Diabetes Control and Complications Trial (1,2), have demonstrated that good glycemic control is essential to preventing and minimizing micro- and macrovascular complications. In the United States, only about half of all people with diabetes achieve their A1C goal, even with knowledge of the benefits of optimal blood glucose control (3). In contrast, close to two-thirds of people with diabetes (57–67%) in the United Kingdom achieve their A1C goals (3). With the prevalence of diabetes expected to increase throughout the next several decades, achieving therapeutic goals, understanding methods to improve adherence to therapies, and initiating insulin early in the disease are of utmost relevance (3).

Insulin is a crucial therapy for achieving and maintaining good glycemic control for all people with type 1 diabetes. Additionally, more than half of all people with type 2 diabetes will eventually require insulin therapy to maintain glycemic control (3).

Despite the broad availability of insulins, ~26% of Americans with diagnosed diabetes (4.9 million patients) use insulin as part of their therapeutic management plan (4). Multiple factors contribute to both patients and health care providers (HCPs) avoiding initiation of insulin, including the complexity of dosing regimens, fear of self-injection, potential side effects, and possible social stigma (5,6). With recognition of these concerns, there has been an increased interest in the development of insulins and devices that will address these barriers.

After insulin analogs became available in the early 2000s, durable and disposable insulin pens were developed to enhance the delivery of these agents (7). Although the market share of insulin pens in the United States has remained moderately low (15%), insulin pens are the standard of care in Europe and Asia (80–90%) (5,6). One element conceivably contributing to this discrepancy is a belief held by some U.S. HCPs that insulin pens are merely gadgets or convenience products, without regard to relevant data related to

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TABLE 1. Subgroup Analysis of Average A1C in Year Before Conversion and Year After Conversion

Quartile	Preconversion A1C (%)	Postconversion A1C (%)	P
1	6.7 ± 0.5	7.3 ± 1.2	<0.001
2	7.7 ± 0.2	8.0 ± 1.0	0.024
3	8.7 ± 0.4	8.9 ± 1.6	0.844
4	10.6 ± 1.1	9.7 ± 1.9	0.001

pens' potential for cost savings and adherence improvement (6).

Insulin pens provide solutions to many concerns of people with diabetes and their HCPs. Insulin pens have been proven to deliver accurate doses over the dosing range, potentially minimizing some patients' fear of hypoglycemia from administering too much insulin. The ease with which patients are able to select the correct dose can provide independence to elderly people with diabetes, who previously relied on assistance to obtain correct doses (6,8). Insulin pens also may allay fears of injection because of continual development of smaller pen needles (6). For HCPs, the time required to teach patients how to correctly administer insulin can be significantly reduced because of the relative simplicity of insulin pens compared to vials and syringes, leaving more time for education about other aspects of diabetes management (6,9). Furthermore, insulin pens consistently have led to improved adherence among patients who switched from vials and syringes (7,10–12). A 2010 study (10) examined the impact of insulin pens on adherence, hypoglycemia, and costs. This study compared patients using an insulin aspart pen to others using insulin aspart administered with vials and syringes and demonstrated improved adherence with reduced hypoglycemia and total health care costs in the pen group.

The study discussed here is a retrospective investigation of clinical outcomes in a cohort of veterans with type 2 diabetes across a period during which they received insulin aspart in

vials and were then switched to insulin aspart pens. Its primary objective was to evaluate change in A1C after a therapeutic conversion from insulin administration through vials and syringes to pen use. To the authors' knowledge, this is the first study of its kind to evaluate whether the improved adherence documented in previous trials translates to improvement in clinical outcomes or whether a change in delivery device has no impact on clinical outcomes.

Research Design and Methods

Sample Selection

A list of potentially eligible veterans was generated from data available in the Veterans Affairs (VA) Computerized Patient Record System at a single VA medical center. Records were reviewed for all veterans receiving their care at this VA facility who were ≥18 years of age, had type 1 or type 2 diabetes, and were initially managed with insulin aspart vials and converted to insulin aspart pens between 1 January 2009 and 31 August 2013. For this study, veterans had to have actively used insulin aspart pens for at least 6 months after converting from vials. Veterans with fewer than two A1C values recorded during either time period—while using insulin aspart vials or while using pens—were excluded. Veterans were also excluded if they were no longer receiving insulin aspart pens; were under the care of a nursing home, assisted living facility, or hospice; or had a diagnosis of gestational diabetes or pregnancy. Of note, the therapeutic conversion from vials to pens was not intentionally carried out as a policy, but rather

was an individualized decision made at the discretion of each provider.

Data Collection

Charts were reviewed to obtain baseline demographics, prescribed doses of insulin aspart, information about additional antidiabetic agents used (both oral agents and intermediate-acting and basal insulins), and A1C values collected during the study period. Data on concomitant antidiabetic agents was collected in an attempt to account for potential confounding factors. This retrospective chart review was approved by the local institutional review board at the study facility.

Outcomes

The primary outcome was change in A1C, assessed by averaging all A1C values collected in the year before conversion and in the year after conversion.

Secondary outcomes included change in insulin aspart dose with conversion from vials to pens, measured in units of insulin aspart per kilogram of body weight per day. Additionally, investigators compared the frequency of hospitalizations and emergency department visits for which the chief complaint was hyper- or hypoglycemia during the 1-year periods before and after conversion.

Data Analysis

At least 83 patient charts needed to be reviewed to detect a difference of 0.4 percentage points, with an alpha of 0.05 and a power level of 85% (3,13). However, all patients meeting the inclusion criteria were included in the data analysis. Data were analyzed using Microsoft Excel 2010 data analysis tools (Microsoft Corp., Redmond, WA). Descriptive data were expressed as mean ± SD, and patients were compared before and after conversion using a paired *t* test. Post-hoc subgroup analysis was conducted by separating the patients into quartiles based on their average A1C in the year before conversion.

Results

A total of 447 patient charts were reviewed. Of these, 209 were included in the analysis (Figure 1). Of patient charts excluded, 113 were excluded because the patient had spent insufficient time (≤ 6 months) using the insulin aspart pen. Another 83 patient charts were excluded because the patient had fewer than two A1C values in the year before or the year after conversion. The last 42 excluded patient charts were omitted because the patients were receiving care in a nursing facility, had switched back to insulin aspart vials, or had switched initially from pens to vials. The mean age of the patients included in the review was 66.7 ± 8.5 years. The majority of patients were male (97.1%, $n = 203$) and had type 2 diabetes (93.8%, $n = 196$). The average time a patient had been using insulin pens was 18 ± 5.6 months.

The change in A1C from the last measurement before conversion and the most recent measurement after conversion to a pen device was not statistically significant (Figure 2). The average last A1C before conversion was 8.4%, and the average most recent A1C while using the pen device was 8.5% ($P = 0.67$). The average A1C in the year before conversion was 8.38%, and the average A1C for the year after conversion was 8.35% (Figure 3). This, too, was not statistically significant ($P = 0.57$).

Although the change in A1C was not statistically significant, the analysis found a significant difference in the number of units per kilogram per day when using the vial versus the pen. The average insulin aspart dose increased after conversion to the insulin pen device. While using insulin aspart vials, patients used an average of 0.545 units/kg body wt/day versus 0.618 units/kg body wt/day while using insulin aspart pens ($P < 0.001$). There was no statistical difference in patient weight after conversion to the pen (105.2 vs. 104.5 kg, $P = 0.11$). Basal insulin doses were similar



FIGURE 1. Flow chart of patients who met inclusion/exclusion criteria in the identified study population.¹ Excluded because they were living in nursing facility or hospice, converted from insulin pen to a vial, switched between delivery devices more than once, never used an insulin vial, or were not receiving the insulin pen from the study facility.

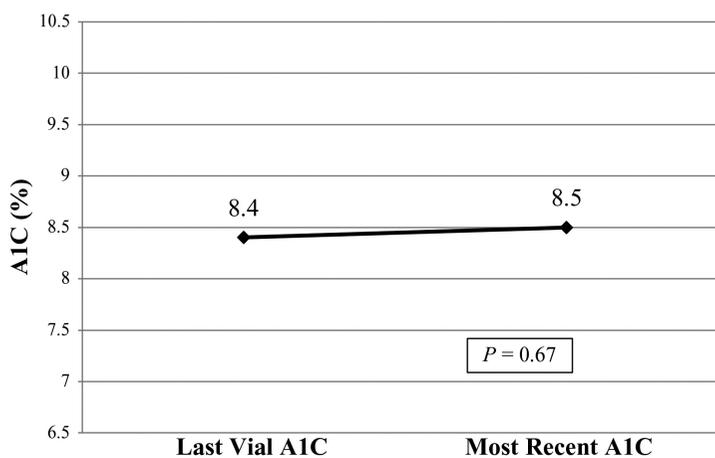


FIGURE 2. Single-point A1C comparison of last measurement while using insulin aspart vials and most recent measurement since converting to insulin aspart pens.

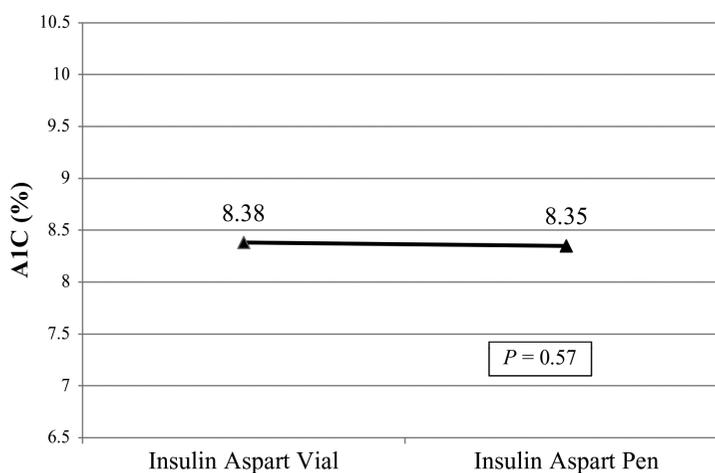


FIGURE 3. Average A1C in year before conversion and year after conversion.

regardless of vial or pen use (63 vs. 65 units/day, $P = 0.16$).

The post-hoc subgroup analysis evaluating patients in quartiles based on their average A1C in the year before conversion found a statistically significant increase in A1C in the first quartile ($P = 0.0137$), but a statistically significant decrease in A1C in the fourth quartile ($P = 0.025$), which included patients with the lowest and highest preconversion A1C values, respectively (Table 1). The second and third quartiles were not statistically significant ($P = 0.39$ and $P = 0.44$, respectively).

Oral agent use also did not change during the study period. The number of prescriptions for basal insulin was significantly higher after than before conversion ($n = 208$ vs. $n = 199$, $P = 0.003$). Intermediate-acting insulin use declined after conversion to the insulin pen by a statistically significant amount ($n = 15$ vs. $n = 4$, $P = 0.002$). It is unknown whether the observed shift to more basal insulin than intermediate-acting insulin prescriptions in any way affected A1C.

The occurrence of hospital admissions to the facility as a result of hyperglycemia was not different in the years before and after conversion ($P = 1.0$). There were no admissions for hypoglycemia during either study period. There were fewer emergency department visits for hyper- or hypoglycemia after conversion. Emergency department visits for hyperglycemia for the study population decreased from 17 to 10, but this was not statistically significant ($P = 0.3$). Visits related to hypoglycemia decreased from 12 to 3 after conversion, which was also not statistically significant ($P = 0.07$).

Conclusion

Although insulin pens have been shown to improve adherence to insulin therapy and reduce hypoglycemia, there is limited research assessing their clinical impact. This retrospective analysis evaluated A1C change after therapeutic conversion from insulin

aspart vials to insulin aspart pens in veterans with diabetes to determine whether this conversion led to an improvement in glucose control, as evidenced by a decrease in A1C.

This study found that conversion from insulin aspart vials to insulin aspart pens yielded no statistically significant change in A1C. However, there was a statistically significant increase in the amount of insulin aspart (units per day) used after conversion to the pen. This could be explained by the additional units necessary for insulin pen priming, which is not required when using insulin vials and syringes. This increase could also be attributed to progression of diabetes and a resulting increase in overall insulin requirements.

The assumption could be made that the use of an insulin device that is shown to improve adherence and reduce hypoglycemia should also improve glucose control with either a similar or possibly decreased insulin dose, if adherence is a major issue when a patient is using vials and syringes. The data presented here would indicate otherwise.

A possible explanation for similar A1C values observed in this study is the decrease in hypoglycemia observed. However, this point would be difficult to prove because those patients who may have experienced frequent hypoglycemia before conversion may have seen an increase in A1C after conversion as a result of having fewer hypoglycemic events.

Additionally, the conversion may have had no effect for some patients and potentially improved A1C for others resulting from a reduction in rebound hyperglycemia after hypoglycemic events. The post-hoc subgroup analysis lends support to this hypothesis, as evidenced by the A1C increase observed in the first quartile subgroup and A1C decrease observed in the fourth quartile. However, because A1C also increased in the second quartile and made no significant change in the third quartile, these results support a conclusion

that conversion from insulin vials to insulin pens does not improve glucose control. This subgroup analysis suggests that if one group were to gain benefit from conversion to the insulin pen then it would be those with the highest A1C levels.

There are some limitations to this study. This is a retrospective study relying heavily on appropriate documentation of current insulin doses in the medication list of the electronic medical record. This documentation may not occur with each insulin adjustment. The assessment of glucose control was done solely by reviewing changes in A1C levels. Various factors may lead to a falsely elevated or falsely low A1C results. Review of self-monitored blood glucose readings, along with A1C levels, would have been beneficial, but these are difficult to ascertain from the electronic record. In evaluating changes in frequency of hypo- and hyperglycemia requiring emergency department care or hospital admission, the data were limited to emergency department visits and admissions at the study facility. Patients living far away from the facility may have received care elsewhere as a matter of practicality.

Another potential limitation is that the reason for conversion to the insulin pen was not consistently documented in the medical record and could not be assessed for this analysis. It is possible that conversion was motivated by patient characteristics such as decreased vision or decreased digit dexterity, which may have made the use of vials and syringes unsafe. Future research is needed to evaluate whether subgroups of patients converted to insulin pens for specific reasons differentially benefit from conversion in terms of adherence and A1C reduction.

Another potential limitation is that a facility-wide conversion in preferred basal insulin therapy occurred concurrently during the analysis period. However, our analysis did not differentiate between basal insulins. Many patients could

have experienced a change in both basal insulin type and bolus insulin delivery device at the same time. Additionally, although the conversion in basal insulin type was intentionally carried out because of a formulary change, the switch from vials to pens was voluntary. This may have limited the population analyzed to patients with adherence issues that providers felt could be addressed with a device conversion.

The results of this study can prompt primary care providers and specialists to consider their intentions in using insulin pens in the diabetes population. Insulin pens have been shown to improve adherence, provide more accurate insulin dosing, and reduce hypoglycemia. Certain patients benefit from pens for these reasons. However, these findings suggest that the insulin pen itself may not lead to a statistically significant improvement in glucose control based on change in A1C. One area for further study may include identifying patients with suboptimal adherence and evaluating their insulin requirements, in addition to their A1C, before and after conversion. Further study in this area is important because it can help providers better understand the reasons for suboptimal adherence and identify more suitable means to assist patients in meeting therapeutic goals. Providers

may want to reconsider initiation of or conversion to insulin pens if their sole purpose is to improve glucose control.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. U.K. Prospective Diabetes Study 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;352:837–853
2. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
3. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with type 1 or type 2 diabetes mellitus: a systematic review. *Diabet Med* 2013;30:512–524
4. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA, U.S. Department

of Health and Human Services, Centers for Disease Control and Prevention, 2011

5. Cuddihy RM, Borgman SK. Consideration for diabetes: treatment with insulin pen devices. *Am J Ther* 2013;20:694–702
6. Magwire ML. Addressing barriers to insulin therapy: the role of insulin pens. *Am J Ther* 2011;18:392–402
7. Leichter S. Is the use of insulin analogues cost-effective? *Adv Ther* 2008;25:285–299
8. Meece J. Effect of insulin pens devices on the management of diabetes mellitus. *Am J Health Sys Pharm* 2008;65:1076–1082
9. Bohannon NJ, Ohannesian JP, Burdan AL, Holcombe JH, Zagar A. Patient and physician satisfaction with the Humulin/Humalog pen, a new 3.0-mL prefilled pen device for insulin delivery. *Clin Ther* 2000;22:1049–1067
10. Baser O, Bouchard J, DeLuzio T, Henk H, Aagren M. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;27:94–104
11. Grabner M, Chu J, Raparla S, Quimbo R, Zhou S, Conoshenti J. Clinical and economic outcomes among patients with diabetes mellitus initiating insulin glargine pen versus vial. *Postgrad Med* 2013;125:204–213
12. Seggelke S, Hawkins RM, Gibbs J, Rasouli N, Wang CC, Draznin B. Effect of glargine insulin delivery device (pen device versus vial/syringe) on glycemic control and patient preferences in patients with type 1 and type 2 diabetes. *Endocr Pract* 2014;20:536–539
13. Koivisto V, Cleall S, Pontiroli AE, Giugliano D. Comparison of insulin lispro protamine versus insulin glargine once daily in basal-bolus therapies with insulin lispro in type 2 diabetes mellitus patients: a prospective randomized open-label trial. *Diabetes Obes Metab* 2011;13:1149–1157