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DOI:10.4158/EP14290.OR

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Original Article

EP14290.OR

ADDING RAPID-ACTING INSULIN OR GLP-1 RECEPTOR AGONIST TO BASAL INSULIN:

OUTCOMES IN A COMMUNITY SETTING

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Running title: Outcomes with add-on RAI or GLP-1

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DOI:10.4158/EP14290.OR

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ABSTRACT

Objective: To evaluate real-world outcomes in patients with type 2 diabetes mellitus (T2DM) receiving basal insulin, who initiate add-on therapy with a rapid-acting insulin (RAI) or a glucagon-like peptide 1 (GLP-1) receptor agonist.

Methods: Data were extracted retrospectively from a U.S. health claims database. Adults with T2DM on basal insulin who added an RAI (basal+RAI) or GLP-1 receptor agonist (basal+GLP-1) were included. Propensity score matching (1 up to 3 ratio) was used to control for differences in baseline demographics, clinical characteristics, and health resource utilization. Endpoints included prevalence of hypoglycemia, pancreatic events, all-cause and diabetes-related resource utilization, and costs at 1 year follow-up.

Results: Overall, 6,718 matched patients were included: 5,013 basal+RAI and 1,705 basal+GLP1. Patients in both groups experienced a similar proportion of any hypoglycemic event ($P = .4079$). Hypoglycemic events leading to hospitalization were higher in the basal+RAI cohort (2.7% vs. 1.8%; $P = .0444$). The basal+GLP-1 cohort experienced fewer all-cause (13.55% vs. 18.61%; $P < .0001$) and diabetes-related hospitalizations (11.79% vs. 15.68%; $P < .0001$). The basal+GLP-1 cohort had lower total all-cause health care costs (\$18,413 vs. \$20,821; $P = .0002$), but similar diabetes-related costs (\$9,134 vs. \$8,985; $P < .0001$) compared with the basal+RAI cohort.

Conclusion: Add-on therapy with a GLP-1 receptor agonist in T2DM patients receiving basal insulin was associated with fewer hospitalizations and lower total all-cause costs compared with add-on therapy using a RAI, and could be considered an alternative to a RAI in certain patients with T2DM, who do not achieve effective glycemic control with basal insulin.

Keywords: databases; diabetes; evidence-based medicine; health-care costs; outcomes

Abbreviations

A1C = hemoglobin A_{1C}; **ED** = emergency department; **GLP-1** = glucagon-like peptide 1;
ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification;
IHCIS = Integrated Health Care Information Services; **NPH** = neutral protamine Hagedorn;
PSM = propensity score matching; **RAI** = rapid-acting insulin; **T2DM** = type 2 diabetes mellitus.

INTRODUCTION

Many patients with type 2 diabetes mellitus (T2DM) will require insulin therapy as an additional treatment on top of metformin to achieve or maintain target glycemic control (1). However, a substantial proportion (estimates ranging from 28–72%) of patients might not achieve glycemic control on basal insulin therapy alone and could require further treatment intensification (2-5). One method of intensifying basal insulin therapy is to add a prandial or rapid-acting insulin (RAI), but treatment intensification with a glucagon-like peptide 1 (GLP-1) receptor agonist might be an effective alternative (1,6). Several clinical trials have reported an association between the addition of a GLP-1 receptor agonist (e.g., exenatide, lixisenatide) to basal insulin therapy (e.g., insulin glargine, insulin detemir, neutral protamine Hagedorn [NPH] insulin) and improved glycemic control, without an accompanying increase in weight or risk of hypoglycemia (7-12). Thus, this combination might represent an additional option for patient management.

Real-world data on the effects of newly-emerging therapeutic options, such as the intensification of basal insulin therapy with a GLP-1 receptor agonist, compared with pre-established regimens are crucial if health care providers, payers, and other decision makers are to continue selecting the most appropriate and cost-effective treatments for patients. The clinical studies reported previously have not included economic outcomes, a necessary component of

current clinical decision-making. This study used the Integrated Health Care Information Services (IHCIS) IMPACT database to evaluate real-world outcomes, both clinical and economic, associated with the use of basal insulin plus a GLP-1 receptor agonist, compared with basal insulin plus an RAI, in patients with T2DM in the United States in a managed-care setting.

METHODS

Study Design

This was a retrospective analysis of U.S. health insurance claims data from the IHCIS IMPACT database, which contains medical and pharmacy claims, eligibility data, and laboratory results from 86.4 million covered lives. Of these, 63.7 million (74%) have pharmacy benefits and 12.6 million (15%) have laboratory results; the database includes all data for individuals in all U.S. census regions and represents 46 health plans. Institutional Review Board approval to conduct this study was not required.

Patient Identification

Data were included from patients aged ≥ 18 years and diagnosed with T2DM; defined as having ≥ 1 inpatient or ≥ 2 office visits (≥ 30 days apart) with a primary or secondary T2DM diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis codes 250.x0 or 250.x2) (13). Patients were treated with a basal insulin (insulin glargine, insulin detemir, or NPH insulin) plus add-on therapy with either an RAI (insulin glulisine, insulin aspart, or insulin lispro; the basal+RAI group) or a GLP-1 receptor agonist (exenatide or liraglutide; the basal+GLP-1 group), initiated between July 1, 2007, and December 31, 2011. In addition, continuous health care coverage for ≥ 6 months before (baseline) and for 12 months after (follow-up) the first GLP-1 receptor agonist or RAI prescription date (index date)

was required for inclusion, and patients had to have been prescribed basal insulin in the quarter before and the quarter after the index date. Subsets of patients with ≥ 1 glycated hemoglobin A1C (A1C) value during the baseline period or aged ≥ 55 years at index were also identified for sensitivity analyses. Data from patients prescribed: premix, prandial, or regular insulin; a GLP-1 receptor agonist; or ≥ 1 type of basal insulin during the baseline period were excluded from the analysis.

Study Endpoints

Clinical outcomes included: hypoglycemic events, defined as a health care encounter (outpatient, inpatient, or emergency department [ED] visit) with a primary or secondary diagnosis code for hypoglycemia (ICD-9-CM diagnosis codes: 250.8x, diabetes with other specified manifestations; 251.0, hypoglycemic coma; 251.1, other specified hypoglycemia; or 251.2, hypoglycemia, unspecified); and pancreatic events, defined as a health care encounter (outpatient, inpatient, or ED visit) with a primary or secondary diagnosis of pancreatic disease (ICD-9-CM diagnosis code 577.xx).

Economic outcomes included all-cause health care resource utilization (outpatient visits, ED visits, inpatient admissions, inpatient length of stay), diabetes-related health care resource utilization (from claims with a primary or secondary diagnosis of diabetes [ICD-9-CM diagnosis code 250.xx]), and health care costs. These were computed as plan-reimbursed amounts of adjudicated claims including inpatient, outpatient, ED, and pharmacy costs. Diabetes-related health care costs comprised those from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM diagnosis code 250.xx), antidiabetes medications, glucose meters, and test strips.

Statistical Analyses

Patient baseline demographics, including age, gender, health plan type, and U.S. geographic region, were assessed at the study index date, whereas baseline clinical characteristics (Charlson Comorbidity Index and individual comorbidities) were observed during the 6 months prior to the index date. Study outcomes were measured at 1-year follow-up.

Propensity score matching (PSM; 1 up to 3 ratio) was used to control for any differences in age, gender, health plan, comorbidity, all-cause health care utilization (including any hospitalization and any ED visit), and hypoglycemic events between cohorts at baseline. Baseline characteristics and clinical and economic outcomes were summarized and compared in matched cohorts, with *P*-values provided by Student *t*-tests for continuous variables, or χ^2 tests for binary and categorical variables, as appropriate; health care costs were reported as mean costs and cost difference in U.S. dollars.

RESULTS

Baseline Demographics and Clinical Characteristics

Patient sample attrition associated with the inclusion criteria for this study is shown in Figure 1. In total, data from 11,338 patients were eligible for inclusion, 1,705 in the basal+GLP-1 group and 9,633 in the basal+RAI group. At baseline, patients in the unmatched basal+RAI group had more comorbidities, higher A1C values, and higher healthcare costs than those in the basal+GLP-1 group (Table 1). After PSM, data from 6,718 patients were retained for the analysis. In the basal+GLP-1 group (*n* = 1,705), 82% of patients used exenatide and 18% used liraglutide. In the basal+RAI group (*n* = 5,013), 49% of patients used insulin aspart, 44% insulin lispro, and 7% insulin glulisine. At baseline, in the PSM-patients overall, 47% of the patients were women, mean age was 54 years, and basal insulin use was 79% insulin glargine, 16% insulin detemir, and 5% NPH.

Selected Clinical Outcomes

Clinical outcomes after 1 year of follow-up are shown in Table 2. The proportions of patients in the basal+GLP-1 and basal+RAI groups who experienced either any hypoglycemic event or any pancreatic event were similar. However, inpatient hypoglycemic events were significantly less common in the basal+GLP-1 group compared with the basal+RAI group (0.12% vs. 0.46%; $P = .0454$) as were hypoglycemic events leading to hospitalization (1.82% vs. 2.69%; $P = .0444$).

Health Care Resource Utilization

In general, fewer health care resources were required by the basal+GLP-1 group. All-cause hospitalizations were significantly less common in the basal+GLP-1 group compared with the basal+RAI group (Fig. 2A), and there were significantly fewer diabetes-related hospitalizations and ED visits in the basal+GLP-1 group compared with the basal+RAI group (Fig. 2B). However, all-cause and diabetes-related endocrinologist visits were significantly higher in the basal+GLP-1 group compared with the basal+RAI group (Fig. 2).

With regard to cost outcomes, mean total all-cause health care costs were significantly lower in the basal+GLP-1 group compared with the basal+RAI group, driven by significantly lower inpatient (cost difference = \$2,051; $P < .0001$) and outpatient costs (cost difference = \$1,682; $P < .0001$) (Fig. 3A). Pharmacy costs were significantly higher in the basal+GLP-1 group versus basal+RAI group (Fig. 3A). For diabetes-related health care costs, the basal+GLP-1 group compared with the basal+RAI group had significantly lower inpatient (cost difference = \$530; $P = .0192$) and outpatient costs (cost difference = \$353; $P < .0001$), and lower costs related to diabetes supplies and testing strips (Fig. 3B). This was offset by significantly lower

diabetes-related pharmacy costs in the basal+RAI group; total costs for diabetes-related health care were not significantly different between groups (Fig. 3B).

Sensitivity Analyses

Similar trends in clinical and economic outcomes were observed in sensitivity analyses conducted in A1C-matched patient cohorts, which comprised approximately 20% of the overall population (Table 3). In this matched cohort, changes in A1C values at 1-year were similar in the basal+RAI and basal+GLP-1 groups (-0.58% vs. -0.60%, respectively; $P = .9104$).

DISCUSSION

This study presented real-world data on clinical, health care resource utilization, and cost outcomes in T2DM patients not achieving glycemic control, who initiated basal insulin therapy combined with a GLP-1 receptor agonist or an RAI in a U.S. managed-care setting.

There were no differences in A1C outcomes in patients adding a GLP-1 receptor agonist or RAI, or in terms of hypoglycemic and pancreatic events, although there were fewer hypoglycemic events leading to hospitalization in the basal+GLP-1 group compared with the basal+RAI group. Intensification of treatment with a GLP-1 receptor agonist was associated with fewer diabetes-related hospitalizations and ED visits than intensification with RAI; however, GLP-1 receptor agonist use was associated with more diabetes-related endocrinologist visits. This could indicate a potential association between GLP-1 receptor agonist usage and increased endocrinologist visits. Other work has suggested that, even as recently as in 2013, endocrinologists feel more confident than other health care providers in identifying patients who would benefit from treatment with a GLP-1 receptor agonist (14).

Inpatient and outpatient health care costs were significantly lower in the basal+GLP-1 group compared with the basal+RAI group, regardless of whether all-cause or diabetes-related

health care costs were being evaluated. In contrast, all-cause and diabetes-related pharmacy costs were significantly higher in the basal+GLP-1 group compared with the basal+RAI group. However, the basal insulin plus GLP-1 receptor agonist regimen cost an average of \$2,408 less annually in terms of total all-cause health care costs compared with the basal insulin plus RAI regimen.

In our study, of the >11,000 patients identified, 85% intensified with an RAI. Although GLP-1 receptor agonist treatment would not be seen as appropriate for all patients, our study has demonstrated that in patients with similar baseline demographic and clinical characteristics there might be reduction in overall costs if a GLP-1 receptor agonist were used. Furthermore, when patients initiating a GLP-1 receptor agonist or RAI were matched according to their baseline A1C values, we continued to observe the difference in overall costs with similar glycemic outcomes.

. Evidence from clinical studies and a recent systematic review also support the consideration of GLP-1 receptor agonist as add-on therapy for treatment intensification in patients on basal insulin therapy (6-9,11,12). However, none of these previous studies included cost outcomes. These favorable clinical trial data were also reflected in another real-world data analysis of 6,500-matched cohort patients. In this other real-world data analysis, treatment intensification using a GLP-1 receptor agonist was associated with similar glycemic control, higher weight loss, and lower incidence of hypoglycemia compared with intensification using an RAI (10), complementing the current study.

Limitations

As with all retrospective database analyses, this study could be subject to selection bias; however, PSM was undertaken to mitigate the effects of confounding factors. Although one-to-many matching has been previously validated as a method to increase precision in cohort

studies as compared with one-to-one matching (15), we were unable to control for certain characteristics at baseline (e.g., A1C values, body weight, and duration of disease) so no causality conclusions can be drawn from this study. These factors are associated with the severity of the disease and may have an important impact on clinical outcomes as well as healthcare utilization and costs.

In addition, the health care claims data used in this study could be subject to coding errors because the presence of an ICD-9-CM diagnosis code on a medical claim does not confirm a positive presence of disease, also a diagnosis might be incorrectly coded or included as a rule-out criterion rather than actual disease. Similarly, hypoglycemia was estimated using diagnostic codes in which only events severe enough to require medical intervention are captured. Furthermore, the current results are from a typical managed-care U.S. population. For example, the proportion of patients in this managed care database aged 65 years and older was low at 6.7% of all members, and fewer than 5% of patients with diabetes had Medicare or Medicaid coverage. Caution should be exercised in the generalization of these results to other populations.

CONCLUSION

Certain patients on basal insulin who are not achieving/maintaining glycemic control targets and who require intensification of their treatment, as their disease progresses, could be considered for add-on treatment with a GLP-1 receptor agonist rather than with an RAI. Longer-term studies are required to further evaluate the potential clinical and economic benefits associated with the use of a GLP-1 receptor agonist in patients not achieving adequate glycemic control on basal insulin plus oral antidiabetes drugs alone.

ACKNOWLEDGMENT

This study was funded by Sanofi U.S., Inc. The authors received writing/editorial support in the preparation of this manuscript provided by Rachel Spice, PhD, of Excerpta Medica, funded by Sanofi U.S., Inc.

DISCLOSURE

Dr. Dalal is an employee of Sanofi U.S., Inc. Drs. Xie and Baser are employees of STATinMED under contract to Sanofi U.S., Inc. Dr. DiGenio is an employee of Isis Pharmaceuticals, Inc., and was an employee of Sanofi U.S., Inc. at the time this study was conducted.

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FIGURE LEGENDS

Fig. 1. Sample attrition. *GLP-1 = glucagon-like peptide 1 receptor agonist; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; RAI = rapid-acting insulin; T2DM = type 2 diabetes mellitus.*

Fig. 2. Health care resource utilization at 1-year follow-up (matched analysis): all-cause (A) and diabetes-related (B). *ED = emergency department; GLP-1 = glucagon-like peptide 1 receptor agonist; RAI = rapid-acting insulin.*

Fig. 3. Health care costs at 1-year follow-up (matched analysis): all-cause (A) and diabetes-related (B). *ED = emergency department; GLP-1 = glucagon-like peptide 1 receptor agonist; RAI = rapid-acting insulin.*

Table 1**Baseline Demographic and Clinical Characteristics (Unmatched Analysis)**

Characteristic	Basal+RAI (n = 9,633)	Basal+GLP-1 (n = 1,705)	P-value
Age, mean (SD), years	54.37 (12.16)	54.36 (9.17)	.9718
Women, n (%)	4,319 (44.84)	805 (47.21)	.0689
U.S. region, n (%)			
Northeast	2,711 (28.14)	466 (27.33)	.4916
South	4,087 (42.43)	731 (42.87)	.7308
Midwest	1,925 (19.98)	337 (19.77)	.8355
West	908 (9.43)	171 (10.03)	.4339
Unknown	2 (0.02)	0	.5518
Health plan type, n (%)			
HMO	1,696 (17.61)	307 (18.01)	.6900
POS	4,841 (50.25)	924 (54.19)	.0027
PPO	2,051 (21.29)	351 (20.59)	.5115
Medicare	404 (4.19)	40 (2.35)	.0003
Medicaid	75 (0.78)	11 (0.65)	.5584
Others	566 (5.88)	72 (4.22)	.0063
CCI, mean (SD)	0.92 (1.59)	0.50 (0.98)	<.0001
A1C			
Evaluable at baseline, n (%)	1,819 (18.88)	401 (23.52)	<.0001
<7.0%	193 (10.61)	56 (13.97)	.0540
≥7.0% to <8.0%	349 (19.19)	93 (23.19)	.0690
≥8.0% to <9.0%	377 (20.73)	99 (24.69)	.0801

Characteristic	Basal+RAI (n = 9,633)	Basal+GLP-1 (n = 1,705)	P-value
≥9.0%	900 (49.48)	153 (38.15)	<.0001
Mean (SD), %	9.23 (2.01)	8.71 (1.68)	<.0001
All-cause health care costs, mean (SD), \$			
Total costs	13,546 (28,216)	7,527 (10,260)	<.0001
Inpatient costs	6,214 (23,458)	1,427 (7,945)	<.0001
Outpatient costs	4,119 (9,898)	2,680 (4,493)	<.0001
ED costs	401 (1,488)	248 (1,044)	<.0001
Treatment costs	2,813 (2,978)	3,173 (2,486)	<.0001
Diabetes-related health care costs, mean (SD), \$			
Total costs	4,898 (10,429)	3,410 (5,288)	<.0001
Inpatient costs	2,372 (9,638)	714 (4,728)	<.0001
Outpatient costs	1,103 (2,681)	928 (1,701)	.0004
ED costs	181 (808)	112 (579)	<.0001
Treatment costs	1,048 (892)	1,475 (1,008)	<.0001
Diabetes supply costs	194 (229)	182 (202)	.0196
Cost of testing strips	155 (210)	138 (188)	.0008

CCI = Charlson Comorbidity Index; ED = emergency department; GLP-1 = glucagon-like peptide 1 receptor agonist; HMO = Health Maintenance Organization; POS = Point-of-Service; PPO = Preferred Provider Organization; RAI = rapid-acting insulin; SD = standard deviation.

Table 2**Selected Clinical Endpoints at 1-Year Follow-Up (Matched Analysis)**

Endpoint	Basal+RAI (n = 5,013)	Basal+GLP-1 (n = 1,705)	P-value
Hypoglycemic events, n (%)			
Any	359 (7.16)	112 (6.57)	.4079
Any inpatient	23 (0.46)	2 (0.12)	.0454
Any ED	117 (2.33)	29 (1.70)	.1215
Any outpatient	254 (5.07)	88 (5.16)	.8782
Leading to hospitalization ^a	135 (2.69)	31 (1.82)	.0444
Pancreatic events, n (%)			
Any	93 (1.86)	20 (1.17)	.0585
Any inpatient	21 (0.42)	3 (0.18)	.1464
Any ED	35 (0.70)	10 (0.59)	.6253
Any outpatient	69 (1.38)	14 (0.82)	.0730

^aDefined as inpatient or ED health care encounters with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia.

ED = emergency department; GLP-1 = glucagon-like peptide 1 receptor agonist; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; RAI = rapid-acting insulin.

Table 3**Clinical and Economic Endpoints at 1-Year Follow-Up (Matched Analysis of Patients With >1 A1C Value During the Baseline Period)**

Endpoint	Basal+RAI (n = 1,127)	Basal+GLP-1 (n = 400)	P-value
Hypoglycemic events, n (%)			
Any	87 (7.72)	24 (6.00)	.2551
Any inpatient	6 (0.53)	0	.1437
Any ED	28 (2.48)	9 (2.25)	.7933
Any outpatient	60 (5.32)	18 (4.50)	.5202
Leading to hospitalization ^a	33 (2.93)	9 (2.25)	.4762
Pancreatic events, n (%)			
Any	25 (2.22)	5 (1.25)	.2306
Any inpatient	1 (0.09)	1 (0.25)	.4436
Any ED	14 (1.24)	2 (0.50)	.2104
Any outpatient	19 (1.69)	4 (1.00)	.3333
All-cause health care resource utilization, n (%)			
Any hospitalization	245 (21.74)	59 (14.75)	.0026
ED visits	377 (33.45)	127 (31.75)	.5341
Office visits	1,126 (99.91)	400 (100)	.5512
Endocrinologist visits	553 (49.07)	219 (54.75)	.0509
Diabetes-related health care resource utilization, n (%)			
Any hospitalization	213 (18.90)	53 (13.25)	.0105

Endpoint	Basal+RAI (n = 1,127)	Basal+GLP-1 (n = 400)	P-value
ED visits	245 (21.74)	81 (20.25)	.5324
Office visits	1,121 (99.47)	398 (99.50)	.9386
Endocrinologist visits	543 (48.18)	217 (54.25)	.0370
All-cause health care costs, mean (SD), \$			
Total cost	22,305 (34,986)	19,230 (18,354)	.0269
Inpatient cost	6,412 (24,913)	3,739 (13,184)	.0072
Outpatient cost	7,940 (15,036)	6,089 (7,659)	.0017
ED cost	593 (1,737)	605 (1,790)	.9073
Pharmacy cost	7,361 (5,172)	8,797 (5,078)	<.0001
Diabetes-related health care costs, mean (SD), \$			
Total cost	9,168 (11,949)	9,522 (9,328)	.5464
Inpatient cost	2,265 (9,765)	1,924 (7,468)	.4706
Outpatient cost	2,283 (4,693)	1,915 (3,388)	.0948
ED cost	274 (1,101)	238 (935)	.5340
Pharmacy cost	3,639 (2,227)	4,929 (2,291)	<.0001
Diabetes supply cost	708 (641)	516 (443)	<.0001
Cost of testing strips	557 (564)	358 (382)	<.0001

^aDefined as inpatient or ED health care encounters with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia.

ED = emergency department; GLP-1 = glucagon-like peptide 1 receptor agonist; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; RAI = rapid-acting insulin; SD = standard deviation

≥1 Prescription order for either GLP-1 or RAI (not both) during identification period
(July 1, 2007 – Dec 31, 2011)
(N = 232,074)

Patients with ≥1 inpatient or ≥2 physician visits dated ≥30 days apart with a primary or secondary T2DM ICD-9-CM code (250.x0 or 250.x2)
(N = 181,033)

Characteristics/ outcomes data for ≥6 months before (baseline) and 6 months after (follow-up) the index date, defined as date of first prescription for GLP-1 or RAI
(N = 85,062)

Patients with GLP-1 or RAI, not prescribed premix insulin or regular insulin
(N = 22,422)

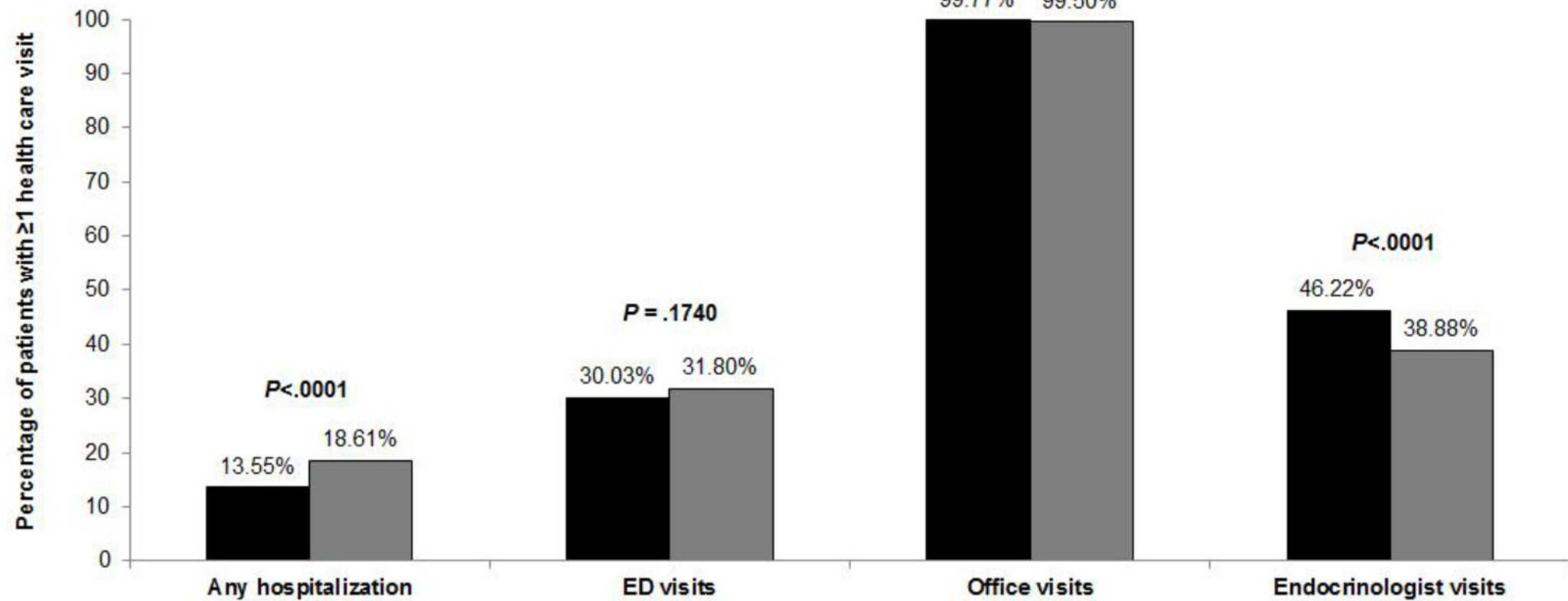
≥1 Basal insulin in the quarter before the index date
(N = 19,488)

No more than 1 type of basal insulin at baseline
(N = 19,265)

≥1 Refill of same basal insulin in the first quarter of follow-up
(N = 15,327)

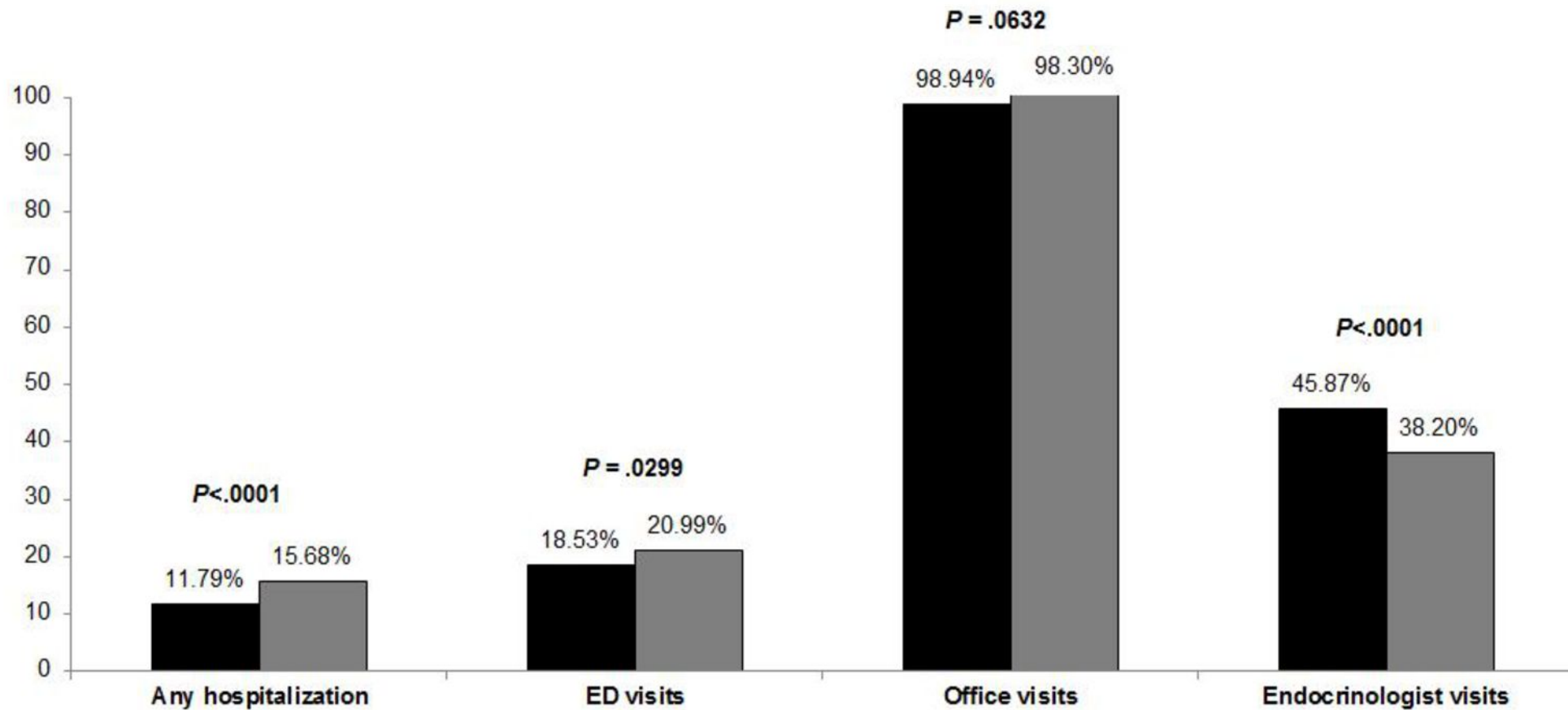
≥1 Year follow-up data available
(N = 11,338)
(unmatched final sample size: basal+GLP-1, n=1,705; basal+RAI, n=9,633)
(matched sample size: basal+GLP-1, n=1,705; basal+RAI, n=5,013)

■ Basal+GLP-1 ■ Basal+RAI

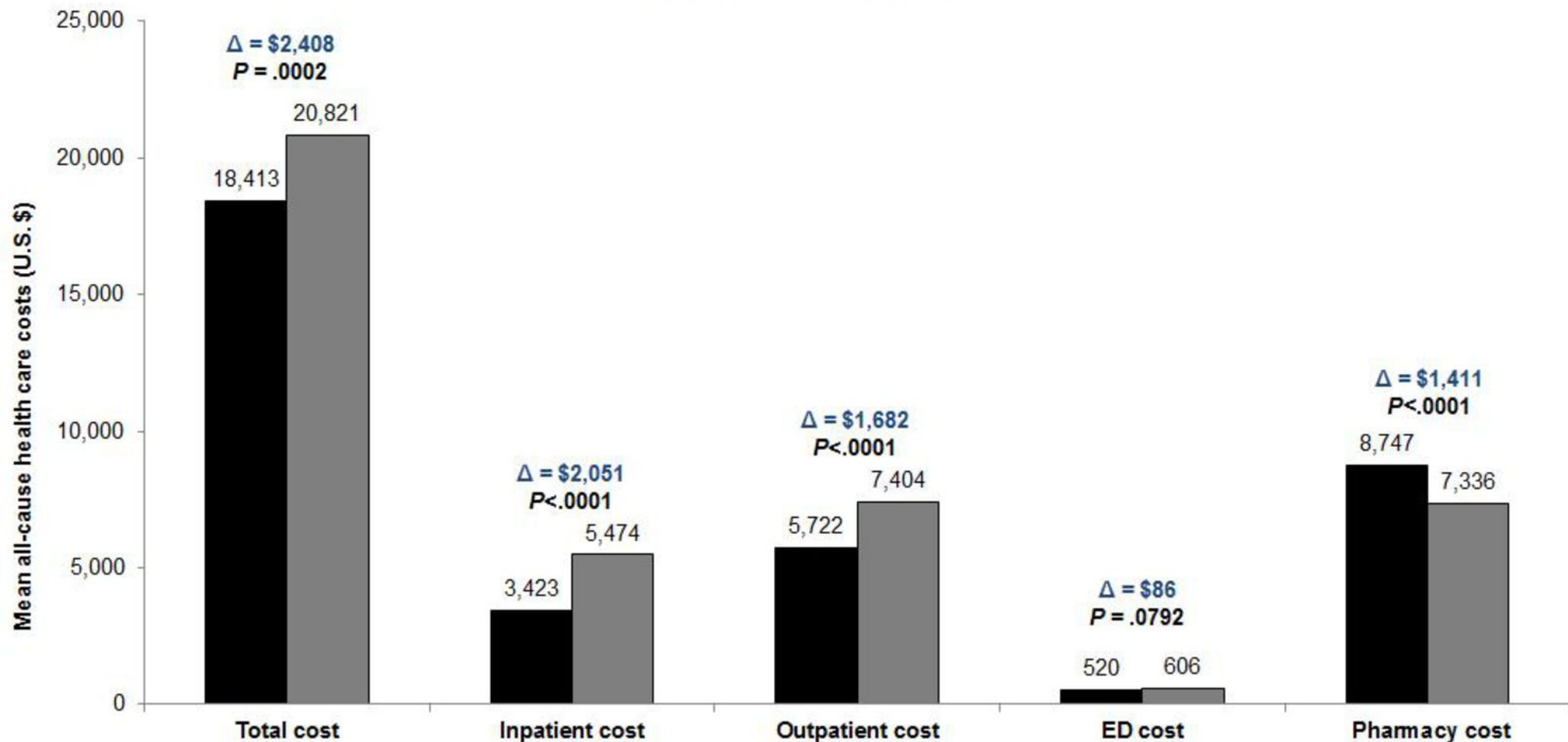


■ Basal+GLP-1 ■ Basal+RAI

Percentage of patients with ≥ 1 health care visit



■ Basal+GLP-1 ■ Basal+RAI



■ Basal + GLP-1 ■ Basal + RAI

