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ORIGINAL RESEARCH

Characteristics, Treatment Patterns, and Economic Outcomes of Patients Initiating Injectable Medications for Management of Type 2 Diabetes Mellitus in Japan: Results from a Retrospective Claims Database Analysis

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ABSTRACT

Introduction: This study's objective was to describe characteristics, treatment patterns, and economic outcomes of type 2 diabetes mellitus (T2DM) patients initiating injectable antidiabetic medications in Japan.

Methods: Adults (≥ 18 years) with T2DM, ≥ 2 claims for injectable antidiabetics between 1 August 2011 and 31 July 2015 (first claim = index date), no evidence of type 1 diabetes mellitus, ≤ 1 claim for insulin, no claims for GLP-1RA before index, and continuous enrollment for 6 months before (baseline) and 12 months after index (follow-up) were selected from the Japan Medical Center Database. Patient characteristics and outcomes during the baseline and follow-up periods were described overall and by provider, using the proxy setting of index medication [hospital (including outpatient departments) for specialists; clinic for general practitioner (GP)].

Results: Of the 2683 patients included (mean age: 50 years, 67% male), 1879 (70%) initiated injectable antidiabetics with specialists and 804 (30%) with GPs. The specialist cohort had a significantly greater comorbidity burden, but lower HbA1c levels during baseline, and was more likely to receive intensified treatment at index than the GP cohort. Almost 40% of patients (almost 30% of GP cohort) did not use antidiabetics during baseline; the remaining patients received oral medications, primarily from GPs. During follow-up, patients used the index medication for approximately 7 months. Independent of specialist vs. GP setting, patients received antidiabetics and medications for T2DM-related comorbidities and complications during the baseline and follow-up periods from the same provider, primarily GPs. The overall average healthcare costs were ¥350,404 during baseline and ¥1,856,727 during follow-up.

Conclusions: In Japan, most T2DM patients initiated injectable antidiabetics with specialists vs. GPs. There were considerable differences in characteristics of patients treated by specialists vs. GPs. After initiation, injectable antidiabetics were largely prescribed by GPs. Future research should evaluate the factors associated with different provider practices and communication

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channels between specialists and GPs to improve patient management.
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Keywords: Costs; Injectable antidiabetic; Resource use; Specialist vs. GP setting; Treatment patterns; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, affected about 7.6% of adults aged 20–79 years in Japan in 2015 [1] and accounted for approximately 4% of the national healthcare expenditure in 2014 [2]. The healthcare costs are particularly high among patients who develop diabetes-related complications, as demonstrated by a Japanese claims data study in 2016 [3]. As such, it is important to effectively manage patients with T2DM in clinical practice. Japanese guidelines for the management of T2DM recommend beginning with lifestyle modifications such as diet and exercise therapy, followed by treatment with oral antidiabetic agents and/or injectable therapy if the glycemic control target is not achieved [4]. Injectable therapies may include the start of an insulin therapy (often basal insulin as the first step of insulin therapy) or glucagon-like peptide-1 (GLP-1) receptor agonists [4]. The Japanese treatment guidelines recommend a stepwise escalation of treatment (in terms of either dose or use of more than one therapeutic agent) along the course and progression of the disease. However, unlike other treatment guidelines such as from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), which recommend use of injectable medications among patients with a more advanced disease stage [5], the recommendations regarding the use of injectable medications and treatment pathway in Japan are not clear. With the increasing prevalence of T2DM [6], as well as the lack of specific recommendations regarding the use of injectable medications in Japan, there is a need for characterizing the treatment pathways followed in practice and subsequent outcomes in T2DM patients initiating injectable antidiabetic medications in Japan. In addition, a better understanding of the roles and relationships between the different types of Japanese health professionals treating T2DM patients is required to inform future policy decisions, particularly given the recent government initiatives to limit specialist care to supporting and advising of non-specialists when necessary [7].

To the best of our knowledge, however, no study to date has provided a comprehensive assessment of the treatment patterns and clinical as well as economic outcomes among T2DM patients initiating injectable antidiabetic medications—overall and by provider type—in Japan. For example, using a hospital-based database, Ikeda et al. [8] found varied treatment and healthcare service utilization patterns among Japanese patients with T2DM who initiated insulin therapy (long-acting, pre-mixed, rapid-acting, or a combination). However, only medium- and large-sized administrative hospitals were included, and outpatient clinics were not considered. In a different study, Hadjiyianni et al. [9] evaluated medication use and economic outcomes among patients initiating basal insulin in Japan and found that continuous use of basal insulin during the year after initiation was associated with lower medical resources and costs. However, the study was limited to basal insulin initiators and did not consider other injectable therapies. Additionally, neither study evaluated practice patterns and outcomes by type of provider prescribing insulin treatment. A few studies that did assess the variation between prescription patterns of general physicians (GPs) and specialists treating T2DM patients in Japan did not evaluate the treatment transitions leading up to and outcomes following insulin treatment. For example, in the insurance-based database, Hidaka et al. [10] found that more patients with T2DM were treated by GPs than by specialists, and prescription patterns between them were different. Specifically, the specialists were more likely to prescribe insulin (19% vs. 6%) and use intensified treatment approaches (e.g., triple combination therapy of biguanides + DPP-4 inhibitors + sulfonylureas) compared with GPs. Another study using administrative claims data

from the Japan Medical Data Center also reported that patients treated in academic hospitals were more likely to receive aggressive treatment, including higher rates of insulin therapy, compared with those treated in clinics [11]. A different study surveyed more than 15,000 patients from clinics and hospitals in Japan and found that patients treated by diabetes specialists were more likely to initiate insulin than those treated by general practitioners [12].

To address this gap in the literature, using de-identified retrospective data for commercially insured patients in Japan, the objectives of this study were to: (1) understand the demographic and clinical characteristics of T2DM patients initiating injectable medications, (2) describe antidiabetic treatment patterns, clinical outcomes, and all-cause and T2DM-related medical resource use and costs during the 6 months before and 12 months after initiation of injectable medications, and (3) provide a better understanding of the types of providers prescribing the oral antidiabetic medications and medications for T2DM-related comorbidities prior to and following initiation of injectable antidiabetic medications. The outcomes were reported for the overall cohort as well as for cohorts stratified by type of medical provider, specialist, or GP, using as a proxy the setting in which the index medication was prescribed [hospital (including outpatient departments) for specialist or clinic for GP].

METHODS

Data and Sample Selection

This study was conducted using data from the Japan Medical Data Center (JMDC) [13, 14]. The JMDC database contains de-identified administrative claims data for beneficiaries of the Kenpo health insurance system who are employed by middle-to-large size companies in Japan and their dependents. The JMDC database currently includes over 4 million unique beneficiaries under age 75 and contains administrative claims for services provided between 1 January 2005 and 31 March 2016. Data contain information on enrollment history, patient demographics, medical and prescription drug claims, and costs. Laboratory values from annual health check-ups for people aged $\geq$ 40 years, as well as the size of the medical facilities, are also available.

The study sample consisted of beneficiaries with T2DM who initiated injectable antidiabetic medications (basal insulin, rapid insulin, basal-bolus therapy, pre-mixed insulin, or GLP-1 receptor agonists) between 1 August 2011 and 31 July 2015. The date of the first observed claim during this time period was defined as the study index date, the 6-month period prior to index date as the baseline period, and the 12-month period following the index date as the follow-up period. Beneficiaries were identified as having T2DM if they met any of the following conditions during the 2 years before and 1 year after the index date: (1) at least two diagnoses for T2DM [International Classification of Diseases (ICD) 10 code: E11.x or E14.x] or (2) at least one diagnosis of T2DM and at least one prescription for a non-insulin antidiabetic medication [9]. Further, beneficiaries were required to have at least two additional claims for the index medication after the index date, be at least 18 years old, and have continuous enrollment with JMDC throughout the baseline and follow-up periods (to ensure availability of complete pharmacy and medical care information). Beneficiaries with evidence of type 1 diabetes mellitus (T1DM; ICD-10: E10.x) before the index date or during the follow-up period not accompanied by oral antidiabetic use were excluded. Additionally, to increase the likelihood of capturing the 'true' initiators of injectable medications (as opposed to those using these medications for acute reasons), beneficiaries with more than one claim for insulin during the baseline period or with any claim for an antidiabetic injectable medication other than insulin prior to the index date were excluded.

The data do not contain information about provider specialty. However, this information can be approximated based on the setting in which care was provided. Specifically, in Japan, primary care is typically provided in clinics (defined as a facility with less than 20 beds),

whereas specialist care is provided in hospital (defined as a facility with at least 20 beds) [11, 15]. Consistent with these definitions, patients in the final analytic sample were stratified into two cohorts depending on the setting of the index medication: the specialist cohort, consisting of patients whose index medication was prescribed in a hospital setting, and the GP cohort, consisting of patients whose index medication was prescribed in a clinic. The hospital setting included in- and outpatient medical claims as well as pharmacy claims associated with a facility with at least 20 beds.

This article is based on previously collected data and does not involve any new studies of human or animal subjects performed by any of the authors.

Patient Characteristics

Patient characteristics were evaluated over the 6-month baseline period prior to the index date or at index date. These included demographics (age and gender), type of index medication (i.e., basal insulin only, rapid insulin only, basal and rapid insulin, pre-mixed insulin only, GLP-1 receptor agonists only, and multiple), Charlson comorbidity index (CCI) [16], and presence of T2DM-related complications and comorbidities (e.g., retinopathy, neuropathy, and congestive heart failure).

In addition, among patients with data from annual health check-ups prior to or at the index date, the test results for specific measures were reported. These included body mass index (BMI), HbA1c levels, fasting blood sugar levels, and blood pressure levels [including systolic blood pressure (SBP) and diastolic blood pressure (DBP)].

Outcomes

Medication Use

Use of antidiabetic medications and other select medications for T2DM-related complications and comorbidities (antihypertensives, statins, or antiplatelet agents, overall and by medication class) was evaluated during the baseline and follow-up periods. In addition, for antidiabetic medications, proportions of patients using monotherapy vs. combination therapy were described. Combination therapy was defined as the concurrent use of at least two medications, each from a different class of antidiabetics, such that the days' supply for the medications overlap by at least 28 days, and there was a new prescription for each of the overlapping antidiabetic therapies after the start of concurrent use. Combination therapy captured the use of a combination of oral medications, orals and injections, or injections and thus potentially included the use of insulin. All patients using at least one class of antidiabetic medication and not meeting the criteria for combination therapy were considered as using monotherapy.

Furthermore, among patients using both antidiabetic medications and medications for T2DM-related complications and comorbidities, the proportions of patients for whom their most recent medications were prescribed in a hospital or clinic setting were described. For the baseline period, the last medication prescribed for each patient before their index date was used; for the follow-up period, the last medication observed during the follow-up period for each patient was used. In addition, the proportions of patients who had the same provider for the most recent use of any antidiabetic and T2DM-related medication were reported for both time periods.

Healthcare Resource Use and Costs

Metrics of all-cause and T2DM-related healthcare resource use as well as associated costs were evaluated during the baseline and follow-up periods. Specifically, proportions of patients with an in- or outpatient visit during the respective period were reported. Additionally, among those with at least one inpatient visit the mean duration of inpatient stay was reported. Similarly, among those with an outpatient visit, the mean number of outpatient visits during the relevant period were reported. Furthermore, healthcare costs including total costs, total medical costs, medical costs by hospital department (inpatient and outpatient), and pharmacy costs during the respective period were reported. The costs represent payments for

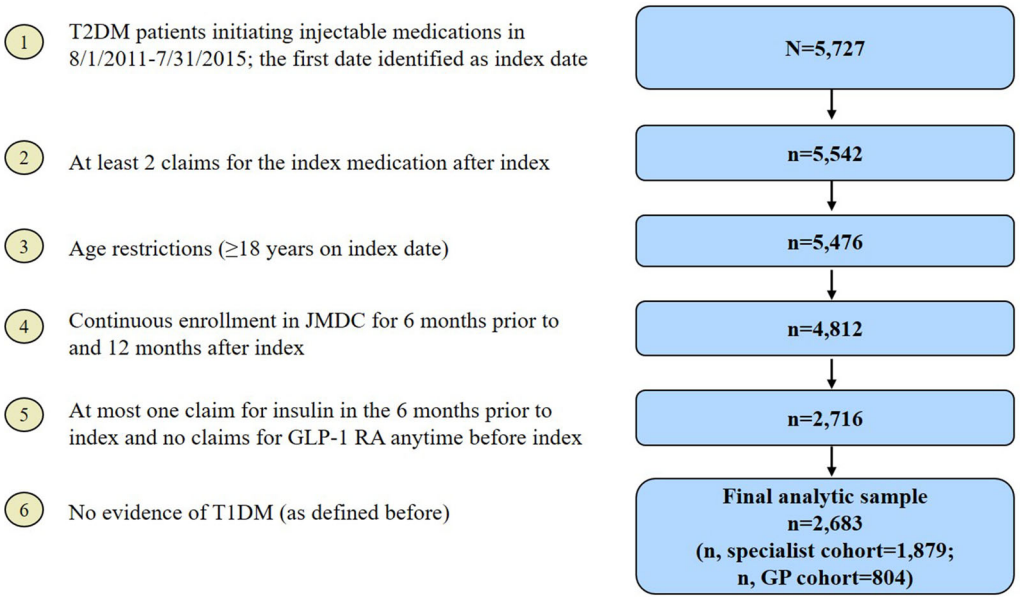

Fig. 1 Sample selection and resulting patient counts. *GLP-1* RA glucagon-like peptide-1 receptor agonists, *GP* general practitioner, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus. Patients were identified as having T2DM based upon having at least two diagnoses for T2DM (ICD-10 codes E11.x and E14.x) or having at least one diagnosis for T2DM and at least one claim for an OAD; T1DM was identified using ICD-10 code E10.x

medical services and prescription drugs. The costs associated with medical care received include the insurance payment and patient copayment amount. Costs were inflated to first semi-annual 2016 Japanese yen (¥) using the medical care component of the Japanese Consumer Price Index (CPI) [17]. T2DM-related healthcare resource use and costs include claims with a diagnosis for T2DM, retinopathy, neuropathy/diabetic foot, nephropathy, cardiovascular disease, congestive heart failure, peripheral vascular disease, stroke, hypertension, dyslipidemia, and severe hypoglycemic event.

Statistical Analyses

Patient characteristics, medication use, healthcare resource use, and healthcare costs were described using means and standard deviations (SD) for continuous variables (e.g., age, CCI) and numbers and proportions for categorical variables (e.g., gender, comorbidity rates). In addition, the median and interquartile range were reported for age, all-cause healthcare resource use, and all cost variables.

Results were reported for the overall cohort as well as stratified by specialist vs. GP provider type at the time of initiation. For the stratified analyses, comparisons between the two cohorts were conducted using Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

A total of 2683 patients were included in the final analytic sample, with 1879 patients (70%) in the specialist cohort and 804 patients (30%) in the GP cohort (Fig. 1).

For the overall population, the mean age at index was 50 years and 67% were male (Table 1). At the last annual health check-up prior to initiating injectable antidiabetic medication, among patients with available data (see

Table 1 Patient baseline characteristics

	Index medication setting			
	Overall (*n* = 2683)	**Specialist (*n* = 1879)**	**GP (*n* = 804)**	***P* value**
Demographics				
Age on the index date				
Mean (SD)	50.0 (10.4)	50.4 (10.8)	49.1 (9.6)	0.0012*
Gender (male), *n* (%)	1799 (67.1%)	1227 (65.3%)	572 (71.1%)	0.0032*
Index medication category, *n* (%)				< 0.0001*
Basal insulin only (not mixed)	774 (28.8%)	349 (18.6%)	425 (52.9%)	
Rapid insulin only	779 (29.0%)	701 (37.3%)	78 (9.7%)	
Basal and rapid insulin	549 (20.5%)	488 (26.0%)	61 (7.6%)	
Pre-mixed insulin only	192 (7.2%)	108 (5.7%)	84 (10.4%)	
GLP-1 receptor agonists only	351 (13.1%)	202 (10.8%)	149 (18.5%)	
Multiple index medications (excluding basal and rapid insulin)	38 (1.4%)	31 (1.6%)	7 (0.9%)	
Index medication route of administration, *n* (%)				< 0.0001*
Pen only	2126 (79.2%)	1330 (70.8%)	796 (99.0%)	
Vial only	322 (12.0%)	315 (16.8%)	7 (0.9%)	
Both pen and vial	235 (8.8%)	234 (12.5%)	1 (0.1%)	
CCI, mean (SD)	1.6 (2.2)	1.9 (2.4)	1.0 (1.4)	< 0.0001*
T2DM-related complications and comorbidities, *n* (%)				
Microvascular conditions				
Retinopathy	17 (0.6%)	13 (0.7%)	4 (0.5%)	0.5611
Neuropathy/diabetic foot	8 (0.3%)	8 (0.4%)	0 (0.0%)	0.1150
Nephropathy	158 (5.9%)	126 (6.7%)	32 (4.0%)	0.0060*
Macrovascular conditions				
Cardiovascular disease	385 (14.3%)	310 (16.5%)	75 (9.3%)	< 0.0001*
Congestive heart failure	261 (9.7%)	226 (12.0%)	35 (4.4%)	< 0.0001*
Peripheral vascular disease	282 (10.5%)	212 (11.3%)	70 (8.7%)	0.0462*
Stroke	201 (7.5%)	155 (8.2%)	46 (5.7%)	0.0227*
T2DM-related comorbidities				
Hypertension	1092 (40.7%)	763 (40.6%)	329 (40.9%)	0.8796
Dyslipidemia	1274 (47.5%)	845 (45.0%)	429 (53.4%)	< 0.0001*
Severe hypoglycemic event	55 (2.0%)	47 (2.5%)	8 (1.0%)	0.0117*

Table 1 continued

	Index medication setting			
	Overall (*n* = 2683)	**Specialist (*n* = 1879)**	**GP (*n* = 804)**	***P* value**
HbA1c levels (%), *n* (%)	1273 (47.4%)	840 (44.7%)	433 (53.9%)	
Mean (SD)	8.9 (2.3)	8.8 (2.3)	9.1 (2.2)	0.0165*
Systolic blood pressure (mmHg), *n* (%)	1446 (53.9%)	960 (51.1%)	486 (60.4%)	
Mean (SD)	130 (18.0)	131 (18.5)	127 (16.8)	0.0003*
Diastolic blood pressure (mmHg), *n* (%)	1446 (53.9%)	960 (51.1%)	486 (60.4%)	
Mean (SD)	80 (11.7)	81 (12.0)	79 (10.9)	0.0016*
Fasting blood sugar levels (mg/dl), *n* (%)	1158 (43.2%)	766 (40.8%)	392 (48.8%)	
Mean (SD)	187 (72.3)	183 (70.9)	194 (74.4)	0.0052*
BMI (kg/m^2), *n* (%)	1447 (53.9%)	961 (51.1%)	486 (60.4%)	
Mean (SD)	26.7 (5.6)	27 (5.8)	27 (5.3)	0.6930

SD standard deviation, *GLP-1* glucagon-like peptide-1, *CCI* Charlson comorbidity index, *T2DM* type 2 diabetes mellitus, *HbA1c* hemoglobin A1c, *BMI* body mass index

*Statistically significant at $p < 0.05$; *p* values estimated using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables

Table 1), the mean HbA1c level was 8.9%, the mean BMI was 27 kg/m^2, and the mean fasting blood sugar level was 187 mg/dl. In terms of the type of index medications, 29% of patients used basal insulin only, 29% rapid insulin only, and 21% basal-bolus treatment (both basal and rapid insulin). Thirteen percent of patients used only GLP-1 receptor agonists as their index medication.

There were several differences in patient characteristics between the specialist and GP cohorts (Table 1). On average, patients in the specialist cohort were slightly older (50 vs. 49 years, $p = 0.0012$) and had a higher comorbidity burden compared with patients in the GP cohort as measured by the CCI, specific microvascular and macrovascular conditions, and other T2DM-related comorbidities. However, at the last annual health check-up prior to injectable initiation, among patients with available data, those in the specialist cohort had slightly, yet statistically significantly lower baseline HbA1c (8.8% vs. 9.1%, $p = 0.0165$) and fasting blood glucose (183 vs. 194 mg/dl, $p = 0.0052$) as well as higher systolic blood pressure (131 vs. 127 mmHg; $p = 0.0003$) and diastolic blood pressure (81 vs. 79 mmHg; $p = 0.0016$), compared with the GP cohort (Table 1). Patients in the specialist cohort were more likely to receive rapid insulin (37%) or basal-bolus treatment (26%) compared with basal insulin only (19%), whereas patients in the GP cohort were more likely to receive basal insulin only (53%) or GLP-1 receptor agonists only (19%).

Medication Use

Baseline Period

During the 6-month baseline period, 39% of the overall cohort did not use any antidiabetic medication, 52% used monotherapy, and 9% used combination therapy (Fig. 2a). Nearly half (54%) of the patients received their most recent prescription for a non-injectable antidiabetic from a GP; only 6% received it from specialists (Table 2). The most commonly used classes of oral antidiabetic medications were dipeptidyl-

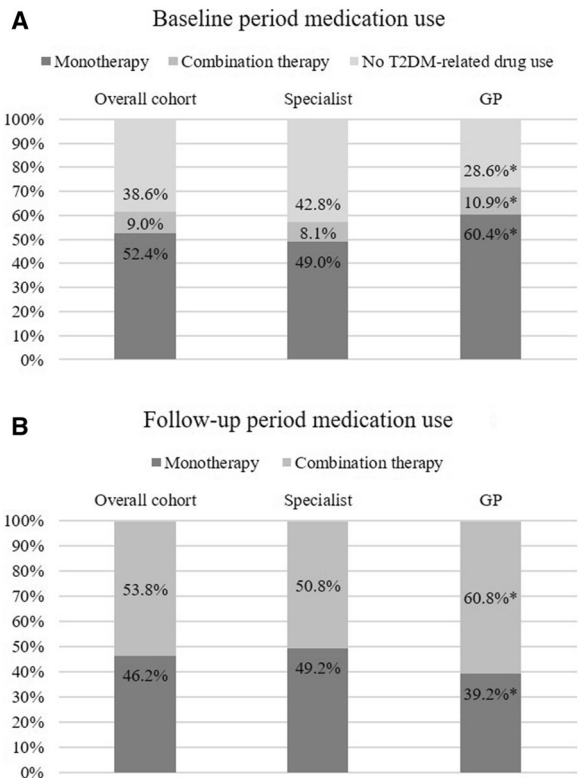

Fig. 2 T2DM-related medication use by cohort. *T2DM* type 2 diabetes mellitus, *GP* general practitioner. *Significant difference between the specialist and GP cohorts, as determined by $p < 0.05$. **a** Baseline period medication use. **b** Follow-up period medication use

peptidase-4 (DPP-4) inhibitors (46%), sulfonylureas (42%), and biguanides (36%). Approximately half of the overall cohort also used medications for select T2DM-related complications and comorbidities. These T2DM-related medications were most commonly (94%) prescribed by the same provider as that for antidiabetic medications (primarily GPs; Table 2).

When evaluating the medication use by index medication setting, patients in the specialist cohort were less likely to have oral antidiabetic use during the 6-month baseline period compared with patients from the GP cohort (57% vs. 70%, $p < 0.0001$) and were generally less likely to have used the various classes of antidiabetic medications (Table 2). Additionally, only 9% of patients who initiated injectable medication with a specialist had received their most recent oral medication during the baseline period from a specialist. Furthermore, patients in the specialist cohort were less likely to have used statins during the baseline (26% vs. 33%, $p < 0.0001$), but had similar rates of use of antihypertensives and antiplatelet agents as the patients from the GP cohort (Table 2). In addition, for patients in the specialist cohort, the most recent medications for T2DM-related comorbidities prior to injectable initiation were generally prescribed by the same provider as those prescribing oral antidiabetic agents (i.e., GPs), suggesting that multiple physicians may be involved in the treatment decisions at initiation of injectable medications (Table 2).

Follow-up Period

On average, patients in the overall cohort used their index medication for 214 days (as approximated by the medication's days of supply) during the 12-month follow-up period and just over half used a combination therapy of antidiabetics (including their index injectable antidiabetic) (Fig. 2b). Nearly 70% of patients received their most recent prescription for an oral antidiabetic from a GP, although 70% initiated the first injectable therapy with a specialist. As in the baseline period, the most frequently used oral agents during the follow-up period were DPP-4 inhibitors (55%), biguanides (49%), and sulfonylureas (41%). Approximately 66% of patients had medication for T2DM-related comorbidities. Most patients (94%) had their most recent antidiabetic medication and medication for T2DM-related comorbidities prescribed by the same provider (Table 3).

Patients in the specialist cohort were more likely to have monotherapy during the 12-month follow-up period compared with patients in the GP cohort (49% vs. 39%, $p < 0.0001$) (Fig. 2b). Additionally, patients in the specialist cohort were significantly less likely to use certain types of oral antidiabetic medications, such as sulfonylureas, biguanides, antidiabetic combinations, and SGLT2 inhibitors, than patients from the GP cohort (Table 3). Furthermore, while on average patients used their index injectable medications for nearly 7 months, the mean duration of use was shorter

Table 2 Baseline period medication use

	Index medication setting			
	Overall (*n* = 2683)	**Specialist (*n* = 1879)**	**GP (*n* = 804)**	***P* value**
T2DM-related drug use, *n* (%)				
Use of antidiabetic medications, overall and by class				
Oral antidiabetic medications				
Any oral antidiabetic medications	1626 (60.6%)	1064 (56.6%)	562 (69.9%)	< 0.0001*
DPP-4 inhibitors	1228 (45.8%)	787 (41.9%)	441 (54.9%)	< 0.0001*
Sulfonylureas	1137 (42.4%)	712 (37.9%)	425 (52.9%)	< 0.0001*
Biguanides	968 (36.1%)	608 (32.4%)	360 (44.8%)	< 0.0001*
Alpha-glucosidase inhibitors	516 (19.2%)	334 (17.8%)	182 (22.6%)	0.0034*
Thiazolidinediones	412 (15.4%)	262 (13.9%)	150 (18.7%)	0.0019*
Meglitinides	114 (4.2%)	84 (4.5%)	30 (3.7%)	0.3846
Antidiabetic combinations	98 (3.7%)	50 (2.7%)	48 (6.0%)	< 0.0001*
SGLT2 inhibitors	10 (0.4%)	7 (0.4%)	3 (0.4%)	1.0000
Setting for most recent use of antidiabetic medications				
Type of provider prescribing oral antidiabetic medication				
Hospital only	169 (6.3%)	166 (8.8%)	3 (0.4%)	< 0.0001*
Clinic only	1442 (53.7%)	883 (47.0%)	559 (69.5%)	< 0.0001*
Multiple	5 (0.6%)	15 (0.8%)	0 (0.0%)	0.0082*
Drug use related to other select complications and comorbid conditions, *n* (%)				
Any drug use	1304 (48.6%)	881 (46.9%)	423 (52.6%)	0.0066*
Antihypertensives	988 (36.8%)	691 (36.8%)	297 (36.9%)	0.9351
Antiplatelet agents	290 (10.8%)	213 (11.3%)	77 (9.6%)	0.1789
Statins	747 (27.8%)	480 (25.5%)	267 (33.2%)	< 0.0001*
Patients with the same provider for medications[a], *n* (%)				
Patients with medications for T2DM-related comorbidities and oral antidiabetics	1111 (41.4%)	729 (38.8%)	382 (47.5%)	< 0.0001*
Patients with the same provider	1042 (93.8%)	677 (92.9%)	365 (95.5%)	< 0.0001*

DPP-4 dipeptidyl peptidase-4, *SGLT2* sodium-glucose co-transporter 2, *T2DM* type 2 diabetes mellitus

*Statistically significant at $p < 0.05$; *p* values estimated using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables

[a] The most recent medication prescriptions observed during the baseline period were used

Table 3 Follow-up period medication use

	Index medication setting			
	Overall (*N* = 2683)	**Specialist (*N* = 1879)**	**GP (*N* = 804)**	***P* value**
Days of index medication use during the follow-up period, mean (SD)	214 (104)	195 (104)	260 (89)	< 0.0001*
T2DM-related drug use, *n* (%)				
Use of antidiabetic medications, overall and by class				
Oral antidiabetic medications				
Any oral antidiabetic medications	2197 (81.9%)	1504 (80.0%)	693 (86.2%)	0.0002*
DPP-4 inhibitors	1466 (54.6%)	1008 (53.6%)	458 (57.0%)	0.1136
Sulfonylureas	1093 (40.7%)	689 (36.7%)	404 (50.2%)	< 0.0001*
Biguanides	1321 (49.2%)	895 (47.6%)	426 (53.0%)	0.0111*
Alpha-glucosidase inhibitors	673 (25.1%)	455 (24.2%)	218 (27.1%)	0.1125
Thiazolidinediones	377 (14.1%)	252 (13.4%)	125 (15.5%)	0.1447
Meglitinides	278 (10.4%)	210 (11.2%)	68 (8.5%)	0.0343*
Antidiabetic combinations	95 (3.5%)	43 (2.3%)	52 (6.5%)	< 0.0001*
SGLT2 inhibitors	43 (1.6%)	23 (1.2%)	20 (2.5%)	0.0170*
Any non-index injectable antidiabetic medications				
Basal insulin (not mixed)	366 (13.6%)	299 (15.9%)	67 (8.3%)	< 0.0001*
Rapid insulin	403 (15.0%)	324 (17.2%)	79 (9.8%)	< 0.0001*
Pre-mixed insulin	119 (4.4%)	95 (5.1%)	24 (3.0%)	0.0170*
GLP-1 receptor agonists	95 (3.5%)	74 (3.9%)	21 (2.6%)	0.0886
Setting for most recent use of antidiabetic medications				
Type of provider prescribing injectable antidiabetic medication				
Hospital only	667 (24.9%)	653 (34.8%)	14 (1.7%)	< 0.0001*
Clinic only	1981 (73.8%)	1194 (63.5%)	787 (97.9%)	< 0.0001*
Multiple	35 (1.3%)	32 (1.7%)	3 (0.4%)	0.0054*
Type of provider prescribing oral antidiabetic medication				
Hospital only	359 (13.4%)	355 (18.9%)	4 (0.5%)	< 0.0001*
Clinic only	1812 (67.5%)	1125 (59.9%)	687 (85.4%)	< 0.0001*
Multiple	26 (1.0%)	24 (1.3%)	2 (0.2%)	0.0127*
Drug use related to other select complications and comorbid conditions, *n* (%)				
Any drug use	1766 (65.8%)	1256 (66.8%)	510 (63.4%)	0.0879
Antihypertensives	1375 (51.2%)	1009 (53.7%)	366 (45.5%)	0.0001*

Table 3 continued

	Index medication setting			
	Overall (*N* = 2683)	**Specialist (*N* = 1879)**	**GP (*N* = 804)**	***P* value**
Antiplatelet agents	423 (15.8%)	334 (17.8%)	89 (11.1%)	< 0.000*
Statins	1011 (37.7%)	700 (37.3%)	311 (38.7%)	0.4845
Patients with the same provider for medications[a], *n* (%)				
Patients with medications for T2DM-related comorbidities and any antidiabetics	1725 (64.3%)	1221 (65.0%)	504 (62.7%)	0.2557
Patients with the same provider	1621 (94.0%)	1140 (93.4%)	481 (95.4%)	0.6819
Patients with medications for T2DM-related comorbidities and injectable antidiabetics	1698 (63.3%)	1197 (63.7%)	501 (62.3%)	0.4936
Patients with the same provider	1499 (88.3%)	1028 (85.9%)	471 (94.0%)	0.0642
Patients with medications for T2DM-related comorbidities and oral antidiabetics	1438 (53.6%)	995 (53.0%)	443 (55.1%)	0.3073
Patients with the same provider	1344 (93.5%)	919 (92.4%)	425 (95.9%)	0.0607

DPP-4 dipeptidyl peptidase-4, *SGLT2* sodium-glucose co-transporter 2, *GLP-1* glucagon-like peptide-1, *T2DM* type 2 diabetes mellitus

*Statistically significant at $p < 0.05$; p values estimated using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables

[a] The most recent medication prescriptions observed during the follow-up period were used

for the specialist cohort than for the GP cohort (195 vs. 260 days). Despite initiating an injectable antidiabetic medication with a specialist, 64% of patients in the specialist cohort received their most recent injectable antidiabetic medication from a GP. Additionally, most patients in the specialist cohort received their most recent antidiabetic medications and other T2DM-related medications from the same provider (Table 3).

Healthcare Resource Use and Costs

Baseline Period

Overall, 12% of patients had an inpatient visit during the 6-month baseline period. A significantly higher proportion of the specialist cohort had an inpatient visit than the GP cohort (15% vs. 3%, $p < 0.0001$) during the baseline period (Fig. 3a), and the average number of inpatient days for patients with at least one visit was also higher (23 vs. 7, $p = 0.0023$). Nearly 90% of all patients had at least one outpatient visit during the 6-month baseline period; the mean number of outpatient visits was 7.

Overall, the average healthcare costs were ¥350,404 during the baseline period, 75% of which were attributable to T2DM (Fig. 3b). The average total and medical costs were significantly greater for patients in the specialist vs. the GP cohort (total costs: ¥418,894 vs. ¥190,338; medical costs: ¥352,022 vs. ¥121,545; all $p < 0.05$); this difference was mainly driven by some extreme medical costs observed for the specialist cohort. However, the difference in average pharmacy costs between the two cohorts was small (¥66,873 vs. ¥68,792, $p = 0.0007$).

Most of the observed resource use and costs were attributable to T2DM (Fig. 3a, c).

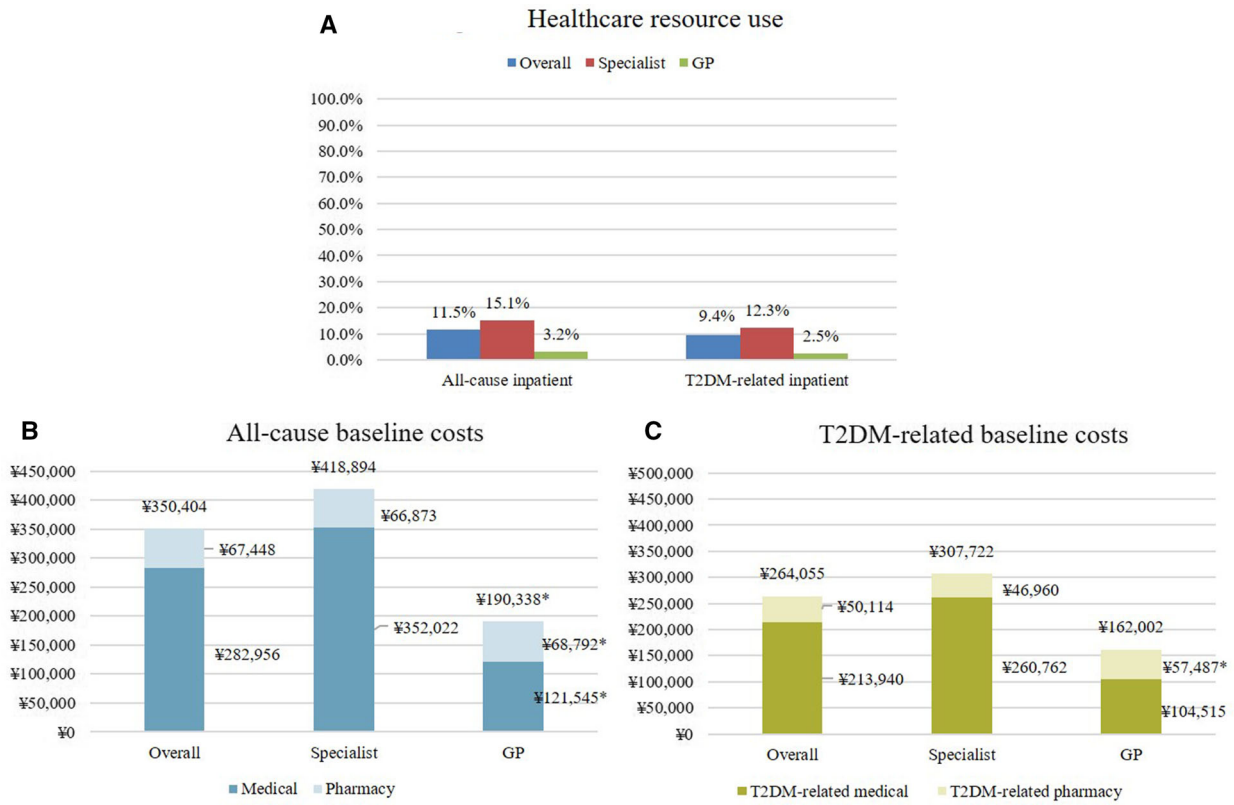

Fig. 3 Baseline period healthcare resource use and costs by cohort. *T2DM* type 2 diabetes mellitus, *GP* general practitioner. *Significant difference between the specialist and GP cohorts, as determined by $p < 0.05$. **a** Healthcare resource use. **b** All-cause healthcare costs. **c** T2DM-related healthcare costs

Follow-up Period

During the 12-month follow-up period, 55% of the overall cohort had at least one inpatient visit, and almost all patients had at least one outpatient visit (Fig. 4a). The average number of outpatient visits in the overall cohort for patients with at least one visit was 16. The average healthcare costs were ¥1,856,727 during the follow-up period (Fig. 4b).

The stratified analyses showed that a significantly greater proportion of patients treated by specialists had an inpatient visit (73% vs. 12%, $p < 0.0001$) during the follow-up period compared with the GP cohort (Fig. 4a), and this difference remained significant when the index month was excluded (51% vs. 12%, $p < 0.0001$). The average number of inpatient days for patients with at least one visit was also significantly higher for patients in the specialist cohort (41 vs. 16 days, $p < 0.0001$).

The average total and medical costs during the 12-month follow-up period were significantly higher for patients in the specialist cohort vs. GP provider cohort (total costs: ¥2,344,988 vs. ¥715,628; medical costs: ¥2,117,343 vs. ¥503,204; all $p < 0.0001$; pharmacy costs: ¥227,645 vs. ¥212,424, $p = 0.0131$) (Fig. 4b).

Most of the resource use and costs during the follow-up period were attributable to T2DM for all cohorts (Fig. 4a, c).

DISCUSSION

In this claims database study of T2DM patients initiating injectable antidiabetic medications in Japan, most (70%) of the patients initiating an injectable antidiabetic medication did so under specialist care as opposed to GP. Independent of

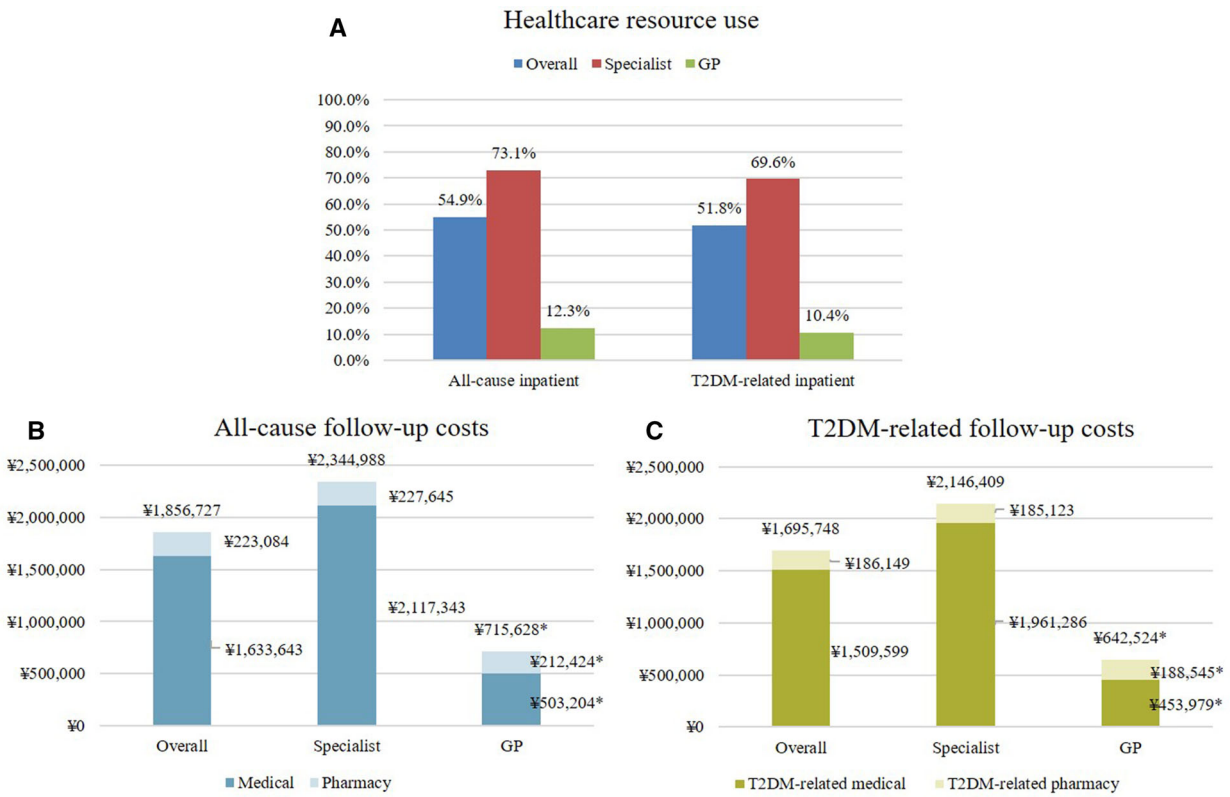

Fig. 4 Follow-up period healthcare resource use and costs by cohort. *T2DM* type 2 diabetes mellitus, *GP* general practitioner. *Significant difference between the specialist and GP cohorts, as determined by $p < 0.05$. **a** Healthcare resource use. **b** All-cause healthcare costs. **c** T2DM-related healthcare costs

the provider type, a large proportion of patients (almost 40%) did not use any antidiabetic medication in the 6-month period prior to initiating injectable medications, suggesting that in Japan, a substantial proportion of patients initiate injectable medications as the first-line treatment. These findings are similar to those reported by Kohro et al. [11] using the same database as the present study. Specifically, in their study of first-line antidiabetic medications, the authors found that nearly 20% of all T2DM patients initiated insulin as the first antidiabetic medication. The proportions were even higher among those treated in academic hospitals vs. clinics (~ 40% vs. ~ 10% in 2011) [11]. Despite the relatively young age (50 years on average), the population had high average HbA1c (8.9%) and fasting glucose levels as well as high rates of T2DM-related comorbidities and complications before initiating injectable medications; this suggests that the high disease burden prior to treatment initiation may have triggered a more intensified treatment approach, such as short-term intensive insulin therapy [18]. Indeed, in the DAWN Japan study, the physicians reported that they would consider initiating insulin at HbA1c levels ≥ 8.7%, and patients reported that insulin was recommended when average HbA1c levels were ≥ 9.6% [19].

In the current study, the average HbA1c levels at the last annual health check-up before the start of injectable antidiabetic medication were slightly higher for those treated by the GPs (9.1% GP vs. 8.8% specialist), suggesting that the GPs may use less intensive approaches to managing T2DM. In this study, patients treated by specialists were more likely to receive intensified treatment regimens involving rapid insulin only (37% vs. 10%) or basal-bolus treatment (26% vs. 8%) and less likely to receive basal insulin only (19% vs. 53%) compared with

those treated by GPs. Additionally, over half of the patients used a combination of antidiabetic medications, including additional oral antidiabetic medications, during the follow-up period. These results are consistent with previous studies in Japan as well as other countries and highlight the considerable variation in physician practice patterns. For example, Ikeda et al. [8] studied Japanese patients with T2DM who initiated insulin therapy in a hospital setting and also concluded that only 11% of the patients were treated with long-acting insulin and that treatment with rapid insulin was the most common therapy (47% of initiators). Additionally, patients treated with more intensified treatments, including with rapid insulin, also tended to be older, have lower HbA1c, and experience more comorbid conditions. A survey of patients treated by general practitioners and diabetes specialists in Japan and a different study using the same database as the present study also found a similar pattern [11, 12]. Such findings could be attributed to the fact that GPs in Japan often have limited resources to facilitate initiation of injectable antidiabetic regimens. For example, in the aforementioned DAWN Japan study, nearly 55% of the non-specialist clinicians reported that "[they] do not have staff (nurse, pharmacists) who can assist with explanations" and that "[it] is difficult to provide guidance and education on insulin injection to patients" compared with 1% and 7% of the specialists reporting the same concerns [19]. With the limited number of diabetes specialists in Japan (4760 as of August 2013) [20], providing adequate education and support systems to the GPs may help improve the management of T2DM patients.

Regarding the outcomes after injectable initiation, we find that patients continued treatment with the index medication for approximately 7 months, independent of the setting in which the treatment was initiated. These findings are consistent with previous research that demonstrated that the probability of discontinuing basal insulin treatment within the first year after initiation in Japan was low (22%) [9]. Despite this, the patients in our sample had considerable resource use and costs in the year after treatment initiation, a finding also consistent with the previously mentioned study by Hadjiyianni et al. [9]. In particular, 55% of all patients had at least one hospitalization in the year after injectable initiation; the average all-cause costs during the 12-month follow-up period were ¥1856,727, approximately 90% of which were attributable to T2DM and related complications and comorbidities. The economic burden was even higher among those initiating the injectable medication with a specialist. Specifically, nearly three-quarters (73%) of the patients in the specialist cohort had an inpatient visit during the 12-month follow-up period compared with 12% in the GP cohort, and among those with an inpatient visit, the average number of inpatient days was significantly higher for patients in the specialist cohort. Consequently, patients in the specialist cohort had higher medical costs relative to those in the GP cohort. However, differences in pharmacy costs across the two cohorts were small. Taken together, our findings suggest that the considerable increase in the proportion of patients with an inpatient visit during the follow-up period was the major driver of the cost increase for patients in the specialist cohort. It is possible that the higher rates of hospital visits are related to continued care management in a hospital setting because of the complexity of the treatment and higher comorbidity burden in the specialist cohort. However, our findings indicate that independent of the index medication setting, after initiating the injectable medication, routine follow-up care may transition to a clinic setting. Specifically, 64% of patients who initiated injectable medications in a hospital setting received their most recent injectable medication during the follow-up period in a clinic setting. Most patients also received their oral medications as well as medications for T2DM-related complications and comorbidities from the same providers, suggesting that use of hospitals and both specialist and GPs for maintenance treatment of T2DM and related conditions is limited. Given this observation, an alternative explanation for the higher observed costs could be related to differences in practice patterns by provider specialty and/or other, unobserved patient characteristics. While this was not studied

directly in the present study, Chin et al. [21] studied the differences in resource utilization among older patients with diabetes in the US who were cared for by endocrinologists, internists, family practitioners, and general practitioners and concluded that patients treated by specialists (endocrinologists and internists) had higher utilization of diabetes-specific process-of-care measures and received a more costly style of care than patients treated by family practitioners and general practitioners. Additional research is warranted to understand how hospital- and clinic-based physicians communicate treatment strategies for T2DM and T2DM-related complications/comorbidities, including who makes the decisions to augment or switch treatments as patients' conditions progress over time and whether patients are referred to specialists in a timely fashion for initiating more complicated treatment regimens.

To the best of our knowledge, this is the first study to provide a comprehensive assessment of the characteristics and outcomes among patients with T2DM initiating their first injectable medication with or without prior oral antidiabetic treatment in Japan, both before and after treatment initiation, using real-world health insurance data. Additionally, the study provides important insight into the characteristics and outcomes of patients treated by specialists (i.e., in a hospital inpatient or outpatient setting) compared with those treated by general practitioners in Japan, which could help inform future policy decisions regarding the coordination of care between different types of providers. This study particularly benefits from the large sample size of the JMDC claims database as well as from the availability of laboratory measures from annual health check-ups. Another advantage of the JMDC database is that it contains a classification of the medical facilities associated with each claim, which aided in the construction of the two study cohorts to approximate provider specialty. However, this analysis was subject to limitations associated with any inaccuracies or incompleteness of the ICD-10 codes and ATC codes used to identify diagnoses and medication use as well as lack of clinical information (e.g., to assess blood glucose control). Relatedly, while the methods used to identify patients with T2DM are consistent with prior studies using the same database, the effect of alternative criteria for identifying T2DM patients on the study findings is not known [3]. In addition, HIV/AIDS information was not available in JMDC, so the CCI may not be precise. Similarly, the specialty of the treating physician was not directly observed in the data, and the proxy used to approximate this attribute may not accurately represent care provided by specialists in hospitals with < 20 beds or by GPs in large hospitals. The JMDC data on laboratory test results were limited to tests performed as a part of the regular annual check-ups for beneficiaries aged at least 40 years and did not include information from tests performed for other reasons (e.g., while in the hospital). Further, the results were limited to tests performed at special facilities performing health check-ups or hospital/clinics recommended by the beneficiaries' insurance provider for their routine annual check-up. Furthermore, findings are limited to people aged under 75 years who have employer-sponsored insurance in Japan and may not generalize to other populations (e.g., may not be representative of patients covered by other insurance programs) as the JMDC database is not representative of the national population in Japan.

CONCLUSIONS

The study findings indicate that in Japan patients with T2DM are more likely to initiate medications with specialists as opposed to GPs. Patients initiating injectable medications with specialists are older and have greater disease severity prior to treatment initiation, but are less likely to be using oral antidiabetic medications in the 6 months prior to initiating injectable medications than patients initiating injectable medications with GPs. Additionally, patients initiating injectable medications with specialists are more likely to receive intensive treatment with rapid insulin or basal-bolus therapy on their index date than those initiating treatment in a clinic setting and are more

likely to have inpatient visits and higher healthcare costs both before and after treatment initiation. However, the majority of patients initiating injectable antidiabetic medications with specialists receive subsequent injectable medication during the follow-up period from the GPs, suggesting that GPs are responsible for maintenance care as opposed to the prescribing specialists. Further research is needed to understand the reasons behind the prescribing patterns and subsequent outcomes among T2DM patients in Japan, as well as to better understand the communication channels between GPs and specialists regarding patients' treatments over time.

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Compliance with Ethics Guidelines. This article is based on previously collected data and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The data used for the current study are not publicly available because they were provided by Japan Medical Data Center (JMDC) to Analysis Group, Inc., and the data license agreement does not permit sharing of data sets with people external to the study team. Interested readers may request the data directly from JMDC.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 7th Edn [Internet]; 2015 [cited 2017 July 27].: http://www.diabetesatlas.org/across-the-globe.html.

2. National Health Expenditure 2014 [Internet]. Ministry of Health, Labour and Welfare; 2014 [cited Aug 9]. http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/14/dl/toukei.pdf.

3. Fukuda H, Ikeda S, Shiroiwa T, Fukuda T. The effects of diagnostic definitions in claims data on healthcare cost estimates: evidence from a large-scale panel data analysis of diabetes care in Japan. Pharmacoeconomics. 2016;34(10):1005–14.

4. Japan Diabetes Society. Treatment guide for diabetes 2014–2015 [Internet]; pp. 15–17. [cited 2016 Sept 30]. http://www.jds.or.jp/modules/en/index.php?content_id=1.

5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. position statement of the american diabetes association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35:1364–79.

6. Charvat H, Goto A, Goto M, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. J Diabetes Investig. 2015;6(5):533–42.

7. Central Social Insurance Medical Council. General assembly 346, function of general practitioner [Internet].2017. [cited 2017 Aug 9]. http://www.mhlw.go.jp/stf/shingi2/0000152389.html.

8. Ikeda S, Crawford B, Sato M. Utilization patterns of insulin therapy and healthcare services among Japanese insulin initiators during their first year: a descriptive analysis of administrative hospital data. BMC Health Serv Res. 2016;16(1):6.

9. Hadjiyianni I, Desai U, Suzuki S, et al. Basal insulin persistence, associated factors, and outcomes after treatment initiation: a retrospective database study among people with type 2 diabetes mellitus in Japan. Diabetes Ther. 2017;8(1):149–66.

10. Hidaka H, Tokumoto K, Hori Y, Homma S, Inoue C. Prescription and quality of diabetes care provided by specialists and general physicians in Japan -an analysis of insurance claim and health checkup data. J Japan Diab Soc. 2014;57(10):774–82.

11. Kohro T, Yamazaki T, Sato H, et al. Trends in antidiabetic prescription patterns in Japan from 2005 to 2011. Int Heart J. 2013;54(2):93–7.

12. Arai K, Takai M, Hirao K, et al. Present status of insulin therapy for type 2 diabetes treated by general practitioners and diabetes specialists in Japan: third report of a cross-sectional survey of 15,652 patients. J Diabetes Investig. 2012;3(4):396–401.

13. Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J Epidemiol. 2010;20(5):413–9.

14. Japan Medical Data Center. http://www.jmdc.co.jp/.

15. International Health Care System Profiles. The Japanese Health Care System [Internet]. The Commonwealth Fund [cited 2017 Dec 11]. http://international.commonwealthfund.org/countries/japan/.

16. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–9.

17. Statistics Bureau, Ministry of Internal Affairs and Communications. Consumer price index [Internet]. Statistics Japan [cited 2016 Sept 30]. http://www.stat.go.jp/english/data/cpi/index.htm.

18. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care. 2004;27(9):2282–3.

19. Ishii H, Iwamoto Y, Tajima N. An exploration of barriers to insulin initiation for physicians in Japan: findings from the Diabetes Attitudes, Wishes and Needs (DAWN) Japan study. PLoS ONE. 2012;7(6):e36361.

20. Present number of medical specialists [Internet]. Japanese Board of Medical Specialties. [cited 2017 Aug 9]. Available from: http://www.japan-senmon-i.jp/hyouka-nintei/data/.

21. Chin MH, Zhang JX, Merrell K. Specialty differences in the care of older patients with diabetes. Med Care. 2000;38(2):131–40.