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Fixed-Dose Combination Antidiabetic Therapy: Real-World Factors Associated with Prescribing Choices and Relationship with Patient Satisfaction and Compliance

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ABSTRACT

Introduction: Compliance with antidiabetic therapy has the potential to impact on the risk for complications by an effect on glycemic control. Fixed-dose combinations (FDCs) offer a simplified dosing regimen that may improve patient compliance. We undertook a retrospective database analysis to understand the real-world association between FDCs, treatment practices, glycated hemoglobin (HbA\textsubscript{1c}) levels, and patient perspectives in type 2 diabetes. Methods: Data were drawn from the Adelphi Diabetes Disease Specific Programme (DSP), a multicenter, patient record-based market research study of primary care physicians and diabetologists/endocrinologists in Europe. The study is based on physician interviews, completion of detailed patient record forms by physicians, and a self-completion questionnaire by patients. Regression analyses were used to identify factors associated with (1) physician-reported dipeptidyl peptidase-4 inhibitor (DPP-4)/metformin FDC prescribing in dual or triple therapy regimens; (2) HbA\textsubscript{1c} of patients prescribed a DPP-4 FDC alone versus free-form DPP-4 plus metformin dual therapy regimens; and (3) differences between patients prescribed any oral antidiabetic therapy (OAD) FDC therapy (alone or in combination with one other OAD) versus those prescribed dual or triple OAD free-form combination therapy. Results: Physician-reported data were available for 5891 patients (mean age 61.5 years, 43% female, mean duration since diagnosis 5.7 years). Factors associated with DPP-4 FDC usage included physicians’ reason for choice being “improves patient compliance.” The relative mean % HbA\textsubscript{1c} level associated with being on a DPP-4 FDC rather than free-form independent of the physician perception of patient compliance was 0.25 lower (CI –0.40 to –0.09). When physician-perceived patient compliance was described as “fairly compliant” rather than “poorly compliant”
or "not at all compliant," the relative mean % HbA1c level was 0.42 lower (CI –0.67 to –0.18). Similarly, being perceived as "fully compliant" rather than "fairly compliant" was associated with a relative mean % HbA1c level that was 0.17 lower (CI –0.31 to –0.02). A significant predictor for the current regimen being any FDC (alone or in combination with one other OAD) regimen was patients' satisfaction with treatment (odds ratio 1.32; 95% CI 1.10 to 1.58; \( P = 0.003 \)).

**Conclusions:** These results suggest that DPP-4 FDC prescribing is considered to be a positive prescribing choice to improve compliance and that choice is associated with improved glycemic control. From the patient’s perspective, the decision to prescribe an FDC is associated with improved satisfaction with treatment.

**Keywords:** compliance; dipeptidyl peptidase-4 inhibitors; real-world; satisfaction; simplified dosage regimen; type 2 diabetes

**INTRODUCTION**

There are currently more than 346 million individuals worldwide living with a diagnosis of diabetes, 90% of whom are diagnosed with type 2 diabetes mellitus (T2D).\(^1\) By 2025 this figure is expected to have increased to 380 million individuals.\(^2\) In Europe, the prevalence of T2D continues to rise.\(^3\) Diabetes is a chronic, progressive disease that imposes a considerable physical, social, and emotional burden on individuals. It is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, and an increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease).\(^3,5\) Diabetes is also associated with a considerable economic burden, mainly due to the cost of managing long-term complications of the disease.\(^6,7\)

As there is currently no known cure for diabetes, management strategies aim to maintain good glycemic control and minimize the known risk factors for complications of the disease, including both microvascular and macrovascular complications.\(^8\) However, despite the availability of effective antidiabetic medications, many patients with T2D do not achieve recommended targets for glycemic control.\(^9-12\) For the majority of individuals this means an ongoing process of treatment intensification, alongside diet and exercise, in an effort to maintain glycemic control using oral antidiabetic medications (metformin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 [DPP-4] inhibitors) as monotherapy, dual or triple combination regimens, and eventually injectable glucagon-like peptide (GLP-1) agonists or insulin-replacement therapy.\(^8,11,14\)

One factor that has been proposed as a potential factor in the failure to reach and maintain clinical targets among patients with T2D is failure to comply with or adhere or concord to their prescribed antidiabetic regimen.\(^15-18\) Compliance has been defined as the extent to which a patient acts in accordance with the physician’s advice.\(^19\) The term adherence is often used synonymously with the term compliance and refers to the extent to which a patient acts in accordance with the recommendations agreed with the physician. Concordance implies the patient understands the recommendations.\(^19\) In the current analysis, the authors have studied compliance with medication as observed by the physician. Satisfaction with treatment may be associated with a patient’s willingness or capacity to adhere to their prescribed medication regimen.\(^20\) Indeed, recent guidelines recognize the need to take into account the willingness of patients to follow and engage positively with their prescribed medication.\(^21\)
Improved patient compliance has been associated with improved glycemic control.\textsuperscript{22} Thus steps to improve compliance may have long-term benefits for patients. Compliance with medication in chronic diseases such as diabetes is a complex, multifactorial issue, but the complexity of the medication regimen in terms of pill burden and dosing frequency may impact on a patient’s willingness to comply with their prescribed therapy. Moreover, simplification of the medication regimen is well established as a method to improve patient compliance.\textsuperscript{23} A retrospective cohort study among patients with T2D suggested that a single-tablet treatment regimen was associated with better adherence to antidiabetic therapy than one involving multiple tablets.\textsuperscript{24} Thus, regimen simplicity may be a relevant factor when considering the needs of individual patients. For patients requiring combination noninsulin antidiabetic therapy a number of fixed dose combinations (FDCs), including DPP-4 FDCs, are now available that are simpler than regimens that require the patient to take two or more pills several times each day. Real-world research is one method that can help us to understand and identify patients who might benefit most from these new regimens.

There is currently a paucity of data on the real-world impact of the new noninsulin antidiabetic FDCs in relation to patient satisfaction and compliance with therapy. Market research data, such as presented in this article, provides valuable insights into real-world current treatment practices outside the clinical trial setting and the perceived place of new medication regimens in the current noninsulin antidiabetic medication armamentarium. Specifically, the analyses presented here were carried out to better understand the association between FDCs and trends in treatment practices and achieved HbA\textsubscript{1c} levels in T2D, physician behavior, and patient behavior, both as observed by physicians and reported directly by patients. Understanding patient needs as determined by physicians and the patients themselves is of considerable value to physicians in selecting the most appropriate treatment for individual patients.

**MATERIALS AND METHODS**

**Study Design**

Data were drawn from the Adelphi Diabetes Disease Specific Programme (DSP),\textsuperscript{25} a large, multinational study that captures a cross-section of robust, real-world data. The DSP is a multi-sponsor survey, conducted under market research guidelines. These data accurately reflect current clinical practice regardless of current national or international clinical guidelines, current symptom prevalence and severity, and physician and patient perception of their health state and its impact on their daily and working life. It collects only information available to the physician/patient at the time of consultation.

The DSP is a patient record-based study of primary care physicians (PCPs) and diabetologists/endocrinologists in France, Germany, Italy, Spain, and the UK of >4000 patients. These physicians contributed to the study on a volunteer basis and received payment for their participation. This study was undertaken between October 1, 2009 and March 31, 2010 and is based on physician interviews, completion of detailed patient record forms by physicians, and a self-completion questionnaire by patients. The data collected using this method include subjective, objective, and clinical information about individual patients, their disease and their treatment. The DSP is not run to test any specific hypotheses, and it is not set up to demonstrate cause and effect (as a prospective longitudinal piece of research would).
The study was performed according to the European Pharmaceutical Market Research Association guidelines and in full accordance with the US Health Insurance Portability and Accountability Act 1996. While ethical approval is not obtained from local authorities, each patient provided consent for de-identified and aggregated reporting of research findings as required by the guidelines. The data are collected by local fieldwork partners and fully de-identified prior to receipt by Adelphi. The data collected in DSP are not audited externally for data quality.

**Physician Eligibility**

To be eligible to participate in the study, PCPs had to have been qualified for ≥2 years and for ≤33 years, to manage >6 patients each month at risk of developing T2D and to be managing >2 patients each month with a diagnosis of type 1 diabetes (T1D). In addition, they were required to manage >25 patients each month with a diagnosis of T2D who were prescribed noninsulin antidiabetic agents with or without insulin. Eligible diabetologists/endocrinologists had to have been qualified for ≥2 years and ≤33 years, to manage >10 patients with a diagnosis of T1D and ≥50 patients with T2D who were prescribed noninsulin antidiabetic agents with or without insulin.

**Patient Eligibility**

Each participating physician completed a detailed patient record form (PRF) for the next six (PCPs) or nine (diabetologists/endocrinologists) eligible patients. This sample is qualified as a “random sample” in this paper because the physicians providing the information had no control over which of the eligible patients in their care presented in their clinic during the data collection period. All responses were anonymized to preserve patient confidentiality.

Physicians provided information from patient records on patient demographics; diabetes history and diagnosis; comorbidities; type of tests performed (and any available results); blood glucose targets and monitoring; lifestyle involvement and engagement with disease; current treatments and reasons for choice; weight management; physician perception of patient compliance (as a single question describing the patient as either “not compliant at all,” “poorly compliant,” “fairly compliant,” or “fully compliant”); hypoglycemic episodes; and healthcare resource utilization including hospitalizations and physician consultations.

Physicians were also asked to invite all consecutive patients for whom they completed a PRF to complete a patient self-completion questionnaire (PSC). As stated above each patient provided consent for de-identified and aggregated reporting of research findings.

**Data Collection**

**Physician Interviews**

Following an initial screening call, physicians who agreed to participate in the study underwent a 1-hour face-to-face interview. During the interview, information was collected about concomitant conditions, lifestyle, and current drug treatment of the patients with diabetes under their care.

**PRFs (Physician Completed)**

Each participating physician completed a detailed PRF for the next six (PCPs) or nine (diabetologists/endocrinologists) eligible patients. This sample is qualified as a “random sample” in this paper because the physicians providing the information had no control over which of the eligible patients in their care presented in their clinic during the data collection period. All responses were anonymized to preserve patient confidentiality.

Physicians provided information from patient records on patient demographics; diabetes history and diagnosis; comorbidities; type of tests performed (and any available results); blood glucose targets and monitoring; lifestyle involvement and engagement with disease; current treatments and reasons for choice; weight management; physician perception of patient compliance (as a single question describing the patient as either “not compliant at all,” “poorly compliant,” “fairly compliant,” or “fully compliant”); hypoglycemic episodes; and healthcare resource utilization including hospitalizations and physician consultations.
All physicians were asked to provide up to three additional retrospective PRFs for patients receiving recently launched noninsulin antidiabetic agents (including, but not exclusively, DPP-4 agents). This was described as the “over-sample.” These patients were not required to be attending for consultation and were not requested to complete a PSC. The over-sample records were maintained separately from the prospectively collected random sample. The over-sample was utilized to improve our understanding of patients prescribed recently introduced antidiabetic agents, including FDCs, by securing additional retrospective records for these patients.

Patient PSC Questionnaire
Using the PSC, information was gathered from the patients’ perspective about their disease (blood sugar control, impact on lifestyle, and information sources), treatment and satisfaction with treatment (Diabetes Treatment Satisfaction Questionnaire [DTSQ]), hypoglycemic events, general health (Euro-QoL-5 Dimensions questionnaire), and the impact of the disease on their ability to work.

Physicians were asked to ensure that all patients from the “random sample” group were given the opportunity to complete the questionnaires in private and to provide patients with an envelope in which to place their completed form and to seal the envelope before returning it to the physician. All responses were anonymized to maintain patient confidentiality.

Study Population
As noted, DSP data are derived from physician- and patient-completed record forms. Not all physicians and patients answered all the questions on the PRF and PSC, respectively. Consequently, the respondent population size may differ for individual questions and thus for certain analyses. The population size (or base) is given for each individual analysis where appropriate and indicates the number of respondents (physician or patient) who provided responses relevant to that analysis.

Study Questions and Statistical Analyses
Three separate analyses were undertaken on three separate populations. Analysis 1 studied physician reported data on patients prescribed DPP-4-FDC or DPP-4 free-form therapy on dual or triple therapy regimens (n=696). Analysis 2 studied physician-reported data on patients prescribed dual DPP-4-FDC or DPP-4 free-form therapy on dual therapy regimens (n=533). Analysis 3 studied patient-reported data on patients prescribed any OAD FDC therapy either alone or in combination with one other OAD compared with those prescribed OAD free-form combination therapy (n=562).

Analysis 1. What are the Physician-Related Factors Associated with Prescription of a DPP-4 FDC versus DPP-4 Free-Form Therapy?
This question was addressed by using matched and combined data from the total patient sample (random sample + over-sample) drawing on information from the physician interview and the PRF. Responses were eligible for inclusion in this analysis if they related to patients receiving dual or triple (or more) agent therapy, without insulin, who were receiving a DPP-4 FDC or free-form combination (that was dose compatible with a DPP-4 FDC) for at least 12 weeks. This was the only stipulation for treatment duration (n=696). A logistic regression analysis was conducted to identify those factors associated with use of a DPP-4 FDC or not. The analysis included the following variables attitudinal responses to
questions relating to frequency of FDC use and their utility for patients with poor compliance with their prescribed antidiabetic medication regimen, physician satisfaction with blood glucose control, and perceived patient compliance, as well as patient characteristics including age, gender, body mass index (BMI), time since diagnosis, and current comorbidities.

Those variables that showed a significant association with DPP-4 FDC prescription were combined for a single regression analysis. Wald testing was used to evaluate the joint significance of a range of potential covariates. Insignificant variables were then removed from the regression model.

**Analysis 2. Is there an Association Between DPP-4 FDC Use, Perceived Level of Compliance, and HbA1c Level?**

The second research question used data from the total patient sample (random sample + over-sample) drawing on data recorded in the PRFs for patients receiving dual therapy only (n=533). Responses were eligible for inclusion in this analysis if they related to patients receiving dual therapy, without insulin, who were receiving a DPP-4 FDC or free-form combination therapy (that was dose compatible with a DPP-4 FDC) for at least 12 weeks. This analysis compared HbA1c levels at the last testing (last HbA1c test taken within the last 12 months) between patients prescribed a DPP-4 FDC for at least 12 weeks and those prescribed a dose-compatible DPP-4 free-form combination. An ordinary least squares (linear) regression analysis (OLS) was conducted using Wald testing to evaluate the joint significance of covariates. Insignificant variables were then removed from the regression. Covariates included patient age, gender, BMI, time since diagnosis, prescription of FDC or free-form therapy, patient compliance (physician perception), time spent on regimen (log transformed data). The exact timing of the HbA1c test in relation to the prescription of the DPP-4 FDC or DPP-4 free-form combination was not collected. Physicians completed one of three tick box responses (test conducted in the last 3 months, test conducted at some time in the period between 3 months and 6 months or test conducted in the last 6-12 months). However, the populations in the DPP-4 free form group and the population in the DPP-4 FDC group did not differ in their responses to the tick boxes. Therefore, while the information available relating to timing of the HbA1c test is a limitation of the current analyses, the limitation applies equally to both groups of patients.

**Analysis 3. Are There Differences Between Patients Prescribed any OAD FDC Therapy (Alone or in Combination with One Other OAD) Compared with Those Prescribed OAD Free-Form Combination Therapy**

This question was addressed by using data recorded in the PSCs and included patients from the random sample only (no PSCs were available for patients included in the over-sample). Consequently, the research question examined prescription of any OAD FDC (alone or in combination with one other OAD) versus OAD free-form combination prescribing as the cohort of patients who received DPP-4 agents and also provided a PSC was regarded as too small for meaningful comparisons to be made. Responses relating to patients receiving OADs alone who were not receiving insulin or other injectable antidiabetic agents were eligible for inclusion in this analysis.

Due to nature of the data, it was important to ensure the results were independent of age, gender, BMI, and the time since the patient was diagnosed with diabetes; therefore, a multivariate approach was used with these as confounding factors. Two sets of logistic regression analyses
were conducted including DTSQ covariates and other relevant covariates from the PSCs as well as the aforementioned confounders. The dependent variable was prescription of an FDC (alone or in addition to one OAD) versus OAD free-form combination therapy. To account for the large number of possible covariates, a variable reduction method was employed using a step-wise iterative approach that allowed sequential exclusion of variables with the largest \( P \)-value until only significant variables remained. Covariates included responses to the DTSQ, patient recollection of factors such as sources of diabetes information, feelings about current blood sugar control, lifestyle adaptations, and the perceived importance of a range of potential benefits of prescribed diabetes treatments.

RESULTS

A total of 641 physicians took part in the study (384 of whom were PCPs and 257 were specialists) and provided data for a total of 5891 patients (Table 1). For the 4354 patients included in the random sample, 2179 were receiving care from a PCP and 2175 were receiving care from a diabetologist/endocrinologist. The demographics and disease and treatment characteristics of the study population are summarized in Table 2.

**Table 1. Patient populations by country included in the Adelphi Diabetes Disease Specific Programme (from which the eligible populations for the three analyses were drawn).**

<table>
<thead>
<tr>
<th>Country</th>
<th>Random sample</th>
<th>Over-sample</th>
<th>Total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>818</td>
<td>295</td>
<td>1113</td>
</tr>
<tr>
<td>Germany</td>
<td>900</td>
<td>371</td>
<td>1271</td>
</tr>
<tr>
<td>Italy</td>
<td>889</td>
<td>177</td>
<td>1066</td>
</tr>
<tr>
<td>Spain</td>
<td>850</td>
<td>322</td>
<td>1172</td>
</tr>
<tr>
<td>UK</td>
<td>897</td>
<td>372</td>
<td>1269</td>
</tr>
<tr>
<td>Total</td>
<td>4354</td>
<td>1537</td>
<td>5891</td>
</tr>
</tbody>
</table>

Analysis 1. What are the Physician-Related Factors Associated with Prescription of a DPP-4 FDC versus DPP-4 Free-Form Therapy?

This analysis was carried out using physician-reported data from the physician interviews and the PRFs available for the random sample as well as the over-sample. A total of 696 patients out of the population of 1834 DPP-4 users (see Table 2) met the inclusion criteria for this analysis and had received a prescription for a DPP-4 either as an FDC (n=482) or as a free-form combination that was dose compatible with a DPP-4 FDC (n=214) on dual or triple therapy regimens, were receiving therapy for at least 12 weeks, were not receiving an insulin, and had a complete dataset for the variables included in the regression analyses. The demographics and treatment profile of these patients is shown in the univariate analysis in Table 3. The univariate analysis was used only to define the population for a logistic regression because the univariate analysis does not account for confounders; therefore, no conclusions regarding associations can be drawn from this analysis. It is necessary to correct for these confounders by using the logistic regression analysis method.

The logistic regression analysis identified eight variables as being significantly associated with prescription of a DPP-4 FDC rather than a DPP-4 free-form combination (Table 4). Three variables were associated with less likely to have been prescribed a DPP-4 FDC versus a DPP-4 free-form combination: most recent HbA1c level elevated (physicians were asked to record the most recent HbA1c test result for each patient); “once daily dosing” as a reason for treatment choice; “cost-effective” as a reason for treatment choice. The association between more recent HbA1c level and the proportion of patients prescribed a DPP-4 FDC rather than a free-form DPP-4 is illustrated in Figure 1.
is derived from the predicted values from the logistic regression model when the other seven independent variables are set to “average” values. The figure illustrates that the proportion of patients prescribed a DPP-4 FDC declined as most recent HbA1c value increased. The remaining five variables were associated with more likely to have been prescribed a

**Table 2.** Type 2 diabetes patients (on noninsulin antidiabetics +/- insulin): demographics and current treatments included in the Adelphi Diabetes Disease Specific Programme (from which the eligible populations for the three analyses were drawn).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Random sample (n=4354)</th>
<th>Over-sample (n=1537)</th>
<th>Total sample (n=5891)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD)</td>
<td>61.9 (11.6)</td>
<td>60.2 (10.7)</td>
<td>61.5 (11.4)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>44</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Time since diagnosis, mean years (±SD)</td>
<td>5.9 (5.8)</td>
<td>5.3 (4.5)</td>
<td>5.7 (5.5)</td>
</tr>
<tr>
<td>BMI, mean kg/m² (±SD)</td>
<td>29.1 (5.2)</td>
<td>29.4 (5.4)</td>
<td>29.2 (5.3)</td>
</tr>
<tr>
<td><strong>Noninsulin OAD (including FDC/GLP-1), n (%)</strong></td>
<td>4354 (100)</td>
<td>1537 (100)</td>
<td>5891 (100)</td>
</tr>
<tr>
<td>Biguanides</td>
<td>3168 (73)</td>
<td>763 (50)</td>
<td>3931 (67)</td>
</tr>
<tr>
<td>SU</td>
<td>1409 (32)</td>
<td>348 (23)</td>
<td>1757 (30)</td>
</tr>
<tr>
<td>TZD</td>
<td>356 (8)</td>
<td>77 (5)</td>
<td>433 (7)</td>
</tr>
<tr>
<td>Prandial glucose regulators</td>
<td>279 (6)</td>
<td>32 (2)</td>
<td>311 (5)</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>155 (4)</td>
<td>120 (8)</td>
<td>275 (5)</td>
</tr>
<tr>
<td>DPP-4 inhibitor*</td>
<td>313 (7)</td>
<td>812 (53)</td>
<td>1125 (19)</td>
</tr>
<tr>
<td>Metformin/DPP-4 inhibitor combination*</td>
<td>233 (5)</td>
<td>481 (31)</td>
<td>714 (12)</td>
</tr>
<tr>
<td>Metformin/TZD combination</td>
<td>150 (3)</td>
<td>18 (1)</td>
<td>168 (3)</td>
</tr>
<tr>
<td>Metformin/SU combination</td>
<td>69 (2)</td>
<td>2 (&lt;1)</td>
<td>71 (1)</td>
</tr>
<tr>
<td>Other OAD†</td>
<td>112 (3)</td>
<td>5 (&lt;1)</td>
<td>117 (2)</td>
</tr>
<tr>
<td><strong>Insulin, n (%)</strong></td>
<td>681 (16)</td>
<td>51 (3)</td>
<td>732 (12)</td>
</tr>
<tr>
<td>Very long acting insulin analogs</td>
<td>470 (11)</td>
<td>40 (3)</td>
<td>510 (9)</td>
</tr>
<tr>
<td>Biphasic insulin/mixtures</td>
<td>145 (3)</td>
<td>4 (&lt;1)</td>
<td>149 (3)</td>
</tr>
<tr>
<td>Very rapid acting insulin</td>
<td>141 (3)</td>
<td>9 (1)</td>
<td>150 (3)</td>
</tr>
<tr>
<td>Intermediate acting insulin</td>
<td>48 (1)</td>
<td>3 (&lt;1)</td>
<td>51 (1)</td>
</tr>
<tr>
<td>Other insulin‡</td>
<td>35 (1)</td>
<td>2 (&lt;1)</td>
<td>37 (1)</td>
</tr>
<tr>
<td><strong>DPP-4 overview, n (%)</strong></td>
<td>543 (12)</td>
<td>1291 (84)</td>
<td>1834 (31)</td>
</tr>
<tr>
<td>(Patients on DPP-4 free-form or DPP-4 FDC combination[s])</td>
<td>313 (7)</td>
<td>812 (53)</td>
<td>1125 (19)</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>46 (1)</td>
<td>193 (13)</td>
<td>239 (4)</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>259 (6)</td>
<td>604 (39)</td>
<td>863 (15)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>8 (&lt;1)</td>
<td>15 (1)</td>
<td>23 (&lt;1)</td>
</tr>
<tr>
<td>(Patients on DPP-4 FDC combination(s)*</td>
<td>233 (5)</td>
<td>481 (31)</td>
<td>714 (12)</td>
</tr>
<tr>
<td>Vildagliptin/metformin</td>
<td>83 (2)</td>
<td>193 (13)</td>
<td>276 (5)</td>
</tr>
<tr>
<td>Sitagliptin/metformin</td>
<td>150 (3)</td>
<td>288 (19)</td>
<td>438 (7)</td>
</tr>
</tbody>
</table>

*Three patients were prescribed a DPP-4 in addition to a DPP-4/metformin FDC.
†Includes alpha glucosidase inhibitors and thiazolidinedione/sulfonylurea FDC.
‡Includes regular insulin and insulin not further specified.

BMI=body mass index; DPP-4=dipeptidyl peptidase-4 inhibitor; FDC=fixed-dose combination; GLP-1=glucagon-like peptide-1 agonist; OAD=oral antidiabetic; SD=standard deviation; SU=sulfonylurea; TZD=thiazolidinedione.
Analysis 2. Is There an Association Between DPP-4 FDC Use, Perceived Level of Compliance, and HbA_{1c} Level?

This analysis was based on physician’s perspectives, drawing on data recorded in the PRFs (random sample and over-sample). To understand differences in HbA_{1c} levels it is important to study dual therapy only with comparable doses. A total of 533 patients met the inclusion criteria for this analysis. Eligible patients had received a prescription for a DPP-4 either as an FDC (n=383) or a free-form combination that was dose compatible with a DPP-4 FDC (n=150); were receiving dual therapy for at least 12 weeks; were not receiving an insulin; had an HbA_{1c} test result available; and had a complete dataset for the variables included in the regression. The exact timing of the HbA_{1c} test in relation to the prescription of DPP-4 FDC or DPP-4 free-form combination was not collected. This limitation applies equally to both groups of patients.

In Table 5, results are presented using an OLS regression analysis. The results identify variables associated with HbA_{1c} level. Three variables or predictors were identified as being significantly associated with the most recent HbA_{1c} level. Predictors significantly associated with a lower mean % HbA_{1c} level at the last testing were: prescription of a DPP-4 FDC rather than a free-form combination; physician perception of patients being “fairly compliant” versus “poorly” or “not at all compliant;” physician perception of patients being “fully” versus “fairly compliant.” Hence, the relative mean % HbA_{1c} level associated with being on a DPP-4 FDC rather than free-form, independent of the physician perception of patient compliance, was 0.25 lower (CI –0.40 to –0.09). However, if physician-perceived patient compliance was described as “fairly compliant” rather than “poorly compliant” or “not at all compliant,” the relative mean % HbA_{1c} level was 0.42 lower (CI –0.67 to –0.18). Similarly, being perceived as “fully compliant” rather than “fairly compliant” was associated with a relative mean % HbA_{1c} level that was 0.17 lower (CI –0.31 to –0.02). There were no interactions between these three significant variables and hence the associations between these three variables and the mean % HbA_{1c} level are additive.
Analysis 3. Are There Differences Between Patients Prescribed any OAD FDC Therapy (Alone or in Combination with One Other OAD) Compared with Those Prescribed OAD Free-Form Combination Therapy

This analysis drew on data recorded in the PSCs, which were available for the random sample only as PSCs were not included in the oversample. Responses relating to 562 patients who were receiving OADs alone and were not receiving insulin or other injectable antidiabetic agents were eligible for inclusion in this analysis. Of these, 155 (28%) were receiving an FDC alone or in combination with a single OAD, and 407 (72%) were receiving OAD free-form combination therapy. Those receiving an FDC had a mean satisfaction with treatment (DTSQ) score of 27.5 (SD±4.69), whilst those on free-form combination therapy had a mean DTSQ score of 26.0 (SD±5.47; P=0.0041).
The logistic regression analyses identified four more patient-focused covariates that were associated with an increased likelihood of receiving an FDC prescription, and four covariates that were associated with an increased likelihood of receiving an OAD free-form combination prescription (Table 6). After correction for confounding factors (age, gender, BMI, and time since the patient was diagnosed with diabetes), a single significant variable remained for the current regimen being any FDC (alone or in combination with one other OAD): increased patient satisfaction with their treatment (as indicated by a higher DTSQ score).

The logistic regression analyses identified four more patient-focused covariates that were associated with an increased likelihood of receiving an FDC prescription, and four covariates that were associated with an increased likelihood of receiving an OAD free-form combination prescription (Table 6). After correction for confounding factors (age, gender, BMI, and time since the patient was diagnosed with diabetes), a single significant variable remained for the current regimen being any FDC (alone or in combination with one other OAD): increased patient satisfaction with their treatment (as indicated by a higher DTSQ score).

Table 4. Physician-related factors associated with DPP-4 FDC versus DPP-4 free-form prescription (random sample and over-sample) for patients receiving dual or triple therapy (n=696; logistic regression model).

<table>
<thead>
<tr>
<th>Significant variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less likely to receive a DPP-4 FDC vs. a DPP-4 free-form combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated log-transformed current HbA1c value</td>
<td>0.09</td>
<td>0.01-0.66</td>
<td>0.018</td>
</tr>
<tr>
<td>“Once-daily dosing” as reason for treatment choice</td>
<td>0.09</td>
<td>0.05-0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>“Cost-effective” as reason for treatment choice</td>
<td>0.14</td>
<td>0.08-0.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>More likely to receive a DPP-4 FDC vs. a DPP-4 free-form combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who physicians described as “poorly compliant,” “fairly compliant,” or “fully compliant” vs. “not at all compliant”*</td>
<td>5.21</td>
<td>1.30-20.91</td>
<td>0.020</td>
</tr>
<tr>
<td>“Improves compliance” as reason for treatment choice</td>
<td>3.35</td>
<td>1.94-5.79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>“Covered by insurance” as reason for treatment choice</td>
<td>3.77</td>
<td>2.35-6.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physicians expressed that they used any FDCs frequently or as a first choice</td>
<td>2.26</td>
<td>1.47-3.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physician agreed or strongly agreed with the statement “I tend to use FDCs more in noncompliant patients”†</td>
<td>2.48</td>
<td>1.44-4.28</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Source: patient record form, Section LQ1a – in your experience, how compliant is this patient with their diabetes treatment? Response options: not at all compliant, has poor compliance, fairly compliant, fully compliant.
†Source: physician interview.
CI=confidence interval; DPP-4=dipeptidyl peptidase-4 inhibitor; FDC=fixed-dose combination; HbA1c=glycated hemoglobin.

Table 5. Variables associated with mean % HbA1c level among patients receiving dual therapy only, either prescribed a DPP-4 FDC or DPP-4 plus metformin at dosages comparable to those of a DPP-4 FDC (random sample and over-sample n=533; OLS regression analysis).

<table>
<thead>
<tr>
<th>Significant variables associated with the relative mean % HbA1c at most recent test</th>
<th>Difference in mean % HbA1c level</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription of a DPP-4 FDC (n=383) vs. DPP-4 free-form combination therapy (n=150)</td>
<td>−0.25</td>
<td>−0.40 to −0.09</td>
<td>0.002</td>
</tr>
<tr>
<td>“Fairly compliant” vs. “poorly compliant” or “not at all compliant”</td>
<td>−0.42</td>
<td>−0.67 to −0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>“Fully compliant” vs. “fairly compliant”</td>
<td>−0.17</td>
<td>−0.31 to −0.02</td>
<td>0.026</td>
</tr>
</tbody>
</table>

BMI=body mass index; CI=confidence interval; DPP-4=dipeptidyl peptidase-4 inhibitor; FDC=fixed-dose combination; HbA1c=glycated hemoglobin; OLS=ordinary least squares (linear) regression analysis.
Covariates were age, gender, BMI, time since diagnosis, prescription of FDC or free-form therapy, patient compliance, and time spent on regimen.
A further analysis of the DTSQ item scores revealed that patients who regarded their current regimen as more convenient (higher score for the question “How convenient have you been finding your treatment to be recently?”) were more likely to have been prescribed an FDC regimen than OAD free-form combination therapy (odds ratio 1.32; 95% CI 1.10 to 1.58; \( P = 0.003 \)). Those receiving an FDC had a mean score of 4.7 (SD±0.96, range 0-6) for this question, compared with 4.4 (SD±1.14; \( P = 0.0055 \)) for those on free-form combination therapy. Patients who regarded pill size and ease of swallowing as important benefits of their current regimen were also more likely to be on any FDC. Patients prescribed any FDC regimen were more likely to be dissatisfied with the cost of their treatment and to lack an agreed target HbA1c. Dissatisfaction with their current treatment, not being able to control their HbA1c, nurses as a source of information about their diabetes (as indicated in response to the question “Which of the following sources have you used for diabetes information?”), older age, and a higher BMI were all significant predictors for the current regimen being OAD free-form combination.

### DISCUSSION

The Adelphi DSPs provide real-world evidence about why disease-management decisions are made, what the decisions are, and the involvement/perspective of the patient. DSP data provide valuable insights into the implications of a disease and its treatment. The relevance and limitations of the Adelphi DSP methodology and cross-sectional design have been published elsewhere.25

Data from the Adelphi Diabetes DSP presented here show that a variety of factors appear to be associated with DPP-4 FDC versus DPP-4 free-form combination prescribing. Physician-related factors associated with DPP-4 FDC prescribing decisions were associated with a desire to improve patient compliance.
Four variables were associated with an increased likelihood of prescribing a DPP-4 FDC rather than a DPP-4 free-form combination (patients described by physicians as having a compliance level of “poor compliance,” “fairly compliant,” or “fully compliant” versus “not at all compliant,” physicians’ reasons for choice being “improves patient compliance” or “covered by health insurance,” physicians who indicated that they used FDCs frequently or as a first choice treatment; physicians who agreed with the statement “I tend to use FDCs more in noncompliant patients”).

Predictors significantly associated with a lower HbA1c level at the last testing were prescription of a DPP-4 FDC rather than a free-form combination; physician perception of patients being “fairly compliant” versus “poorly” or “not at all compliant;” physician perception of patients being “fully” versus “fairly compliant.” The significant associations of these three variables with the mean % HbA1c level were additive as there were no interactions between them. Therefore, if a patient is on a DPP-4 FDC rather than free-form DPP-4 and is perceived by the physician to be “fairly compliant,” having previously been “poorly compliant” or “not at all compliant,” the mean % HbA1c level would be 0.25+0.42 giving an overall 0.67 lower level. These results suggest that using DPP-4 FDCs for “not at all compliant” or “poorly compliant” patients would independently facilitate an improvement in mean % HbA1c level and may assist an improvement to “fairly compliant”, which would give rise to the best incremental gain in blood sugar control.

Having corrected for the confounding factors age, gender, BMI, and time since the patient was diagnosed with diabetes, significant predictors for the current regimen being any FDC (alone or in combination with one other OAD) were greater patient satisfaction with their treatment (shown by a higher DTSQ score), patients perception of their current regimen as more convenient (from the DTSQ), and patients regarding pill size and ease of swallowing as important benefits of their current regimen. Patients prescribed any OAD FDC regimen were more likely to be dissatisfied with the cost of their treatment and to lack an agreed target HbA1c. Dissatisfaction with their current treatment, not being able to control their HbA1c, nurses as a source of information about their diabetes, older age, and a higher BMI were all significant predictors for the current regimen being OAD free-form combination therapy. A previous study has shown that lower levels of treatment satisfaction may be associated with difficulties in taking medications and attending follow-up visits. Identifying and employing strategies to improve patient satisfaction with treatment may thus prove beneficial in improving patient compliance.

In conclusion, the three analyses undertaken in this retrospective database study suggest that DPP-4 FDC prescribing is considered to be a positive prescribing choice to improve compliance. From the patient’s perspective, the decision to prescribe an FDC is associated with improved satisfaction with treatment. These results are consistent with the results of a systematic literature review that suggested that FDC therapy is associated with improved medication taking and treatment satisfaction. Finally, both better compliance and DPP-4 FDC use are independently associated with a lower HbA1c level, leading to the assumption that better treatment compliance leads to better real-world effectiveness. The associations identified in this study provide support for the hypothesis that prescription of DDP-4 FDCs may indeed lead to improved effectiveness of glucose-lowering drugs in the real world. Longitudinal studies are now required to confirm and extend the observations reported here.
ACKNOWLEDGMENTS

The authors acknowledge that AstraZeneca and Bristol-Myers Squibb commissioned this retrospective database analysis of the Adelphi Diabetes DSP, proposed the questions to be tested, provided input to the analyses to be performed, reviewed the results, and provided direct input to the manuscript. The authors also acknowledge the editorial support provided by Dr Tracey Lonergan (Adelphi Real World) in the preparation of the manuscript. M.B. is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

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REFERENCES


The relationship between glucose-lowering medications, adherence and outcomes in patients with type 2 diabetes

ISPOR, Milan, November 9th 2015

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Background and Objectives

- Adherent type 2 diabetes (T2DM) patients are more likely to have good glycaemic control than non-adherent patients, potentially resulting in better outcomes.

- We investigated the association between the number of glucose-lowering therapies, adherence and their impact on glycaemic control and quality of life (QoL).
Methodology - Data Collection

Data source
The Adelphi Real World Diabetes Disease Specific Programme (DSP®) is a cross-sectional survey of consulting patients with T2DM

Countries
France, Germany, Italy, Spain, UK

Patient criteria
Patients 18 years and older with a diagnosis of T2DM

Data collection timings
Q1 2013

PRO = patient reported outcome; EQ-5D-3L = EuroQol 5 Dimension – 3 Level
QoL = Quality of Life; MMAS-8 = Morisky Medication Adherence Scale
Methodology - Total Survey Sample

Physicians included the next 10 consulting T2DM patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Physicians</th>
<th>Physician-Completed Record Form</th>
<th>Patient Self Completion Questionnaire¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>PCP² Specialist</td>
<td>Total PCP Specialist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>125</td>
<td>75 50</td>
<td>1,247 750 497</td>
</tr>
<tr>
<td>Germany</td>
<td>125</td>
<td>75 50</td>
<td>1,250 750 500</td>
</tr>
<tr>
<td>Italy</td>
<td>125</td>
<td>75 50</td>
<td>1,250 750 500</td>
</tr>
<tr>
<td>Spain</td>
<td>125</td>
<td>75 50</td>
<td>1,260 760 500</td>
</tr>
<tr>
<td>UK</td>
<td>125</td>
<td>74 51</td>
<td>1,237 734 503</td>
</tr>
<tr>
<td>EU total</td>
<td>625</td>
<td>374 251</td>
<td>6,244 3,744 2,500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Patient self-completion questionnaires were voluntary. Patients provided written consent.
² PCP: Primary Care Physician
Methodology – Analysis Cohort

Patients with physician-completed questionnaire
N=6,244

Patients with patient-completed questionnaire
N=3,773

Current regimen duration (6m to 5y)
N=1,957

Available HbA1c measure
N=1,722

All variables completed for final model
N=1,209

- There was a reduction in patient numbers due to inclusion criteria
- The real-world element of this survey allows for missing values. Questionnaires with missing values were excluded, thus further reducing the final patient numbers

HbA1c = Glycosylated Haemoglobin

1 219 patients did not have HbA1c values and 16 patients were excluded as reported HbA1c <4%
2 Variables included were Age; Body Mass Index; Time from diagnosis to start of current regimen; Time since start of current regimen; Daily diabetes pill count; Daily non-T2DM pill count; Daily diabetes injection count; Level of lifestyle adaptation, MMAS-8 and EQ-5D-3L
Patient Reported Outcomes Tools Used

• EuroQol 5 Dimension 3 level (EQ-5D-3L)
  • Generic instrument for assessing health-related QoL across five dimensions: 
    **mobility, self-care, usual activities, pain/discomfort, anxiety/depression**¹.
  • A single summary score is derived where 1 represents perfect health and 
    lower scores indicate poorer health states.

• Morisky Medication Adherence Scale (MMAS-8)
  • 8 question self-report generic instrument for assessing adherence to 
    medication².
  • A single summary score is derived where 8 represents high adherence and 
    lower scores indicate lower adherence.
  • Reported in 3 levels: **low, medium and high adherence**.

## Demographic and Clinical Characteristics

### Table 1: Demographic characteristics (n=1209)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>60.7 (10.3)</td>
</tr>
<tr>
<td>Male</td>
<td>57.9%</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²), mean (SD)</td>
<td>28.6 (4.7)</td>
</tr>
<tr>
<td>Time since T2DM diagnosis (years), mean (SD)</td>
<td>4.0 (4.0)</td>
</tr>
</tbody>
</table>

### Table 2: Clinical characteristics (n=1209)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oral diabetes medication pills per day, mean (SD)</td>
<td>2.21 (1.16)</td>
</tr>
<tr>
<td>Number of diabetes injections per day, mean (SD)</td>
<td>0.36 (1.03)</td>
</tr>
<tr>
<td>Most recent % HbA₁c mean (SD)</td>
<td>6.94 (0.80)</td>
</tr>
<tr>
<td>Most recent diastolic blood pressure (mmHg), mean (SD)</td>
<td>79.3 (8.8)</td>
</tr>
<tr>
<td>Most recent systolic blood pressure (mmHg), mean (SD)</td>
<td>134.4 (13.0)</td>
</tr>
</tbody>
</table>

HbA₁c = Glycosylated Haemoglobin; mmHg = millimeter of mercury; SD = Standard Deviation  

*Derived from height/weight calculation (physician-reported)*  
*Base n=1070 due to missing values*  
*Base n=1071 due to missing values*
Methodology - Modelling Technique

• Selection of Structural Equation Model (SEM)
  
  • Chosen as it allows a multivariate approach with multiple causal pathways to be modelled simultaneously and reflects complexities and realities of managing T2DM in clinical practice.

  • The software required a path model to be constructed to define the SEM.
We took into account the following confounders:

- Age
- Body Mass Index
- Time from diagnosis to start of current regimen
- Time since start of current regimen
- Daily non-T2DM pill count
- Level of lifestyle adaptation
Results

- Patients with low daily pill/injection count have better adherence compared to patients with a high pill/injection count.
- Higher adherence levels are associated with lower, most recent HbA1c levels, thus improving glycaemic control.
- Subsequently, patients with good glycaemic control have a better QoL than those whose glycaemic levels are not controlled.

**Statistically significant**  
0.00  
Figures indicated the effect of a unit increase in the causal variable
Path Model Strengths and Limitations

- The path model enabled the separation of the 2 conflicting causal pathways between HbA$_{1c}$ and number of medications. On the one hand, a worse HbA$_{1c}$ may mean more medications; yet on the other, less medications means improved HbA$_{1c}$, through improved adherence.

- The model assumes linear relationships.

- The model is relatively simple. There are variables not included that could have an influence, e.g. the type of pill or injectable is not detailed, just the daily number.
Controlling for important clinical and demographic factors, a lower number of daily glucose-lowering therapies is associated with greater adherence which, in turn, is associated with better glycaemic control and improved QoL.

Further research is required to investigate if these associations vary depending on the specific medication taken or other patient-related parameters not considered here and to ascertain the clinical importance in the change of HbA$_{1c}$ observed.
Characterization and patient-reported perceptions and outcomes of insulin use amongst pre-insulin versus insulin type 2 diabetes mellitus (T2DM) populations in USA

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Adelphi Real World, Bollington, Cheshire, UK

PDB55

Objectives

- Guidelines endorse a patient-centered approach to the management of T2DM, recommending insulin therapy as a 2nd or 3rd line therapy option.
- Insulin is typically introduced when all non-insulin therapy has been optimised but better glycaemic control is still required.
- This analysis aimed to assess perceptions of insulin usage amongst pre-insulin and current insulin T2DM populations and establish differences in patients’ feelings between the cohorts.

Methods

- Data were drawn from 5 years (2010-2014) of the Adelphi Real World Diabetes Disease Specific Programmes (DSPs) in T2DM patients cared for across the USA.
- The Diabetes DSP is a real-world, cross-sectional survey involving face-to-face interviews with endocrinologists (ENOs), primary care physicians (PCPs) and completion of physician-reported questionnaires for their next 10 consulting T2DM patients.
- The same patients were invited to complete an unassisted, voluntary questionnaire.

- Physician inclusion criteria included being personally responsible for diabetes management decisions. Patient inclusion criteria were aged ≥21 years; on at least 1 non-insulin prescribed drug with or without insulin therapy. The same patients were not followed year on year.
- Physicians and patients provided de-identified data in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Prior to analysis, responses were aggregated. Full details of the methodology have been published.
- Statistical methods: Percentages and descriptive statistics were used. Pairwise comparisons were made using t-tests, χ2 tests or Fisher’s exact tests, depending on the type of variable tested (numeric/categorical). Mean results over the 5 surveys were calculated.

- Patient-perceived feelings towards starting insulin therapy and how patients currently on insulin feel about injecting themselves were measured using a 4-point scale ‘very happy’, ‘fairly happy’, ‘fairly unhappy’ and ‘very unhappy’.
- Adherence was measured using the validated Morisky Medication Adherence Scale (MMAS-8) and reported in 3 levels: low (3-8), medium (1-2) or high (0) adherence.

Results

- Aggregated data from the five annual surveys provided a total of 13,527 patients from 504 ENOs and 626 PCPs for analysis.
- Of these, 6,504 patients completed a patient-reported form, of which, 4,575 patients were pre-insulin and 1,929 patients were currently on insulin.
- Few pre-insulin patients reported any degree of happiness about starting insulin, (very/fairly happy: PCP 4.6%; ENDO 7.3%).
- Most patients were very unhappy at the prospect of starting insulin.
- Once taking insulin, however, patients’ feelings were more likely to be positive (very/fairly happy: PCP 47.4%; ENDO 42.5%) (Figure 1).

- Main barriers to insulin uptake among pre-insulin users included dislike of injections (PCC 73.9%; ENDO 63.6%), accepting their diabetes is now more advanced (PCC 52.9%; ENDO 50.5%) and failure to control their diabetes (PCC 40.3%; ENDO 39.8%) (Figure 2).

Conclusions

- Pre-insulin users have higher concerns towards taking insulin compared with those currently receiving insulin.
- Once on insulin, patients’ concern levels around therapy improve due to positive experiences around feeling better.
- It would appear exposure to other injectable therapy (GLP-1 RA) ahead of insulin mitigates pre-insulin patient concerns towards insulinization.
- Irrespective of whether current insulin patients feel happy or unhappy since starting insulin, similar positive feelings of therapy are reported.
- Patients happy injecting insulin results in improved adherence to medication.
- It appears pre-insulin patient concerns around injecting are reduced once patients do inject (either GLP-1 RA or insulin). Education via physician-patient and current insulin to pre-insulin patient interactions could be beneficial in alleviating concerns around injecting. This may maximize adherence which then has the potential to improve outcomes.

References


Table 1: Pre-insulin patients (i) vs (ii) fairly unhappy injecting (%) (i) Very unhappy (ii) Fairly unhappy

| All differences are statistically significant (p<0.05) (i) Pre-insulin patients vs other pre-insulin patient groups (ii) All current insulin patients

<table>
<thead>
<tr>
<th>Current treatment</th>
<th>(PCP)</th>
<th>(ENDO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pre-insulin medications</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Concerned around starting insulin</td>
<td>93.4</td>
<td>92.9</td>
</tr>
<tr>
<td>Nervous, anxious</td>
<td>72.9</td>
<td>72.3</td>
</tr>
<tr>
<td>Worried about being judged</td>
<td>69.6</td>
<td>68.8</td>
</tr>
<tr>
<td>Concerned about gaining weight</td>
<td>56.8</td>
<td>56.5</td>
</tr>
<tr>
<td>Concerned because of family</td>
<td>55.9</td>
<td>55.5</td>
</tr>
</tbody>
</table>

Table 2: Current insulin patients (i) vs fairly unhappy injecting (%)

<table>
<thead>
<tr>
<th>Current treatment</th>
<th>(PCP)</th>
<th>(ENDO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pre-insulin medications</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Concerned around starting insulin</td>
<td>85.7</td>
<td>85.6</td>
</tr>
<tr>
<td>Nervous, anxious</td>
<td>68.2</td>
<td>67.3</td>
</tr>
<tr>
<td>Worried about being judged</td>
<td>60.2</td>
<td>59.6</td>
</tr>
<tr>
<td>Concerned because of family</td>
<td>59.6</td>
<td>59.4</td>
</tr>
<tr>
<td>Concerned because of weight gain</td>
<td>54.3</td>
<td>54.5</td>
</tr>
</tbody>
</table>

Figure 1: Pre-insulin patients: feeling towards starting insulin - Current insulin patients’ feelings towards injecting (% overall mean)

Figure 2: Barriers to starting insulin

Figure 4: Reasons for feeling better since starting insulin

Figure 5: Thirty-six percent of current insulin patients felt fairly unhappy since starting insulin (% overall mean)
The major 5 European markets and Japan operate generally socialized healthcare systems. The USA has a mixed system of healthcare funding involving public and insurance based systems. Each system has different structures and organizations to assess the value of medical interventions, and a number of different decision makers who act on the basis of these assessments to ensure efficient use of healthcare resources. These decision makers are collectively referred to as payers.

A key objective of the payer is to influence prescribing behavior and healthcare resource use in order to contain healthcare costs while simultaneously allowing an acceptable minimum quality of care. To achieve this they use a number of administrative approaches which vary according to the care setting.

Less clear is the extent to which these administrative controls are effective tools to influence prescribing behavior; the extent to which prescribers feel these are appropriately implemented, or how this varies between countries or therapy areas.

We have previously demonstrated that prescribing is affected by such controls in high-cost specialist therapies such as oncology.1 In this analysis we explore the impact on prescribing decisions in diabetes, a more common and arguably less specialized therapy area, and whether regulatory impact on prescribing decisions, their impact on prescribing behavior, and how they are perceived by prescribers.

The major 5 European markets and Japan were aggregated. Full details of the DSP regulations. Prior to analysis, responses for Economic and Clinical Health (HITECH) and Health Information Technology (HIPAA) and Health Information Technology (HITECH) were grouped. Differences between these regulatory frameworks were highlighted. The objective of this analysis is to assess the extent to which prescribing decisions for T2DM are influenced by payer-implemented controls.

Methods

Data were drawn from the Adelphi Real World Diabetes Disease Specific Programme (DSP) conducted across France, Germany, Italy, Spain, UK, USA and Japan in Q2 2015. The DSP is a real-world, cross-sectional survey of physicians and their consulting patients.

The data drawn from the DSP included 390 endocrinologists and 560 primary care physicians (PCPs) who complete physician-reported patient record forms for their next 10 consulting T2DM patients. In addition to clinical considerations, physicians were asked to record the impact of administrative controls on their prescribing and the processes they followed. For analysis, the responses were grouped into popularized sets to allow for international comparisons.

Three categories were devised for this analysis:

- Control had no impact on prescribing
- Controls influenced prescribing
- Controls lead to non-preferred prescribing

A Fisher’s Exact test was used to test the null hypothesis that the differences between markets were due to chance, with Bonferroni adjustment to account for multiple testing.

Physicians and patients provided identified data in a Diabetes Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) compliant manner. All statistical responses were aggregated. Full details of the DSP methodology has been published previously.1

This research demonstrates that prescribing in all countries studied is influenced by administrative controls to which payers contribute, with differences between nations and regions. The greatest impact was seen in Germany, the USA and Japan.

In diabetes, although prescribers commonly take account of formulary and other payer restrictions, in the majority of cases they did not believe these restrictions altered their choices, and in very few cases do they feel that they have not been able to prescribe an appropriate drug.

One possible conclusion for these observations is that payer controls are generally aligned with what prescribers see as good clinical practice. It may also reflect the situation in which controls do not generally affect the ability to prescribe a given class of drug, instead focusing on indicating which product within a class is preferred. This is further supported by the low number of cases where prescribers report being unable to use a drug that they consider to be appropriate.

Despite apparently good alignment between payers and prescribers, we have observed that in a small number of cases payer controls can lead to prescribing of diabetes treatments considered non-ideal by prescribers. This was seen more in the UK and USA than in other markets.

Further research will help to establish whether differences between markets reflect actual differences in the nature and implementation of payer controls, or simply differing levels of alignment between prescribers’ and payers’ objectives or opinions.

In either case, further insights into this issue have the potential to inform discussions between prescribers and payers about rational use of medicines and patients’ access to medicines.

Understanding national funding and control dynamics is likely to be important in framing these discussions.

It is interesting to observe that these findings are in agreement with those that we have previously reported in Multiple Sclerosis (MS) in Europe1 to observe that in diabetes the degree to which prescribers feel they have been compelled to make a non-ideal or non-preferred prescribing decision is lower.

IMPLICATIONS:

- It has been shown that payer-based controls drive treatment selection in the majority of patients; these controls should therefore be designed and implemented with great care and due clinical consideration.

- There is room for greater alignment between prescribers and payers to ensure that the former understand why formulary decisions represent the best clinical practice for their patients.

- Enhanced and refined insight tools to capture these influences on prescribing behavior with a focus on interaction based outcomes will help to illuminate this dynamic further and inform future decisions.

References


Exceptions were the UK (1 in 50; statistically significant) and the USA (1 in 33; different from all except UK p<0.001).

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Background: Despite the availability of a variety of treatments, many patients with type 2 diabetes mellitus (T2DM) are not achieving glucose control. We analyzed successive waves of the Adelphi Real World Diabetes Disease Specific Programmes (DSPs) to assess treatment patterns reported by primary care physicians (PCPs) and specialists and the effect of treatment on levels of glucose control.

Methods: Data were collected between 2000 and 2015 in the US and EU5 (France, Germany, Italy, Spain, and the UK). Physicians completed patient record forms for the next 10 patients consulting with T2DM. Key aspects captured were change over time in therapy usage, time to insulin introduction, and glycated hemoglobin (HbA1c) levels.

Results: Over 12 DSP waves, 3,555 specialists and 5,109 PCPs completed questionnaires for 70,657 patients. Treatment patterns changed considerably over time as new agents were introduced. The number of agents prescribed per patient increased over time, as did HbA1c levels at which physicians stated they would introduce insulin. The greatest improvements in HbA1c levels occurred during 2000–2008, with little improvement since 2008.

Conclusion: In this real-world setting, the proportion of patients with T2DM achieving good glucose control has not increased greatly since 2008. A better understanding of how to individualize treatment pathways may be required to improve control in these patients.

Keywords: insulinization, real world, type 2 diabetes, treatment trends

Introduction

The array of treatment options available to patients with type 2 diabetes mellitus (T2DM) has increased markedly in recent years, as reflected in recent treatment guidelines. Current recommendations involve commencing metformin monotherapy if dietary and lifestyle modifications are not sufficient, with the addition of other agents if the patient’s glycated hemoglobin (HbA1c) target is not met after 3 months. Available agents include sulfonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and insulin. Triple therapy may be needed if the HbA1c target is not reached on dual therapy, with the addition of insulins if required. Glucose control or homeostasis is the focus of treatment for patients with T2DM. Current guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a personalized approach to glycemic control rather than a universal goal for all patients; an HbA1c level of 7% is often used as a cutoff point. Despite comprehensive treatment guidelines and the
availability of a range of therapeutic options, many patients continue to have poorly controlled diabetes. In the US, 48% of people with diabetes in the National Health and Nutrition Examination Surveys (NHANES) had an uncontrolled HbA1c >7% between 2007 and 2010, with 13% of patients having an HbA1c >9%. In an audit of over 2 million patients with diabetes in England and Wales, 35% of patients with T2DM had HbA1c >7.5%. These data suggest that, despite the availability of a range of therapeutic options and guidelines, patients may be treated inadequately or are not taking control of their condition effectively, for example, via lack of lifestyle improvements or non-adherence to medication regimens.

Using data from successive waves of the Adelphi Real World Diabetes Disease Specific Programme (DSP), the aim of these analyses was to assess treatment patterns reported by primary care physicians (PCPs) and specialists involved in the management of patients with T2DM and the subsequent impact on levels of glycemic control. Key aspects of these analyses were to assess changing T2DM therapy usage since the launch of newer drug classes; review the role of polypharmacy; identify the trigger point at which physicians introduce insulin therapy in patients with T2DM; review any changes in time to insulin introduction; and analyze if any identified changes in treatment have ultimately affected HbA1c levels over an extended period in this patient population.

Methods
Data were drawn from successive waves of the Diabetes DSP conducted between 2000 and 2015 in the US and EU5 (France, Germany, Italy, Spain, and the UK). These were prospective, cross-sectional surveys of physicians and their patients presenting in a real-world clinical setting. Although not longitudinal in nature, each wave provides an independent snapshot of cross-sectional data, which can be used to explore patterns over time. DSPs are large, multinational surveys conducted in clinical practice that describe current disease management, disease-burden impact, and associated treatment effects (clinical and physician-perceived). The survey methodology is designed to facilitate collection of up-to-date data from the following three key sources of information: physician face-to-face interviews, physician-reported workload questionnaires, and patient record forms. A complete description of the methods of the survey has been previously published.

Using a check box, patients provided informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt, and as a result, data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such it does not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996, the European Pharmaceutical Marketing Research Association guidelines, and Health Information Technology for Economic and Clinical Health Act legislation.

Participating physicians and patients
For each DSP wave, physicians were eligible to participate in this research if they were personally responsible for treatment decisions and management of patients with T2DM. Inclusion criteria for patients were aged ≥18 years, a physician-confirmed diagnosis of T2DM, receiving antidiabetic non-insulin therapy (with or without insulin regimens), and consulting the physician on the day of assessment. Each wave of data collection was independent of the others, ensuring the same physicians and patients were not included year on year.

Eligible physicians completed a face-to-face interview. Of particular importance to our study objective was the question included from 2004 onward that specifically asked physicians what HbA1c level would prompt initiation of insulin therapy. Physicians then completed a workload page for the next 5 working days. This provides a holistic view of T2DM management including prescribed and nonprescribed approaches. Irrespective of which patients were recruited for the survey, physicians recorded the total number of patients with T2DM consulting per day who were being managed with the following treatment approaches: 1) diet and exercise only; 2) non-insulin drug treatment only; 3) non-insulin drug treatment plus insulin; and 4) insulin only.

Physicians were then instructed to complete a patient record form for the next 10 consecutive consulting patients with a physician-confirmed diagnosis of T2DM and receiving prescribed antidiabetic therapy (with or without insulin), regardless of the reason for the consultation. The physician-reported forms reflected physicians’ knowledge about their treatment decisions and assessment of health status in patients seeking routine care, including information on patients’ demographics, clinical assessments, clinical outcomes, diabetes medication use, and history. The physician-reported forms also collected information on the time to insulin initiation. Market updates from year to year necessitated minor amendments to some questions (refer Table S1 for specific questions administered in each wave).
It should be noted that as each survey was designed to facilitate understanding of real-world clinical practice, physicians could only report on data they had to hand at the time of the consultation. Therefore, this represents the evidence they had when making any clinical treatment and other management decisions at that consultation. No tests, treatments, or investigations were performed as part of this survey.

Statistical analyses
Patient characteristics were analyzed descriptively for the total study sample. Categorical variables were described by proportion of respondents, excluding any missing values. Continuous numerical variables were described by their mean.

As the time from diagnosis of T2DM to the survey date was different in each patient within each wave, the time to initiation of insulin was compared against the year the patient was diagnosed, rather than the survey year in which the patient was included. For example, a patient recruited in 2015 diagnosed with T2DM 5 years earlier was considered the same as a patient recruited in 2011 diagnosed for 1 year, as their diabetes management would have started in the same year.

Survival analysis was used to analyze the time from diagnosis to the first insulin regimen. This method was chosen as patients who had not received any insulin regimen by the time of the survey could be included; therefore, a patient’s time from diagnosis to the point of data collection was used even if a patient had not yet received insulin, as they could potentially receive insulin at some point in the future.

Kaplan–Meier failure curves were plotted by time of diagnosis, where “failure” in this analytical setting infers the initiation of insulin. A log-rank test was used to assess significant differences in the time taken for patients to receive insulin.

Results
Patients and physicians
A total of 3,555 specialists and 5,109 PCPs participated in the 12 DSP waves conducted between 2000 and 2015. A total of 88,681 patients with T2DM were counted via the 5-day workload page, providing the holistic prescribed and non-prescribed antidiabetic cohort; 70,657 patients with T2DM were recruited via the physician-reported questionnaires providing the prescribed antidiabetic therapy (non-insulin therapy with or without insulin) cohort (Figure 1).

Baseline characteristics of patients treated by PCPs and specialists were generally consistent over time (Table 1). No changes were apparent in mean age at diagnosis, current age, and body mass index. However, a slight increase was observed in the mean number of antidiabetic agents prescribed. This was more pronounced among specialists, who prescribed an average of 1.6 agents per patient in 2000, increasing to 2.1 per patient in 2015. This increase was

Figure 1 Analyses cohort diagram.
Note: Specialist here refers to a diabetes specialist (diabetologist, endocrinologist).
Abbreviations: PCP, primary care physician; T2DM, type 2 diabetes mellitus.
Therapy patterns over time

In order to obtain an overview of treatment received by patients with diabetes, PCPs and specialists were asked to record what therapies their patients were receiving: diet and exercise only; non-insulin drug treatment only; non-insulin drugs plus insulin; and insulin only. As shown in Figure S1, the majority of patients were prescribed non-insulin agents only. Insulin-only regimens and diet and exercise only played a minor role, being used in <20% and <10% of patients, respectively, with these proportions remaining relatively unchanged over time. Both PCPs and specialists have consistently reported prescribing a higher proportion of both non-insulin-only regimens and – especially among specialists – non-insulin plus insulin regimens, and this generally remained static between 2004 and 2015. Owing to these therapy dynamics, subsequent analyses excluded patients on insulin-only regimens and diet and exercise only.

The range of individual regimens used for the treatment of patients with T2DM has changed greatly since 2000, as demonstrated by the introduction of new agents from 2006 onward (Figure 2). Metformin monotherapy was most commonly prescribed by PCPs, increasing to a peak of 44% of patients in 2012 before dropping to 36% in 2015. The use of non-insulin-only combinations containing the new drug classes is derived from the addition of metformin plus DPP-4 inhibitor usage to all other non-insulin regimens containing single or combined use of DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 RAs. Non-insulin-only combination use of these newer drug classes increased among PCPs from 4% of patients in 2008 to 33% in 2015, in particular, metformin plus DPP-4 inhibitors predominantly in free form but also included fixed-dose combinations. This pattern was observed to a greater extent among specialists, where the use of the newer non-insulin-only classes, alone or in combination, increased from 1% of patients in 2006 to 43% in 2015. Specialist use of regimens containing non-insulin drugs plus insulin increased over the time period, being prescribed for 16% of patients in 2000 and 29% of patients in 2015, whereas PCP use of these regimens remained relatively static.

Insulin initiation: perception versus reality

The proportion of physicians stating they would introduce insulin at HbA1c <8% decreased from 24% of PCPs and 34% of specialists in 2004 to 7% for both PCPs and specialists in 2015 (Figure S2). A corresponding increase in the proportion of physicians waiting until HbA1c was ≥9% was observed over this time period, from 36% of PCPs and 24% of specialists in 2004 to 42% of PCPs and 39% of specialists in 2015.

In line with physicians’ perceptions of insulin being initiated at higher HbA1c levels, mean actual HbA1c level at the time of insulin initiation increased over the study period, as shown in Figure S3, with the most pronounced increase being observed between 2011 and 2014 for PCPs (2011: 8.7%; 2014: 9%) and between 2011 and 2015 for specialists (2011: 8.8%; 2015: 9.7%).

Time to insulin initiation

Figure 3 shows time to insulin initiation, with patients receiving insulin significantly sooner after diagnosis in more recent years (P<0.001; log-rank test). An overall trend toward a shorter time to insulin initiation was observed;
Table 1 (Continued)

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Table 1: Demographics and clinical characteristics by survey year of patients with T2DM treated by PCPs and specialists.

this was most pronounced among specialists. For example, a specialist-treated patient diagnosed before 1999 had an 8% likelihood of receiving insulin within the first 5 years after diagnosis compared with 17% for a patient diagnosed between 2004 and 2007 and 19% for a patient diagnosed between 2008 and 2011.

Glucose control as measured by most recent HbA1c
The proportion of patients with HbA1c <7%, the goal recommended by many guidelines, is shown in Figure 4. In 2015, 50% of PCP-treated patients were likely to have controlled diabetes compared with 36% of specialist-treated patients. As expected, specialists treated a higher proportion of patients with HbA1c >9% compared with PCPs. Although improvements were seen in both groups of patients between 2000 and 2015, the majority of this progress was achieved between 2000 and 2008; glucose control has improved little since then.

Discussion
Real-world data spanning prolonged time intervals provide an opportunity to gain insights into treatment patterns and how they change over time. The diabetes suite of DSP analyses has assessed clinical trends and treatment patterns almost annually since 2000, providing a real-world view of the changing T2DM environment over this period.

The present analysis of treatment patterns in patients with T2DM over the period between 2000 and 2015 began with a holistic overview of four main treatment classes: diet and exercise only; non-insulin drug treatment only; insulin only; and insulin plus a non-insulin drug. The most apparent changes over time were an increase in the use of insulin plus an oral non-insulin (oral antidiabetic agent with or without GLP-1 RA) and a reduction in the use of oral antidiabetic non-insulin agents alone. This is in line with treatment guidelines, which provide clear recommendations on when insulin should be added to oral non-insulin therapy, and agrees with the notion that physicians do not appear to feel constrained by payer or formulary influences when prescribing antidiabetic therapies.

Examination of drug treatment patterns over this time period revealed that specialist use of non-insulin plus insulin regimens doubled between 2000 and 2006, whereas PCP use increased only slightly. Since 2006, there have been large increases in the use of the DPP-4 inhibitors, GLP-1 RAs, and SGLT-2 inhibitors by PCPs and specialists. This coincided with a decline in the use of regimens containing older agents such as SUs, TZDs, prandial glucose regulators, and alpha-glucosidase inhibitors. The use of TZDs may have been affected by the introduction in 2007 of a black box warning for rosiglitazone; this may have resulted in an increase in the use of insulin in 2008. In their study of prescribing in the UK primary care population, Sharma et al reported an increase in metformin from 55% of treated patients in 2000 to 84% in 2013, while prescription of SUs decreased from 65% to 41%, results that are in agreement with the findings of this analysis.

Our analysis also showed that the mean number of antidiabetic drugs per patient increased slightly between 2000 and 2008, a trend that was more noticeable in patients treated by specialists. Interestingly, the mean number of antidiabetic drugs has remained static since 2006 among PCPs and increased only slightly among specialists, suggesting that PCPs are more likely to switch therapy, while specialists add agents in an effort to achieve glycemic control. Among patients treated by specialists, fewer received
metformin monotherapy and more received insulin therapy compared with patients treated by PCPs; this is consistent with more advanced disease at the time of referral to the specialist. Although we observed increased use of newer agents, use of metformin monotherapy remained relatively static, suggesting no move toward introduction of multiple therapies earlier in the treatment path.

Between 2010 and 2015, an increase was observed in the HbA1c level at which physicians stated they would initiate insulin. In-line with these perception data, the HbA1c level at which insulin was actually initiated also increased. Current ADA/EASD guidelines recommend introducing insulin to the regimen for HbA1c levels ≥10%–12%; therefore, our findings are suggestive of adherence to guideline recommendations.
Figure 3  Time to initiation of insulin in patients with T2DM for (A) PCPs and (B) specialists.

Notes: All patients were receiving ≥1 non-insulin antidiabetic treatment and could also have been receiving insulin, but insulin-only patients were excluded. As time to diagnosis of T2DM to the survey date was different in each patient within each wave, time to initiation of insulin was compared for the year the patient was diagnosed, rather than the survey year in which the patient was included. Data collected in Diabetes Disease Specific Programme 2011–2015, physician-completed patient record form. Base: year of diagnosis: pre-1999 (n=2,032), 2000–2003 (n=2,695), 2004–2007 (n=4,959), 2008–2011 (n=10,264), 2012–2015 (n=7,456).

Abbreviations: T2DM, type 2 diabetes mellitus; PCPs, primary care physicians.
Despite insulin now being initiated at higher HbA1c levels than in earlier years, the actual time to insulin initiation decreased over the study period, suggesting that insulin-naive patients are reaching these higher HbA1c levels sooner. Coupled with our data also showing that patient age at diagnosis has not changed over the survey time period, this would suggest that more patients are reaching the point of needing insulin treatment sooner in their disease progression.

A key finding of our research was that, despite the increased range of antidiabetic agents now available, HbA1c levels did not appear to be substantially better in 2015 than in 2000 in specialist-treated patients, although a small reduction was observed in patients treated by PCPs. This is likely to be a consequence of referral bias, with specialists seeing patients with more advanced, complex disease after failure of more straightforward therapy. In-line with our own findings, the
The prevalence of patients achieving HbA1c <7% reported in the US NHANES study increased from 43% in the 1988–1994 report to 57% in NHANES 2003–2007 report as a result of the availability of newer agents, before falling to 53% in 2007–2010. Further research is needed to establish why the development of new and effective antidiabetic agents has not led to better glucose control; however, as the mean change in HbA1c achieved is <1% for many of the glucose-lowering agents and >1% for only the SUs, GLPs, and insulins, the challenge faced by clinicians is considerable.

Some limitations of this analysis should be considered. Different waves of the Diabetes DSP surveys are based on questionnaires and interviews that changed over time depending on market changes, needs, and prescribing environments. This evolution of the DSP facilitates the collection of more timely and relevant data, which can be used to monitor trends in a changing landscape. For example, introduction in recent surveys of a key question such as “At what HbA1c level would you initiate insulin?” enhances disease management understanding in today’s market where newer agents offer pre-insulin options that did not previously exist. Information regarding the time from diagnosis to insulin initiation was recorded differently in the various surveys. Questions administered in 2011 and 2012 captured this information via a direct question to the physician in each patient form. Data collected during 2013–2015 derived this information via treatment history information, although it must be borne in mind that it is possible that there may be missing information as physicians might not have had access to the complete patient record from diagnosis, particularly if patients changed their physician (or insurer). Patients included in the surveys may not reflect the general diabetes population, as patients in these analyses are consulting their physician and represent those who are likely to consult more frequently.

Despite these limitations, real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials. Patients included in clinical trials represent a small proportion of the consulting population as a result of age restrictions and failure to meet stringent eligibility criteria. Patients treated in the real-world setting may be less likely to be adherent to medication than those included in clinical trials. As a result, data from real-world studies can complement clinical trials and provide insight into the efficacy of interventions in patients commonly seen in clinical practice.

**Conclusion**

Treatment choices after metformin monotherapy have increased markedly for patients with T2DM, as specialists in particular take advantage of the range of antidiabetic agents and insulins now available. The proportion of patients achieving good glucose control (HbA1c <7%) increased most between 2000 and 2008. However, despite the availability of the newer agents and earlier introduction of insulin regimens, no improvement in the proportion of patients achieving HbA1c <7% has been observed since that time. It would seem that further clarification is required to establish which T2DM treatment pathways should be utilized in individual patient types to achieve improved and sustained glycemic control.

**Acknowledgment**

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**Disclosure**

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**References**


Evidence for validity of a national physician and patient-reported, cross-sectional survey in China and UK: the Disease Specific Programme

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ABSTRACT
Objective: Diabetes represents a significant challenge for Chinese healthcare providers. Healthcare decision-making is generally based on many data sources, including randomised controlled and real-world studies; however, good-quality data from Chinese diabetes patients are scarce. We performed an initial validation to assess the representativeness of one source of real-world data—the Diabetes Adelphi Disease Specific Programme (DSP) in China.

Setting: China, UK.

Participants: The Chinese DSP included 2060 patients with previously diagnosed type 2 diabetes mellitus (T2DM) sampled by 200 physicians. The reference Chinese population comprised 238 639 patients with previously diagnosed T2DM. The UK DSP contained 1481 patients with T2DM sampled by 125 physicians; the reference UK population comprised 289 patients with diabetes.

Primary and secondary outcomes: The primary outcome was comparison of unweighted China DSP and reference data for sex, body mass index (BMI), blood pressure (BP), patients achieving glycosylated haemoglobin (HbA1c)<7%, total cholesterol, coronary heart disease and dyslipidaemia. The secondary outcome was comparison of weighted UK DSP and reference data for BMI, BP, mean HbA1c, total cholesterol, smoking and insulin status.

Results: Comparison of unweighted China DSP and reference data revealed statistical equivalence for BMI, systolic BP, proportion of patients achieving HbA1c<7%, total cholesterol, coronary heart disease and dyslipidaemia. Sex, age, diabetes duration, diastolic BP and mean HbA1c level were not equivalent, although differences were generally small. Weighting of data did not substantially affect the results. A similar pattern was observed for UK data.

Conclusions: This study provides evidence that the methodology used for the China and UK parts of the Diabetes DSP produces representative samples that are comparable with other independent sources of patient treatment outcomes data, which may ultimately inform public health decision-making. Although this method could be used in other countries, the current validation applies to UK and China. Further research is required for other countries.

INTRODUCTION
The International Diabetes Federation estimated the national prevalence of diabetes to be 9.32% for China in 2014,1 a significant increase from the <1% prevalence reported in 1980.2 This translated into an estimated 96 million individuals with diabetes and 1.2 million diabetes-related deaths in 2014.1 This represents a significant challenge; public health planners making formulary and reimbursement decisions must decide how to meet changing priorities by efficiently allocating funding and ensuring appropriate access to medicines. To date, treatment guidelines have largely been based on

Strengths and limitations of this study
- The Adelphi Real World Disease Specific Programme (DSP) is a valuable source of information on patients with type 2 diabetes in China, a region where reliable and up-to-date information is lacking.
- This analysis has demonstrated, by comparison with a large, reference population-based, cross-sectional survey, that the DSP population is representative of patients with type 2 diabetes in China.
- The representativeness of the DSP population was further supported by comparison of the UK Diabetes DSP with diabetes data gathered in the Health Survey for England.
- Limitations of the study include the selection of patients included in the DSP samples, which depends on the physician’s diagnostic skills, and the potential for over-representation of patients with more severe disease than the general population.
- Patient-level data were available for the DSP and Health Survey for England populations but not the Chinese reference population, for which only aggregate data were available; as a result, possible design bias could not be addressed in the Chinese reference population.
Evidence from non-Asian populations, although an increasing number of randomised clinical trials are now in progress in China.3

Currently, decisions regarding the availability and reimbursement of medicines are made at the government, regional, local and hospital level in China. Decision-makers have differing evidentiary requirements and varied data are required to support the value of specific interventions. Data need to be current, treatment-specific, valid at a patient level, relevant and obtained from a representative sample. Outcomes data are also required, including safety and drug surveillance information, and efficacy, cost and resource-use data. Such data may be scarce and not readily available.

Although considered the gold standard for questions relating to efficacy and safety, data from randomised controlled studies are often unrepresentative of the population in which the intervention will be used because of strict inclusion criteria. Renal and cardiovascular complications may lead to the exclusion of many patients with diabetes from randomised clinical studies.1 For example, only half of Finnish patients with diabetes beginning treatment with statins for diabetic dyslipidaemia would have qualified for inclusion in the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study.5 Epidemiological or ‘real-world’ studies provide information on larger, more representative populations but are generally not accessible to patient-level interrogation.

One source of real-world data for Chinese patients with diabetes is the Adelphi Real World Disease Specific Programme (DSP) for diabetes. DSPs, which are cross-sectional surveys generating data from real-world clinical practice, collect current patient demographic data and treatment practices, in addition to resource-use and quality-of-life data, in specific therapy areas and meet the majority of the criteria described above.6 DSPs have been conducted for a variety of therapy areas, including diabetes, in countries with varying healthcare systems and following societal changes, such as seen in China.

One important consideration of DSP validation is determining the representativeness of the data compared with wider populations. With that aim, we compared DSP diabetes data for China against a reference Chinese data source. To support this analysis, we performed a similar validation of the DSP in a developed western market with a contrasting socioeconomic and healthcare system to China, to demonstrate the adaptability of the data collection methodology. We selected the UK for this confirmatory validation because the availability of a reliable reference data source made it possible to assess the representativeness of DSP diabetes data for the UK compared with the wider UK population. We hypothesised that, viewed together, these analyses would provide evidence for the representativeness of the DSP as a source of real-world evidence for patients with diabetes in China.

**METHODS**

**Disease Specific Programmes**

DSPs are large, multinational surveys of clinical practice that describe current disease management, disease-burden impact and associated treatment effects (patient-reported, clinical and physician-reported). The survey method is designed to adapt to any country, culture or disease area, with rapid implementation facilitating collection of up-to-date data. DSPs collect qualitative and quantitative data from four key sources of information: physician interviews, physician workload questionnaires, patient record forms completed by the doctor and questionnaires completed by the same patients. Physicians are selected for participation based on their eligibility to participate in the DSP in terms of specialty, location (hospital or office), whether they are personally responsible for treatment decisions and how many patients they see in a typical week. Candidate physicians who meet these criteria are invited to participate in the DSP; those who agree to participate are reimbursed for their time according to national reimbursement rates in their country. Patients are recruited only once and have no further follow-up as each DSP is a point-in-time survey. DSPs are repeated every 1 or 2 years, depending on the disease area, introduction of new treatments and how often guidelines are updated. The stages of DSP development are summarised in online supplementary figure S1; full details of DSP methodology have been published previously.5

The Diabetes DSPs selected for this analysis were conducted in China in 2012 and in the UK in 2013; these versions were chosen to match the time of data collection for the reference data sources. Geographically representative primary care physicians and specialists (hospital physicians only in China) were asked to sample the next 10 patients presenting with type 2 diabetes mellitus (T2DM), aged >18 years and currently taking antidiabetic drugs. Additional criteria that applied specifically to the present analysis, over and above those used to recruit patients for the DSP and in order to match the criteria of the comparator study, were that patients were not to be presenting for the first time with T2DM and insulin monotherapy was not allowed. Physicians completed a patient record form for these patients and gave them a patient self-completion form. Physicians recorded information on patient demographics, clinical characteristics (including glycaemic control and hypoglycaemic events in the Diabetes DSP), medications administered and resource use. The questions used in this analysis in China and the UK are shown in online supplementary appendices 1 and 2, respectively. Although not used in this analysis, the voluntary patient self-completion forms collected information about how diabetes affected the patient’s everyday life, together with their opinions and understanding of their medications and glycaemic control. Patients could complete any or none of the questions and were instructed to complete the form without help from their healthcare practitioner.
The DSP is research involving survey procedures and as such does not require ethics committee approval. Patients provide informed consent for use of their anonymised and aggregated data for research and publication in scientific journals. This is achieved by means of a check box on the front page of the patient-completed survey. Data are collected in such a way that patients and physicians cannot be identified directly, with all data being aggregated and de-identified before receipt by Adelphi Real World. DSPs are performed in accordance with the European Pharmaceutical Marketing Research Association (EphMRA) guidelines and the US Health Insurance Portability and Accountability Act 1996.

Comparator data
The Chinese reference data set was based on a multicentre, cross-sectional survey of outpatients with T2DM in 606 hospitals across China between April and June 2011. The first seven patients entering the facilities and meeting the following criteria were included: diagnosed with T2DM; one or more previous outpatient medical record pertaining to diabetes; aged ≥18 years; and treated with oral antidiabetic agents, either alone, with insulin or with glucagon-like peptide-1 agonists.

The UK Diabetes DSP data were compared against the Health Survey for England (HSFE) 2011 (10 617 patients). This is a cross-sectional, country-wide health survey that monitors health trends across the general population, estimating proportions of people with specified health conditions and the prevalence of risk factors and combinations of risk factors associated with these conditions. The 2011 HSFE had a special focus on cardiovascular disease, hypertension and diabetes, and included diabetes-related variables, for example, age at diagnosis and insulin treatment, in addition to standard demographic data and information on other disease areas. The HSFE included patients taking antidiabetic medication and those managing their condition with insulin alone or with diet and exercise alone; we applied exclusion criteria to identify those with T2DM who were treated with an antidiabetic medication.

To ensure comparability of the UK DSP and HSFE populations, patient characteristics were matched as closely as possible. This required exclusion of patients aged ≤18 years; diagnosed before age 35 years and treated with insulin (a proxy for type 1 diabetes in the absence of an explicit indicator in this database); and those not receiving endocrine drug treatment (a broad term used in the HSFE coding system and used in the current analysis to exclude patients managing their condition with diet and exercise). Pregnant women were also excluded.

Statistical analysis
Clinical and demographic characteristics common to the China DSP and Chinese reference population and the UK DSP and the HSFE data were compared to assess the validity of the UK and China DSPs. In order to compare the DSP and reference populations, weighting was needed to correct for imbalances between the groups. In the DSPs, patients consulting more frequently have a greater chance of selection and for a given frequency of visiting, a patient’s chance of being sampled is a function of the total number of patients managed by the doctor, that is, the more patients a doctor manages, the less likely it is that any individual will be sampled. Inverse probability weighting was used to account for this, incorporating the frequency of visits made by the patient in the last 12 months (adjusted to 12 months if the patient had been managed for <12 months) and the total number of patients managed by each doctor (in conjunction with the number of patients sampled by each doctor). A random sample of patients with T2DM would include very few patients diagnosed on the same day as the study sampling, whereas the DSP population contained a relatively high number of patients attending for initial diagnosis because patients were sampled on days when they consulted their doctor. To better approximate a random sample, as well as matching the inclusion criteria for the comparator study in China, patients diagnosed on the day of the sample were excluded from the weighted analysis. The HSFE 2011 used a clustered stratified multistage sampling design. Similar to the weighting applied to the DSP, weights were applied to the HSFE data, according to guidance issued by the HSFE, to account for selection and non-response bias. Missing data were assumed to be missing at random and were not imputed.

Standard tests, such as the t-test and χ² test, assume a null hypothesis that the two comparator groups are the same. Only if the p value is <0.05 can that hypothesis be rejected and a significant difference be claimed. A p value ≥ 0.05 does not allow the claim that there is no difference. Therefore, standard tests were not appropriate in this analysis, where the aim was to show no difference and tests for ‘equivalence’ were required. Variables common to each pair of data sets were compared using two one-sided tests aimed at testing for equivalence. Two means are considered equivalent if they occur within a predefined ‘distance’ or tolerance of each other. A sensible tolerance is the minimum important difference (MID). If the MID is unknown, assuming an MID of 25–50% of the overall SD is considered reasonable. In the present analysis, an MID of 25% was assumed for all variables. For proportions of patients (eg, proportion with hypertension), an MID of 25% of that proportion was used.

RESULTS
China
The Chinese DSP included 2060 patients with T2DM sampled by 200 physicians. A total of 398 patients were receiving insulin only and were excluded in line with the reference population; the Chinese unweighted DSP
population therefore included 1662 patients with T2DM. Table 1 shows clinical and demographic variables collected in both surveys. Patients’ mean body mass index (BMI) was on the upper limit of normal at 24.3 kg/m². Mean diastolic blood pressure (DBP) and systolic blood pressure (SBP) were high (83.2 and 132.7 mm Hg, respectively), mean glycosylated haemoglobin (HbA1c) level was high (7.4%) and the proportion of patients with HbA1c <7% was low (33%). Weighting of data to account for DSP design bias led to the exclusion of 79 patients but did not substantially change any disease characteristics other than the proportion of patients with comorbidities.

The reference Chinese population comprised 238 639 patients with T2DM. Patients had a mean age of 58.7 years, mean BMI of 24.4 kg/m² and mean diabetes duration of 5.6 years (table 1). Mean DBP and SBP were high (81.0 and 131.9 mm Hg, respectively); mean total cholesterol level was normal at 183 mg/dL, although mean HbA1c level was high (7.9%) and the proportion of patients with HbA1c <7% was low (32%).

Comparison of the unweighted China DSP and Chinese reference populations revealed statistical equivalence for BMI, SBP and the comorbidities coronary heart disease and dyslipidaemia (table 1). Variables for which there was not enough evidence for equivalence were sex, age, duration of diabetes, DBP and HbA1c level, although the proportion of patients achieving an HbA1c level <7% was equivalent in both populations. Weighting of the DSP data did not substantially affect these differences.

**United Kingdom**

The UK DSP contained 1481 patients with T2DM sampled by 125 physicians; 1213 patients were eligible for inclusion in the analysis of unweighted data. In total, 268 patients were not eligible because they had type 1 diabetes (n=244), were diagnosed before the age of 35 years and treated with insulin only (n=19) or were pregnant (n=5). Weighting resulted in exclusion of another 41 patients who were diagnosed with diabetes on the day of the survey; the weighted analysis population thus comprised 1172 patients.

Overall, 8610 adults and 2007 children were interviewed for the 2011 HSFE; 2296 were excluded as they were under the age of 18 years, 7878 did not have a diagnosis of diabetes and 244 were not receiving an endocrine agent and were also excluded. The UK reference population therefore comprised 289 patients. Variables collected in both surveys are given in table 2. Total cholesterol levels were normal in both groups, as was DBP, SBP and BMI were high in both groups.

Comparison of the unweighted UK DSP and HSFE populations revealed statistical equivalence in sex, age at diagnosis, BMI and total cholesterol level (table 2). Some exceptions, where equivalence could not be demonstrated, were observed. DSP patients were younger, had a shorter time since diagnosis, lower HbA1c level and higher SBP and DBP than HSFE patients. Weighting of the UK DSP population did not substantially affect these differences, with the exception of total cholesterol level, which became statistically equivalent after weighting.

**DISCUSSION**

Public health planners in China face a diabetes epidemic and must make treatment recommendations complicated by a paucity of good-quality data obtained in relevant populations in a timely manner. While collection and reporting of data is improving, data are scarce that satisfy all the criteria required to meet the needs of Chinese decision-makers. DSPs offer one solution to this issue, being sufficiently up to date, collected rapidly and frequently and containing information on a breadth of clinical, demographic and outcome variables that can inform public health decision-making when used with other supporting data.

The current analysis was undertaken to demonstrate the representativeness of DSP data compared with the Chinese T2DM population. Comparison of the China DSP and reference Chinese populations identified equivalence in many variables common to both studies. Some areas of non-equivalence were observed: time since diagnosis of diabetes was longer in patients in the reference population and DBP values were non-equivalent, although the difference was small (<2 mm Hg) and its clinical relevance questionable. Mean HbA1c level was non-equivalent, although the proportion of patients achieving HbA1c <7% was equivalent. This suggests that the reference data set may have contained more patients with high values, which would have a greater impact on mean HbA1c than on the proportion with HbA1c <7%.

The between-group difference is within the bounds of natural variation, as reflected by the SDs and the mean baseline HbA1c levels of 7.0–8.3% reported in other observational and phase IV studies or surveys. The comparison of UK DSP and HSFE diabetes data, which was performed to substantiate the findings of the Chinese comparison, also provided evidence for the representativeness of the DSP, with equivalence in many of variables. Although equivalence was not demonstrated for some, including patient age and time since diagnosis, this may reflect different characteristics of presenting patients in the DSP versus the randomly selected HSFE group. HbA1c and SBP were non-equivalent, although between-group differences were small (<0.2% and 2.5 mm Hg, respectively), within the bounds of natural variation as reflected by the SDs and of questionable clinical relevance.

In line with other observational and real-world studies, several limitations of the data sources should be considered. The primary limitations of the DSP relate to selection and diagnosis of patients. Physicians were asked to include the next 10 presenting patients with T2DM to reduce selection bias. The integrity of this process...
depends on the physician’s diagnostic skills as no formal entry criteria were specified. In addition, this process favours patients presenting more frequently, as more frequent consultation increases the likelihood of selection. Although we corrected for this using a weighting process, the possibility cannot be excluded that patients with more severe disease or complications might be over-represented in the DSP population. No patient-level data were available for the Chinese reference source and aggregated evidence was used instead. As a result, design bias could not be corrected through weighting. This means that even if the DSP data were perfectly corrected to be representative of the Chinese diabetes population, some differences would still be observed. We noted differences between the DSP and reference populations that were not corrected either by looking only at the prevalent population or by weighting; further research is required to identify potential reasons for such differences. The HSFE also has limitations, including oversampling in underpopulated areas, lack of response and differences in how study visits and procedures were performed. These limitations were addressed using a complex weighting strategy. Potential bias relating to non-response as a result of ill health was however, not accounted for in the HSFE. These limitations must be taken into consideration before generalising the findings to other populations.

The strengths of the DSP approach should be considered. Although the DSPs are exploratory studies that complement rather than replace larger studies, advantages include the ability to rapidly perform studies in relatively small populations that nonetheless provide insights into diseases, attitudes and outcomes that might otherwise be difficult to obtain in such a timely manner.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chinese reference population (n=238 639)</th>
<th>DSP unweighted n=1662</th>
<th>Missing</th>
<th>p Value*</th>
<th>DSP weighted† n=1583</th>
<th>Missing</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>52.2</td>
<td>47.7</td>
<td>0</td>
<td>1.0000</td>
<td>46.7</td>
<td>0</td>
<td>1.0000</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>58.7 (11.7)</td>
<td>56.1 (11.3)</td>
<td>0</td>
<td>0.1423</td>
<td>56.4 (11.1)</td>
<td>0</td>
<td>0.0063</td>
</tr>
<tr>
<td>Mean time since diagnosis, years (SD)</td>
<td>5.6 (5.3)</td>
<td>3.3 (3.6)</td>
<td>34</td>
<td>1.0000</td>
<td>3.5 (3.5)</td>
<td>34</td>
<td>1.0000</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>24.4 (3.2)</td>
<td>24.3 (3.1)</td>
<td>6</td>
<td>0.0000</td>
<td>24.5 (3.2)</td>
<td>6</td>
<td>0.0000</td>
</tr>
<tr>
<td>Mean total cholesterol level, mg/dL (SD)</td>
<td>182.9 (57.2)</td>
<td>185.4 (39.6)</td>
<td>399</td>
<td>0.0000</td>
<td>186.9 (41.5)</td>
<td>379</td>
<td>0.0000</td>
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<tr>
<td>Mean HbA1c, % (SD)</td>
<td>7.9 (1.7)</td>
<td>7.4 (1.0)</td>
<td>73</td>
<td>1.0000</td>
<td>7.3 (1.0)</td>
<td>71</td>
<td>0.9990</td>
</tr>
<tr>
<td>HbA1c &lt;7%, %</td>
<td>31.8</td>
<td>32.8</td>
<td>73</td>
<td>0.0000</td>
<td>33.3</td>
<td>71</td>
<td>0.0000</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg (SD)</td>
<td>81.0 (11.1)</td>
<td>83.2 (8.6)</td>
<td>54</td>
<td>0.0962</td>
<td>83.1 (8.1)</td>
<td>51</td>
<td>0.1439</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg (SD)</td>
<td>131.9 (15.1)</td>
<td>132.7 (12.3)</td>
<td>54</td>
<td>0.0000</td>
<td>133.4 (11.8)</td>
<td>51</td>
<td>0.0000</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td>10.9</td>
<td>9.2</td>
<td>0</td>
<td>0.0000</td>
<td>8.8</td>
<td>0</td>
<td>0.0000</td>
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<tr>
<td>Coronary heart disease</td>
<td>19.7</td>
<td>22.8</td>
<td>0</td>
<td>0.0000</td>
<td>25.6</td>
<td>0</td>
<td>0.0193</td>
</tr>
</tbody>
</table>

Values in bold are p>0.05, that is, evidence is not strong enough to show equivalence.

*p Value for comparison with Chinese reference population.
†Weighted to account for design bias in the DSP.
BMI, body mass index; BP, blood pressure; DSP, Disease Specific Programme; HbA1c, glycosylated haemoglobin.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HSFE (n=289)</th>
<th>DSP unweighted n=1213</th>
<th>Missing</th>
<th>p Value</th>
<th>DSP weighted* n=1172</th>
<th>Missing</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>58.2</td>
<td>58.4</td>
<td>0</td>
<td>0.0001</td>
<td>57.7</td>
<td>0</td>
<td>0.0003</td>
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<tr>
<td>Mean age, years (SD)</td>
<td>63.9 (13.7)</td>
<td>61.5 (12.7)</td>
<td>32</td>
<td>0.1747</td>
<td>61.8 (12.5)</td>
<td>12</td>
<td>0.117</td>
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<tr>
<td>Mean age at diagnosis, years (SD)</td>
<td>54.1 (14.1)</td>
<td>54.6 (11.5)</td>
<td>98</td>
<td>0.0011</td>
<td>54.7 (11.5)</td>
<td>98</td>
<td>0.0027</td>
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<tr>
<td>Mean time since diagnosis, years (SD)</td>
<td>9.7 (9.1)</td>
<td>6.9 (6.2)</td>
<td>87</td>
<td>0.989</td>
<td>7.3 (6.1)</td>
<td>87</td>
<td>0.925</td>
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<tr>
<td>Current smoker, %</td>
<td>14.3</td>
<td>16.1</td>
<td>32</td>
<td>0.0002</td>
<td>15.7</td>
<td>32</td>
<td>0.0018</td>
</tr>
<tr>
<td>Insulin treated, %</td>
<td>21.0</td>
<td>26.3</td>
<td>0</td>
<td>0.0281</td>
<td>25.5</td>
<td>0</td>
<td>0.018</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>32.3 (6.3)</td>
<td>31.6 (6.6)</td>
<td>46</td>
<td>0.0241</td>
<td>31.5 (6.7)</td>
<td>46</td>
<td>0.0374</td>
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<tr>
<td>Mean total cholesterol level, mg/dL (SD)</td>
<td>172.1 (51.1)</td>
<td>178.3 (55.9)</td>
<td>121</td>
<td>0.0619</td>
<td>176.7 (54.7)</td>
<td>101</td>
<td>0.0349</td>
</tr>
<tr>
<td>Mean HbA1c, % (SD)</td>
<td>8.0 (1.6)</td>
<td>7.8 (1.7)</td>
<td>17</td>
<td>0.0754</td>
<td>7.8 (1.7)</td>
<td>13</td>
<td>0.063</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg (SD)</td>
<td>71.1 (11.3)</td>
<td>76.8 (9.6)</td>
<td>216</td>
<td>1.0000</td>
<td>76.7 (9.5)</td>
<td>206</td>
<td>1.0000</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg (SD)</td>
<td>132.6 (16.5)</td>
<td>134.9 (15.4)</td>
<td>216</td>
<td>0.0700</td>
<td>135.1 (15.6)</td>
<td>206</td>
<td>0.0109</td>
</tr>
</tbody>
</table>

Values in bold are p>0.05, that is, evidence is not strong enough to show equivalence.
*Weighted to account for design bias in the DSP.
BMI, body mass index; BP, blood pressure; DSP, Disease Specific Programme; HbA1c, glycosylated haemoglobin; HSFE, Health Survey for England.
and at in-depth patient level. A consistent methodology is used for DSPs across countries and economic environments, enabling cross-country comparisons. This may not be possible using registries or databases designed to be specific for a particular country or region. DSPs can also include elements related to patient-reported outcomes and impact on usual activities, providing insights into aspects not routinely assessed in randomised clinical trials.

Observational studies, such as performed by Ji et al., provide important epidemiological information in rapidly changing healthcare environments. This reference population comprised patients from 606 hospitals representing every region of mainland China other than Tibet and was designed to represent all regions of the Chinese mainland. Other strengths include the population size and census-style data. All patients were consulting a physician, similar to the DSP, and physicians sampled consecutive presenting patients in both studies. The strength of the HSFE lies in its epidemiological robustness in terms of general population coverage and collection of comprehensive clinical data and patient-reported symptom and burden outcomes from a representative cross section of England, repeated annually with a consistent methodology. Both sources complement the DSPs as a result of consistency of overlapping variables; the depth of information provided by the DSPs on a smaller number of patients also complements the larger but less detailed data presented by Ji et al and the HSFE.

Ultimately, no single source provides all the data needed by every stakeholder. The China DSP and reference study are complementary and valid as variables common to both studies are consistent. Importantly, the independence of each study allows validation of the other. The HSFE and UK DSP have also been shown to be complementary, each validating the other. The DSPs can therefore be used to complement data from clinical trials performed in well-defined but potentially unrepresentative populations to provide an update on data otherwise obtained from large-scale but costly and time-consuming epidemiological studies. Based on the results of the present analysis and considering the limitations discussed above, the Chinese and UK DSP data could be considered appropriate for inclusion in submissions for health technology assessments. While the DSPs are a useful additional tool for modelling and health technology authority requirements, further validation is required to determine whether data from countries other than China and the UK can be extrapolated to larger populations.

In conclusion, the present analysis indicates that the China Diabetes DSP with appropriate weighting applied, is an epidemiologically valuable source of information on patients with T2DM that is representative of the wider diabetes population in China, as indicated by comparability of data collected in the DSP and a reference population-based cross-sectional survey. Comparison of the UK Diabetes DSP and a reference UK diabetes population derived from the HSFE provides further support for this approach in the diabetes setting. Together, these findings highlight the need for good-quality data collected using standardised collection methodologies and suggest that data generated using the DSP methodology may complement other data sources of information on patients with T2DM by filling a need for up-to-date patient treatment outcome data, which may ultimately inform public health decision-making in China.

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Collaborators Victoria Higgins and Andrea Leith.

Contributors SMB, BC, TH, GM and JP jointly designed the study and GM performed the statistical analyses. All authors participated in drafting and revising the manuscript. All authors read and approved the final manuscript.

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Competing interests SMB and BC are employed by and shareholders in Eli Lilly & Co. TH, GM and JP are employed by Adelphi Real World.

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Evidence for validity of a national physician and patient-reported, cross-sectional survey in China and UK: the Disease Specific Programme

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Adherence among type 2 diabetes mellitus (T2DM) patients: real-world physician and patient views and characterisation

Introduction/Objectives

- The prevalence of type 2 diabetes mellitus (T2DM) is high and continues to increase due to aging populations and rising obesity rates across the world.1
- Increasing diabetes prevalence is concerning, especially when these patients are already at increased risk for comorbid conditions compared with non-diabetic patients resulting in multiple chronic medication use.3
- While the ultimate goal of diabetes therapy is to achieve good glycaemic control, many patients are not achieving optimal control due to non-adherence factors.1

This analysis investigates the differing views of adherence among physicians and their patients and characteristics non-adherent versus adherent T2DM patients.

Data/methodology

- Methods were drawn from the 2015 Adelphi Real World Diabetes Disease Specific Programme (DSP) in T2DM conducted across the US and EU between May and August. The DSP methodology has been published previously.6
- The DSP is a real-world, cross-sectional survey involving specialists (endocrinologists and diabetologists) and primary care physicians (PCPs) who were asked to complete the next 10 consulting T2DM patients. Data collection includes information regarding current therapy, HbA1c, values and physician-perceived assessment of patient compliance.

- The same patients were invited to complete an unassisted, voluntary survey when they next attended the clinic. The T2DM DSP is a real-world, cross-sectional survey involving specialists (endocrinologists and diabetologists) and primary care physicians (PCPs) who were asked to complete the next 10 consulting T2DM patients. Data collection includes information regarding current therapy, HbA1c, values and physician-perceived assessment of patient compliance.18

- The patient groups, injectable naïve and injectable experienced, were asked how they would be starting an anti-diabetic injectable medicine, defined as understanding of need for injectable medicine versus how concerned they would be taking injectable medicine. Each used a scale of 1 to 7, where 1 was ‘Do not understand need for injectable medicine’/‘Very concerned about taking injectable medicine’ and 7 was ‘Fully understand need for injectable medicine’/‘Not at all concerned about taking injectable medicine.’

Conclusions

- These real-world research findings suggest that poorly adherent T2DM patients, as measured by a patient-reported validated tool, are greatly under-recognised by physicians.
- Patients with low adherence are more likely to smoke heavily, be from a lower socio-economic demographic, have obesity and lifestyle concerns, and present with higher number of products for all conditions (diabetic and non-diabetic), both with poor glucose monitoring and control resulting in a higher number of hypoglycaemic episodes.1
- Coupled with high product burdens and patient-perceived low needs for medicine, it is clear that improved healthcare practitioner and patient awareness could result in better adherence to diabetes therapy, which could in turn, improve glucose control.

References

Objectives

- Guidelines endorse a patient-centered approach to the management of T2DM, recommending GLP-1 RA and/or insulin therapy as 2nd or 3rd line options.1
- Diabetes patients transitioning to GLP-1 RA and/or insulin therapy use can often have controversies about gastrointestinal disturbances, weight gain, hypoglycaemic episodes, needle phobias/reactions and fears of advancing disease.

This analysis explores T2DM patients on injectable therapies (GLP-1 RA and/or insulin) with/without oral anti-diabetics, their needs versus concerns around injecting, impact on compliance and associated characteristics.

Methods

- Data were drawn from the 2015 Adelphi Real World Diabetes Disease Specific Programme (DSP) in T2DM conducted across the US and 5 EU markets (France, Germany, Italy, Spain and the UK).
- The Diabetes DSP is a real-world, cross-sectional survey of 600 endocrinologists and primary care physicians completing physician-reported questionnaires for their next 10 consulting T2DM patients.
- The same patients are invited to complete an unassisted, voluntary questionnaire.
- Full details of the methodology and validation of the sample have been published.2,3
- The DSP inclusion criteria were T2DM patients aged ≥18 years and receiving at least one anti-diabetic therapy.
- Patients were excluded from this analysis if they did not receive at least one anti-diabetic injectable therapy (GLP-1 RA and/or insulin).
- Physicians and patients provided de-identified data in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Prior to analysis, personal identifiers were removed.
- Patients currently on injectable medication were asked how they felt about injecting themselves, defined as understanding of need for injectable medication and how concerned they are when injecting medication. Each used a scale of 1 to 7, where 1 was ‘Do not understand need for injectable medication’/Very concerned about taking injectable medicine’ and 7 was ‘Fully understand need for injectable medication’/Not at all concerned about taking injectable medicine’.
- Patients were classified into quadrants based on their perceived need versus concern levels around injectables:
  - low concern/low need (LCLN)
  - low concern/high need (LCHN)
  - high concern/low need (HCLN)
  - high concern/high need (HCHN).
- Adherence was measured using the patient-reported validated Morisky Medication Adherence Scale (MMAS-8) and reported in the following intervals: 0-2 (0-5), 3-5 (6-7) or high (8-9) adherence.4
- Statistical methods: Percentages and descriptive statistics were derived. Pairwise comparisons were made using Kruskal-Wallis on χ² tests, depending on the type of variable tested (continuous/categorical). Fractional logistic regression was used to model the relationship between needs and concerns, and the MMAS-8.

Results

- Of the total 8,368 patients included in the Diabetes DSP, 3,585 were eligible for this analysis, i.e. receiving an injectable therapy and had provided a patient-completed form with a corresponding physician-reported form.
- Figure 1 shows the proportion of patients in each need versus concern quadrant for SEU/US.
- Majority of patients were LCHN in both regions (SEU 73%; US 71%), but in 12 patients were HCLN (7% US 8%).

![Figure 1: Patient-reported need vs concern regarding anti-diabetic injectable medicine](image)

Table 1: Current injectable patients (i) LCLN vs (ii) LCHN vs (iii) HCLN vs (iv) HCHN

<table>
<thead>
<tr>
<th>Region</th>
<th>LCLN (n=141)</th>
<th>LCHN (n=141)</th>
<th>HCLN (n=141)</th>
<th>HCHN (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEU</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>US</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

- Compared with the other 3 quadrants, SEU HCLN patients were most likely to be male (61.3%), have the worst Hba1c (8.3%), the most comorbidities (4.7), the highest physician-reported ‘very high’ cardiovascular (CV) risk (12.5%) and the highest overall burden pill (8.9) [see Table 1].
- Some differences were observed between SEU and US HCLN patients. US HCLN patients had the same profile except they are less likely to be male (US 34.3% vs SEU 61.3%), have fewer comorbidities (3.7 vs 4.7) and lower physician-reported ‘very high’ CV risk (9.9% vs 12.5%). Interestingly, US HCHN patients are mostly likely to mirror the SEU HCLN patient profile.

![Figure 2: Influence of patient-reported need vs concern regarding anti-diabetic injectable medicine on patient-reported adherence](image)

Conclusions

- Patient-reported needs versus concerns towards injectable therapy influence adherence.
- Patients with HCLN towards injectables appear least adherent with poor Hba1c, highest CV-risk and pill burden, suggesting they do not understand their high clinical need.
- Such lack of patient understanding coupled with high concerns warrants attention.
- It must be noted that this analysis did not distinguish between different dosing schedules, ranging from multiple daily injections through to once-weekly. Further research will be needed to assess the impact of injection frequency on the needs and concerns described in this analysis.

References