Patient-reported outcomes of dipeptidyl   peptide-4 inhibitors: a systematic review.

Background
- The individualization of treatment is key in type 2 diabetes mellitus (T2DM) patients according to guidelines.2
- Besides efficacy and safety outcomes, patient preferences, treatment adherence and health-related quality of life (HRQoL) should be taken into account in treatment choice.3
- Recent systematic reviews including dipeptidyl-peptide-4 (DPP-4) inhibitors have explored clinical or economic outcomes, but patient-reported outcomes (PROs) have not been considered.

Objective
- To synthesize the available information on the therapeutic value of DPP-4 inhibitors for T2DM treatment considering published data on PROs.

Materials and methods
- A systematic review was performed on Spanish (IBECS, MEDES) and international (PubMed, ISI WOK, Scopus, Cochrane Library) databases.
- Observational studies regarding HRQoL, adherence, persistence, satisfaction or preferences assessed in T2DM patients receiving DPP-4 inhibitors. The selected studies were published in English or Spanish until June 2013.

Results
- Of 1,713 references identified, 13 full-text articles were evaluated for eligibility and 4 publications met inclusion criteria (Figure 1).

Figure 1. Results of systematic review
- The characteristics of the selected publications are described in table 1.

Table 1. Characteristics of selected publications

<table>
<thead>
<tr>
<th>First author, publication year, country, OCEBM</th>
<th>Design</th>
<th>Population</th>
<th>PROs evaluated</th>
<th>Adherence</th>
<th>Satisfaction</th>
<th>Preferences</th>
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<tbody>
<tr>
<td>Curkendall M, 2013, USA (2c)</td>
<td>Observational retrospective study</td>
<td>79,518 T2DM patients (18+ years old) receiving DPP-4 inhibitors, GLP-1 analogs, SU or T2D by 2 year</td>
<td>Adherence: Proportion of days covered (adherent if PDC ≥0.8)</td>
<td>Persistence: Time to discontinuation</td>
<td>0.71</td>
<td>0.46 (0.40, 0.52)</td>
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<tr>
<td>Genovese S, 2013, Italy (3b)</td>
<td>Observational prospective study</td>
<td>1,448 T2DM patients (18+ years old) not adequately controlled with metformin which received DPP-4 inhibitors/metformin (fixed combination) as a second step observed for up to 1 year from prescription</td>
<td>Adherence: Diabetes Treatment Satisfaction Questionnaire (DTSQ) 5-item (all satisfied): 1 year from prescription</td>
<td></td>
<td>0.69</td>
<td>0.71 (0.65, 0.77)</td>
</tr>
<tr>
<td>Rathmann W, 2013, Germany (2a)</td>
<td>Observational retrospective study</td>
<td>19,184 T2DM patients receiving DDP-4 inhibitors and S1,110 receiving SU</td>
<td>Adherence: Continuously refilling the prescription within 90 days of the previous dispensing.</td>
<td>0.76</td>
<td>0.71 (0.65, 0.77)</td>
<td>0.04 (0.01, 0.08)</td>
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<tr>
<td>DiBonaventura M, 2013, USA, France, Italy, Germany, Spain and United Kingdom (2a)</td>
<td>Observational cross-sectional study</td>
<td>T2DM patients receiving metformin monotherapy. n = 2,402 completed a first wave. A second wave was conducted because newer data became available after wave 1 from a head-to-head trial (sitagliptin and linagliptin)</td>
<td>Adherence: Patients were asked which medication profile they would prefer. Both profiles included 4 attributes: frequency and mode of administration, efficacy in HbA1c reduction, side effects (hypoglycemia, nausea, vomiting and diarrhea), other effects (changes in weight, blood pressure).</td>
<td></td>
<td>0.71</td>
<td>0.46 (0.40, 0.52)</td>
</tr>
</tbody>
</table>

References:

Two studies reported information about adherence/persistence, one about satisfaction and another one about preferences. No information about HRQoL was identified.

Adherence and persistence
Curkendall et al., evaluated adherence and persistence in patients receiving DPP-4 inhibitors, GLP-1 agonists, SU and TZD showing that:
- Patients receiving DPP-4 inhibitors were more likely to be adherent than those treated with GLP-1 agonists [Odds Ratio, OR=0.49; 95% CI[0.37-0.62], SU [OR=0.49; 95% CI[0.46-0.52] or TZD [OR=0.54; 95% CI[0.51-0.57].
- Patients receiving DPP-4 inhibitors were more persistent compared with GLP-1 agonists, SU and TZD (OR reported graphically).
- Compared with DPP-4, the probability of discontinuation was 71% higher for those taking GLP-1 analogs, 63% higher for those taking SU, and 55% higher for those taking TZD.
- Adherence may be better with DPP-4 inhibitors due to a better tolerability than with the other medications.

Rathmann et al., evaluated treatment persistence to DPP-4 inhibitors and sulfonylureas showing that:
- DPP-4 inhibitors were associated with a lower risk of treatment discontinuation (non-persistence: 39%) compared with SU (49%) [Hazard Ratio=0.74; 95% CI[0.71-0.76].
- In this study, previous hypoglycemia was related to a future risk of hypoglycemic events. The authors suggested that this fact could contribute to non-persistence.

Patient satisfaction
The results of the study conducted by Genovese et al., showed that:
- Combination of DPP-4 inhibitors and metformin increased patient's satisfaction a 30% compared with metformin monotherapy.
- The proportion of patients ‘very satisfied’ with treatment increased from baseline by 44.7%; patients who perceived themselves as hyperglycemia-free increased a 37% from baseline (from 6.3% to 26.9%) and those who perceived as hypoglycemia-free increased a 15.2% (from 29.8% to 40.9%).
- The authors supported these findings with clinical data: improvement of HbA1c in 54% of patients and stabilization of HbA1c in 41%.

Treatment preferences
DiBonaventura et al., study showed that:
- Most patients preferred the DPP-4 inhibitor profile over the GLP-1 agonist profile (wave 1: 81.9% vs. 18.1%; wave 2: 84.4% vs. 15.6%; p<0.001).
- Most patients preferred to take first the DPP-4 inhibitor profile over GLP-1 agonist profile, if they could switch later (wave 1: 82.8% vs. 17.2%; wave 2: 85.0% vs. 15.0%; p<0.001).
- Most patients believed they could take the DPP-4 inhibitor profile longer than the GLP-1 agonist profile (wave 1: 83.4% vs. 16.6%; wave 2: 86.5% vs. 13.5%; p<0.001).
- In the Spanish population (n=188), the proportion of patients preferring DPP-4 inhibitors was even higher (90.4% vs. 9.6%; p<0.001).

Conclusions
- PROs in DPP-4 inhibitors are poorly described in the literature.

Nevertheless, DPP-4 inhibitors are preferred as first option and are associated with higher persistence and satisfaction levels, mainly due to higher perception of glycemic control and lower hypoglycemia risk.