

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists (CHADIG Study): a cross-sectional multicentre study in Spain
AUTHORS	Conget, Ignacio; Mauricio, Didac; Ortega-Basagoiti, Rafael; Detournay, Bruno

VERSION 1 - REVIEW

REVIEWER	Carlo Bruno Giorda Diabetes & Metabolism Unit ASL TORINO 5 via Demaria, 1 10023 Chieri TO ITALY
REVIEW RETURNED	29-Oct-2015

GENERAL COMMENTS	<p>This study reports the result of rather small survey on the mode of prescription of GLP-1 RA in Spain.</p> <p>The main limitation of the manuscript is its lack of novelty and originality. These results may raise some interest at a local level but have little appeal at the international level. The findings are largely expected as they reflect the well-known indications for choosing a GLP1-RA therapy in the clinical setting.</p> <p>It presents a major limitation :</p> <p>There is no comparison with a similar (or matched) cohort of type 2 patients treated with other oral agents in the same period of time. Comparison with previous Spanish data is not the same. Usually, in post marketing survey, both treated and differently treated groups are observed.</p> <p>2 other minor points</p> <ol style="list-style-type: none">1. There is some problem with the prevalence of diabetes (Introduction). The figure (13,8%) is abnormally high: was it population aged > 40 ? Check, all over Europe the prevalence of diabetes is 5-7 %.2. Complications only declared by patients raise some question in terms of reliability <p>My conclusions: This paper has a major flaw It may have some value in a national journal not in an international Journal. It is clearly written</p>
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REVIEWER	Sten Madsbad Hvidovre hospital Denmark
REVIEW RETURNED	29-Jan-2016

<p>GENERAL COMMENTS</p>	<p>In the present report data on clinical use and sociodemographic profile of patients initiating treatment with GLP-1 RA in Spain are reported from a cross-sectional, observational study performed in Spanish specialist outpatient clinics.</p> <p>403 patients initiated treatment with a GLP-1 RA. Age was 58 years, diabetes duration 9.9 years and BMI about 36 kg/m². Mean HbA1c 8.4 % and 14 % had a HbA1c < 7.0 %. 54 % was treated with OAD and 45 % with insulin alone or with insulin plus OAD. OAD treated patients were mostly treated with only one drug (65%). 45 % of the patients switched from a DPP-4 Inhibitor to a GLP-1 RA.</p> <p>The authors conclude that in Spain GLP-1 RA is started with OAD or the combination of OAD plus insulin, roughly a decade after diagnosis and with relatively high BMI. The latter could be explain by Spanish regional payers limited reimbursed prescription to patients with a minimum BMI threshold of 30 kg/m² or > 35 kg/m² in some regions.</p> <p>The study provides insight into the description of GLP-1 RA's in Spain. The manuscript is thoroughly written both in relation to presentation of results and discussion of the data. As expected the prescribing pattern followed payer's restrictions to GLP-1 RA's in Spain. The strength and limitation of the study is summarized very well in the conclusions.</p> <p>A limitation is of course that no followed –up data in relation to effect on HbA1c and weight is presented. Of interest is also how many of the patients stop GLP-1 RA's treatment, i.e. during the first year of treatment.</p> <p>A problem with the study is of course, how interesting the results is for people outside Spain, and maybe it better deserves to be published in a national journal of diabetes.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Carlo Bruno Giorda, Diabetes & Metabolism Unit ASL TORINO 5 via Demaria, ITALY.
 Response to reviewer 1: First, we gratefully appreciate the rigorous feedback of reviewer 1 which has triggered a deeper and more careful review of our paper, which hopefully will now have been improved. Nevertheless, we would like to clarify some aspects that may have not been clearly apparent in the previous version.

a) This study reports the result of rather small survey on the mode of prescription of GLP-1 RA in Spain.

We would like to make clear that this is not a survey (as the one just published by Matza et al); actually, it is a cross-sectional study of real practice. We would also like to clarify that it is not addressing “mode of prescription”, because that is already “fixed” by the SPC and the payers framework for reimbursement. Rather, the study tries to find out the prescription drivers and the patient profiles for subjects receiving GLP-1 Ra for the first time. We, of course, respect the qualification of “small”, but would want to mention that there is (Methods section) a statement about the calculation of the sample size.

b) The main limitation of the manuscript is its lack of novelty and originality. These results may raise some interest at a local level but have little appeal at the international level. The findings are largely expected as they reflect the well-known indications for choosing a GLP1-RA therapy in the clinical setting.

We acknowledge this comment and hopefully have made now clear, in the new version (see our response to the Editorial comments above) that the study is indeed new in its approach and we think

may provide useful learnings and insights to the international readers. We think it is a useful and new complement to the retrospective analyses and surveys published from other countries (eg. the UK, as mentioned in the references which we have included in the paper).

c) It presents a major limitation: There is no comparison with a similar (or matched) cohort of type 2 patients treated with other oral agents in the same period of time. Comparison with previous Spanish data is not the same. Usually, in post marketing survey, both treated and differently treated groups are observed.

We thank this comment which also has helped us in making the intention of the study more clear. There is no comparison because, as explained, the requirements and circumstances for prescribing other antidiabetics in Spain are different and therefore, in essence, not comparable. What we were trying is to find out and describe patient profiles for diabetic subjects receiving GLP-1 treatment for the first time. As this is done in Spain mainly by Specialists because of payers' restriction, comparison vs other drugs (oral or injectable) which can be prescribed by Primary Care physicians without restrictions, might have been informative, but, biases apart, would have been different in scope to the present study. We would therefore agree with the reviewer's comment about this limitation had the objective of the study been a comparison of treatments or effectiveness of treatments in real life. However, the aim of the present study was not to compare treatments or effectiveness, but to assess patient profiles of subjects getting a first script of a definite class of drugs, and therefore we think the mentioned limitation is not applicable to this study.

d) other minor points

1. There is some problem with the prevalence of diabetes (Introduction). The figure (13,8%) is abnormally high: was it population aged > 40 ? Check, all over Europe the prevalence of diabetes is 5-7 %.

Thank you so much for the comment. We agree that the figure would appear to be above the figure across Europe, but we think the statement in the paper is clear in that this includes known and unknown diabetes, with the figure of unknown diabetes being 6%, therefore the prevalence of known diabetes would be 7.8%, which we think is more or less in line with the European figure. The statement in the paper reads as follows:

In Spain, the overall prevalence of diabetes mellitus adjusted for age and sex was estimated in a representative sample of the population to be 13.8%, of which about half (6.0%) had unknown diabetes2..

2. Complications only declared by patients raise some question in terms of reliability.

We acknowledge this and therefore have focused the discussion in the "observed" (i.e. truly "real") data.

Reviewer: 2 - Sten Madsbad - Hvidovre hospital, Denmark

In the present report data on clinical use and sociodemographic profile of patients initiating treatment with GLP-1 RA in Spain are reported from a cross-sectional, observational study performed in Spanish specialist outpatient clinics.

403 patients initiated treatment with a GLP-1 RA. Age was 58 years, diabetes duration 9.9 years and BMI about 36 kg/m². Mean HbA1c 8.4 % and 14 % had a HbA1c < 7.0 %. 54 % was treated with OAD and 45 % with insulin alone or with insulin plus OAD. OAD treated patients were mostly treated with only one drug (65%). 45 % of the patients switched from a DPP-4 Inhibitor to a GLP-1 RA.

The authors conclude that in Spain GLP-1 RA is started with OAD or the combination of OAD plus insulin, roughly a decade after diagnosis and with relatively high BMI. The latter could be explain by Spanish regional payers limited reimbursed prescription to patients with a minimum BMI threshold of 30 kg/m² or > 35 kg/m² in some regions.

The study provides insight into the description of GLP-1 RA's in Spain. The manuscript is thoroughly written both in relation to presentation of results and discussion of the data. As expected the prescribing pattern followed payer's restrictions to GLP-1 RA's in Spain. The strength and limitation of the study is summarized very well in the conclusions.

A limitation is of course that no followed –up data in relation to effect on HbA1c and weight is

presented. Of interest is also how many of the patients stop GLP-1 RA's treatment, i.e. during the first year of treatment.

A problem with the study is of course, how interesting the results is for people outside Spain, and maybe it better deserves to be published in a national journal of diabetes.

Response to reviewer 2:

First, we sincerely appreciate the comments from reviewer 2. We agree of course that having a follow-up of the effects on HbA1c and weight would have been interesting, but think it would have been quite beyond the scope of this descriptive, cross-sectional study, which, as explained before, had the aim to find out the patient profiles and decision drivers for prescribing a GLP-1Ra in Spain, taking into consideration the payers' restrictions. We also agree that the prescribing pattern is more or less in line with those restrictions, but we also would like to emphasize that there were some intriguing findings as well, such as a relevant subgroup (14%) which got a script with an HbA1c value <7%. This would not appear to be much aligned with the payers' instructions. With regard to the interest of the study for people outside Spain, we hope that we have been able to address this more clearly in the new version of the paper, also in line with the feedback from reviewer 1 and the Editor, as explained above in this document.

VERSION 2 – REVIEW

REVIEWER	Carlo B. Giorda Diabetes and Metabolism Unit ASL Torino 5 Italy
REVIEW RETURNED	27-Feb-2016

GENERAL COMMENTS	<p>I have carefully read the authors' response and appreciated the effort to clarify the most important negative comments on the manuscript.</p> <p>However I am still convinced that:</p> <p>This study is based on a limited number of patients: It analyses the patients characteristics (and possible drivers) underlying GLP-1RA prescription in a Spanish environment. The relevance of the subject to an international readership is low.</p> <p>Being retrospective is not a fault. However, including patients who had initiated GLP-1RA 3 months before inclusion visit sounds as in part retrospective</p> <p>As regards possible prescription drivers (not treatment effectiveness), there is no comparison with a similar (or matched) cohort of type 2 patients treated with other agents in the same period of time. Comparison with previous Spanish data is not the same. This make the study in interesting internal audit not a scientific result.</p> <p>The prevalence of diabetes in Spain can not be 13,8%, even if you include undiagnosed forms. It would be one of the highest in the world including Finland, Oceania and Sardinia which rank first in the list of top diabetes prevalence.</p>
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REVIEWER	Sten Madsbad Dept of Endocrinology Hvidovre hospital University of Copenhagen
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REVIEW RETURNED	19-Mar-2016
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GENERAL COMMENTS	The authors have changed the manuscript in accordance with the suggestions from the Editor and reviewers. I have no more comments on the report.
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VERSION 2 – AUTHOR RESPONSE

Response to comments by Reviewer 1

Reviewer Name: Carlo B. Giorda

Institution and Country: Diabetes and Metabolism Unit, ASL Torino, Italy

I have carefully read the authors' response and appreciated the effort to clarify the most important negative comments on the manuscript.

We gratefully acknowledge that the most important negative comments on the manuscript have been addressed.

We will try to address and comments on the remaining concerns.

This study is based on a limited number of patients: It analyses the patients characteristics (and possible drivers) underlying GLP-1RA prescription in a Spanish environment. The relevance of the subject to an international readership is low.

Response: As stated in our previous response, even if we of course respect the qualification of "small" for the number of patients in the study, the number needed was estimated as explained in the Methods section, and therefore, would seem adequate for the purpose (and as such considered by the Ethics Committee which approved the study). We have addressed the other comment about relevance for the international readership in our previous response and have tried to provide additional context in the manuscript to emphasize the interest for such audience. However, this interest is, to a significant degree, a matter of personal opinion (for example reviewer 2 would seem to have now a different perspective), and we still think the matter may be of interest for the prospective international reader.

Being retrospective is not a fault. However, including patients who had initiated GLP-1RA 3 months before inclusion visit sounds as in part retrospective

The study is essentially cross-sectional. The proportion of patients who had initiated GLP-1 RA in the 3 months before inclusion is very small, and we allowed for that to facilitate the data collection since the use of GLP-1 RA in Spain was (and still is) very limited. In a disease with such a long-term course and very long treatments, going just 3 months backs would not seem to alter the essentially cross-sectional nature of the study. In accordance with this, but in the interest of clarity, we have maintained the cross-sectional qualification for the study but have deleted the mention of non-retrospective.

As regards possible prescription drivers (not treatment effectiveness), there is no comparison with a similar (or matched) cohort of type 2 patients treated with other agents in the same period of time. Comparison with previous Spanish data is not the same. This make the study in interesting internal audit not a scientific result.

This was addressed also in our previous response, and as a consequence several modifications to the paper were made. We appreciate the reviewer's opinion on this matter but respectfully think that the changes and additions already made address his comments on the above point. This include mentions of those aspects as potential limitations of the study.

The prevalence of diabetes in Spain cannot be 13,8%, even if you include undiagnosed forms. It would be one of the highest in the world including Finland, Oceania and Sardinia which rank first in the list of top diabetes prevalence.

The response about this is included in the answer to the editor requests at the beginning. We think

the figure of 7.8% for known T2DM in subjects ≥ 18 is well in line with other estimates (eg. IDF), and the total of 13.8% would include 6% of unknown DM which is in line as well with other estimates.

Reviewer: 2

Reviewer Name: Sten Madsbad

Institution and Country: Dept of Endocrinology, Hvidovre hospital, University of Copenhagen

The authors have changed the manuscript in accordance with the suggestions from the Editor and reviewers. I have no more comments on the report.

We are glad that we have been able to address the comments by reviewer 2 and gratefully appreciate his constructive feedback.

Correction

Conget I, Mauricio D, Ortega R on behalf of the CHADIG Study investigators, *et al.* Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): a cross-sectional multicentre study in Spain. *BMJ Open* 2016;**6**:e010197. doi: 10.1136/bmjopen-2015-010197

Four of the Collaborator names were written incorrectly. 'Francisco Merino Torres' should have been written 'Juan Francisco Merino-Torres', 'Fernando Gómez Peralta' as 'Fernando Gomez-Peralta', 'Diego Bellido Guerrero' as 'Diego Bellido' and 'Miguel Ángel Mangas' as 'Miguel Angel Mangas-Cruz'.

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