PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study
AUTHORS	Nishimura, R; kato, haruka; Kisanuki, Koichi; Oh, Akinori; Hiroi, Shinzo; Onishi, Yoshie; Guelfucci, Florent; Shimasaki, Yukio

VERSION 1 – REVIEW

REVIEWER	Thomas Wilke Institut für Pharmakoökonomie und Arzneimittellogiostik, University of Wismar, Gernany Received honoria from different pharmaceutical companies, such as Boehringer, Novo Nordisk and GSK
REVIEW RETURNED	27-Aug-2018

GENERAL COMMENTS	your Research is important, and your mainly descriptive results are important to be published. However, I have some concerns around the description of methodology of this paper: 1. You describe throughout the paper differences/similarities between the two datasets. The question is: why? Is it not more important to get numbers for the Overall Population? 2. The Abstract Needs to be improved. Include numbers in the results section - Statements like "most common add-on therapy" etc. are not helpful. Present a bit less Facts, but Support them by numbers. 3. I did not understand what the difference between Switch and add-on therapy is. How EXCACTLY did you define both? If someone received a DPP-4 mono, and then Metformin was prescribed - was it a Switch or add-on? Or did you require another DPP-4 prescription after Metformin for add-on? If yes, say that and explain that. I did not understand the definition in the methods section. 4. Methods - study Population: write that all patients started a new therapy. 5. Do not talk about "adequate" time - adequacy should be evaluated by others. 6. What is about death after index date? Did you exclude all patients who died within 12 months after index date? 7. Why did you exclude GLP-1s? Here, Treatment Patterns are very clear, and adherence & persistence can be analyzed.

	8. How did you define discontinuation of an index therapy - what was the critical gap? 9. How did you calculate the prescribed days? Did physicians Report that in the prescriptions, or did you use the DDD? 10. From when to when did you calculate the PDC (first to last prescription?)? 11. How did you deal with hospitalization periods in Terms of adherence/persistence measurement? How did you deal with stockpiling? 12. For which period did you assess add-on/Switches - also 12 months? Obviously, patients with a longer follow-up have a higher Chance to experience add-on/Switch. 13. Pages 12/13 - too many numbers, maybe not all to be described in the text, the tables are sufficient. 14. Sometimes you define the adherence rate as percentage with a PDC>80%, sometimes as mean PDC in a sample. Use uniform wording. 15. You did not explain the Regression Analysis in the methods. 16. I would strongly recommend to run a multivariable Cox Regression for time until discontinuation/Switch of therapy - you obviously ran only univariate statistics, which is not sufficient from my perspective. 17. fferentiated

REVIEWER	Andrew McGovern University of Exeter, UK Previous research funding from Eli Lilly, AstraZeneca, and Pfizer.
REVIEW RETURNED	30-Aug-2018

GENERAL COMMENTS	This is a very interesting analysis of the current medication trends in type 2 diabetes in Japan. I think this will be of interest to a general audience and therefore merits publication in the BMJ open. My main concern is the possible bias towards discussion of DPP4 inhibitors - I do not feel that the manuscript in it's current format provides a neutral overview of the data. This could be addressed by following the suggested amendments I have listed below. Abstract: The concept of an index date is not explained in the abstract - either please explain or remove the reference to this date. The message in the conclusion is somewhat biased - I don't feel that this paper confirms the 'key role of DPP4 inhibitors' as there is no data on important patient outcomes here. A more neutral conclusion which states that DPP4 inhibitors are the most commonly used therapy and have a high level of adherence and persistence would be more appropriate. Strengths and limitations: I would not consider the observational nature of the study to be a limitation here. The question is what about happens in the real world

	- the best study design to answer this is an observational study. This comment also applies to the discussion section. Introduction This provides an excellent overview of the area and the first two paragraphs are of particular use to the international reader. I would like to see a brief overview of the type of healthcare system used in Japan - is all healthcare private or is some provided by the state? Who would be captured by the claims databases used and who would be missed - these issues are not clear. Again this is important for the international reader. (This could go in the methods section if the authors feel that would be more appropriate) Given the focus on DPP4 inhibitors here I think it would be useful to explain their positioning in the national Japanese guidelines also. The authors cite two meta analyses (refs 17 and 18) demonstrating the additional effectiveness of DPP4 inhibitors in Asians. Additional data which has been published since then and should be cited here comes from the TECOS trial: https://onlinelibrary.wiley.com/doi/pdf/10.1111/dom.13242 Methods In the outcomes section the definition and relevance of switching therapy is unclear. The author claim to have calculated PDC for adherence but their formula provided looks to have calculated medication possession ratio (MPR) - please explain how this was done in more detail. It is not clear how adherence was calculated where two (or more) medications were taken in combination. Was adherence >0.8 required for both therapies or just the newly added medication? Results The first paragraph of the results claims that all patients with at least one prescription for the index drug were included but the methods state two prescriptions were required - please clarify. Please provide follow up statistics as median duration of follow up (with IQR) in years; this data is easier to interpret. The following sentence is a bit unclear: In PT patients (fig 2b), the most common index therapy was combination therapy Does this refer to fixed dose combination products or the number or people who are on dual, triple or higher therapy when compared with those switching medications but remaining on monotherapy? I am assuming the latter but I think this could be described more clearly. On line 57, pg 13 DPP4i is written as DPP-41 Discussion This is well written and interesting. I have only a few comments: The finding of low adherence to SGLT2 inhibitors is interesting and in contrast with the CVOTs and RWE elsewhere in the world. In the discussion the authors state: Between May and October 2015, prescribing of SGLT2i was restricted to 14−28 days' therapy, which may have

	impacted on usage rates. Can the authors expand on this point. What does restricted to 14-28 days therapy mean? Did people subsequently have to buy it themselves? If so this might explain this observation. The authors state that: There is broad recognition that DPP-4i are more effective in Asian than non-Asian patients. Whilst this is probably true what is not clear is if they are more effective than other medication in east Asians. This should be mentioned here unless the authors are aware of comparative data to suggest they are. In Caucasian populations DPP4 inhibitors are probably slightly less effective than other commonly used oral agents. The authors claim that: it is worth remembering that no significant association between DPP-4i and possible pancreatic disorder was observed in several large-scale studies. However there is some evidence to suggest a very slight increased risk of pancreatitis with DPP4is: http://care.diabetesjournals.org/content/diacare/40/2/161.full.pdf The authors should also highlight that there is no current evidence that DPP4 inhibitors have better glycaemic, microvascular or macrovascular outcomes when compared to metformin or other oral agents in Japanese patients although where adherence is an issue they could be a better treatment option.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:	**Responses**
Reviewer: 1	
Reviewer Name: Thomas Wilke Institution and Country: Institut für Pharmakoökonomie und Arzneimittellogiostik, University of Wismar, Gernany Please state any competing interests or state 'None declared': Received honoria from different pharmaceutical companies, such as Boehringer, Novo Nordisk and GSK	Thank you for your suggestion. We state our competing interests in the " **Competing interests**" section as follows**:** RN has received speaker honoraria from Astellas Pharma Inc, Nippon Boehringer Ingelheim Co. Ltd, Eli Lilly Japan K.K., Kissei Pharmaceutical Co. Ltd, Medtronic Japan Co. Ltd, MSD, Novartis Pharma K.K., Novo Nordisk Pharma Ltd, Sanofi K.K., and Takeda Pharmaceutical Co. Ltd.; and

	contract research fees for collaborative research with the Japan Diabetes Foundation.
your Research is important, and your mainly descriptive results are important to be published. However, I have some concerns around the description of methodology of this paper:	Many thanks for your review and suggestions for improvements.
1. You describe throughout the paper differences/similarities between the two datasets. The question is: why? Is it not more important to get numbers for the Overall Population?	It was our view that the respective database populations were too different to pool. Analyzing the databases separately was expected to (and did) provide insight into whether there were differences in antidiabetic drug utilisation trends and persistence and adherence patterns between a younger and healthier population (JMDC) *vs* an older population with more comorbidity (MDV), even though, as it turned out, DPP-4i was the most commonly used antidiabetic drug class in both datasets.
2. The Abstract Needs to be improved. Include numbers in the results section - Statements like "most common add-on therapy" etc. are not helpful. Present a bit less Facts, but Support them by numbers.	Some additional results have been added to the Abstract as per your suggestion. However, because there are four distinct subgroups to report, i.e. UT and PT patients in each database (JMDC and MDV), providing numbers for all results would be cumbersome and would increase the word count beyond the limit.
3. I did not understand what the difference between Switch and add-on therapy is. How EXCACTLY did you define both? If someone received a DPP-4 mono, and then Metformin was prescribed - was it a Switch or add-on? Or did you require	An ‘add-on’ occurred when a new antidiabetic drug class was prescribed in addition to an existing drug class(es) for more than 21 days

another DPP-4 prescription after Metformin for add-on? If yes, say that and explain that. I did not understand the definition in the methods section.	(e.g. DPP-4i <<add-on event>> DPP-4i + metformin). A 'switch' occurred when at least one new antidiabetic drug class was prescribed *in place of an existing drug class(es)* within the grace period which was 1.5 times the median prescription duration for a given drug class (e.g. DPP-4i <<switch event>> metformin). *Methods >> Outcomes* has been revised accordingly.
4. Methods - study Population: write that all patients started a new therapy.	*Methods >> Study population* has been amended as per your suggestion. A new sentence has been added.
5. Do not talk about "adequate" time - adequacy should be evaluated by others.	*Methods >> Study population* has been amended as per your suggestion. The word 'adequate' has been deleted.
6. What is about death after index date? Did you exclude all patients who died within 12 months after index date?	The exclusion criterion of '<12 months of continuous enrolment in the database before or after the index date' ensured that patients who were not under the insurance society within 12 months of the first prescription (index date) were not eligible for inclusion. Thus, enrolees who died within 12 months of the index date were not included for analysis.
7. Why did you exclude GLP-1s? Here, Treatment Patterns are very clear, and adherence & persistence can be analyzed.	In *Methods >> Antidiabetic drug classes of interest*, it is explained that:

	"Data for insulin and GLP-1 receptor agonists were excluded from the persistence and adherence analyses mainly because of inconsistent database information regarding the duration of therapy for these injectable drug classes."
8. How did you define discontinuation of an index therapy - what was the critical gap?	Discontinuation of an index therapy was defined when no index therapy wasprescribe d within the specified 'grace period' after the end of a treatment line. Thegrace period was defined as 1.5 times the median prescription duration in days for oral antidiabetic drugs; and as 90th percentile of the gap between two prescriptions for injectable antidiabetic drugs.
9. How did you calculate the prescribed days? Did physicians Report that in the prescriptions, or did you use the DDD?	The JMDC and MDV databases both contain a field corresponding to the number of days' supply of a medication. These data were used to calculate the number of prescription days. The *Methods >> Outcomes* section has been revised accordingly.
10. From when to when did you calculate the PDC (first to last prescription?)?	Yes, the PDC was calculated from the first to last prescription; in other words, from the index (first prescription) date to the first discontinuation of index treatment. The *Methods >> Outcomes* section has been revised accordingly.
11. How did you deal with hospitalization periods in Terms of adherence/persistence measurement? How did you deal with	Adherence/persistence were calculated according to the number

stockpiling?	of antidiabetic drug prescription days, without differentiating between inpatient/outpatient prescribing. No information was available about possible pill dumping or stockpiling and this is study limitation. The *Methods >> Outcomes* section has been revised accordingly.
12. For which period did you assess add-on/Switches - also 12 months? Obviously, patients with a longer follow-up have a higher Chance to experience add-on/Switch.	Add-ons/Switches were also assessed for 12 months. The titles of Tables 2-5 have been updated accordingly (e.g. Table 2 Changes to index therapy: add-on treatment *over 12 months* ….).
13. Pages 12/13 - too many numbers, maybe not all to be described in the text, the tables are sufficient.	Many thanks for the suggestion. The numbers have been deleted to improve readability and to avoid repetition with the data in the tables.
14. Sometimes you define the adherence rate as percentage with a PDC>80%, sometimes as mean PDC in a sample. Use uniform wording.	Thank you for the suggestion. For consistency, we have used ≥80% throughout the manuscript .
15. You did not explain the Regression Analysis in the methods.	The Methods >> Statistical analyses had been revised accordingly.
16. I would strongly recommend to run a multivariable Cox Regression for time until discontinuation/Switch of therapy - you obviously ran only univariate statistics, which is not sufficient from my perspective.	This study focused on treatment patterns in a descriptive manner. Therefore, only descriptive statistics were reported.
17. fferentiated	Unfortunately, the majority of this referee comment was missing.
Reviewer: 2	

Reviewer Name: Andrew McGovern Institution and Country: University of Exeter, UK Please state any competing interests or state 'None declared': Previous research funding from Eli Lilly, AstraZeneca, and Pfizer.	
This is a very interesting analysis of the current medication trends in type 2 diabetes in Japan. I think this will be of interest to a general audience and therefore merits publication in the BMJ open. My main concern is the possible bias towards discussion of DPP4 inhibitors - I do not feel that the manuscript in it's current format provides a neutral overview of the data. This could be addressed by following the suggested amendments I have listed below.	Many thanks for your review and suggestions for improvements.
Abstract: The concept of an index date is not explained in the abstract - either please explain or remove the reference to this date.	The Abstract has been amended to indicate that index date means 'first prescription' date.
The message in the conclusion is somewhat biased - I don't feel that this paper confirms the 'key role of DPP4 inhibitors' as there is no data on important patient outcomes here. A more neutral conclusion which states that DPP4 inhibitors are the most commonly used therapy and have a high level of adherence and persistence would be more appropriate.	Agreed. The Abstract has been amended accordingly. The conclusions section of the Abstract now reads: "The findings indicate that DPP-4i is the most commonly used antidiabetic drug class in Japanese patients with T2DM, and has a high level of persistence and adherence". The Conclusions and implications section of the Discussion has also been amended to provide a more neutral interpretation of the findings.
Strengths and limitations: I would not consider the observational nature of the study to be a limitation here. The question is what about happens in the real world - the best study design to answer this is an observational study. This	We agree. Many thanks for the suggestion. The Abstract and the Discussion have been amended

comment also applies to the discussion section.	accordingly.
Introduction This provides an excellent overview of the area and the first two paragraphs are of particular use to the international reader. I would like to see a brief overview of the type of healthcare system used in Japan - is all healthcare private or is some provided by the state? Who would be captured by the claims databases used and who would be missed - these issues are not clear. Again this is important for the international reader. (This could go in the methods section if the authors feel that would be more appropriate)	Thank you for your valuable comments. Japan has a compulsory insurance system whereby all residents are legally obligated to be covered by some form of public insurance: 1) Health Insurance for general employees; 2) Seamen's Insurance; 3) Mutual aid associations for national and local public employees, and private school teachers/staffs; 4) National Health Insurance (NHI) for farmers, self-employed, retired persons under employees' health insurance; and 5) Medical care system for the elderly aged 75 and over. The largest number of subscribers are on systems 1) and 4) as of March 2016. The JMDC dataset is created by 6% insured (4.2 million of 66.3 million) among total subscribers to system 1). The MDV dataset is derived from in- and outpatient records of the 20% DPC hospitals in Japan. A sentence has been added to the Introduction to briefly explain about Japan's compulsory insurance system.
Given the focus on DPP4 inhibitors here I think it would be useful to explain their positioning in the nationalJapanese guidelines also.	The Introduction has been revised to include JDS treatment recommendations for T2DM. The JDS stance on oral antidiabetic therapy is explained further in the

	Discussion.
The authors cite two meta analyses (refs 17 and 18) demonstrating the additional effectiveness of DPP4 inhibitors in Asians. Additional data which has been published since then and should be cited here comes from the TECOS trial: https://onlinelibrary.wiley.com/doi/pdf/10.1111/dom.13242	Thank you for the suggestion. The Introduction has been amended to include this citation and the references have been renumbered accordingly.
Methods In the outcomes section the definition and relevance of switching therapy is unclear.	The sentence has been amended for greater clarity.
The author claim to have calculated PDC for adherence but their formula provided looks to have calculated medication possession ratio (MPR) - please explain how this was done in more detail. It is not clear how adherence was calculated where two (or more) medications were taken in combination. Was adherence >0.8 required for both therapies or just the newly added medication?	We confirm that the formula is PDC: Total number of prescription days coveredfor defined drug class of interest / Total number of days in the follow-up period. MPR would have been: Total number of prescription days' supplyfor defined drug class of interest / Total number of days in the follow-up period. For days covered, an overlap between prescription is considered once. For days' supply, an overlap between prescriptions is considered twice e.g. 2 prescriptions with a duration of 30 days each and 15 days of overlap PDC=45 ; MPR=60 Adherence with combination therapy was calculated only for those patients with at least two prescriptions for the five most

	frequent index antidiabeticdrug combinations during the 12-month post-index follow-up period. A new figure (fig 6) has been added for greater clarity.
Results The first paragraph of the results claims that all patients with at least one prescription for the index drug were included but the methods state two prescriptions were required - please clarify.	In Methods it is stated: Eligible patients were adults (≥18 years) with a diagnosis of T2DM (International Classification of Diseases [ICD]-10 code: E11 or E14) who had been issued *at least one prescription* for an antidiabetic drug during the target selection period of January 2011 to December 2015. Thus, Methods corresponds with Results. By definition, adherence analyses could be performed only for patients with *at least two prescriptions* of the index antidiabetic drug class(es) during the 12-month post-index follow-up period.
Please provide follow up statistics as median duration of follow up (with IQR) in years; this data is easier to interpret.	Table 1 has been amended accordingly.
The following sentence is a bit unclear: In PT patients (fig 2b), the most common index therapy was combination therapy Does this refer to fixed dose combination products or the number or people who are on dual, triple or higher therapy when compared with those switching medications but remainingon monotherapy? I am assuming the latter but I think this could be described more clearly.	Fig 2b shows the antidiabetic drug classes that were prescribed to PT patients as *index therapy.* The most common index prescription was for combination therapy (74.6% of JMDC patients; 81.1% of MDV patients). The five most common combinations are shown individually in the figure key. Myriad other combinations were prescribed at

	lower frequency and are combined in the 'other' category. Combinations could consist of single agents in combination, FDC, or FDC + single agents in combination. The *Results << Index date therapy* section has been amended to improve clarity.
On line 57, pg 13 DPP4i is written as DPP-41	The typo has been fixed. Thank you.
Discussion This is well written and interesting. I have only a few comments:	
The finding of low adherence to SGLT2 inhibitors is interesting and in contrast with the CVOTs (cardiovascular outcome trials) and RWE (real-world evidence) elsewhere in the world. In the discussion the authors state: Between May and October 2015, prescribing of SGLT2i was restricted to 14−28 days' therapy, which may have impacted on usage rates. Can the authors expand on this point. What does restricted to 14-28 days therapy mean? Did people subsequently have to buy it themselves? If so this might explain this observation.	When SGLT2i were first approved for use in Japan, the Japanese Pharmaceuticals and Medical Devices Agency limited the prescribing duration to 14 days' therapy so that patients would have to undergo regular and frequent evaluation for effectiveness and safety during the initial stages of treatment with this new class of drugs in Japan. The Strengths and limitations section of the Discussion has been updated accordingly.
The authors state that: There is broad recognition that DPP-4i are more effective in Asian than non-Asian patients. Whilst this is probably true what is not clear is if DPP-4i are more effective than other antidiabetic medication in east Asians. This should be mentioned here unless the authors are aware of comparative data to suggest they are. In Caucasian	Thank you. We agree with your comments. The sentence has been amended as follows: "Based on numerous studies involving mainly Japan or Chinese patients, there is broad recognition

populations DPP4 inhibitors are probably slightly less effective than other commonly used oral agents.	that DPP-4i are more effective in East Asian than non-Asian patients[1,17-19,30] and, in Japan, >70% of patients treated with antidiabetic drugs receive incretin-based therapies." References: Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives. J Diabetes Investig 2016;7 Suppl 1:102-9. doi: 10.1111/jdi.12490 pmid: 27186364. Kim YG, Hahn S, Oh TJ, et al. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia 2013;56:696-708. doi: 10.1007/s00125-012-2827-3 pmid: 23344728. Kim YG, Hahn S, Oh TJ, et al. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:900-9. doi: 10.1111/dom.12293 pmid: 24655583. Davis TME, Mulder H, Lokhnygina Y, et al. Effect of race on the glycaemic response to sitagliptin: Insights from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab.

	2018;20:1427-34. Ito Y, Ambe K, Kobayashi M, et al. Ethnic difference in the pharmacodynamics-efficacy relationship of dipeptidyl peptidase-4 inhibitors between Japanese and non-Japanese patients: a systematic review. Clin Pharmacol Ther 2017;102:701-8. doi: 10.1002/cpt.692 pmid: 28378919.
The authors claim that: it is worth remembering that no significant association between DPP-4i and possible pancreatic disorder was observed in several large-scale studies. However there is some evidence to suggest a very slight increased risk of pancreatitis with DPP4is: http://care.diabetesjournals.org/content/diacare/40/2/161.full.pdf	Many thanks for the suggestion. The sentence has been amended as follows: “Although no significant association between DPP-4i and possible pancreatic disorder was observed in several large-scale studies,[25,32-34], it is important to remain vigilant for potential safety signals[35] since DPP-4i-related pancreatitis is a low but established risk”.[36] 36. DeVries JH, Rosenstock J. DPP-4 inhibitor-related pancreatitis: rare but real! Diabetes Care 2017;40:161-3. doi: 10.2337/dci16-0035.
The authors should also highlight that there is no current evidence that DPP4 inhibitors have better glycaemic, microvascular or macrovascular outcomes when compared to metformin or other oral agents in Japanese patients although where adherence is an issue they could be a better treatment option.	The Conclusions have been amended accordingly.

VERSION 2 – REVIEW

REVIEWER	Thomas Wilke University of Wismar Received honoria from different pharmaceutical companies, such as Boehringer, Novo Nordisk and GSK
REVIEW RETURNED	09-Nov-2018

GENERAL COMMENTS	You addressed most of my comments, many thanks. I still think that the recommended Cox Regression could improve the Quality of the paper, but I leave that to you.

REVIEWER	Dr Andrew McGovern University of Exeter, UK Previous research funding from Eli Lilly, AstraZeneca, and Pfizer
REVIEW RETURNED	10-Oct-2018

GENERAL COMMENTS	My previous comments have all been satisfactorily addressed. I feel this paper makes a very useful and interesting contribution to the existing literature. There is a now a slight typo in the Abstract: "with treatment as 12 months." should read "with treatment at 12 months."