PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Metformin use and long-term risk of benign prostatic hyperplasia. A population-based cohort study.
AUTHORS	Nørgaard, Mette; Darvalics, Bianka; Thomsen, Reimar

VERSION 1 – REVIEW

REVIEWER	Teemu Murtola Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland Consultation fees Astellas Pharma and Janssen-Cilag, stockholder Arocell Ab
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	This is a cohort study of estimating risk of benign prostatic hyperplasia among Danish men starting metformin or sulphonyrureas as antidiabetic treatment during 2000-2006. The research hypothesis driven by preclinical studies is that the risk would be lower among men using metformin compared to sulphonylurea users. Both drugs were recommended as first line treatment of type 2 diabetes at the time, yet differences in several baseline covariates are found between the comparison groups, and are being adjusted for in the analysis. A slighlty lowered risk for some BPH endpoints is observed among metformin users, which mostly disappears after multivariable adjustment. The authors conclude accordingly that no marked difference in risk of BPH exist between users of metformin and sulphonylureas. My main concern is how well these resutls can be generalized to average diabetic men. The study population has been selected according to several strict rules: the participants had to have two filled prescriptions of metformin or sulphonylureas in 2000-2006, with no prescriptions before that but still having a recorded diagnosis of diabetes in an inpatient or outpatient setting before the first prescription. The registry data on DM diagnoses extends back to 1977, so the cohort participants could have had diabetes for years, even decades before their first drug prescription. This suggests that men in the study population have either been uncompliant to start antidiabetic treatment earlier or alternatively that their diabetes has been so early-stage that it has been managed only with diet and exercise. Either way such restrictions limit generalizability of the results. Further, only men who remained on metformin or sulphonylurea monotherapy for the first 6 months of follow-up were included in the study. Again this is very restrictive, likely limiting the study population to those with very early stage diabetes only. Therefroe it should not be surprising to see only little or no effect of antidiabetic treatment on BPH risk. The findings could be different in

	men with more advanced diabetes. These limitations should be discussed and acknowledged in the text. Small comments: - Materials nad methods, Outcome-section, 1st paragraph: Alpha-blockers are being used in clinical management of a range of lower urinary tract symptoms, not only in BPH. Would results change if you defined BPH by 5alpha-redcutase inhibitor usage only? - Materials nad methods, Diabetes severity-section, 1st paragraph: How did you define the cut-points for HbA1c? - Materials nad methods, Statistical analysis-section, 5th paragraph: Why did you adjust the analysis for alcohol-related disease or glucocorticoid use? They are not known risk factors for BPH, thus uncertain to cause confounding. Were they significant predictors of BPH risk in this analysis? - Results, page 13, 2nd paragraph: check the numbers in confidence interval for crude HR for hospital-related BPH

REVIEWER	Amr Ahmed EL-Arabey Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University, Egypt.
REVIEW RETURNED	11-Sep-2020

GENERAL COMMENTS	The topic for that study is interesting because there are a lot of controversial data in that area. In fact, the current study was proposed to examine whether metformin use affects the risk of BPH by comparing the risk of BPH in men with type-2 diabetes who initiated first-line treatment with either metformin or sulfonylurea monotherapy between 2000 or 2006 in Northern Denmark. Therefore, I recommend the publication for the current study after minor revision as the following: 1- The authors should examine the sensitivity of analyses. 2- Please, refer to the transporter of metformin in prostate and the clinical trials which were done regarding the action of metformin on prostate cancer; Reference: El-Arabey AA, Abdalla M, Ali Eltayb W. Metformin: Ongoing Journey with Superdrug Revolution. Adv Pharm Bull. 2019;9(1):1-4. doi:10.15171/apb.2019.001 3- Although, it is well known that Metformin used off-label for weight reduction; Reference: El-Arabey AA. Update on off label use of metformin for obesity. Prim Care Diabetes. 2018;12(3):284-285. Could the authors further discuss obesity as a critical risk factor for BPH and highlight that the characteristic baseline of hospital recorded obesity in the present study was highest in metformin users (12.7%) versus sulfonylurea (5.3%). Moreover, authors should clarify how that factor may impact these results?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. Comments from the Editor:

Please accept our apologies for the delay in reaching a decision on your manuscript. This is largely due to the increase in workload since the COVID-19 pandemic along with a need to prioritise manuscripts related to the pandemic.

Response: We appreciate the explanation – thank you.

- Please revise your patient and public involvement statement so that it is in line with the description in our Instructions for Authors (http://bmjopen.bmj.com/pages/authors/). The statement should outline patient and public involvement in the planning and design of the study. Please see our blog for further information regarding PPI: http://blogs.bmj.com/bmjopen/2018/03/23/new-requirements-for-patient-and-public-involvement-statements-in-bmj-open/
Response: We have revised the PPI statement so that it says: "Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research".

- How many participants were lost to follow up? Please include this number in the Abstract. Do you have any data on participants that were lost to follow up?
Response: Our loss to follow-up was negligible. Less than 5 persons were censored due to emigration and we are not allowed to provide data on such a low number of persons due to patient confidentiality. We have added this information in the abstract and in the results section. Please see page 11 bottom line.

- Please provide side headings in the Discussion to guide the reader
Response: We have provided side headings as suggested.

Reviewer(s)' Comments to Author:

Reviewer: 1 Teemu Murtola
This is a cohort study of estimating risk of benign prostatic hyperplasia among Danish men starting metformin or sulphonyrureas as antidiabetic treatment during 2000-2006. The research hypothesis driven by preclinical studies is that the risk would be lower among men using metformin compared to sulphonylurea users. Both drugs were recommended as first line treatment of type 2 diabetes at the time, yet differences in several baseline covariates are found between the comparison groups, and are being adjusted for in the analysis.
A slighlty lowered risk for some BPH endpoints is observed among metformin users, which mostly disappears after multivariable adjustment. The authors conclude accordingly that no marked difference in risk of BPH exist between users of metformin and sulphonylureas.

1. My main concern is how well these resutls can be generalized to average diabetic men. The study population has been selected according to several strict rules: the participants had to have two filled prescriptions of metformin or sulphonylureas in 2000-2006, with no prescriptions before that but still having a recorded diagnosis of diabetes in an inpatient or outpatient setting before the first prescription. The registry data on DM diagnoses extends back to 1977, so the cohort participants could have had diabetes for years, even decades before their first drug prescription. This suggests that men in the study population have either been uncompliant to start antidiabetic treatment earlier or

alternatively that their diabetes has been so early-stage that it has been managed only with diet and exercise. Either way such restrictions limit generalizability of the results.

Response 1.1

It is correct that we included patients who were first-time starters of anti-diabetic treatment because we wanted to use a new user design. We did not, however, require a recorded diagnosis of diabetes before their first prescription. We have presented diabetes duration in Table 1 and 58.9% of metformin initiators and 63.1% of men who started sulphonylurea did not have a registered diabetes diagnosis before their start of treatment. Actually, less than 15% of the study population had a diabetes duration of more than a year, i.e., 85.4% of metformin users and 86.0% of sulfonylurea users had diabetes duration of less than 1 year.

2. Further, only men who remained on metformin or sulphonylurea monotherapy for the first 6 months of follow-up were included in the study. Again this is very restrictive, likely limiting the study population to those with very early stage diabetes only. Therefroe it should not be surprising to see only little or no effect of antidiabetic treatment on BPH risk. The findings could be different in men with more advanced diabetes. These limitations should be discussed and acknowledged in the text.

Response 1.2

We agree that we were rather restrictive when designing this study. However, our major concern was the internal validity and specifically to avoid immortal time bias and avoid comparing men at different stages of their diabetes. Still, we had a median follow-up of 10 years and were able to follow some men for up to 17 years so we did not only include information on early stage diabetes. The fact that the cumulative 10-year incidence of BPH was 25% also reassured us that this was a relevant study population. Moreover, when stratified by achieved HbA1c we did not see any BPH protective effect in those with poor glycemic control. Still, we cannot rule out that men with more advanced diabetes could have a beneficial effect of metformin regarding BPH risk. We have elaborated on this in the discussion on page 15.

Small comments:

- Materials and methods, Outcome-section, 1st paragraph: Alpha-blockers are being used in clinical management of a range of lower urinary tract symptoms, not only in BPH. Would results change if you defined BPH by 5alpha-redcutase inhibitor usage only?

Response 1.3

Although alpha-blockers have been first line treatment for LUTS/BPH for several years, these drugs may also be used for LUTS due to other causes and they are used for arterial hypertension as well. We may therefore overestimate the rate of BPH when defining BPH based on these prescriptions. Still, according to the national statistics (https://medstat.dk/) in 2015, 75,090 individuals filled at least one prescription for an alpha blocker. Of these, 71,300 (95%) were men and 69276 (92%) were men

aged 45 years or older. We therefore feel reassured that these drugs are predominantly used for symptomatic BPH. As a sensitivity analysis, we reanalyzed data restricting our BPH definition to either a recorded diagnosis or a prescription for 5-alpha-redcutase inhibitor usage. This lowered the BPH rate while the adjusted hazard ratios did not change substantially, please see figure below. We have added this sensitivity analysis to the manuscript.

	Intention to treat analysis		As treated analysis	
	Metformin	Sulfonylurea	Metformin	Sulfonylurea
BPH diagnosis or use of 5 alpha-reductase inibitors				
Rate per 1,000 PY (95% CI)	8.24 (7.31-9.17)	12.42 (11.46-13.39)	7.94 (6.90-8.98)	12.80 (11.65-13.96)
Crude HR (95% CI)	0.66 (0.58–0.76)	(ref)	0.62 (0.53–0.73)	(ref)
Adjusted HR (95% CI)	0.92 (0.78–1.10)	(ref)	0.85 (0.70–1.04)	(ref)

- *Materials and methods, Diabetes severity-section, 1st paragraph: How did you define the cut-points for HbA1c?*

Response 1.4

We made these cut points *a priori* based on The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” (see Diabetes Care 2020 Jan; 43(Supplement 1): S66-S76 for the most updated version). According to these, an HbA1c goal for many non-pregnant adults of <7% (53 mmol/mol) is appropriate, less stringent HbA1c goals (such as <8% [64 mmol/mol]) may be appropriate for some patients, while HbA1c >8% [64 mmol/mol]) is considered not well controlled diabetes.

We have clarified this in the manuscript on page 9 first line.

- *Materials and methods, Statistical analysis-section, 5th paragraph: Why did you adjust the analysis for alcohol-related disease or glucocorticoid use? They are not known risk factors for BPH, thus uncertain to cause confounding. Were they significant predictors of BPH risk in this analysis?*

Response 1.4

We identified our potential confounding factors *a priory*. Alcohol-related disease is not strongly associated with to BPH but we considered alcohol-related diagnoses to be a marker for a general unhealthy lifestyle which may potentially be associated with BPH. Use of glucocorticoids could be related to both choice of antidiabetic treatment and degree of inflammation and was considered relevant. In our analyses we found that both variables were associated with BPH. Use of glucocorticoids versus non-use yielded a hazard ratio = 1.13 (95% CI, 0.70-1.83), while alcoholism versus no alcoholism yielded a HR of = 1.32 (95% CI, 0.77-2.29). Since these variables were slightly skewed between the two exposure groups, we kept them as potential confounders in our analysis.

- *Results, page 13, 2nd paragraph: check the numbers in confidence interval for crude HR for hospital-related BPH*

Response 1.4

Thank you for pointing to this. It was a typo. The correct estimate is 0.62 (95% CI 0.53 to 0.74). This has been corrected.

Reviewer: 2 Amr Ahmed EL-Arabey

The topic for that study is interesting because there are a lot of controversial data in that area. In fact, the current study was proposed to examine whether metformin use affects the risk of BPH by comparing the risk of BPH in men with type-2 diabetes who initiated first-line treatment with either metformin or sulfonylurea monotherapy between 2000 or 2006 in Northern Denmark. Therefore, I recommend the publication for the current study after minor revision as the following:

1- The authors should examine the sensitivity of analyses.

Response 2.1

We agree that sensitivity analyses are of importance in observational studies. We also did check the sensitivity in several ways – we conducted both an ITT and an as treated analysis, we stratified our analyses and we used several different definitions for BPH. We have additionally added a sensitivity analysis in which we define BPH-treatment as a diagnosis of BPH or a prescription of 5-alfa reductase inhibitors. We are of course willing to do additional specified sensitivity analyses if requested.

2- Please, refer to the transporter of metformin in prostate and the clinical trials which were done regarding the action of metformin on prostate cancer;

Reference: El-Arabey AA, Abdalla M, Ali Eltayb W. Metformin: Ongoing Journey with Superdrug Revolution. Adv Pharm Bull. 2019;9(1):1-4. doi:10.15171/apb.2019.001

Response 2.2

We have added the suggested reference in the introduction. Please see page 5 line 9.

3- Although, it is well known that Metformin used off-label for weight reduction;

Reference: El-Arabey AA. Update on off label use of metformin for obesity. Prim Care Diabetes. 2018;12(3):284-285.

Response 2.3

We have added the suggested reference in the discussion on page 16, first line.

Could the authors further discuss obesity as a critical risk factor for BPH and highlight that the characteristic baseline of hospital recorded obesity in the present study was highest in metformin

users (12.7%) versus sulfonylurea (5.3%). Moreover, authors should clarify how that factor may impact these results?

Response 2.4

We agree that the role of obesity is highly relevant and that lack of BMI information is a major weakness. We based our information on hospital recorded obesity which is known to be underreported and residual confounding could potentially mask a beneficial effect of metformin. The HR for BPH in men with a recorded obesity diagnosis compared with those without was 1.028 (95% CI, 0.694 – 1.524) so we did not observe a very strong effect of measured obesity in our study. We have added this information to the discussion. Please see page 16.

VERSION 2 – REVIEW

REVIEWER	Teemu J Murtola Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	I am satisfied with the responses. I have no further comments.

REVIEWER	Amr Ahmed El-Arabey Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University, Egypt
REVIEW RETURNED	27-Oct-2020

GENERAL COMMENTS	The authors have successfully addressed all comments.