PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-tem evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study
AUTHORS	ODERIS, GEERT; Van Pottelbergh, gijs; Truyers, Carla; Van Casteren, Viviane; De Clercq, Etienne; Van Den Broeke, Carine; Buntinx, Frank

VERSION 1 - REVIEW

REVIEWER	Barzilay, Joshua Kaiser Permanente, Endocrinology
REVIEW RETURNED	05-Oct-2013

GENERAL COMMENTS	This paper examines retrospectively a cohort of people with DM regarding renal function over time. There are several issues that need clarification. I present them in order of appearance: 1.INTRO- end of 2nd paragraph, " ...The use of eGFR alone.. could represent an age related functional decline" - please rewrite this sentence. What you mean to say is that a reduced eGFR at one point in time does not tell one if the low eGFR is a stable finding or a sign of a dynamic process of decline. 2. METHODS - end of the paragraph beginning with "The eGFR was calculated.." remove the last sentence "In this definition, CKD 1 and 2 were excluded" It sounds like this group is totally removed from the paper and yet in Table 1 these stages appear. 3. METHODS - from where did you take your criteria for rapid vs non-rapid eGFR decline? The studies I am aware of show decline of greater than 3 ml per year to be high. In the ACCORD study, in an article to appear shortly, the mean eGFR decline was 1 ml per year (Barzilay J et al..Clin J Am Soc Nephrol. 2013 Aug 29. [Epub ahead of print]. See also the article by Krolewski AS about rate of eGFR decline in type 1 DM. Curr Opin Nephrol Hypertens. 2009 May;18(3):233-40. doi: 10.1097/MNH.0b013e3283293db1. Review. PMID: 19300247 [PubMed - indexed for MEDLINE] . 4. METHODS- why did you settle on 3 yrs of anti diabetic drug dispensing as a criterion for diabetes? I have never seen such a strict criterion and I have never seen anyone else use it. 5. METHODS - please provide in this section or the RESULTS section how many people had 2, 3 , 4, etc...creatinine levels during follow up. If a large proportion had only 2 values for slope calculation this could be a problem and not too relable. You may then wish to repeat analyses without this group to see if your results hold up.

	6. In the INTRO you never mentioned the concept of severe drop or "certain drop." It now becomes an important part of the RESULTS section. You have not prepared the reader for this. Also please note that severe drops may not be a sign of renal disease but random variation due to an imperfect MDRD formula that may not be all that accurate in older adults. If you really want to get into this issue you would need a much more accurate means of assessing eGFR with cystatin C. Alternatively you can compare MDRD to the CKD Epi formula. The "certain drops" may not be so certain and actually be random variation. Consider dropping this whole notion and removing from the DISC section 7. RESULTS - the first logistic model shows that if the "severe drop" is not due to random variation from the MDRD formula then the drop in eGFR is indeed a true drop. This is circular reasoning. If one is dropping > 10ml/yr and the drop is true then of course they will be in ESRD quite quickly. 8. DISC - keep it simple and stay away from sudden declines in eGFR. The data for that is weak. Concentrate on the beautiful graphs that you have of stable CKD and rapid progressors. This information is not well known and if you emphasizze these results the paper should be fine.

REVIEWER	Trond Jenssen Oslo University Hospital, Rikshospitalet, Department of Nephrology and Oslo Diabetes Research Centre
REVIEW RETURNED	18-Oct-2013

GENERAL COMMENTS	The paper is of general interest for clinicians and scientists working with diabetes and/ or nephrology. The methods have som unfortunate limitations, escpecially that the authors were not able to include albuminuria/proteinuria in their estimates. Thus, from this paper we do not know anything about the course of diabetic nephropathy or any other renal disease, but it is rather a "real-life" descpription of what we might expect in evolution of renal funciton among patients with type 2 diabetes. This is an important information in itself given the cardiovascular risk that strikes diabetic patients with reduced renal function. This paper describes the course of renal function in a cohort of type 2 diabetic patients. The cohort is observed for up to 10 years, which gives the study some merit. A major limitiation is that albuminuria/ proteinuria measurements were not available, this is adequately discussed in the paper by the authors, as is also the lack of body weight indices. Some clarifications are however needed. 1. GPs recruting data to the registry applied for participation. This may indicate selecation problems in the cohort. We need to know, if possible, patient demographics in neighbouring GP practices. 2. I am puzzled that the CKD-EPI equation is not used instead of the MDRD equation, it is a more accurate estimate at least at higher levels of renal function, e.g., borderline stage 3. Why is that, and would the results be different with the CKD EPI equation?

	3. It is stated in the last paragraph of page 6 that HbA1c is stable over time unless some intervention is carried out. This is not true given the natural course of beta cell function in type 2 diabetes, also confounded by changes in body weight. This statement should be omitted. 4. What is the rationale for dividing the patients in 3 specific age groups, and what is the rationale for the specific cut-offs (page 7)? 5. Please give us more evidence for the representativity of the cohort (my previous point) other than a foreign language publicatoin (ref 29), and discuss in more detail on representativity issues, e.g. ethnicity which is not described in table 1. 6. We need to know the number of observations at each given year in figs.1a-c 7.In para 2, page 5 it should also be stated that loss of muscle mass in elderly patients may falsely give reduced estimates of renal function. The equation corrects for age, but does not eliminate the impact of muscle mass.

VERSION 1 – AUTHOR RESPONSE

First Reviewer

This paper examines retrospectively a cohort of people with DM regarding renal function over time. There are several issues that need clarification. I present them in order of appearance:

1.INTRO- end of 2nd paragraph, " ...The use of eGFR alone.. could represent an age related functional decline" - please rewrite this sentence. What you mean to say is that a reduced eGFR at one point in time does not tell one if the low eGFR is a stable finding or a sign of a dynamic process of decline.

We rewrote the sentence using the reviewer's suggestion: " because a reduced eGFR a one point in time does not tell if it is a stable finding or a sign of a dynamic process of decline. "

2. METHODS - end of the paragraph beginning with "The eGFR was calculated.." remove the last sentence "In this definition, CKD 1 and 2 were excluded" It sounds like this group is totally removed from the paper and yet in Table 1 these stages appear.
The sentence has been removed.
3. METHODS - from where did you take your criteria for rapid vs non-rapid eGFR decline? The studies I am aware of show decline of greater than 3 ml per year to be high. In the ACCORD study, in an article to appear shortly, the mean eGFR decline was 1 ml per year (Barzilay J et al..Clin J Am Soc Nephrol. 2013 Aug
29. [Epub ahead of print]. See also the article by Krolewski AS out rate of eGFR decline in type 1 DM. Curr Opin Nephrol Hypertens. 2009 May;18(3):233-40. doi:10.1097/MNH.0b013e3283293db1. Review.
PMID: 193 00247 [PubMed - indexed for MEDLINE] .

We based our definition on severe progression of CKD on the work of Al Aly Z et al, "Rate of kidney function decline associates with mortality. J Am Soc Nephrol
2010; 21(11):1961-1969" who defined it as a decline > 4 ml/min per year (as we did). Motivation: it is

one of the rather few articles discussing kidney function decline and it finds an association between kidney function decline and mortality (see table below):

We are aware that there is need of more evidence to point out the optimal cut off value to determine ‘severe decline’. We added a sentence in the discussion section “To determine “Severe Decline”, we used the definition of Al Aly who found an association between SD based on this cut off value and mortality. However, in the literature, there is no consensus on how renal function decline should be reported and what cut off value should be used to determine ‘Severity’. For example, Perkins and Krolewski used percentages to report decline while Barzilay found that A 1 ml/min per 1.73 m2 per year eGFR decline had a borderline association with decline in tests of cognitive function in patients with diabetes. We are thus in need of more research and a consensus procedure on this issue.”

4. METHODS- why did you settle on 3 yrs of anti diabetic drug dispensing as a criterion for diabetes? I have never seen such a strict criterion and I have never seen anyone else use it.

This is a misundertstanding. Diabetes was defined by the diagnosis, coded in the registry. We did not use any proxy to find out what patients were diabetic. Diabetes medication was accepted if it was registered in 2010.Other medication – and we focused on chronic medication use of use of ACE inhibition, other antihypertensive medication, platelet inhibition, lipid lowering drugs and NSAID – was accepted if prescribed for three years or more. As such we wanted to exclude the effect of short medication use on the kidney function.

5. METHODS - please provide in this section or the RESULTS section how many people had 2, 3 , 4, etc...creatinine levels during follow up. If a large proportion had only 2 values for slope calculation this could be a problem and not too relable. You may then wish to repeat analyses without this group to see if your results hold up.

We propose to add in the results section following sentence:
“As to the number of creatinin levels, 126 patients (3%) had 2 measurements, 150 (4%)had 3 measurements, 187 (4%) had 4 measurements and 3578 (89%) had five or more measurements.”
In our opinion, the number of patients with only 2 measurements is too little to do supplementary analyses.

6. In the INTRO you never mentioned the concept of severe drop or "certain drop." It now becomes an important part of the RESULTS section. You have not prepared the reader for this. Also please note that severe drops may not be a sign of renal disease but random variation due to an imperfect MDRD formula that may not be all that accurate in older adults. If you really want to get into this issue you would need a much more accurate means of assessing eGFR with cystatin C. Alternatively you can compare MDRD to the CKD Epi formula. The "certain drops" may not be so certain and actually be random variation. Consider dropping this whole notion and removing from the DISC section.

We added a sentence in the introduction: ”Finally, severe decline may follow different ‘routes’ in different patients. In some patients, decline may be constant and gradual, while in other patients, stable periods may be alternate with “certain drops”. In extreme situations, CKD may be a lifelong complication of acute kidney injury.(1)”
We considered dropping the concept of “certain drop”, but decided not to do. Not all patients with T2DM are equal to CKD. Decline of kidney function is an important factor, but what determines decline? The introduction of “certain drop” allows to show that there are different ways in which the renal function can decline eventually suggesting different underlying causes. This is a hypothesis worth formulating it. Our data showed that in patients with severe decline, prevalence of at least 1 certain drop was considerably higher than in patients without severe decline: 86% (CI 95% 81-90) versus 54% (CI 95% 51-57) in patients with CKD and 77% (CI 95% 70-83) versus 46% (CI 95% 44-

48) in patients without CKD. How can these differences be explained if they are due to random variation in mdrd?
We fully agree that the MDRD equation gives an estimation of the GFR who is often imprecise especially in older persons. So we agree that in older persons our estimated GFR values could differ largely compared to if we would measure the GFR measure by a reference method in the same persons. however in this paper we analyzed the evolution of the eGFR (always measured by the same equation) for every individual patient. So estimating the GFR might lead to an eGFR who might differ with the true GFR but individual changes over time in eGFR cannot be explained by the equation used but by changes in serumcreatinine values.
Finally we also agree that it would be interesting to repeat the analyses with cystatine C based equation of the CKD-EPI equation. However we don't have Cystatine C values of this large cohort since it is not used in clinical practice in our country now for more than 10 years ago. Using the CKD-EPI equation on this data would also include new bias since the CKD-EPI equation can only be used with IDMS traceable creatinine values and most of the creatinine values in this cohort were measured before 2007 (the year of publishing of this new serum creatinine standardization). So we used the MDRD equation who has two versions: one who can be use on creatinine values for the standardization before the IDMS traceability of 2007 and one with this traceability.
7. RESULTS - the first logistic model shows that if the "severe drop" is not due to random variation from the MDRD formula then the drop in eGFR is indeed a true drop. This is circular reasoning. If one is dropping > 10ml/yr and the drop is true then of course they will be in ESRD quite quickly.

This is partly a misunderstanding. The first logistic model talks about severe decline (> 4 ml/min/year over the whole period), not about 'certain drop'. This model essentially tells us that according to our data, no other independent factors than the severity of decline determine grade 5 CKD. It may indeed be somehow trivial, but we emphasize this to strengthen our statement that the definition of CKD should take into account the change in eGFR and not just look about cross sectional values.

8. DISC - keep it simple and stay away from sudden declines in eGFR. The data for that is weak. Concentrate on the beautiful graphs that you have of stable CKD and rapid progressors. This information is not well known and if you emphasizze these results the paper should be fine.

We added a sentence in the beginning of the discussion section:
"As shown in figure 1, most patients remain stable for years."

However, as explained above, we maintained the discussion about 'rapid decline' as hypothesis worthwile formulating it. Therefore we added these sentences:
"The concept of certain drop is somehow controversial. Eventually, the obtained results could be due to random variation in the MDRD formula, but random variation cannot explain the differences in certain drop between patients with and without CKD and with and without severe decline. Moreover, our data show that not all patients with T2DM are equal with regards to CKD. The severity of decline of kidney function is an important factor, but what determines decline? The introduction of "certain drop" allows for showing that there are different ways in which the renal function can decline eventually suggesting different underlying causes. Indeed, some previous studies already suggested an association between ESRD and periods of rapid decline."

Second reviewer.

The paper is of general interest for clinicians and scientists working with diabetes and/ or nephrology. The methods have som unfortunate limitations, escpecially that the authors were not able to include albuminuria/proteinuria in their estimates. Thus, from this paper we do not know anything about the course of diabetic nephropathy or any other renal disease, but it is rather a "real-life" descpription of

what we might expect in evolution of renal funciton among patients with type 2 diabetes. This is an important information in itself given the cardiovascular risk that strikes diabetic patients with reduced renal function.

This paper describes the course of renal function in a cohort of type 2 diabetic patients. The cohort is observed for up to 10 years, which gives the study some merit. A major limitiation is that albuminuria/ proteinuria measurements were not available, this is adequately discussed in the paper by the authors, as is also the lack of body weight indices.

Some clarifications are however needed.

1. GPs recruting data to the registry applied for participation. This may indicate selecation problems in the cohort. We need to know, if possible, patient demographics in neighbouring GP practices.

The privacy commission in our country imposes strict rules about patients' anonymity. Researchers do not have access to the place where these patients are living. We therefore cannot compare with direct neighbours. We can compare with national statistics and these show that concerning age and gender distribution, the intego population is representative for the general Flemish population.

2. I am puzzled that the CKD-EPI equation is not used instead of the MDRD equation, it is a more accurate estimate at least at higher levels of renal function, e.g., borderline stage 3. Why is that, and would the results be different with the CKD EPI equation?

The discussion about with equation to use to estimate the GFR is a very complex discussion. There might be a slight advantage for the CKD-EPI equation over the MDRD equation in older adult but in the oldest old this advantage is uncertain and other equations like the BIS equations are proposed. However the reason why we use the MDRD equation in this cohort is different from this complex discussion. Using the CKD-EPI equation on this data would include new bias since the CKD-EPI equation can only be used with IDMS traceable creatinine values and most of the creatinine values in this cohort were measured before 2007 (the year of publishing of this new serum creatinine standardization). So we used the MDRD equation who has two versions: one who can be use on creatinine values for the standardization before the IDMS traceability of 2007 and one with this traceability.
We wrote a sentence in the discussion section about this issue (see also last comment). "Secondly, the MDRD formula presents several weaknesses as a proxy for the real kidney function. E.g. loss of muscle mass in elderly patients may falsely give reduced estimates of renal function. However, the formula corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same persons, a change in formula does not affect the model outcomes."

3. It is stated in the last paragraph of page 6 that HbA1c is stable over time unless some intervention is carried out. This is not true given the natural course of beta cell function in type 2 diabetes, also confounded by changes in body weight. This statement should be omitted.

The statement has been removed.

4. What is the rationale for dividing the patients in 3 specific age groups, and what is the rationale for the specific cut-offs (page 7)?

This division is based on previous work(2) as well as other studies (3) in which we showed that change in kidney function is different in the different age groups. We added the sentence "Based on the results of previous work as well as other studies, " with the reference.

5. Please give us more evidence for the representativity of the cohort (my previous point) other than a foreign language publicatoin (ref 29), and discuss in more detail on representativity issues, e.g. ethnicity which is not described in table 1.

1. We do not have data on ethnicity, but the registering practices are dispersed over the whole Flemish region (see map).

2.We did research about representativeness in the past by comparing patients' demographic data with databases on the whole population of Flanders regarding age, gender and income (reference 29). The Intego population is similar as the whole Flemish population for the three parameters (see figure and table below).
Age (intego versus Flemish population)

Evolution of age groups between 1994 & 2008 (intego & Flemish population)

Income in the Flanders region versus the municipilaties of the Intego population
Mean income per tax bill Median income per tax bill Mean income per person
Municipalities of Intego-population 25.765 19.919 14.872
Flanders 26.187 19.991 15.032

3. Finally,the diabetes population of intego has been compared with other datasources about diabetes. As shown in the figure below, data are similar to other sources as to prevalence of diabetes and age-related prevalence of diabetes.(4)

We added following sentence in the discussion section:"The Intego-population is comparable to the total Flemish population regarding age, gender and income distribution. Data on ethnicity are lacking but the registering practices are dispersed on the whole Flemish Region. Comparison of the Intego diabetes population with other data sources shows comparable global prevalence and similar distribution of age-related prevalence."

6. We need to know the number of observations at each given year in figs.1a-c
The numbers have been added to the figures

7.In para 2, page 5 it should also be stated that loss of muscle mass in elderly patients may falsely give reduced estimates of renal function. The equation corrects for age, but does not eliminate the impact of muscle mass.

We fully agree that changes in muscle mass can effect eGFR values. However we don't have a solution for this problem.
We wrote a sentence in the discussion section about this issue. "Secondly, the MDRD formula presents several weaknesses as a proxy for the real kidney function. E.g. loss of muscle mass in elderly patients may falsely give reduced estimates of renal function. However, the formula corrects for age that can act as a proxy for muscle mass. However, since we were interested in the evolution of kidney function in the same persons, a change in formula does not affect the model outcomes."

Third reviewer.

This is an interesting population based study of factors influencing the decline in renal function measured by the MDRD equation, in a 10-year period, in 4000 general practice-patients with type 2-diabetes above the age of 40, in Flanders in Belgium.
The study seems to be well planned and conducted, and there are a lot of relecant data incorporated in the logistic regression models.
Although the research question is interesting, there are, however, some serious data flaws. No data on BMI, microalbuminuria nor proteinuria, or the development of ESRD of the mortality of the patients are present, and these data are very important in the interpretation of the data.

Indeed, these are flaws due to the "real-life" description of what we might expect in evolution of renal function among patients with type 2 diabetes (cfr. 2nd reviewer, Prof. Trond Jenssen). The registry has its weaknesses that may be solved in the future if we are able to increase the routine collection and registration in the electronic file of these data. It is not just a problem of registration, but also a lack of real medical follow-up and thus these figures also reflect the quality of medical follow-up of type 2DM in Belgium with regards to micro-albuminuria, etc….

In the conclusion ESDR is mentioned, but no data on ESRD were available?

We rewrote the sentence: “grade V CKD (used as proxy for ESRD)”
Moreover, the associations found to be associated with a more severre decline in eGFR like statin therapy, ACE inhibition, other antihypertensive agents and antidiabetic drugs including insulin therapy are rather a description of the patients severe multimorbid condition rather than the cause for a decline in renal function, and I believe it is a 'closed loop' interpretation.
Some probably are (insulin therapy). Statin is rather a ‘protective’ factor, therefore we dropped from the list in the conclusion section, in order to avoid confusion. But also for statins, it is not possible to conclude on any causal relationship. In order to picture this important issue, we rewrote the last sentences using the reviewers’ suggestion: “Some of them may rather be a description of the patients’ severe multimorbid condition rather than the cause for a decline in renal function. Because of its retrospective character, this study is able to formulate hypotheses, but unable to determine any causal relationship. Further prospective observational and experimental research is needed to clarify the nature of those associations.”