Author’s response to reviews

Title: Management of type 2 diabetes and its prescription drug cost before and during the economic crisis in Greece. An observational study.

Authors:  
Stavros Liatis (sliatis@med.uoa.gr)  
Stavroula Papaoikonomou (drstpapaoikonomou@yahoo.gr)  
Asimina Ganotopoulou (asimigio@gmail.com)  
Athanasia Papazafiropoulou (pathan@ath.forthnet.gr)  
Constantinos Dinos (costasdinos@hotmail.com)  
Marios Michail (mariosmichael@yahoo.com)  
Apostolos Xilomenos (xylom_ap@yahoo.gr)  
Andreas Melidonis (melidonisa@yahoo.com)  
Stavros Pappas (pathan@ath.forthnet.gr)

Version: 3  
Date: 23 February 2014

Author’s response to reviews:

Athens, 22/2/2014

Dear Professor Magliano

Thank you for giving us the opportunity to revise our paper and resubmit it to BMC Endocrine Disorders.

We are pleased to send you now a revised manuscript in order to reevaluate our work. We would also like to thank both reviewers for their constructive comments and remarks. Below, you may find our point-to-point replies. All changes made to the manuscript are in red, bold-face text. Furthermore, we have performed the formatting changes as required.

We confirm that the revised paper has been read and approved by all author.

Sincerely

Dr Stavros Liatis, MD  
1st Department of Propaedeutic Internal Medicine  
Diabetes Center  
Laiko General Hospital  
Athens University Medical School  
Athens  
Greece

Replies to reviewers’ comments
Reviewer #1

1. Is there any major difference in interpretation between the present results and those of the authors’ earlier publication? If so, please highlight.

The major difference between the two studies lies in the fact that between 2006 and 2012 we found no improvement in glucose and blood pressure control indices, as we did in our first report. This might be due to several factors. “The enthusiasm produced after the publication of the UKPDS results in 1998 in contrast to the scepticism that was generated from the ACCORD and VADT trials in 2009, might provide some explanation. On the other hand, the economic crisis might have contributed as well”. We highlighted those differences in the discussion, as suggested.

2. In the Discussion, the study’s limitations would benefit from further analysis.

We have further highlighted the study’s limitations, as suggested, by including a separate paragraph in the last section of the discussion and adding the following remarks: “The main limitation, however, of the present analysis is the questionable representativeness of the study population... We cannot exclude the possibility that several patients, especially in the midst of a major economic crisis, may not afford a 5€ fee. Furthermore, unemployed/uninsured patients may not visit the diabetes clinics, due to their inability to meet financial obligations associated with medical advises/prescriptions. Costs associated with transportation might be a barrier as well. In addition, patients followed by general practitioners or in the private setting are not included in this analysis”.

3. Please do not start sentences with numbers. We have corrected the text as suggested.

Minor discretionary corrections:

1. Some minor improvements in spelling to attain homogeneity (i.e. British spelling) are necessary.

We did our best to improve spelling (e.g., we replaced glycaemia by glycemia and hyperlipidaemia by hyperlipidemia).

Reviewer #2

1. The authors highlight, in several parts of the manuscript, the use of the expensive incretin therapies (DPP-4 inhibitors and GLP-1 analogues) as a possible explanation for the increase of the drug prescription cost. Although this may be true, the results of this study showed that even when incretin therapies were excluded, the cost was still increased. Only when both the incretin therapies and the insulin analogues were excluded, the cost decreased to its previous values. As a result, the role of incretin therapies should be toned down.

Thank you for your remarks. Our intention was by no means to underestimate the role of incretin-based therapies as a valuable strategy against hyperglycemia, but to highlight the increased direct cost that new therapies are associated with. In order to clarify this issue we added the following paragraph in the discussion:

“It has been repeatedly reported that the largest components of medical
expenditures attributed to diabetes are associated with treatment of complications (hospital inpatient care and medications to treat these complications) rather than direct prescription cost to treat hyperglycemia [new Ref nr 28&29]. Hence it can be argued that the benefit derived from reduced incidence of hypoglycemia (including severe hypoglycemia) and reduction (or at least not increase) of body weight, counterbalance the higher medication price. Prospective studies with hard diabetes-related endpoints and independent cost-effectiveness studies of high quality are needed to establish cost-utility of new therapies. In any case, current guidelines issued by the ADA/EASD and the American Association of Clinical Endocrinologists encourage the use of GLP-1 based therapies as second-line options”.

2. The authors report as principal finding of the study (page 8 first 3 lines) that “there is no deterioration of clinical indices related to cardiovascular risk factors of patients with T2D, after the emergence of a major economic crisis in Greece”. However, it must be added that this is a finding concerning the certain indices of glucose, lipid and blood pressure control and the certain population visiting the 3 diabetes outpatient clinics. It is well known that a large number of unemployed individuals cannot afford the 5 euros charge for visiting a diabetes centre and/or the 10-25% cost of the drug prescription. The effects of the crisis on these individuals remain unknown. In any case, although this study provides some evidence about the effects of the crisis on some clinical indices, the effects of the crisis itself on cardiovascular diseases and costs as regards to the treatment (including hospitalisation) of diabetic complications may need a considerable number of years to become evident. From this point of view the role of the new expensive therapies (incretin therapies and insulin analogues) on the rate of major hypoglycaemic events (needing hospitalisation) and the prevalence of diabetic complications (and its costs) should also be carefully assessed, before making any definite claims about the value of these agents in diabetes treatment. These points must be made clear by the authors since it is a major point which will help the health authorities to design their financial policy.

We thank you again for these important comments. We have now included these concerns in the discussion as follows: (a) representativeness of the population has been indicated as an important limitation: “The main limitation, of the present analysis is the questionable representativeness of the study population… We cannot exclude, however, the possibility that several patients, especially in the midst of a major economic crisis, may not afford a 5€ fee. Furthermore, unemployed/uninsured patients may not visit the diabetes clinics, due to their inability to meet financial obligations associated with medical advises/prescriptions. Costs associated with transportation might be a barrier as well. In addition, patients followed by general practitioners or in the private setting are not included in this analysis”. In addition, in the beginning of the discussion section we emphasized that our findings refer to “patients with T2D who are regularly visiting public outpatient diabetes clinics” (b) the role of new and expensive therapies: this issue has been covered in our reply to the previous comment

3. The last sentence of the conclusions (page ) must be rephrased. The
introduction of new categories of agents (such as incretin mimetics and insulin analogues) has definitely helped patients to have a better control of their blood glucose and lipid levels and probably avoid future complications (although this may have to be proved) which will dramatically increase the cost of treatment several fold to the cost of the agents themselves.

Taking into account your comments, the conclusion has been rephrased as follows: “In conclusion, we observed that during the Greek economic crisis, cardiovascular risk management indices of T2D patients being examined at three major diabetes outpatient clinics of the GNHS, did not deteriorate and in the case of LDL-C and triglycerides, they improved. A 15% increase in the associated total prescription cost was observed, mainly due to the higher cost of glucose-lowering related medications. The introduction of new medications in this field (as opposite to the unchanged armamentum against hypertension, dyslipidemia and hyperthrombotic state), although responsible for an increased direct cost, might, on the other hand, provide long-term benefits associated with a favorable profile in terms of hypoglycemic risk and body weight. Long-term prospective studies with hard diabetes-related endpoints and independent cost-effectiveness studies of high quality are needed, in order to clarify cost-effectiveness of new therapies”.