Reviewer's report

Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study

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Reviewer: Edoardo Mannucci

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Major Compulsory Revisions

1) The analysis is based on the assumption that improvement of metabolic control can substantially reduce cardiovascular morbidity and mortality. Although epidemiological data show that a higher HbA1c is associated with higher incidence of fatal and nonfatal cardiovascular disease, results of RCTs are not unequivocal. To date, the only trial showing an improvement of macrovascular outcome as a result of stricter metabolic control in type 2 diabetes is the UKPDS Legacy (UKPDS 80) - with an effect much smaller than that assumed in the paper, while the other available trials (UKPDS 33, ACCORD, ADVANCE, and most recently VADT) failed to detect a similar benefit. Based on current evidence, the effect of reduction of HbA1c on CVD morbidity seems to be smaller than that predicted on the basis of observational studies, whereas the benefit in terms of mortality could be null. On this basis, the effects of early insulin therapy should be recalculated, assuming a beneficial effect on microvascular complications, without any effect on macrovascular complications or all-cause mortality.

2) Another assumption is that the reduction of HbA1c leads to the same long-term outcomes, irrespective of the therapeutical tools used. This point is controversial. The authors should acknowledge that, in the only long-term comparative trial available to date, insulin was associated with a higher mortality in comparison with an oral drug (metformin); furthermore, the epidemiological analysis of the DIGAMI-2 trial showed a significant association of insulin therapy with a poorer outcome in comparison with oral treatments. The observational data associating insulin with a higher cancer-related mortality should also be recollected. Although available data are not sufficient to establish a difference in outcomes between different pharmacological treatments, this possibility should be more clearly and extensively recognized in the Discussion. The authors should also mention the fact that many clinicians believe that reaching the therapeutic targets by non-pharmacological means (diet and exercise), whenever possible, could grant a more favorable outcome than any drug therapy.

3) Early insulin is presented as a "more realistic" approach than oral therapies for reaching and maintaining glycemic targets in type 2 diabetes. While this may well be the case, it should be recognized (in the Discussion) that the introduction of new classes of drugs (e.g., GLP-1 receptor agonists), and the growing use of triple combinations, could change the scenario, providing physicians with some
more valid alternative to insulin therapy.

Minor Essential Revisions
1) Ref. 13 is the epidemiological analysis of the UKPDS; the main analysis (UKPDS 33) is a more appropriate reference.
2) Ref. 15 is a meta-analysis of observational studies, and not of RCTs; this should be specified in the text.
3) Ref. 14 is not by Patel et al. (it is the ADVANCE study)
4) Ref. 18 could be changed with the more recent (2008) edition of the ADA/EASD Consensus Algorithm by Nathan et al.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have received speaking fees, consultancy fees, and/or research grants from manufacturers of insulin (Ely Lilly, Novo Nordisk, Sanofi Aventis) and from manufacturers of hypoglycemic drugs potentially alternative to insulin (the same as above, plus Novartis, Merck Sharp & Dohme, Glaxo SmithKline, Takeda, Merck KgA, Guidotti, Abiogen).