Reviewer’s report

Title: Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy

Version: 1 Date: 20 March 2008

Reviewer: Jan SAG SA Schouten

Reviewer’s report:

Dear Mrs. Norton,

Please find below our review of the manuscript “Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy.”

This is an interesting manuscript dealing with the question whether there is a difference in adherence between patients treated with hydrochlorothiazide monotherapy and patients treated with fixed-dose combinations containing hydrochlorothiazide. We compliment the authors with the large number of included patients. We do have some questions and recommendations.

Discretionary revisions:

1. We have some questions regarding the study utilization metrics and definitions as mentioned in figure 1. We think your definitions are a little bit confusing. To our knowledge, adherence represents the percentage of days that the patient has medication available. Adherence can be calculated by dividing the total number of prescribed pills by the total number of elapsed days. The last recorded prescription in the observation period is often not included in the analysis. Persistence mostly represents the duration that a patient continued to fill prescriptions after his or her first prescription. However, in your article, adherence is defined as the percentage of individuals having an MPR# 80%; persistence is defined as the percentage of patients remaining on therapy. We think the authors should be careful in comparing their results with results of other studies that use different definitions of adherence and persistence. Is there any reason why the authors have chosen these definitions?

2. The authors have chosen to exclude patients who received prescription fills for antihypertensive medications in addition to the study index medication on their study index date. In statistical analysis the authors adjust for independent variables, like other antihypertensive drugs not equal to the initial therapy subsequent to the index pharmacy claim date. The authors also calculated discontinuation of therapy. What if a patient switched therapy from HCTZ monotherapy to fixed-dose combination therapy because of a medical indication? Did the authors measure it only as nonpersistence to HCTZ or did they adjust for this situation in one or another way?
3. The authors compare adherence and persistence to diuretic fixed-dose combination therapy to diuretic monotherapy. It is possible that the severity of hypertension has determined whether a patient received monotherapy or combination therapy as initial antihypertensive treatment. The authors recognize this possibility and hypothesize that patients prescribed HCTZ alone may be healthier patients than those prescribed a fixed-dose combination therapy. The authors mention that statistical analysis was employed to control for differences in patient co-morbidity. To our opinion, however, the difference in disease severity could have led to bias, as patients who suffer from more severe hypertension without suffering from co-morbidity are possibly more adherent or persistent. Severity of hypertension is not included in the patient characteristics used for the propensity score weight. We think the authors should complete the first paragraph of page 14 by mentioning this.

4. Patients were included if they received # 1 prescription of one of the indexed medications. It is possible that patients did not refill their second prescription because continued use might not be indicated medically rather than because of nonadherence. Did the authors make allowance for this possibility. If not, the authors should mention this point in the Discussion section.

5. Was it possible for patients to refill their prescription at a different pharmacy than where they are registered? If yes, can this have led to missed registrations of refills and caused any bias in this study?

6. One advantage of using pharmacy records for measuring adherence, is that pharmacy records can cover an extended period of time. The authors mention in the Discussion section that one study found that persistence declines to 75% during the first six months of treatment and declined to 55% after three years time. Why did the authors choose for a follow-up period of only one year?

7. On page 13, the authors discuss the cost implications resulting from differences between antihypertensive drug regimens for patient medication adherence and persistence. Do the authors have any information to estimate if a switch from HCTZ monotherapy to fixed-dose combination therapy as initial antihypertensive therapy could be cost-effective in terms of improving adherence, taking account for the higher costs associated with a fixed-dose combination therapy? The authors could mention this point in the discussion section.

Minor essential revisions:

8. We think the sentence starting on line 20 on page 12 is not complete.

9. We think the definition of “days to therapy discontinuation” is not complete.

10. We think the word “in” on line 12 on page 13 had to be changed in “an” (important role).

11. In the last sentence of the Abstract, the authors mention that further research is needed to determine the relationship between improved persistence and
adherence with blood pressure control. We can’t find this statement in the discussion section of the manuscript. We don’t think it is of common use to mention new information in the abstract.

We hope the authors will respond to our questions and our recommendations.

Yours sincerely,

J.G.M.M. Hoevenaars, M.D.
J.S.A.G. Schouten, M.D., PhD

What next?: Accept after discretionary revisions

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 declare that I have no competing interests