TIME TO TREATMENT INTENSIFICATION IN PATIENTS ON DUAL PHARMACOTHERAPY FOR TYPE 2DIABETES: METFORMIN+DIPEPTIDYL PEPTIDASE INHIBITOR VERSUS METFORMIN+SULPHONILURA

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Background: Due to the progressive nature of type 2diabetes mellitus (T2DM), all available hypoglycemic drugs eventually lose efficacy. When T2DM patients experience secondary treatment failure, they require a treatment intensification (TI) in order to maintain glycemic control. Pre-clinical studies suggested the possibility that dipeptidyl peptidase inhibitor (DPP4i) could delay the time to IT in T2DM patients, although available clinical evidence on this topic are not conclusive. The aim of this study was to verify whether adding a dipeptidyl peptidase inhibitor (DPP4i) to initial metformin (MET) monotherapy, rather than a sulfonylurea (SU) can delay the time to further treatment intensification in patients with T2DM.

Methods: A retrospective cohort study was performed using administrative data from three Italian geographic areas (Piedmont,Tuscany, Umbria, Caserta) were used, corresponding to a total source population of about 10 million subjects. A distributed database network approach was adopted. Patients receiving a DPP4i or a SU between 2008and 2015were selected. The first dispensing of DPP4i or SU was the index date. Patients were included if at index date they: i) were ≥18years old, ii) had ≥1year of look-back into the database, iii) had been on MET monotherapy for≥60 days, iv) were persistent to MET (no treatment gap ≥90 days)and had no record of any other antidiabetic drug during the year preceding index date. The study cohort was followed up to 31st, December 2017, the occurrence of censoring events (discontinuation of MET, DPP4i or SU, switch, cancer, death, end of data) or the study outcome, i.e. TI, whichever occurred first. TI was defined as insulin dispensing or add-on of a third non-insulin hypoglycaemic. Patients experiencing TI within 180 days from index date were censored (i.e. primary treatment failure). Patients initiating DPP4i were matched 1:1to SU initiators by sex, age band and year of index date. The Hazard Ratio (HR), with 95confidence intervals (95CI), for the occurrence of TI in patients treated with MET+DPP4i versus MET+SU was estimated with a multivariable Cox regression model. Matching covariates, MET treatment duration at index date, comorbidities and concomitant pharmacotherapies were included into the model. To explore the robustness of results, the following sensitivity analyses were conducted: A) including hospital admissions as a censoring criterion, B) matching at 180 days after index date C) including number of HbA1c measurements before index date as matching criterion D) intention to treat approach E) matching by duration of MET treatment.

Results: The cumulative unmatched study cohort from the three areas included 22,691patients. Of these, around 50% of patients were from Tuscany. At time of the present abstract submission, definitive results were available for Tuscany only. The matched Tuscan cohort included 2,281patients in each treatment group, corresponding to 7.332person-years. Patients on MET+SU were more frequently censored because of discontinuation of MET (21% vs 13%) or index drug (47% vs 30%). Median follow-up time in years was 1.5(interquartile range: 0.5-3.1) for MET+DPP4i and 0.5(0.3-1.6) for MET+SU. The primary outcome occurred in 250 patients in the MET+DPP4i group and in 119patients within the MET+SU. In the primary analysis, the HR for TI in patients exposed to MET+DPP4i versus MET+SU of 1.05(95CI 0.82–1.33). Sensitivity analyses (A-C) confirmed the results of the primary analysis. Conversely, analyses D) (HR=1,34; 1,14-1,58) and E) (HR=1,38; 1,07-1,78) showed an higher risk of TI in patients on MET+DPP4i.

Conclusions: Results from the Tuscan cohort suggested that adding a DPP4i to MET rather than SU does not delay the time to TI in T2DM patients. Sensitivity analyses confirmed this finding. Due to the observational nature of the study, however, residual bias cannot be excluded. The analysis of the other three participating databases will increase precision and robustness of the overall study results.