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Pharmacogenomics Bias – Systematic Distortion of Study Results by Genetic Heterogeneity

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Background

Decision analyses of drug treatments in chronic diseases require modeling the progression of disease and treatment response beyond the time horizon of clinical or epidemiological studies. In many such models, progression and drug effect have been applied uniformly to all patients; heterogeneity in progression, including pharmacogenomic effects, has been ignored.

Objective

We sought to systematically evaluate the existence, direction and relative magnitude of a pharmacogenomics bias (PGX-Bias) resulting from failure to adjust for genetic heterogeneity in both treatment response (HT) and heterogeneity in progression of disease (HP) in decision-analytic studies based on clinical study data.

Methods

We performed a systematic literature search in electronic databases for studies regarding the effect of genetic heterogeneity on the validity of study results. Included studies have been summarized in evidence tables.
In the case of lacking evidence from published studies we sought to perform our own simulation considering both HT and HP. We constructed two simple Markov models with three basic health states (early-stage disease, late-stage disease, dead), one adjusting and the other not adjusting for genetic heterogeneity. Adjustment was done by creating different disease states for presence (G+) and absence (G-) of a dichotomous genetic factor. We compared the life expectancy gains attributable to treatment resulting from both models and defined pharmacogenomics bias as percent deviation of treatment-related life expectancy gains in the unadjusted model from those in the adjusted model. We calculated the bias as a function of underlying model parameters to create generic results.
We then applied our model to lipid-lowering therapy with pravastatin in patients with coronary atherosclerosis, incorporating the influence of two TaqIB polymorphism variants (B1 and B2) on progression and drug efficacy as reported in the DNA substudy of the REGRESS trial.

Results

We found four studies that systematically evaluated heterogeneity bias. All of them indicated that there is a potential of heterogeneity bias. However, none of these studies explicitly investigated the effect of genetic heterogeneity. Therefore we performed our own simulation study.
Our generic simulation showed that a purely HT-related bias is negative (conservative) and a purely HP-related bias is positive (liberal). For many typical scenarios, the absolute bias is smaller than 10 %. In case of joint HP and HT, the overall bias is likely triggered by the HP component and reach-

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es positive values > 100 % if fractions of „fast progressors" and „strong treatment responders" are low.
In the clinical example with pravastatin therapy, the unadjusted model overestimated the true life-years gained (LYG) by 5.5 % (1.07 LYG vs. 0.99 LYG for 56-year-old men).

Conclusions

We have been able to predict the pharmacogenomics bias jointly caused by heterogeneity in progression of disease and heterogeneity in treatment response as a function of characteristics of patients, chronic disease, and treatment. In the case of joint presence of both types of heterogeneity, models ignoring this heterogeneity may generate results that overestimate the treatment benefit.