IS IT POSSIBLE TO PREDICT THE MARKET ACCESS OF A NEW PHARMACEUTICAL IN GERMANY? A SYSTEMATIC EVALUATION OF FEDERAL JOINT COMMITTEE DECISIONS ON EARLY BENEFIT ASSESSMENTS ACCORDING TO THE GERMAN LAW FOR REFORMING THE MARKET OF PHARMACEUTICALS

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Abstract

Objectives: As of 1st January 2011 the German drug market is regulated by the act of the reorganization of the pharmaceutical market (AMNOG). Since then the normal procedure for reimbursement of a new pharmaceutical is an early benefit assessment by the joint federal committee (G-BA) which determines one of six additional benefit levels. According to AMNOG any specification of the reimbursement price shall be based on the outcomes of the early benefit assessment. Hence this assessment takes a key role for market access of a new drug in Germany which poses the question whether it is possible to predict the level of additional benefit that will be established by the G-BA.

Methods: In order to evaluate a possible predictor of G-BA decisions, the 'evaluation of pharmaceutical innovations (EVITA)' score was calculated and retrospectively compared with 40 published G-BA decisions. The EVITA algorithm evaluates a new compound for a given indication and in relation to a relevant comparator on the basis of randomized controlled trial (RCT) evidence. EVITA translates the RCT outcomes on the therapeutic benefit and risk profile into rating points, which are expressed as a total EVITA score.

Results: Univariate ordinary least squares and ordered logit regression analyses show statistically significant correlations between EVITA scores and the G-BA additional benefit levels. Moreover, for the prediction of an additional benefit level of at least 'minor', an EVITA score cutpoint of ≥ 3 is associated with a sensitivity of 100% and a specificity of 80%. For the prediction of an additional benefit level of at least 'considerable', an EVITA score cutpoint of ≥ 7.5 is associated with a sensitivity of 100% and a specificity of 93.1%.

Conclusions: The present investigation indicates that the EVITA score may have the potential for the prediction of G-BA decisions related to AMNOG early benefit assessments.

Introduction

- On January 1st 2011 the German act on the reform of the market for medicinal products (Arzneimittelmarktneuordnungsgesetz - AMNOG) became effective [1].
- Due to this act the means of obtaining cost reimbursement for pharmaceuticals from the German statutory health insurance (SHI) have changed significantly. The prices for most pharmaceuticals with new active ingredients which the SHIs reimburse will now be negotiated during the first year after their market launch.
- The results of an early benefit assessment are the basis of these price negotiations. In order to provide evidence for an additional benefit the pharmaceutical companies need to submit a dossier to the joint federal committee (G-BA), that summarizes the benefit/risk profile and the budgetary consequences of a new compound in comparison to a specific 'appropriate comparator' defined by the G-BA.
- Once the manufacturer dossier was submitted (in time) the G-BA usually commissions the Institute for Quality and Efficiency in Health Care (IQWiG) with assessing the benefits of the new drug.
- Using the manufacturer's submission and the IQWiG assessment as basis, the G-BA determines one of the following six additional benefit levels to rate the benefit of a new drug versus the 'appropriate comparator': (1) major additional benefit, (2) considerable additional benefit, (3) minor additional benefit, (4) non-quantifiable additional benefit, (5) no additional benefit, (6) worse than the comparator.
- According to AMNOG, specification of the reimbursement price of a new drug is based on the results of early benefit assessment. Hence, expectations regarding the level of benefit are of major interest at any stage of market access of a new drug in Germany which poses the question whether it is possible to predict the level of additional benefit that will be established by the G-BA.
- In order to answer this question, which is of particular importance for the pharmaceutical industry, the aim of our study was to evaluate a possible predictor for the G-BA additional benefit level on the basis of the comparative benefit risk profile of a new compound, which was assessed by the 'EValuation of pharmaceutical Innovations with regard to Therapeutic Advantage (EVITA)' approach [2].

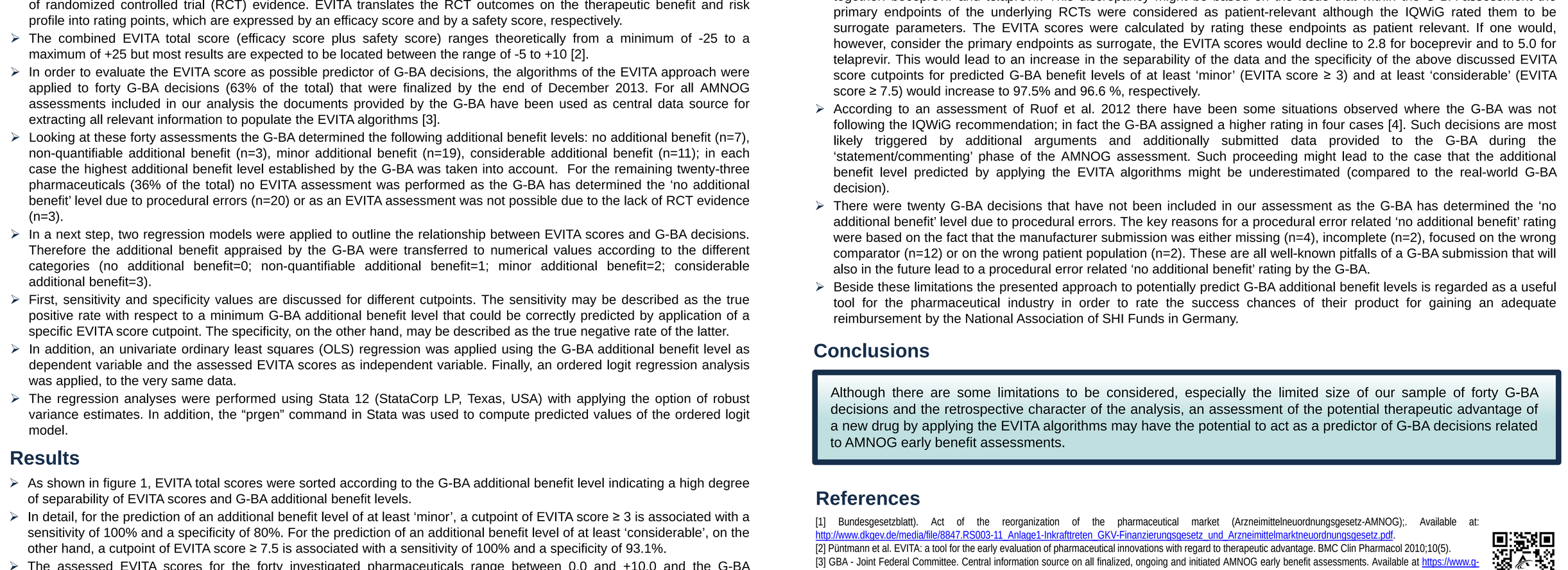
Material and Methods

- Using the EVITA approach [2], developed by the University of Bremen, we investigated whether the level of benefit assessed by the G-BA can be predicted by the EVITA total score.
- The EVITA algorithm evaluates a new compound for a given indication and in relation to a relevant comparator on the basis of randomized controlled trial (RCT) evidence. EVITA translates the RCT outcomes on the therapeutic benefit and risk profile into rating points, which are expressed by an efficacy score and by a safety score, respectively.
- The combined EVITA total score (efficacy score plus safety score) ranges theoretically from a minimum of -25 to a maximum of +25 but most results are expected to be located between the range of -5 to +10 [2].
- In order to evaluate the EVITA score as possible predictor of G-BA decisions, the algorithms of the EVITA approach were applied to forty G-BA decisions (63% of the total) that were finalized by the end of December 2013. For all AMNOG assessments included in our analysis the documents provided by the G-BA have been used as central data source for extracting all relevant information to populate the EVITA algorithms [3].
- Looking at these forty assessments the G-BA determined the following additional benefit levels: no additional benefit (n=7), non-quantifiable additional benefit (n=3), minor additional benefit (n=19), considerable additional benefit (n=11); in each case the highest additional benefit level established by the G-BA was taken into account. For the remaining twenty-three pharmaceuticals (36% of the total) no EVITA assessment was performed as the G-BA has determined the 'no additional benefit' level due to procedural errors (n=20) or as an EVITA assessment was not possible due to the lack of RCT evidence (n=3).
- In a next step, two regression models were applied to outline the relationship between EVITA scores and G-BA decisions. Therefore the additional benefit appraised by the G-BA were transferred to numerical values according to the different categories (no additional benefit=0; non-quantifiable additional benefit=1; minor additional benefit=2; considerable additional benefit=3).
- First, sensitivity and specificity values are discussed for different cutpoints. The sensitivity may be described as the true positive rate with respect to a minimum G-BA additional benefit level that could be correctly predicted by application of a specific EVITA score cutpoint. The specificity, on the other hand, may be described as the true negative rate of the latter.
- In addition, an univariate ordinary least squares (OLS) regression was applied using the G-BA additional benefit level as dependent variable and the assessed EVITA scores as independent variable. Finally, an ordered logit regression analysis was applied, to the very same data.
- The regression analyses were performed using Stata 12 (StataCorp LP, Texas, USA) with applying the option of robust variance estimates. In addition, the "prgen" command in Stata was used to compute predicted values of the ordered logit model.

Results

- As shown in figure 1, EVITA total scores were sorted according to the G-BA additional benefit level indicating a high degree of separability of EVITA scores and G-BA additional benefit levels.
- In detail, for the prediction of an additional benefit level of at least 'minor', a cutpoint of EVITA score ≥ 3 is associated with a sensitivity of 100% and a specificity of 80%. For the prediction of an additional benefit level of at least 'considerable', on the other hand, a cutpoint of EVITA score ≥ 7.5 is associated with a sensitivity of 100% and a specificity of 93.1%.
- The assessed EVITA scores for the forty investigated pharmaceuticals range between 0.0 and +10.0 and the G-BA additional benefit level range between 0 (no additional benefit) and 3 (considerable additional benefit).

Figure 1: Overview of EVITA scores grouped by the GBA additional benefit level



Results (continued)

- As shown in table 1, the two regression models indicate a correlation between the EVITA score and the G-BA additional benefit level. Irrespective of the regression analyses approach a statistically significant correlation between the EVITA score and the G-BA additional benefit level has been obtained.

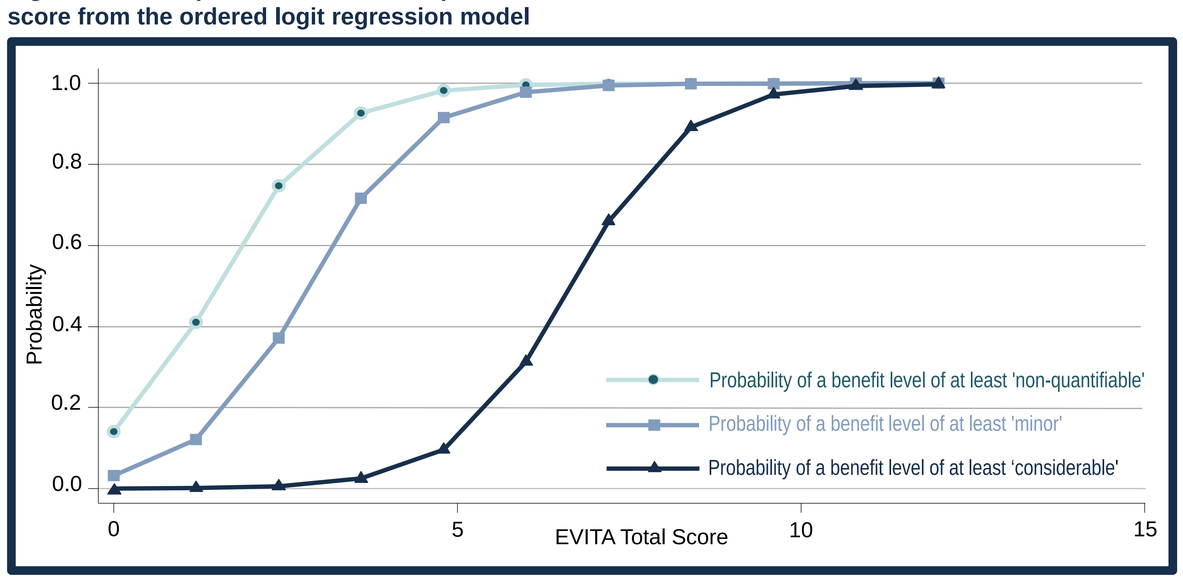
Table 1: Results of the univariate OLS and ordered logit (ologit) regression models using the four ordered categories of G-BA benefit level as dependent variable

	Model 1 (OLS)		Model 2 (ologit)	
EVITA Score	0.292***	(<0.001)	1.209**	(0.008)
Intercept (1 / 2 / 3)	0.441*	(0.020)	1.815* / 3.427** / 8.041**	(0.034) / (0.004) / (0.005)
N	40		40	
R^2 [adj. R^2]	0.689	[0.681]	0.484±	

p-values in parentheses; * p < 0.05, ** p < 0.01, *** p < 0.001; ± pseudo R^2; Regression model (1) provides the results of an univariate ordinary least squares regression analysis with numerical values according to the different categories of G-BA decisions (no additional benefit=0; non-quantifiable additional benefit=1; minor additional benefit=2 and significant additional benefit=3) as dependent variable and the results of the EVITA score as independent variable. Regression models (2) provides the results of the ordered logit regression analysis applied to the very same data. All regression analyses were performed using Stata 12.

- Figure 2 shows the predicted cumulative probabilities according the results of the ordered logit regression model as presented in table 1 (model 2).
- As shown in figure 2 a 50 % probability of an additional benefit level of at least 'considerable', for instance, is reached with an EVITA score of around 7.
- Analogously, a 50 % probability of an additional benefit level of at least 'minor' is reached with an EVITA score of around 3.

Figure 2: Plot of predicted cumulative probabilities of G-BA additional benefit level versus EVITA score from the ordered logit regression model



Discussion

- As shown in figure 1, there are two substances where the G-BA benefit level and EVITA score results do not fit well together: boceprevir and telaprevir. This discrepancy might be based on the issue that within the G-BA assessment the primary endpoints of the underlying RCTs were considered as patient-relevant although the IQWiG rated them to be surrogate parameters. The EVITA scores were calculated by rating these endpoints as patient relevant. If one would, however, consider the primary endpoints as surrogate, the EVITA scores would decline to 2.8 for boceprevir and to 5.0 for telaprevir. This would lead to an increase in the separability of the data and the specificity of the above discussed EVITA score cutpoints for predicted G-BA benefit levels of at least 'minor' (EVITA score ≥ 3) and at least 'considerable' (EVITA score ≥ 7.5) would increase to 97.5% and 96.6 %, respectively.
- According to an assessment of Ruof et al. 2012 there have been some situations observed where the G-BA was not following the IQWiG recommendation; in fact the G-BA assigned a higher rating in four cases [4]. Such decisions are most likely triggered by additional arguments and additionally submitted data provided to the G-BA during the 'statement/commenting' phase of the AMNOG assessment. Such proceeding might lead to the case that the additional benefit level predicted by applying the EVITA algorithms might be underestimated (compared to the real-world G-BA decision).
- There were twenty G-BA decisions that have not been included in our assessment as the G-BA has determined the 'no additional benefit' level due to procedural errors. The key reasons for a procedural error related 'no additional benefit' rating were based on the fact that the manufacturer submission was either missing (n=4), incomplete (n=2), focused on the wrong comparator (n=12) or on the wrong patient population (n=2). These are all well-known pitfalls of a G-BA submission that will also in the future lead to a procedural error related 'no additional benefit' rating by the G-BA.
- Beside these limitations the presented approach to potentially predict G-BA additional benefit levels is regarded as a useful tool for the pharmaceutical industry in order to rate the success chances of their product for gaining an adequate reimbursement by the National Association of SHI Funds in Germany.

Conclusions

Although there are some limitations to be considered, especially the limited size of our sample of forty G-BA decisions and the retrospective character of the analysis, an assessment of the potential therapeutic advantage of a new drug by applying the EVITA algorithms may have the potential to act as a predictor of G-BA decisions related to AMNOG early benefit assessments.

References

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