A novel approach for non-adherence measurement based on prescription data: The example of oral diabetics in the therapy of type 2 diabetes mellitus patients

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Baltimore, May 2011

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Introduction

Up to 50% of patients do not follow prescribed therapies (non-adherence; NA), and therefore present a considerable challenge to the provision of health care. NA is correlated with detrimental clinical outcomes and higher health care costs. The results achieved in the treatment by means of oral hypoglycaemic agents (OHA), of type 2 diabetes mellitus (T2DM) patients show a similar situation. The literature shows NA rates between 30 and 50%, which can lead to worse blood glucose levels, higher rates of acute metabolic events, increased risk of hospitalization and mortality and health care costs that are higher than necessary. It seems that NA of patients may be one of the main challenges in health care provision. In support of this view, authors of a Cochrane review (Haynes et al.) concluded as early as 2002 that "… increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".

A commonly used methodology for NA measurement is the analysis of pharmacy prescription data. However, existing NA-analyses for OHA based on prescription data show an astonishing variance of results; one review shows NA rates (percentage of NA patients based on all observed patients) of between 54 % and 93 %. Such a range may induce differences in the health care provision. As most of the investigations have been conducted using American prescription data, and is therefore based on similar care provision systems, it can be assumed that there are also other explanations of the results. The probability exists that the differences in the NA research results are in part due to methodological differences in the analyses.

If such methodological differences were to exist, it would be desirable to systemize the methodological basis of NA measurements made using prescription data, and to determine the parameters that influence such analyses. Unless an investigation intended to clear such matters is made, both the results of NA research (the extent of NA) and the evaluation of the effectiveness of NA interventions may have considerable deficits. It is the aim of our research, building on the scientific debates that have already taken place concerning NA measurements made on the basis of prescription data, to describe as fully as possible the different parameters and the variety of assumptions on which present NA research using prescription data is founded. The case of OHA in T2DM therapy will be taken as an example. In addition, the quantitative significance of each variation of each parameter will be displayed using a secondary data set. Finally, a statement will be made concerning which combination of parameters is to be strived for in the sense of finding the novel approach which will need to be followed if the NA rate found during research is to contribute to an optimal explanation of diabetes-related hospitalization and clinical events.

Methodology

Parameters of a NA analysis

All the parameters that influence an analysis of NA were drawn from a review (MEDLINE, Embase and Cochrane Database of Systematic Reviews; strings: diabetes oral agents administrative database; diabetes oral agents secondary data; diabetes oral agents medication possession ratio; diabetes oral agents proportion of days covered; 47 contributions). A total of 12 parameters were identified (only main options are shown here).

Parameter	Option A	Option B	Option C
1 Sample inclusion criteria: number and source of diagnoses	At least 2 outpatient T2DM diagnoses in 2 different quarters OR at least 1 inpatient T2DM diagnosis	At least 2 outpatient T2DM diagnosis (irrespective of diagnosis date) OR at least 1 inpatient diagnosis	At least 1 inpatient T2DM diagnosis
2 Analyzed patient sample	All patients meeting inclusion criteria	Only newly treated patients (OAD prescriptions in 2007, but no OAD prescriptions in index year 2006)	
3 Minimum number of prescriptions	At least 3 prescriptions in observation period (2006-2008) in at least 1 OAD-ATC class	At least 2 prescriptions in observation period (2006-2008) in at least 1 OAD-ATC class	
4 Observation period	2006-2008 (3 years)	Yearly analysis	
5 Definition of required daily dose	DDD	(1) Guidelines (2) Individual historical profiles	Based on prescriptions (prescribed days of supply)
6 Calculation approach	Prescription based (first until last prescription), excluding last prescription	Interval-based (first prescription until end of observation period)	Interval-based (calendar period)
7 NA measure	MPR (medication possession ratio; arithmetic mean of ATC-group-specific MPRs)	PDC (percentage of days covered; a day is classified as covered by medication if any of the analyzed medications was available)	Other, e.g. CMG (continuous measure of medication gaps)
8 Stockpiling	With stockpiling	Without stockpiling	
9 Dealing with adherence > 100 % on patient level	Truncation to 100 %	No truncation	
10 Analyzed medication classes	All patients (mono- and multimedication), analysis of all medication classes	Only patients with monomedication: only one prescribed ATC class in the whole observation period (here: Metformin)	All patients (mono- and multimedication), but only analysis of one or certain medication classes
11 Consideration of hospitalization periods	Without consideration	With consideration	
12 If NA measure is dichotomized: Used NA threshold	NA if MPR/PDC < 80 %	NA if MPR/PDC < 90 %	Use of other thresholds

Scenario analysis of parameter influence

The influence of the 12 identified parameters on the results of NA analysis were quantitatively simulated using a German secondary data set. Data concerning patients was drawn from a German statutory health insurance fund that insures 7.6 million individuals. 5.4 million people were insured by the fund without interruption within the observation period, (1 January 2006 to 31 December 2008) and this pool of patients provided us with samples for our investigations. In principle, all the patients in this pool who had been given two ambulant diagnoses of T2DM or one stationary diagnosis of T2DM were included; later, analyses used in part more restrictive sample definitions on the basis of parameters 1 to 4. Based on the originally included 247,401 patients who met the inclusion criteria defined above, the insurance fund's specific T2DM prevalence was about 4.6% in 2008.

Our medication adherence analysis covered most of prescribed OHA-ATC classes that exist in Germany (A10BA - Biguanides, A10BB/A10BC - Sulfonamides, A10BF - Alpha-glucosidase inhibitors, A10BG - Thiazolidinediones, A10BH - Dipeptidyl-peptidase-4-inhibitors, A10BX – other blood glucose lowering drugs, excluding insulins). We only excluded combination preparations of oral blood glucose lowering drugs (A10BD) and all the patients that got these drugs but had OHA prescriptions for any other OHA ATC classes were not completely excluded from the sample; however, adherence measurement was based on the remaining OHA-ATC classes only.

Two sensitivity analyses were conducted to measure the quantitative influence of the alternative parameters on the results of the NA analysis:

1. An analysis base case was formulated in the context of a univariate analysis (option A). In the base Case, all the patients considered had received at least 2 ambulant T2DM diagnoses in 2 different quarters of the year, or a stationary T2DM diagnosis as well as at least 3 prescriptions for an OHA-ATC class medicine in the observation period 2006-2008 (113,108 patients). For all the patients, the analysis took place over three years (this was not only done using newly treated patients). Starting with the base case, each of the parameters with the potential to alter the results was changed in an univariate manner (cet. par.), so that 19 scenarios resul-ted. The results were expressed as the average availability of medication (MPR/ PDC) and as the proportion of the patients affected by NA (NA quota; dichotomized).

2. While the univariate analysis measures the individual influence exerted by each parameter, it is possible that specific combinations of parameters have a special influence on the extent of NA. To test this, 144 alternative methodological cases were distinguished using a decision tree structure, and each case was characterized by a specific combination of 8 of the 12 parameters that had been identified. These were parameters 5-12. The parameters 1-4 define different samples and were therefore not included in this analysis, because the focus of the simulation was not on the definition of patient samples, but on the selection of parameters in a prescription data based NA analysis.

Logistical regression estimates were used to seek those combinations of parameters that best explained statistically the diabetes-related hospitalization as well as the diabetes-related clinical events in the sample in the years 2006-2008. The main hospital ICD code E11 was used to indicate diabetes-related treatment. The clinical incidents considered as relevant in the context of diabetes were stroke (ICD I63) and heart attack (ICD I21). Consequently, the dependent variable was thus a combination of the above-mentioned hospitalization/events, that were dichotomized. The medication availability in the cases being considered was used as the independent variable. Further and controlling independent variables that were in each estimation (logistical regression) were the age, gender, the number of co-morbidities (limited to hypertension, asthma, COPD, rheumatism, KHK and malignancy) the level of dependency on care by third parties, possible insulin intake, intake of circulatory system medication (VKA or antiarrhythmics or antihypertensives) and participation in a disease management programme.

Results (I)

Socio-demographic characteristics of the sample

	BASE CASE(1)
N	113,108
Age (2008/12/31)	Ø 65.42 (SD: 10.42)
Gender	Female: 36,199 (32.00%) Male: 76,909 (68.00%)
Nb. of different prescribed ATC codes in observation period(2)	Ø 13.78 (SD: 7.85)
Nb. of prescriptions for all prescribed ATC codes in observation period(2)	Ø 72.13 (SD: 46.10)
Nb. of different prescribed OHA ATC codes in observation period(2)	Ø 1.67 (SD: 0.86)
Nb. of prescriptions for all prescribed OHA ATC codes in observation period(2)	Ø 15.84 (SD: 10.64)
Nb. of all-cause hospitalizations in observation period(2)	Ø 1.22 (SD: 2.12) [Ø duration: 7.97 days]
Nb. of Diabetes-related hospitalizations in observation period(2); ICD10 E11	Ø 0.74 (SD: 1.40) [Ø duration: 8.67 days]

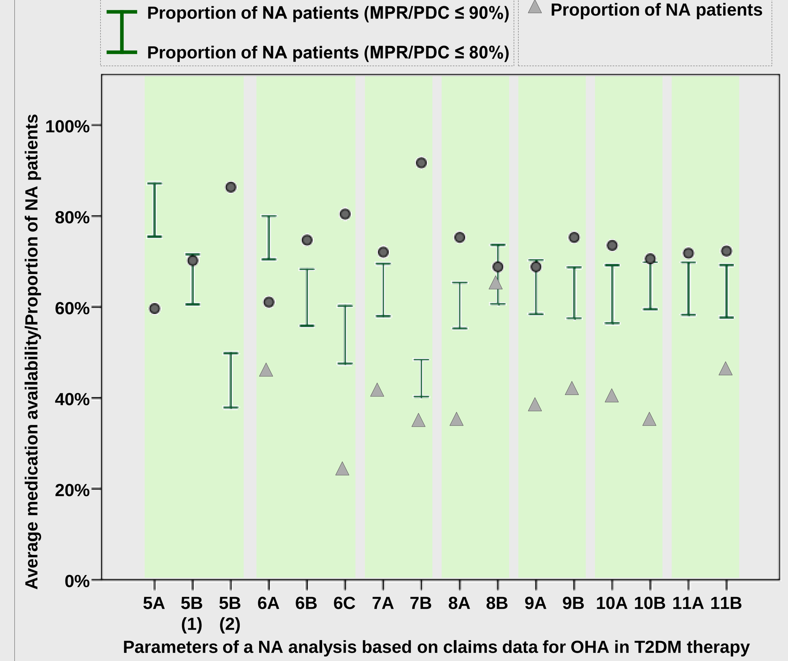
Medication profiles of the sample(1)		
Mono-therapy consistent	Class A	60.879 (53,82 %)
Single-Drug Switcher	Class A, Class B	6.660 (5,89 %)
Single-Drug Add-On	Class A, Class B	19.162 (16,94 %)
Poly-therapy consistent	Class A, Class B	5.377 (4,75 %)
Poly-therapy Add-On	Class A, Class B, Class C	4.321 (3,82 %)
Poly-therapy Drop-Off	Class A, Class B	5.924 (5,24 %)
Poly-therapy Switcher	Class A, Class B, Class C	1.861 (1,65 %)
Multiple-Drug Add-On	Class A, Class B, Class C	8.924 (7,89 %)

(1) BASE CASE: All T2DM patients with at least 2 outpatient T2DM diagnoses in 2 different quarters or 1 inpatient T2DM diagnosis and at least 3 OAD prescriptions for one specific OAD ATC-code in three years (2) 2006-2008

Univariate analysis of parameter changes

	Sample definition				Approaches								Results		
	1. Inclusion criteria	2. Newly treated	3. Nb. of pres-crip-tions	4. Length of obser-vation period	5. Definition of required daily dose (per ATC class)	6. Calculation approach	7. Used NA measure	8. Stock-piling	9. Dealing with adherence > 100 %	10. Analyzed medication classes: Only analysis of patients with mono-medication?	11. Hospi-ta-lization	12. Dichoto-mized defi-nition of NA	Nb. of patients	Average MPR/ PDC (difference to base case in percentage points)	% of NA patients with dichotomized NA definition (difference to base case in percentage points)
Base Case	1A. 2 subsequent outpatient T2DM diagnosis in two different quarters OR at least 1 inpatient T2DM diagnosis	2A. All patients	3A. 3	4A. 3 years	5A. DDD	6A. Prescription-based excluding last prescription	7A. MPR	8A. Multi: Yes within ATC classes; no for different ATC classes	9A. Truncated to 100 %	10A. All patients (Mono + Multi)	11A. Exclu-ded	12A. 80%	113,108	68.16%	61.24%
Case 1	2 outpatient T2DM diagnosis or at least 1 inpatient diagnosis	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	116,671	68.02% (-0.14)	61.43% (+0.19)
Case 2	At least 1 inpatient diagnosis	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	45,458	68.34% (+0.18)	60.97% (-0.27)
Case 3	c. p.	Only newly treated	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	20,251	62.96% (-5.20)	69.55% (+8.31)
Case 4	c. p.	c. p.	2	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	120,155	66.95% (-1.21)	62.61% (+1.37)
Case 5	c. p.	c. p.	c. p.	2006	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	73,021	74.56% (+6.40)	51.47% (-9.77)
Case 6	c. p.	c. p.	c. p.	2007	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	81,294	75.50% (+7.34)	49.38% (-11.86)
Case 7	c. p.	c. p.	c. p.	2008	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	91,593	76.68% (+8.52)	47.04% (-14.20)
Case 8	c. p.	c. p.	c. p.	c. p.	Guideline	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	75.32% (+7.16)	49.34% (-11.90)
Case 9	c. p.	c. p.	c. p.	c. p.	ind. historic profile	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,065	85.40% (+17.24)	29.11% (-32.13)
Case 10	c. p.	c. p.	c. p.	c. p.	c. p.	prescr.- based, incl. last prescr.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	70.64% (+2.48)	58.76% (-2.48)
Case 11	c. p.	c. p.	c. p.	c. p.	c. p.	interval-based, last prescr. cut at 31.12.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	65.73% (-2.43)	65.43% (+4.19)
Case 12	c. p.	c. p.	c. p.	c. p.	c. p.	interval-based, last prescr. no cut	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	67.66% (-0.50)	61.94% (+0.70)
Case 13	c. p.	c. p.	c. p.	c. p.	c. p.	interval-based, 1.095 days	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	56.43% (-11.73)	75.30% (+14.06)
Case 14	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	PDC	c. p.	c. p.	c. p.	c. p.	c. p.	113,108	75.53% (+7.37)	45.44% (-15.80)
Case 15	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	No for all	c. p.	c. p.	c. p.	c. p.	113,108	63.57% (-4.59)	72.46% (+11.22)
Case 16	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	no trunc.	c. p.	c. p.	c. p.	113,108	76.77% (+8.61)	57.81% (-3.43)
Case 17	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	Mono	c. p.	c. p.	33,996	59.48% (-8.68)	74.44% (+13.20)
Case 18	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	incl.	c. p.	113,108	68.72% (+0.56)	60.39% (-0.85)
Case 19	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	c. p.	90%	113,108	68.16% (±0.00)	74.50% (+13.26)

Influence of parameters in comparison with literature

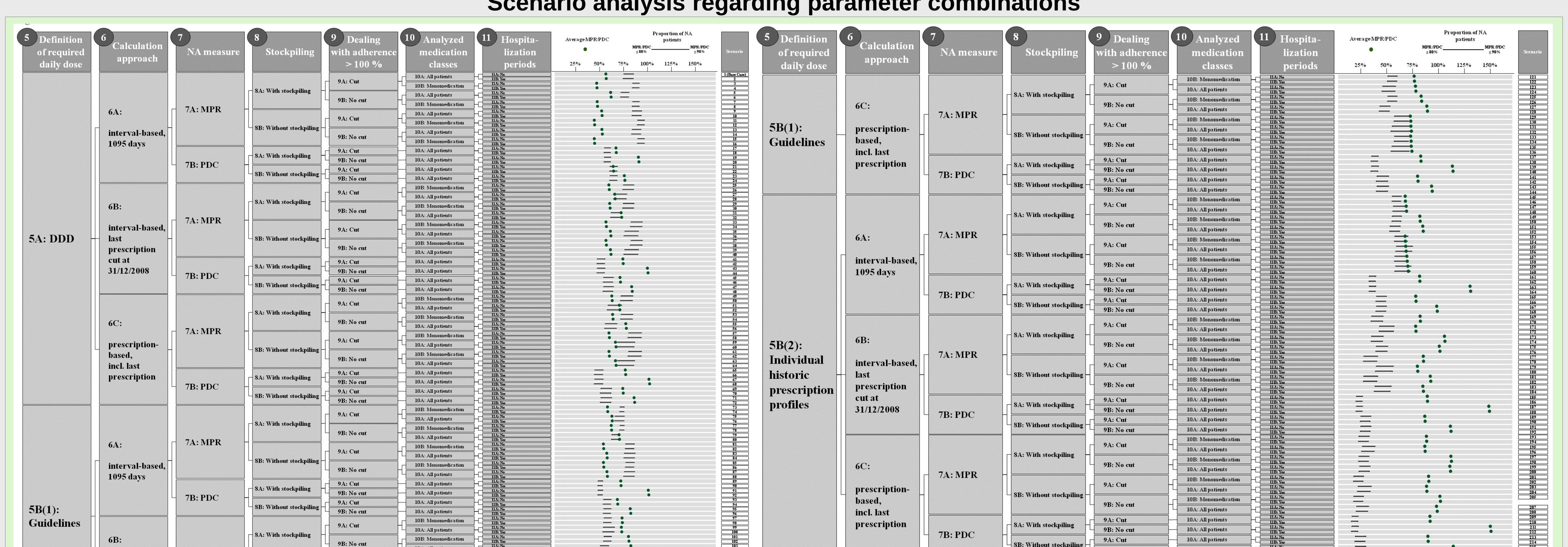


Parameters of a NA analysis based on claims data for OHA in T2DM therapy

Definition of required daily dose (per ATC class)	
DDD (German version)	5A
Guideline (average of recommended dosages)	5B(1)
Individual historic prescription profiles	5B(2)
Calculation approach	
Interval-based (2006/01/01 - 2008/12/31)	6A
Interval-based (first prescription - 2008/12/31)	6B
Prescription-based	6C
NA measure	
MPR	7A
PDC	7B
Stockpiling	
With stockpiling	8A
Without stockpiling	8B
Dealing with adherence > 100 % on patient level	
Truncation to 100 %	9A
No truncation	9B
Analyzed medication classes	
All medication classes (Multi- and Monomedication)	10A
Only patients with metformin-therapy (Monomedication)	10B
Hospitalization	
Without consideration of hospitalization periods	11A
With consideration of hospitalization periods	11B

Results (II)

Scenario analysis regarding parameter combinations



Adherence (MPR/PDC)
MIN: 44.3 %
MAX: 151.2 %

NA-quota (threshold: MPR/PDC < 80%)
MIN: 15.7 %
MAX: 90.0 %

Results of logistic regression estimates (best 3 scenarios)

	n	p value	OR ranges for all 144 logistic regression estimates; only OR for specific adherence measures (scenario) are shown separately[a]	95% CI[b] for OR: Lower	95% CI[b] for OR: Upper	Nagelkerke R^2
Gender						
Female	36,199		1.000[c]			
Male	76,909	0.000 - 0.000	1.125 - 1.134	1.094 - 1.103	1.157 - 1.166	
Age in years	113,108	0.000 - 0.000	1.021 - 1.022	1.019 - 1.021	1.022 - 1.023	
Dependency on care by third parties						
Level 0	109,832		1.000[c]			
Level 1	2,008	0.000 - 0.000	2.946 - 3.028	2.654 - 2.728	3.271 - 3.360	
Level 2	1,013	0.000 - 0.000	3.166 - 3.274	2.732 - 2.827	3.668 - 3.793	
Level 3	255	0.000 - 0.000	3.001 - 3.180	2.272 - 2.406	3.965 - 4.203	
Number of co-morbities	113,108	0.000 - 0.000	1.513 - 1.520	1.493 - 1.501	1.532 - 1.540	
Disease Management Programme						
No	67,002		1.000[c]			
Yes	46,106	0.000 - 0.002	0.947 - 0.959	0.922 - 0.934	0.972 - 0.984	
Insulin taken						
No prescription	85,625		1.000[c]			
At least one prescription	27,483	0.000 - 0.000	1.807 - 1.945	1.754 - 1.888	1.862 - 2.004	
Circulatory system medication						
No prescription	36,784		1.000[c]			
At least one prescription	76,324	0.000 - 0.000	1.955 - 1.975	1.896 - 1.916	2.016 - 2.037	
Constant		0.000 - 0.000	0.027 - 0.049			
Scenario 111: MPR (0-1)	113,108	0.000	0.579	0.548	0.612	0.175
Scenario 107: MPR (0-1)	113,108	0.000	0.576	0.545	0.610	0.175
Scenario 179: MPR (0-1)	113,108	0.000	0.563	0.531	0.598	0.175

a Odds ratios
b Confidence interval
c Reference group

Conclusions/Discussion

For the first time, 12 parameters with the potential to influence NA analyses have been systematically and completely identified. The simulation of the parameters with a secondary data set shows that with the appropriate choice of parameters, a nearly random result can be achieved in estimating the NA rates and the percentage of patients who are affected by NA. The classification of a total of 47 OHA NA analyses made on the basis of prescription data that was in addition conducted during this study makes clear that there is a definite lack of transparency in the character of the parameters that are used in such analyses, and also confirms in general terms the results of the simulation of the influence of the parameters.

Our own simulation and validation of the NA parameter combinations demonstrates that – with an appropriate choice of parameters – medication availability (adherence) as an outcome can explain diabetes-related hospitalization/events. Many of the parameter combinations show that an increase in the availability of medication is related to a lower incidence of diabetes-related hospitalization/events. A few parameter combinations (40 scenarios – 27.8 %) show the opposite relationship; all of these consider hospitalization days (statistical effect because hospitalizations are both an analysis parameter and an outcome) .

The three parameter sets with the greatest explanatory power do not use the DDD as a target profile, are interval-based beginning with the first prescription, and use the MPR. Furthermore, none of the 3 scenarios takes account of stockpiling. Evidently, the assumption that a medication package a patient has received via a prescription will be further used by that patient until it is finished is methodically understandable, but empirically spoken not relevant to the sample. The superiority of the MPR over the PDC shows that is clinically insufficient to have any OHA available on a specific day. Instead, the entire prescribed combination of medications should ideally be available.

Much of the variation in NA rates depicted in the literature is to be attributed to the methodological differences in its measurement rather than to a lack of validity of NA as a criterion of measurement. The importance of our analysis results from an increasing commercial interest in adherence programs, also and even especially in countries in which the prescribed number of days of supply are not available in prescription claims standards. Such programs are dependent on the valid segmentation of patients into groups (the identification of patients with program requirements) and a reliable system of program evaluation. The parameters we have identified show the importance of a stable methodological foundation for these sorts of analyses.

From a scientific perspective, the parameters we have identified also allow the setting up of good practices for the adherence measurement based on prescription data. Methodological transparency in the conduct of prescription-based NA analyses should be given far more attention than is now the case. In future, the assumptions made by studies should be transparently and completely listed for each of the 12 parameters that have been identified here. This applies not only to analyses that focus on OHA.

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