METHODOLOGICAL DIFFICULTIES OF COMPLIANCE ANALYSES BASED ON REAL-WORLD DATA

Péter Andriska[1], Tamás Komáromi[1], Róbert Frigyesy[1], Balázs Salfer[1]
[1]Healthware Consulting Ltd.

Background and objectives

The patients' adherence pattern, considering the regular filling of their prescribed therapy, is a key factor of therapeutic effectiveness of medication treatments, applied in case of chronic diseases. The therapy effectiveness, increased in course of appropriate patient-adherence, may grant direct or indirect advantages for all stakeholders of the health care system. These advantages may occur from the patients' aspect in the positive changes in the disease status, just as avoided negative change, avoided out- or inpatient episodes, avoided death, from the financer's perspective in the cost burden of avoided episodes, from the manufacturers' point of view in the increased brand loyalty and higher sales indicators. The extent of medication adherence can be measured in course of the analysis of part share of medication therapy covered period within a given time interval. [1]

In international practice it can be observed in general, that 80% or over therapy-covered period ratio is mentioned by professionals as adequate adherence pattern, and the patients' individual indicators are compared to this threshold value. [2] Regarding adherence analysis numerous ratios can be found in international scientific literature with simpler or more complex methodology. In our analysis we tend to reveal, that choosing an adequate ratio is not sufficient itself, it is essential to know the difficulties case of pitfalls of the data management and methodology to the objective assessment of the chosen ratio. The chief aim of our study to demonstrate factors in course of practical examples in three indication areas, which may substantially influence the results and the right conclusions, if these factors are modified.

Methods

Parameters	Basic setting	Modification
Time frame criteria for inclusion and exclusion	At least 1 therapy-covered day in 2013	COPD: no fill in 2012
Therapy specific inclusion and exclusion criteria	E.g. ICD-10 codes (COPD: J44; Diabetes: E11; Prostate cancer: C61)	-
Observation period	01.01.2012 - 31.12.2014	-
Index date	1st therapy-covered day in 2013	COPD: 1st fill in 2013
Index period	From index date to 31.12.2013	COPD: index date + 364 days or death
Mortality	If death observed within index period, medication vectors and end of period are truncated	Prostate: death not considered
Oversupply	Therapy vectors overlapping a new fill or end of index period are truncated	-
Gap (grace period)	1 day	Diabetes: 15, 30, 60 days
DDD	Based on SPC DDD and dosing	-
Hospitalization	Not considered	-
Combinations, comedication, polytherapy	Not considered	-

Table1: Parameters influencing PDC ratio

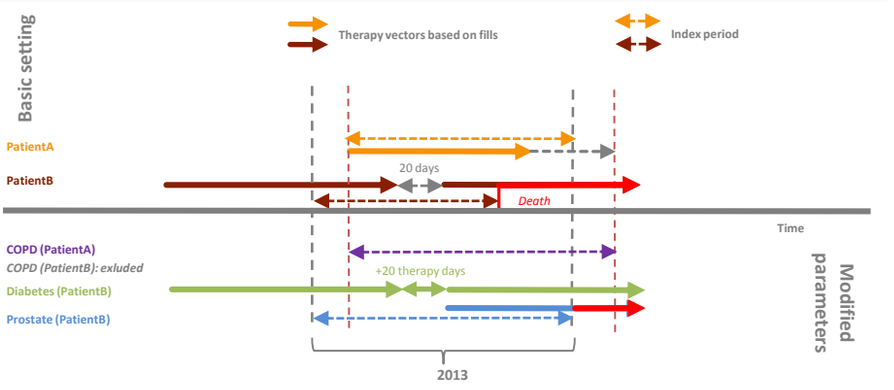

Figure 1: Differences between basic and modified settings

The adherence analysis is based on prescription filling data of database of the Hungarian Health Fund in the field of the following indications: diabetes, COPD, prostate cancer. Drug medications data are not available in the database, only prescription fillings. In the three therapeutic areas we analyzed the adherence ratio in 2013 from the reimbursed pharmacy agents in case of an ultra-long-acting beta-adrenoceptor agonist (indacaterol) in COPD, in case of a GLP-1 agent (exenatide) in diabetes, and in case of a GnRH agent (goserelin) in prostate cancer. From the ratios available in scientific literature, the methodology PDC (Proportion of Days Covered) was chosen as a basis, which is such a ratio, which compares the number of therapy-covered days to the number of days that can be spent theoretically on the therapy in a given period. [3, 4, 5] The value of the PDC ratio is ranging between 0 and 1, where 1 means complete therapy coverage. In course of the indications a basic setting was established to calculate PDC ratio, then after changing each specified parameter one by one (ceteris paribus), the ratio was recalculated.

In course of the **basic setting**, number of therapy-covered days, then the PDC ratio of the patients were determined as follows. We examined each day within the index period, whether it was covered by filled DOT (Days of therapy) or not. If yes, the given day was considered as a therapy-covered day, if not, the given day was not considered as a day spent on therapy. DOT values of the fills served as a basis for the calculation. In case of a fill if more than one unit from products belonging to a given agent were filled (same-day fill), then the DOT values were considered as additive. In case of a fill if a another refilling was observed yet within the period covered by the first fill ("oversupply"), than the part of the therapy vector (the length of the therapy-covered period based on the filled DOTs of the first fill) of the first fill, which overlapped the second fill, was truncated. Therapy-length of each patient is the sum of days covered by therapy. As it is a real phenomenon in practice that the patients' next fill occurs after the end of the therapy vector of the previous fill some days later, we allowed a 1-day grace period (furthermore Gap). According to the applied Gap, if a fill occurred within 1 day after the end of the previous therapy vector, the therapy was considered as continuous. In course of the study we applied a dynamic approach, thus both the beginning and the end of the index period was censored, if it was needed. In case of a new patient (who appears later than the first day of the period, for instance 01.01.2013), only the number of days that can be spent theoretically on the therapy are considered in the denominator of PDC ratio instead of the whole period. In the same way, in case of death within the index period, also only the number of days that can be spent theoretically on the therapy are considered in the denominator instead of the whole period, thus number of days between death and index date is excluded from the value of the denominator. After the calculation if the patients' individual PDC ratio, the median value of the ratio is applied from the descriptive statistical indicators.

In case of **settings different from the basic setting** the following parameters we examined as influencing factors: in case of COPD the patient inclusion and exclusion criteria (364-day PDC ratio calculated from first fill of new patients in 2013); in case of diabetes the Gap (15-day, 30-day and 60-day grace period); in case of prostate cancer the mortality (no censor applied in case of death). In course of the analysis the PDC ratio was calculated based on SPC DOT values in each case.

Results

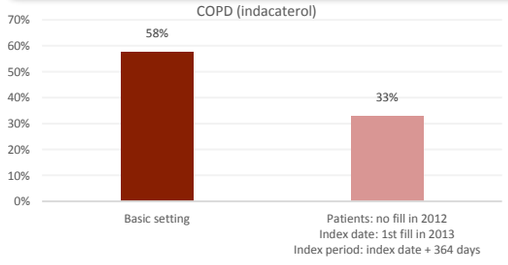

Figure 2: Median of PDC ratio in case of modifying the time frame criteria

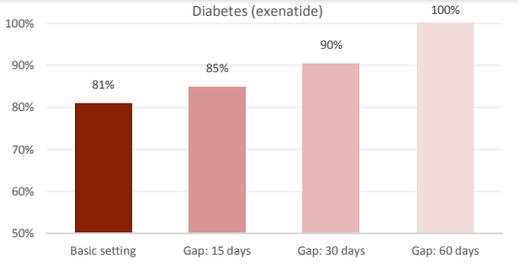

Figure 3: Median of PDC ratio in case of modifying the Gap (grace period)

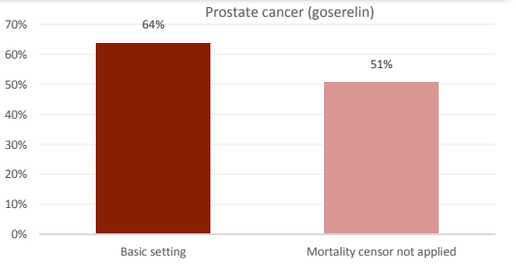

Figure 4: Median of PDC ratio in case of modifying the mortality

In case of the modified settings considering indacaterol (Figure 1.) the therapy coverage was examined only in case of new patients in 2013 (no indacaterol fills observed in 2012), the index period was the period from the first fill + 364 days (or death, if it occured within the 364 days). It is displayed on Figure 1., that more than 20% -point difference can be observed between the two median PDC ratios calculated by the two approaches, in case of basic setting the PDC ratio is close to 60%, while with the modified setting it is 33%. The chief cause of the difference, that the new patients starting indacaterol therapy in the second half of 2013 have less theoretically chance to drop out or switch off until the end of the index period, thus they pull up aggregated median value. The result calculated based on the modified parameter reflects the practical and real therapy coverage ratio better compared to the basic setting, based on the results implementation of this modification in course of calculation PDC ratio is adequate. In case of exenatide (Figure 2.) the grace period was modified, the strict 1 day value based on the basic setting was eased to 15, 30 and 60 days. The PDC ratio resulted a value above 80% in case of the basic setting, by softening the Gap with 15, 30 and 60days the ration increased to 85% and 90%, then reached the 100% median value. Modifying the Gap we eased the strictness requirements, it is worth determining the level of strictness based on the specificities and characteristics of the indication area in course of PDC calculation. In case of prostate cancer (Figure 3.) the mortality parameter was modified, if a patient died within the index period, then neither the part of the therapy vector overlapping after death (nominator), nor the period between death and the end of index period (denominator) was truncated. Based on the results the mortality as a parameter should be managed in course of PDC calculation, censoring the time period after death is required in course of calculation both nominator and denominator. [6]

Conclusions

In course of the study it was proven, that value of the chosen PDC ratio is influenced by several parameters, and the ratio is sensitive to the modifications of these parameters. In course of therapy coverage analysis it is highly important to handle these parameters, in all cases it is required to set them individually considering the specificities of the therapeutic area and the observed therapy, with the focus of the original aim of the study. In the three examples we drew attention to sensitivity of three parameters, but the analysis can be implemented with the same analogy also in case of the other parameters. In order to draw conclusions based on the results as correct as possible, if the parameters, influencing the adherence are set properly and consistently in accordance with the aim of the study and the characteristics of the therapeutic area. It is also important to consider the conclusions above in course of evaluating results of comparative studies. For instance comparing the results of studies with the same methodology (or even the same parameter setting), but concerning different therapeutic areas, or even comparing results concerning the same therapeutic area or a given agent, but from studies with different methodology.

References

[1] Allison B. Rosen, MD, MPH, ScD; Alicen B. Spaulding, MPH; Dan Greenberg, PhD; Jennifer A. Palmer, MS; and Peter J. Neumann, ScD - patient Adherence: A blind spot in Cost-effectiveness Analyses?, AJMC, September 2009
[2] Jeannie K. Lee, PharmD; Karen A. Grace, PharmD; Allen J. Taylor, MD - Effect of a Pharmacy Care Program on Medication Adherence and Persistence, Blood Pressure, and Low-Density Lipoprotein Cholesterol, JAMA. 2006;296(21):2563-2571.
[3] Sudeep Karve, BPharm, MS, Mario A. Cleves, PhD, Mark Helm, MD, Teresa J. Hudson, PharmD,Donna S. West, RPh, PhD, Bradley C. Martin, PharmD, PhD - Prospective Validation of Eight Different Adherence Measures for Use with Administrative Claims Data among Patients with Schizophrenia, Value In Health, 2009, Volume 12.
[4] Lisa M Hess, Marsha A Raebel, Douglas A Conner, and Daniel C Malone - Measurement of Adherence in Pharmacy Administrative Databases: A Proposal for Standard Definitions and Preferred Measures, Annals Of Pharmacotherapy, July 2006, Volime 40.
[5] Isabelle Arnet, Ivo Abraham, Markus Messerli, Kurt E. Hersberger - A method for calculating adherence to polypharmacy from dispensing data records, Springer, November 2013
[6] Source of data: National Health Insurance Fund Administration, Hungary

This poster is compiled by Healthware Consulting Ltd.
ISPOR 18th Annual European Congress, Milan, 7-11 November 2015.

Healthware Consulting Ltd. / H-1093 Budapest, Közraktár str. 32. River Park Offices, VII. floor
Phone.: +36 1 324 2050 / Fax: +36 1 324 2051 / www.healthware.hu

Download our ISPOR posters directly from our webpage:

Poster code: PRM58