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ORIGINAL REPORT

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Using the "proportion of patients covered" and the Kaplan-Meier survival analysis to describe treatment persistence

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Abstract

Purpose: Standard Kaplan-Meier (KM) survival analysis is often used to study treatment persistence estimating the proportion of patients who have not yet experienced a treatment break by a given day after treatment initiation. This method only allows patients to be studied until their first treatment break. The "proportion of patients covered" (PPC) method is another approach to study treatment persistence. It measures the proportion of live patients currently covered by treatment. We aimed to describe the PPC method, show how the KM survival analysis and the PPC method can describe treatment persistence, and discuss the interpretation/application of the methods.

Methods: We identified new users of statins, selective serotonin reuptake inhibitors, hormone replacement therapy, and ibuprofen. We used KM estimates and the PPC to describe persistence in the 3 years post treatment initiation, using a grace period of 90 days to define a treatment break.

Results: Three years after statin initiation, approximately 40% of patients were still in continuous treatment (KM survival) and 60% of patients still alive were in current treatment (PPC). Corresponding numbers were 12% and 25% for selective serotonin reuptake inhibitors and 9% and 29% for hormone replacement therapy. At 1 year, numbers were 5% and 10% for ibuprofen. The PPC showed markedly less variability than the KM survival analysis with different choices of grace periods.

Conclusions: The KM survival analysis and the PPC method can be used to study different aspects of treatment persistence. Together, they provide a more complete picture of treatment persistence and drug use patterns.

KEYWORDS

drug utilization, Kaplan-Meier survival curves, medication persistence, pharmacoepidemiology, proportion of patients covered, survival analysis

1 | INTRODUCTION

Treatment persistence is the extent to which patients continue prescribed treatment. It is a widely studied measure in pharmacoepidemiology[1,2] as it provides important knowledge on real-life drug utilization patterns.

Using administrative claims data, treatment persistence is often estimated using standard Kaplan-Meier survival analysis (drug survival analysis) where an individual's persistence is expressed as the time until discontinuation of drug therapy, usually defined as a gap between prescription refills exceeding a predefined threshold.[2] The drug survival analysis thereby only considers an individual's first treatment episode, and it should thus strictly be interpreted as depicting the proportion of patients that did not yet experience a treatment

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break by a given day after treatment initiation. As the drug survival analysis usually only considers naïve drug users and their first treatment episode, and as it is highly sensitive to the choice of grace period,[3,4] the clinical interpretation might be difficult.

Another approach to study treatment persistence is by considering the proportion of patients covered by treatment on a given day after treatment initiation. In this method, consideration is given not only to the first episode but to all treatments over follow-up. The "proportion of patients covered" (PPC) method has recently been used in a number of studies to measure treatment persistence and treatment duration.[5-8] The PPC method provides a simple measure of the proportion of live patients on a given day after treatment initiation who are in current treatment (ie, covered), regardless of prior treatment breaks. As such, it provides a population-level estimate of treatment persistence, with no consideration of whether the individual has or has not experienced a treatment break in the past.

Whereas the drug survival analysis has been described systematically in the literature,[2] the PPC method is less well known to pharmacoepidemiological researchers. The aim of this study was therefore threefold: (1) to describe the PPC method, (2) to demonstrate how the drug survival analysis and the PPC method can be used to describe treatment persistence, and finally (3) to provide a discussion of the interpretation of the 2 methods and their application.

KEY POINTS

- Kaplan-Meier survival analyses are often used to study treatment persistence. In these analyses, a patient is considered persistent until the first treatment break.
- Another approach to study treatment persistence is by charting the proportion of live patients who are covered by a prescription on any given day, ie, the "proportion of patients covered" (PPC) method.
- The PPC method and the survival analysis reflect different aspects of treatment persistence.
- The PPC method is less sensitive to changes in grace periods.
- When used in conjunction, the 2 methods provide a more complete picture of treatment persistence and drug use patterns.

2 | THE PROPORTION OF PATIENTS COVERED METHOD

The PPC method estimates the proportion of live patients who are covered by treatment on a given day after treatment initiation. The numerator consists of patients that are currently covered by their latest prescription regardless of prior treatment breaks, and the denominator consists of patients that are eligible for treatment, ie, those alive.

To illustrate the principle behind the PPC method, consider 100 patients initiating treatment on day zero. The PPC on this day is 100% (100/100). Let us assume that on day 50, 20 of the initial 100 patients have died, and 60 of the remaining 80 patients are currently covered by their latest prescription. The PPC on this day is 75% (60/80). If, on day 70, the same 80 patients are eligible for treatment, but 65 patients are currently covered by their latest prescription, we obtain a PPC of 81% (65/80) on day 70. As this example illustrates, the PPC method allows patients to reenter the numerator once they resume treatment and thus allows the PPC curve to increase with time.

3 | THE DRUG SURVIVAL ANALYSIS

The survival analysis approach has been described in detail elsewhere.[9] In brief, it displays the cumulative probability of survival in a population over time. When used to display drug survival, the analysis estimates the proportion of patients that have received continuous treatment (have "survived") after a certain number of days after treatment initiation. As such, it displays the cumulative probability of drug survival in a population over time, ie, the probability of having no treatment breaks where a break is defined by the occurrence of a gap that exceeds the length of the prescription duration plus the grace period.[2] The event of interest is the first break in treatment, and patients survive until they experience the event. In a drug survival analysis, patients are thus irreversibly excluded from the analysis once they experience the first break in their treatment. Subsequent prescriptions and treatment episodes are therefore not considered in a drug survival analysis.

4 | METHODS

We used prescription registry data to identify new users of 4 commonly used drug therapies. By using the PPC method and the drug survival analysis, we estimated treatment persistence for each of the 4 drug therapies. In the main analysis, we defined a treatment break as a gap between 2 prescription refills exceeding the length of the duration of the prescription plus 90 days.

4.1 | DATA SOURCES

We used data from Odense Pharmacoepidemiological Database (OPED),[10] a Danish regional prescription register that holds information on all reimbursable prescription drugs filled by residents of Southern Denmark since 2007.[10] For every reimbursable prescription filled, OPED holds information on the person identifier, the dispensing date, the product code, and the dispensed quantity in defined daily doses.[10,11] Drugs are categorized according to the Anatomical Therapeutic Chemical classification system.[11] Similar to other Danish sources of prescription data, information on days' supply and prescribed daily dose is not available in OPED.[10,12] Information on death and migration was extracted from OPED's demographic module.

4.2 | Study drugs and population

We included new users of 4 commonly used drug therapies: hormone replacement therapy (HRT) (Anatomical Therapeutic Chemical code: G03C and G03F), statins (C10AA), selective serotonin reuptake inhibitors (SSRIs) (N06AB), and ibuprofen (M01AE01). These 4 drug therapies were chosen as they represent therapies used both long term (eg, statins) and short term (eg, ibuprofen) and were therefore expected to show different patterns of treatment persistence. Our study population included all new users of these drug therapies from 2010 and until 2012 (new user defined as first fill of these drugs since January 2007). The date of filling the first prescription during the study period marked the index date. We restricted our study population to adults (≥18 years) at index date. Each individual was followed for at least 3 years unless they migrated or died.

4.3 | Analysis

For each drug therapy, we applied the PPC method and the drug survival analysis and depicted treatment persistence during the first 3 years after index date. To estimate the expected duration of a prescription, we assumed a daily dose of 1 tablet per day for users of HRT, statins, and SSRIs. For users of ibuprofen, we assumed a daily dose of 600 mg. Based on the assumed daily dose and the dispensed quantity, we then estimated the duration of the single prescription fill. To each prescription, we added a grace period of 90 days to allow for irregular prescription refills and stockpiling. We considered a new user as having a break in drug treatment when he/she failed to fill a new prescription within the estimated prescription duration plus this 90-day grace period. In both analyses, new users were censored upon death or migration.

From the literature, it is well known that the drug survival analysis is sensitive to changes in grace periods.[3,4] Therefore, to demonstrate how the PPC is affected by such variations, we changed the grace period in both the PPC and drug survival analyses to 60, 120, and 180 days.

4.4 | Other

All calculations were performed using STATA Release 14.2 (StataCorp, College Station, TX, USA). This study was approved by the Danish Data Protection Agency. According to Danish law, purely registry-based studies do not need approval from an Ethics Committee.[13]

5 | RESULTS

We included 23 928 new users of HRT, 49 073 new users of statins, 48 845 new users of SSRIs, and 154 031 new users of ibuprofen during the study period. Figure 1A-D shows the treatment persistence for new users of the 4 drug therapies when applying the PPC method and the drug survival analysis. As expected, the treatment persistence for new users of the 4 drug therapies showed very distinct patterns. For new users of statins, the drug survival curve showed that 3 years after treatment initiation, around 40% of patients were still in continuous treatment (assuming a grace period of 90 days), while the PPC showed that at 3 years after treatment initiation, around 60% of patients who were alive were on current statin therapy (Figure 1B). Similar numbers for new users of HRT were around 9% (Kaplan-Meier survival analysis) and 29% (PPC) (Figure 1A), and for new users of SSRIs around 12% (Kaplan-Meier survival analysis) and 25% (PPC) (Figure 1C). For new users of ibuprofen, the drug survival curve showed that 1 year

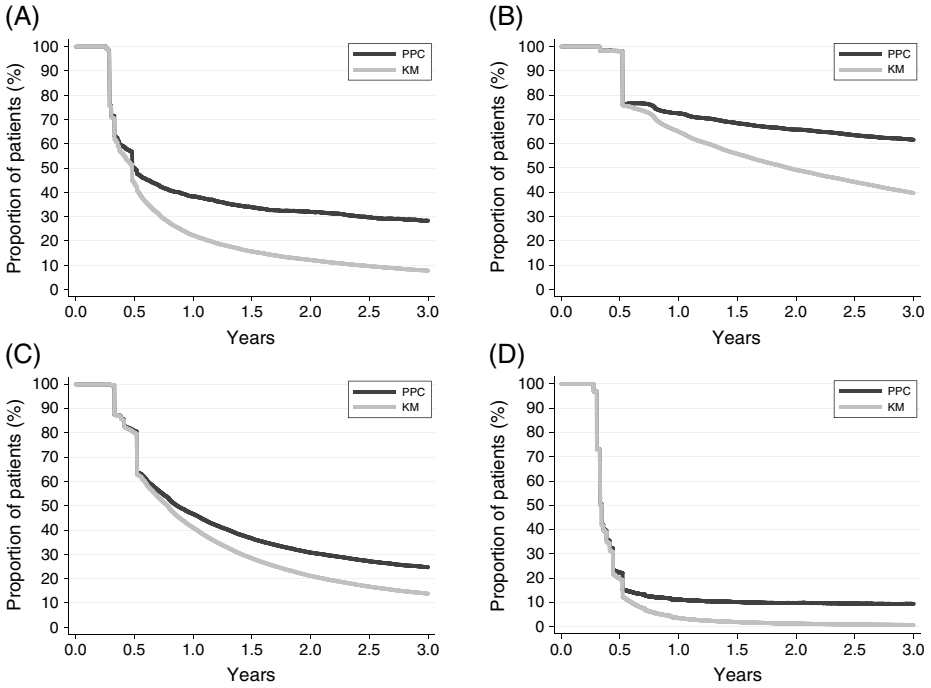

FIGURE 1 A-D, Treatment persistence patterns for users of hormone replacement therapy (A), statins (B), selective serotonin reuptake inhibitors (C), and ibuprofen (D) during 3 years after treatment initiation using the proportion of patients covered method (in black) and the drug survival analysis (Kaplan-Meier) (in grey). The applied grace period is 90 days

after treatment initiation, only around 5% were still in continuous treatment, while the PPC showed that around 10% of patients who were alive were on current treatment (Figure 1D).

Figure 2 shows the treatment persistence of new users of statins when applying the PPC method and the drug survival analysis using different grace periods. In general, the PPC method was less sensitive to changes in grace periods compared to the drug survival analysis. When extending the grace period from 60 to 180 days using the PPC method, there was a difference of 5.3%, compared to a 23.8% difference with the drug survival analysis. Except for new users of ibuprofen, we observed similar patterns for new users of SSRIs and HRT, albeit with a smaller difference between the PPC and drug survival analysis (Supplementary Figure 1S-3S).

6 | DISCUSSION

In this study, we have provided a description of the principle behind the PPC method and we have shown how the PPC and the drug survival analysis can be used to describe 2 different aspects of treatment persistence. The PPC reflects the proportion of live patients who started treatment who were on treatment at any given time, while the drug survival analysis reflects the proportion of patients who had not stopped treatment by that time, ie, were still on continuous treatment.

Several measures of treatment persistence have been proposed in the literature, reflecting the fact that there is no clear consensus of how to measure or define persistence.[1,2,14] Ultimately, the choice of a specific measure should be based primarily on the research question to be answered, while also weighing the specific strengths and limitations of the given persistence measure.[1] Previously, it has been described that measures of treatment persistence should preferably capture both duration and adherence to therapy.[14] Unlike the drug survival analysis, the PPC method does not exclude patients with low adherence to their medication. Patients who have a low level of adherence will have longer intervals between prescription refills than expected. In a drug survival analysis, these patients will fall out of the analysis, but they will reenter the PPC analysis once they fill a new prescription. Although this allows patients with low adherence to contribute in a PPC analysis, the extent with which they, on a population level, do so correlates with the degree of nonadherence in the population, which can complicate interpretation of the PPC curve. Combining the PPC method with the drug survival analysis might, however, provide knowledge on both duration of therapy and adherence patterns. The advantage of combining several persistence measures has already been discussed.[14]

As illustrated by our results, the PPC was less sensitive to changes in grace periods compared to the drug survival analysis, especially for long-term therapies. When measuring treatment persistence, or defining the allowable gap in a drug survival analysis,[1] it is important to consider how the length of the treatment break impacts on the therapeutic benefit, ie, the forgiveness of the drug therapy. A treatment where a short, temporary break in treatment does not affect the therapeutic effect of the specific drug therapy might be considered a forgiving treatment, while a treatment where even a short break could have profound consequences might be considered a nonforgiving treatment. Forgiving treatments are characterized by a cumulative effect, ie, the longer the patients have remained on the treatment, the larger the effect. At reinitiation, the therapeutic effect will be retained. This does not apply for nonforgiving treatments. Examples of nonforgiving treatments are antiretroviral drugs, antiplatelets, and anticoagulants, while antihypertensives and statins are examples of forgiving treatments. However, an interaction between the drug therapy and patient characteristics, eg, age, or disease characteristics might also influence the forgiveness of the therapy. One example of the interaction between drug therapy and disease characteristics is the use of antihypertensives in patients with aortic aneurysm. In these patients, a short break in treatment can have profound consequences for the patient. When measuring treatment persistence of forgiving drug therapies with the simple aim of ensuring the benefit of drug therapy, it might be important to allow patients to have a short break in treatment (ie, allow patients for some degree of nonpersistence), eg, by using the PPC method. Conversely, when measuring persistence of nonforgiving drug therapies, it might be more appropriate to use the drug survival analysis and only consider the first treatment episode.

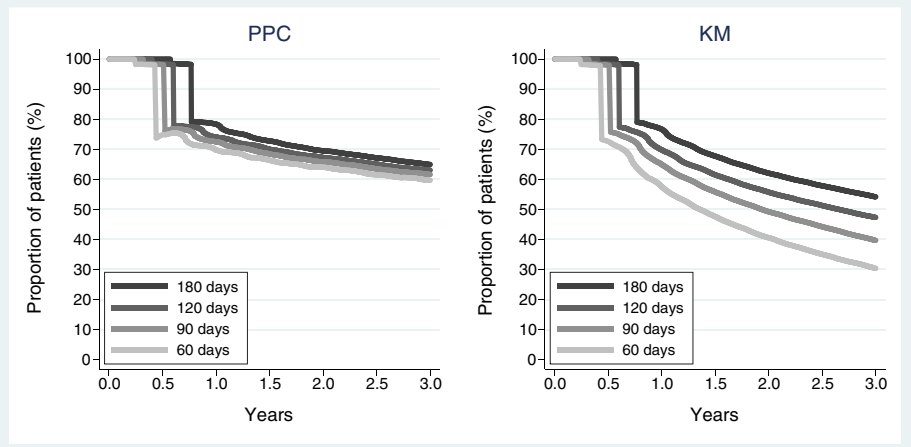

FIGURE 2 Treatment persistence patterns for users of statins during 3 years after treatment initiation using different grace periods. The proportion of patients covered method is shown to the left, and the drug survival analysis (Kaplan-Meier) is shown to the right

Like other treatment persistence measures, the PPC method and the drug survival analysis are most relevant for chronic treatments (eg, statins) or long-term treatments expected to have a duration spanning several refills (eg, HRT). Ibuprofen is an example of a drug therapy, which may not be suitable for either of the 2 methods; here, almost all users only fill 1 prescription, as illustrated in Figure 1. Both analyses may be suitable for episodic treatments (eg, SSRIs), as long as the length of the time window is considered in the interpretation of the observed persistence patterns (see below).

The main limitations of the drug survival analysis are the potential underestimation of persistence to chronic therapies as illustrated in Figure 1. B with statins and the sensitivity to changes in the allowable gap as illustrated in Figure 2. While the PPC method is less sensitive to these, the PPC method has a number of other limitations. First, the PPC method provides no information on the length of the treatment break for the single drug user. Second, the PPC method does not differentiate between multiple treatment episodes. As such, the PPC method provides no information on whether a treatment is stopped/restarted because of remission/relapse of a disease rather than nonpersistence. This should be considered when interpreting persistence patterns of episodic treatments such as antidepressants, and it might be preferable to restrict the time window used. In general, the PPC curve does not provide knowledge on the reasons for the underlying anatomy of the curve, eg, whether a decrease/rise in the PPC is because of low adherence, low persistence, a shift in therapy, remission of disease, etc. Finally, as the PPC is by definition a proportion among those still alive, a high mortality among drug users will affect the interpretation of the PPC curve, while also impeding direct comparison with estimates from a drug survival analysis.

The PPC method and the drug survival analysis have different advantages and limitations which will depend on the particular drug studied. Using the 2 methods in conjunction when studying persistence gives information on 2 different aspects of treatment persistence, and may provide a more complete picture of treatment persistence and drug use patterns.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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