Real-World Adherence to Oral Anticoagulants in Atrial Fibrillation Patients. A Study Protocol for a Systematic Review and Meta-analysis.

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SUPPLEMENTARY FILE 3

RATIONALE FOR THE APPRAISAL OF METHODOLOGICAL CHARACTERISTICS OF DAYS' SUPPLY ADHERENCE MEASURES IN ORAL ANTICOAGULATION ADHERENCE STUDIES USING DATABASES.

Introduction

Accurate secondary adherence measurement with refill databases must take into account some elements in the selection of patients, the construction of days' supply adherence measures, the censoring of cases at follow-up and the analysis, in order to reduce as much as possible flaws in obtaining real-world adherence estimators and bias in adherence comparisons between different drugs for the same condition. Note that some problems with biasing in adherence estimates may not be a quality problem in the context of one specific study.

Checklists for adherence studies mainly check formal aspects and there is little consensus on their use. So, and for initial use in our systematic review of adherence to oral anticoagulant (OAC) in atrial fibrillation (AF) patients, we develop a series of items to assess methodological aspects that could bias PDC values, limit their generalization to the general population of patients with Non-Valvular Atrial Fibrillation (NVAF), or bias the PDC comparisons between two or more OACs.

The first series of items (see **Table 2** in the protocol manuscript) has been designed for use in all studies with estimations of adherence using days' supply measures, while the second series of items (see **Table 3** in the protocol manuscript) includes additional criteria designed for comparative studies of adherence between two or more drugs and has been intended for use in conjunction with the first series. Both lists respond to a conceptual framework rather than the empirical importance of each potential bias on the PDC values.

We present below the rationale for these series of items, together with a series of questions designed to help reviewers in the assessment of each item and the criteria that the authors have agreed (by consensus) for their use in our systematic review of adherence to oral anticoagulants.

Methodological characteristics of adherence studies

A01. Does the study use a prescription-dispensation data design (vs. dispensation-only data design)?

Prescription-dispensation designs, with prescription and dispensation information available and linkable at the individual level, use the date of the first prescription filled or not as the index date to start the follow-up time. The PDC denominator is defined by the days that the physician's

prescription is maintained (in the time interval until the end of the follow-up) and the PDC numerator is defined by the number of days of treatment covered by the prescriptions filled.

Dispensation-only designs are based on dispensation information and use the date of the first prescription filled as the index date. The PDC denominator is defined by the number of days until the end of follow-up regardless of whether the doctor has interrupted the prescription or not. The PDC numerator is the same as in the prescription-based designs: the days covered by the prescriptions filled.

Prescription-dispensation designs account for primary non-adherence (not filling the first prescription), patients not filling several initial prescriptions but with further restarts, and patients who do not fill any prescription (which are accounted for as PDC = 0), while dispensation-only designs (that account for follow-up time from the first filled prescription) do not consider such periods, thus overestimating PDC values. On the other hand, in the case of treatment discontinuation decided by a doctor, prescription-dispensation design censures the case (loss of adherence is not considered if there is not an active doctor's prescription) while dispensation-based designs ignore the doctor's discontinuation, considering these periods as non-adherence and underestimating PDC.

Because most databases do not have information about prescription, studies with prescription-dispensation designs are very scarce, so most of the published papers use dispensation-only designs that predictably over-estimate adherence when the temporal follow-up is short, and have a more uncertain effect with long follow-ups, where the increase in a doctor's discontinuation (due to adverse effects or the success of alternative treatments) could lead to an underestimation of adherence. This last effect will be more intense in new user cohorts, as periods of physician discontinuation are more frequent (when compared with experienced users).

Some dispensation-only studies censure cases if the patient receives a cardioversion or an atrial ablation, or if they suffer a major haemorrhage, which assumes a greater probability of medical suspension of the treatment. The effect on PDC estimates with this practice is uncertain, depending on the proportion of patients affected and for how long they are maintained with OAC after the intervention or event.

A02. Do the sociodemographic and clinical criteria for patient selection allow for an approximate representation of the general population of patients with NVAF?

Age (less adherence in young people), gender, deprivation (less adherence in deprived people, especially with cost-sharing schemes) and some other patient sociodemographic characteristics are associated with adherence. In this sense, the adherence figures obtained in specific populations may not be generalizable to the general population of patients with the condition of interest. In the same way, a patient's clinical characteristics, especially severity and some comorbidities, are associated with adherence (e.g. more adherence in patients with previous ischemic stroke or higher CHA_2DS_2-VASc, less adherence in patients with mental health problems), therefore –and as with sociodemographic characteristics– cohorts with different clinical conditions will have different adherence results and in descriptive studies the adherence of patients with restricted clinical conditions may not be generalizable to other patient groups.

In general, for NVAF patients we expect a population of around 70±5 years of mean age, with 40%±5% of women, a vast majority of patients having a CHA_2DS_2-VASc ≥2 and a high proportion of chronic diseases distributed among the common diagnoses in patients of this age group (diabetes, hypertension, ischemic heart disease) and more discrete but relevant proportions of COPD, depression, heart failure, renal failure, dementia and other conditions.

Note that while databases of countries with National Health Service (NHS) systems tend to adjust to these characteristics because of their population-based nature, in the United States there may

be large differences between the databases of Medicare, Medicaid, private insurance associated with the labour activity, the Veterans Administration, and some others. This also applies to countries with multiple health-plan insurance systems. Note also that this "flaw" should not be considered a bias of the study evaluated (whose results refer to the population under study and can be of high practical value since they offer information on specific subpopulations). Rather, the item refers exclusively to the possibility of generalization of the PDC values obtained for the general population of patients with NVAF, not to the intrinsic quality of the study.

A03. Is there a baseline (lookback) period before the index date of at least 12 months?

A baseline period of time before the index date (look-back period, washout period) is necessary for collecting information about patient clinical characteristics and previous treatments for differentiating between incident and prevalent users [1,2]. In the absence of a baseline period of data of at least 12 months duration before the index date, information about the clinical characteristics or the previous treatments of the studied cohorts is not warranted,[3] and risk adjustment techniques or cohort matching cannot be performed.

A04. Does the study use a new-user design (vs. inclusion of prevalent or experienced users)?

Experienced (prevalent) users are more adherent patients than new users as, by definition, they exclude patients who have previously abandoned treatment.[4-8] Some studies, particularly industry funded ones, are self-defined as “new-user design” but delimit as “experienced users” those patients that are previous users of the index drug, but not previous users of other OAC drugs (usually switchers from a previously marketed OAC). These “false” new-users are, in fact, experienced users, and therefore more adherent than true "new users”. We can expect that the inclusion of experienced users (or “false” new users) in adherence studies to increase PDC values. The greater the proportion they suppose in the cohort, the more PDC values are increased

A05. Does the design avoid requiring a minimum number of treatments filled for inclusion?

Ideally, the adherence analysis should be performed as the difference between the treatment prescribed by the doctor and the one dispensed to the patient (prescription-dispensation design). Because refill databases (the most common type used) do not usually contain information about prescribing, adherence studies generally use the dispensation-only design that requires the patient to fill at least one prescription to be included in the study. Nevertheless, some studies use a metric developed by the Pharmacy Quality Alliance (PQA) to ensure that patients are on chronic therapy, which requires filling at least two fills on two separate dates with ≥180 days apart and at least 60 days supply for the inclusion of patients in the follow-up cohort [9,10], while the standard dispensation-only design requires only one single OAC claim.

Although it is possible that PQA metric has some utility as a comparative indicator of the quality of healthcare organisations, it is obvious that it selects highly adherent populations and that in many cases (especially in studies with short follow-ups) it determines very high PDC values by itself, only generalisable to the highly adherent populations that meet this demanding inclusion criterion. In the same way, studies that require at least one dispensation for the inclusion of patients lose the cases of primary non-adherence (which are at a greater risk of secondary non-adherence) and thus overestimate the adherence of patients (and are generalisable only to patients who comply with their first prescription, but not to the whole population of patients).

A06. Is there a fixed time-window for the number of follow-up days?

In a follow-up cohort, persistence with treatment declines over time, therefore the longer the duration of treatment the lower the adherence. For this reason, an accurate comparison of

adherence figures from different studies (or different cohort drugs in the same study) requires the use of a fixed time window (e.g. 12 months) from the index date. The shorter the time window from the index date, the higher the adherence values. Variable time-window bias is common in studies comparing a pre-existing drug (with a long follow-up time) with one recently incorporated into the market (with a very short follow-up time) that favours the newcomer.

Maintaining the follow-up for patients who lose coverage or die increases non-adherence figures because it is assumed that they should keep filling-up the medication after health plan disenrollment or death. For this reason, continuous enrolment in the Health Plan during the follow-up window is necessary to identify the prescriptions filled by the patient. Alternatively, patients can be censored if they lost coverage or died (although many refill databases do not have the date of death or only when it occurred in the hospital). Because in countries with universal coverage people always keep the “health plan” entitlement, this bias is likely to be unimportant (limited to patients that moves their homes to another country), so we do not consider this bias in NHS countries with universal coverage. In databases with information on doctors’ prescriptions, patients must be censored when the medical prescription ceases.

A07. Does the design avoid censoring non-persistent patients and switchers?

Some studies, particularly industry funded ones that compare adherence between different OACs or DOACs vs. VKAs, consider a patient as non-adherent when a switch with respect to the OAC index occurs, irrespective of the fact that the patient continues to be adherent to the new treatment. These studies alternatively censor these cases at the time of switching (increasing adherence estimates) or continue monitoring the patient but considering them as “non-adherent” (thus decreasing adherence estimates). When the study additionally admits "false” new users, these patients could be enrolled as "new users" of a second index drug (typically introduced in the market later) and, in a drug-adherence version of Schrodinger's paradox, could be considered both non-adherent (to the first index drug) and adherent (to the new index drug).

Similarly, most studies that combine adherence and persistence measures use the date of discontinuation (defined for measuring persistence) as a censure date in the number of days’ supply based adherence measures. These studies (which additionally usually use a variable time-window) tend to overestimate adherence measures.

A08. Does the study account for periods of immeasurable time?

Immeasurable time refers mostly to periods under hospitalization (both acute and long-term care) because hospital dispensation is not usually available in refill databases. As hospitals usually provide the necessary medications to hospitalized patients, patients should be considered adherent while they remain hospitalized (given the close hospital control, even if a patient does not receive the medication under study, it should be considered that this suspension is due to medical orders). Some studies that have evaluated this aspect consider that neglecting hospitalization days does not produce an important bias in adherence estimates [11,12]. Although accounting for hospitalization days is an indicator of refinement in the development of the study, if hospitalisation days are reported then the assessment of this aspect can be considered in terms of its importance.

A09. Does the study account for stockpiling?

The number of days covered by one prescription filled may overlap with another if the patient fills a second prescription before the end of the period covered by the first (at the dose established in the doctor’s prescription). Adherence studies may suppress overlapping prescriptions or allow the patient to stockpile overlapping doses, incorporating the days covered by the second treatment

after the end of the days covered by the first. Drug stockpiling is a habitual practice in the behaviour of patients and its non-consideration overestimates non-adherence. However, it also seems reasonable to limit the accumulation to a plausible period, which may vary according to the type of drug (e.g. allow a maximum of 2-3 months of stockpiling).

A10. Is the days' supply measure capped at 1 or 100%?

If the number of days of medication supplied in the observation period is higher than the number of days in the observation period, which is possible when using the MPR measure, the MPR should be truncated at 1 or 100% so as not to overestimate adherence.

Methodological characteristics of comparative adherence studies

Table 3 in the protocol manuscript shows the 5 items in the methodological appraisal for comparative adherence studies. Note that these items do not evaluate the accuracy of the adherence estimators, which could be flawed in all drugs compared and should be valued with the previous criteria, but the reliability of the comparison between drugs. In this sense, these items should be used in addition to the previous ones.

C01. Matched-cohort designs vs. disparate-cohort designs.

Because different patients have different behaviour regarding adherence, refill database studies comparing PDC values of cohorts using different drugs should use some form of risk-adjustment to allow for an accurate comparison. This adjustment is especially important when, as in the case of OAC studies, drugs have been introduced at different points in time and may have some specific indications or contraindications.

The most appropriate way to adjust PDC values for drug comparison is to use some type of matching (preferably inverse probability weighting matching) including the most relevant variables in the adjustment. Some studies also present unadjusted PDC values to subsequently perform some type of multivariate regression. In these cases, although the coefficients or odds ratios of the model allow for analysing relative adherence, the PDC values remain unadjusted and should not be used in the adherence comparisons.

C02. Similar follow-up time for drug cohorts in comparison.

As previously mentioned, OAC drugs have been introduced at different points in time, it being common for database studies to use long follow-up times for the older drugs and very short follow-up periods for drugs newly incorporated into the market. As adherence decreases over time, this artefact tends to decrease adherence in pre-existing drug cohorts vs. more recently marketed drug cohorts.

C03. Differences in the proportion of prevalent users between drug cohorts.

Prevalent users (and "false" new users) increase PDC values, influencing the comparisons if one of the cohorts has a greater proportion of these patients. As OACs have been introduced at different points in time, the inclusion of prevalent users in the cohorts favours the newer drugs (which receive experienced users of the pre-existing drugs), while older drugs make up cohorts of new users (because they cannot receive experienced patients from the new drugs). In comparative studies this practice allows the comparison of a cohort with a larger proportion of new users in the pre-existing treatment, with a combination of new users and experienced users (switching from a previous OAC), thus increasing adherence in the cohort with more switched patients (usually, the most recently marketed OAC with respect to the previous ones).

C04. Intention to treat approach.

As previously mentioned in the item about switching, studies that consider patients as non-adherent to the OAC index when a switch occurs tend to decrease PDC values associated with the index drug, while increasing adherence to the new drug (Schrodinger's drug adherence paradox). Since switching almost always occurs from a pre-existing medication to a new one, this bias also tends to decrease adherence in pre-existing drug cohorts vs. more recently marketed drug cohorts.

C05. Chronological time for starting the follow-up.

As previously mentioned, OAC drugs have been made available at different points in time. While patients today can be prescribed any OAC, patients starting treatment years ago had fewer therapeutic choices. Assuming that the choice of OAC by physicians is not strictly random, it can be assumed that patients who are currently treated with a VKA (with 4 treatment alternatives with NOAC) may be different from patients treated with VKAs at the time when VKAs were the only available drugs. For example, a patient could receive a VKA for having difficulty paying the higher NOAC price, and this characteristic could be associated with others (in many countries, co-payment for active workers is higher than that for retired people), which is in turn associated with adherence (active workers are younger and less adherent than retired people).

In summary, the cohorts that start when one of the drugs to be compared is not yet available (initiators with older drugs) are more heterogeneous than the cohorts of patients that initiate with newer drugs, and the information on relevant differences is not always available in the refill databases. Therefore, an adequate comparison between drugs should be initiated at a time when all the drugs to be compared are available on the market.

A reference design to estimate secondary adherence using days' supply measures

Our approach to the assessment of flaws in days' supply adherence measures is based on a reference framework, which, essentially, includes the elements considered in Table 1:

1) Only new users should be selected.
2) No fill-up requirements should be made for inclusion.
3) The date of the first prescription, filled or not, should be used as the index date.
4) Days' supply or PDC numerator should account for all the days covered by filled medication from the index date to the end of the follow-up number of days, provided they are covered by a medical prescription.
5) PDC denominator or follow-up days should account for all the days in a fixed time-window of at least 12 months.
6) Censoring should only be allowed if death, loss of continuous health plan coverage or if doctors discontinue the prescription, and periods not covered by a medical prescription during the fixed window of time for follow up should also be censored.

Studies implementing designs and analysis plans that diverge from any or some of the components of this reference pattern tend generally to overestimate adherence, but in some cases the effects on estimates can be mixed. Nonetheless, this divergence will produce flawed PDC values that, even if in some cases may be justified by the objectives of the study, will report secondary adherence defectively.

Table 3. Reference design for secondary adherence studies with days' supply measures: a new user prescription-dispensation design with a fixed time-window of at least 12 months.	
Previous treatments	Only (true) new users should be selected.
Fill requirements	No prescription filled is required for inclusion
Index date	Date of first doctor's prescription (filled or not)
Numerator (supply days)	Days covered by filled medication from the index date to the end of the follow-up days, provided they are covered by a medical prescription.
Denominator (follow days)	The 365 days immediately after the index date, provided they are covered by a medical prescription.
Censoring previous to the end of study date	At the date of death, loss of continuous health plan coverage, or if the doctor discontinues the prescription. No other causes of censoring are allowed. Periods not covered by a medical prescription during the 12 months of fixed follow-up window are also censored.

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