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CURRENT OPINION
Atrial fibrillation

Methodological considerations for investigating oral anticoagulation persistence in atrial fibrillation

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Aims Reports of long-term oral anticoagulant (OAC) therapy for atrial fibrillation (AF) reveal highly variable, and generally suboptimal estimates of medication persistence. The objective of this review is to summarize current literature and highlight important methodological considerations for interpreting persistence research and designing studies of persistence on OAC treatment.

Methods and results We summarize differences in study methodology, setting, timing, treatment, and other factors associated with reports of better or worse persistence. For example, prospective compared with retrospective study designs are associated with higher reported persistence. Similarly, patient factors such as permanent AF or high stroke risk, and treatment with non-vitamin K oral antagonists relative to vitamin K antagonists are associated with higher persistence. Persistence has also been reported to be higher in Europe compared with North America and higher when the treating physician is a general practitioner compared with a specialist. We propose a framework for assessing and designing persistence studies. This framework includes aspects of patient selection, reliability and validity of measures, persistence definitions, clinical utility of measurements, follow-up periods, and analytic approaches.

Conclusions Differences in study design, patient selection, treatments, and factors such as the countries/regions where studies are conducted or the type of treating physician may help explain the variability in OAC persistence estimates. A framework is proposed to assess persistence studies. This may have utility to compare and interpret published studies as well as for planning of future studies.

Keywords Atrial fibrillation • Oral anticoagulation • Persistence • Methodology

Introduction

Medication persistence, an important facet of managing disease, has been linked to patient-important outcomes,[1] and may be especially germane for chronic illnesses requiring long-term treatments. Persistence, the focus of this discussion, refers to 'the duration of time from the initiation to discontinuation of therapy', which is one part of the spectrum within the concept of adherence which comprises the period from initiation, through implementation (reflecting the accurate intake of medications inclusive of dose, frequency, and required schedule), to discontinuation.[2,3] Drug discontinuation and its opposite, drug persistence are terms used interchangeably to measure how long patients remain on treatment.

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A comprehensive understanding of the factors linked to discontinuation and how these affect clinical outcomes will be meaningful to patients and clinicians. This is especially true for treatments unrelated to symptom relief with a substantial risk of adverse events, such as oral anticoagulants (OAC) for atrial fibrillation (AF). AF is an arrhythmia with growing prevalence[4] which requires long-term anticoagulation for those with additional stroke risk factors. Suboptimal OAC persistence in AF is a recognized concern, as the absolute risk of discontinuation is high.[5,6]

Poor persistence to warfarin has been established in the literature with estimates of <50% of patients remaining on treatment after 2 years.[7] When absolute rates of discontinuation are high, investigating persistence as a first step is reasonable, given its' relative ease in measurement compared with more complex measurements of adherence that include dosage, timing, and frequency of use.[3] However, measuring adherence may also have merit, especially in the case of medications such as non-vitamin K OACs (NOAC) which have a relatively short half-life whereby even single missed doses could represent potentially important gaps in treatment.[8–11]

With NOACs increasingly being prescribed over Vitamin K antagonists for anticoagulation initiation, whether persistence is improved due to ease of use or worsened due to absence of routine monitoring is important to establish. The estimates of discontinuation even in large randomized controlled trials (RCTs) are highly variable and inconsistent,[12] making comparisons less reliable and lowering assurance that we have an adequate understanding of the problem.

Furthermore, understanding the reasons and predictors of non-persistence is essential to establish; the former which are imperative for developing constituents of effective interventions (appreciating that some reasons may be more amenable to intervention than others), and the latter to target our attention on patients who are most vulnerable to discontinue, thereby maximizing the potential benefit of delivered interventions. Failure to focus interventions on the group of least adherent patients has been put forth as a potential explanation for the lack of important effects detected in intervention trials to improve adherence.[13]

Methodological differences in the way OAC persistence is explored require consideration to ensure appropriate interpretation of results. Variability in study designs, definitions of persistence, and assessment of outcomes, as well as patient factors and environmental considerations, may at least in part explain the differences observed.

We aim to describe some of the main considerations for OAC persistence research in AF, by elaborating on three broad areas related to study, patient, or other external factors (*Figure 1*), summarizing factors that may be associated with higher or lower persistence (*Figure 2*), and finally, providing a framework for assessing reliability, validity, outcome measures, and clinical utility for designing interventions in studies of persistence (*Table 1*).

Study factors

Study designs

Much of the current knowledge of NOAC persistence comes from retrospective analyses of available data such as those from established national health registries,[14–17] surveys,[18] electronic medical databases,[19,20] and prescription claims databases.[6,21,22] While exploring and synthesizing information from these typically large datasets provides extensive and systematically collected information around patterns of use and discontinuation, there are limitations to keep in mind. One of the main limitations is missing data.[23] Furthermore, critical information may not be available such as explicit reasons why medications are discontinued, and important biases may exist that affect selection of patients and controls, thereby introducing risk for unmeasured confounding.[24] These studies may be restricted to certain patient segments such as databases comprising older patients (e.g. Medicare[25]) or target a sociodemographic subset of patients such as those with continuous health coverage,[6,26] or those based in certain geographic locations.[16,27]

As the nature of these studies is retrospective, treatment exposure and pre-specified collection of important outcomes cannot be controlled, and the accuracy or comprehensiveness of information cannot be fully substantiated. However, these databases offer an important opportunity to evaluate large, representative patient groups relatively efficiently from a cost and resource perspective and thus offer a powerful source of information to evaluate persistence. Generally, measurements of persistence in retrospective clinical practice studies are reported to be lower than their prospective counterparts.[28]

Prospective studies offer some advantages which can include determining: when and how treatments will be administered; which patients, and respective controls, if applicable, will be enrolled; how outcomes will be measured in advance of measurement (e.g. including actual intake and discontinuation dates); and additional critical information, such as reasons for discontinuation without which, studies will have limited utility to enact effective interventions. Although prospectively documenting discontinuation dates may have greater precision and less missing data, such measurements are generally less objective and require relatively more time, resources and cost to conduct these studies. Patients and their healthcare providers may also potentially modify their behaviours as a consequence of knowing their behaviours are being monitored (Hawthorne effect),[29] with the effect of patients remaining on medication longer or healthcare providers implementing additional support to enhance drug continuation. Certain objectives and clinical questions may be inherently better answered by prospective studies, as is the case when the aim is to assess effectiveness of clinical interventions.

Randomized controlled trials (RCTs) can effectively mitigate the potential for unmeasured confounding and allow us to more confidently state that observed differences between groups are due to the presence or absence of an intervention. However, RCTs are designed to test interventions which may independently influence persistence. Furthermore, the ecological validity of measurement is compromised in such controlled settings where contact will likely be more intensive than would be the case in routine clinical practice and follow-up of relatively shorter duration. The patients included in RCTs typically represent a narrow segment of the overall population of patients who may eventually receive the treatment. As drugs are provided free of charge to the patients, the cost element which may drive discontinuation is eliminated. Observational studies in clinical practice settings can lend greater generalizability and clinical utility than RCTs in this regard.

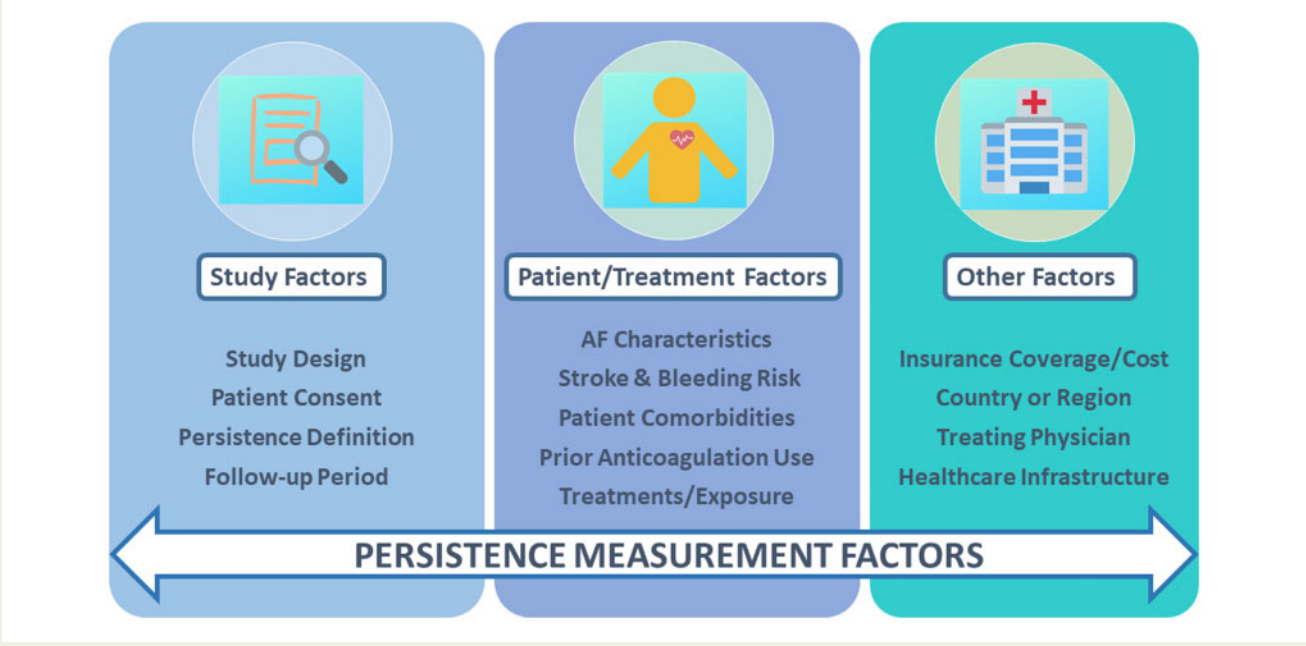

Figure 1 Broad factors which may impact oral anticoagulation persistence or adherence.

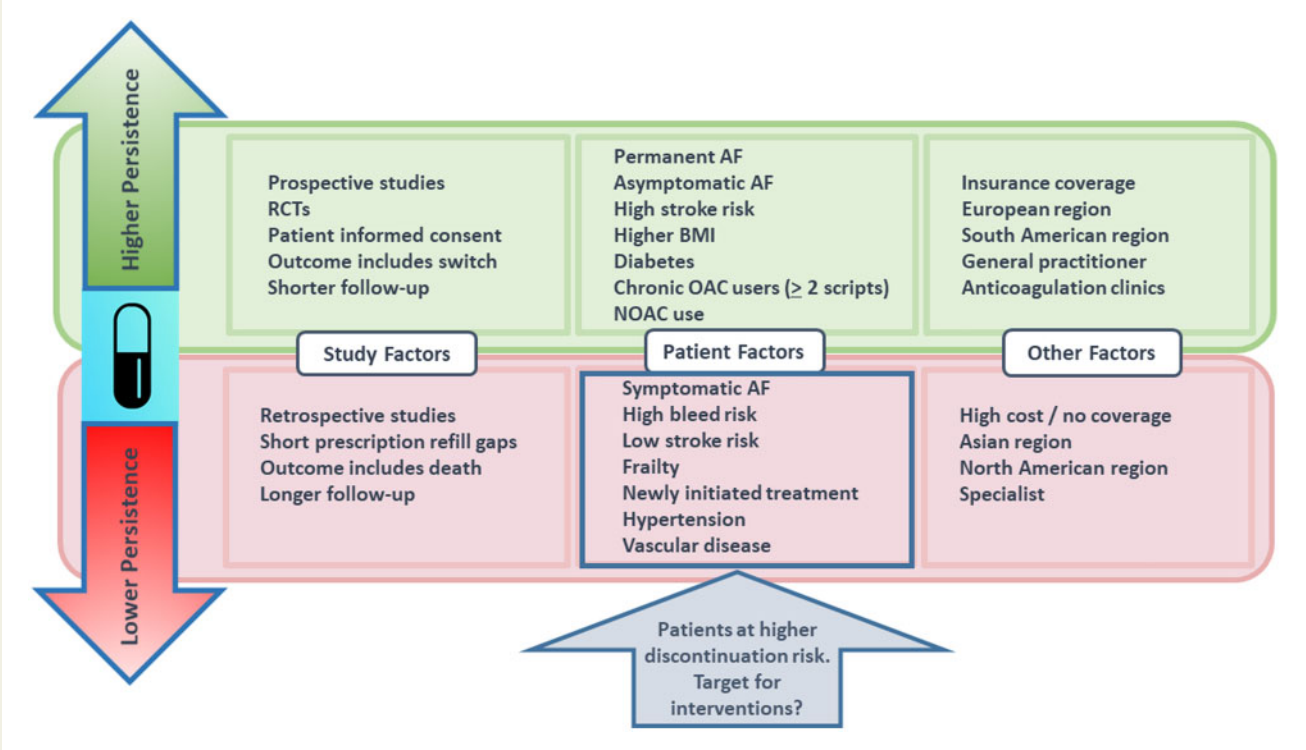

Figure 2 Factors potentially associated with OAC persistence or adherence. AF, atrial fibrillation; BMI, body mass index; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; RCT, randomized controlled trial.

Discontinuation rates reported are generally lower in RCTs than in observational studies. For example, discontinuation rates in an RCT for one of the NOACs (dabigatran) were <15% at 1 year and ~20% at 2 years of follow-up[8] but prospective observational studies of the same NOAC reported higher discontinuation rates in clinical practice settings at ~30% at 2 years.[30] For retrospective

Table 1 **Classification of OAC persistence studies—methodology, patient selection, and utility**

Assessment domains Mandatory domains (# domains)						Optional domain (# domains)
Patient selection (3)	**Reliability (3)**	**Validity (2)**	**Definition of persistence (3)**	**Clinical utility to develop interventions (3)**	**Outcome and follow-up (2)**	**Analyses (3)**
Includes only patients with confirmed AF at risk for stroke with indication for OACs	*Complete:* Low 'missingness' (estimate <10% missing data)	Ecological validity (clinical practice or 'real world' setting)	Includes medication switch as persistent	Includes predictors of discontinuation	Includes follow-up >6 months for majority of population	Comparative analyses control for important patient co-morbidities
Includes incident population, newly diagnosed and starting treatment	*Precise:* High precision for medication start and stop (use of exact dates not ranges)	Concurrent measure of medication intake and not only prescriptions (e.g. patient confirmation of intake)	Discusses or controls for impact of temporary discontinuation	Includes reasons for discontinuation	Patient-important outcomes after discontinuation measured (e.g. stroke, bleeding, mortality)	Adjusts for time-dependent factors (e.g. follow-up time)
Unobtrusive (patient not aware and no consent required)	*Objective:* Consistent/objective measures (e.g. prescriptions, chart reviews)		Excludes competing outcome of death	Considers healthcare delivery or infrastructure such as treating physician and reimbursement or medication cost		Considers and analyses differences in formulation or dosing

The number of applicable areas is summed to comprise the denominator (mandatory, $n = 16 +$ optional, $n = 3$). For all applicable items, allocate '1' if affirmative, '0' if Negative/Unknown/Not Reported. The percentage is the total affirmed responses over the total denominator of applicable items (range 0–100%).

observational studies of the same NOAC, 1-year discontinuation rates ranged from 30% to 51%.[31,32]

Definitions of persistence and measurement of outcomes

Researchers may be interested in persistence, defined as 'the act of continuing the treatment for the prescribed duration' or 'the duration of time from initiation to discontinuation of therapy'[2] or in its related counterpart, discontinuation, defined as the termination of medication[33] by some period in which the medication is not taken. The stringency of the definitions will affect estimates.

The strengths and limitations of varying definitions of persistence or discontinuation require consideration when interpreting rates or comparing across studies. For example, defining discontinuation by treatment gaps of 14 days[34] or less could include temporary discontinuations due to procedures or other brief interruptions resulting from acute illness which may inflate estimates of discontinuation. Indeed, shorter prescription refill gaps for defining non-persistence have been associated with higher non-persistence.[35] In contrast, defining discontinuation by significantly longer intervals to allow for periodic dose adjustments or variable timing of prescription refills (such as those defined by prescription refill gaps of 60 days or longer[6,36]) may be less clinically meaningful or may produce overly liberal and unrealistically optimistic estimates of persistence. In one study, which defined warfarin non-persistence by gaps of 180 days, the 1-year persistence estimate was relatively high compared with other estimates, with close to three quarters of patients identified as persistent after 1 year.[37] Interpretation of results should be made with due caution applied when comparing studies with variable measurements of persistence.

Of critical importance is also how persistence is defined. For example, if persistence only measures the time to first discontinuation and does not consider patients who switch to equally efficacious therapies to be persistent, the predicted clinical course may be assumed to be unnecessarily bleak. An investigation of patients who discontinued dabigatran in fact showed that approximately half of discontinuations were associated with re-start of other NOACs or VKAs,[30] similarly seen in other analyses.[19] Considering these issues, general persistence measures of all anticoagulation treatments (considering patients who switch as persistent) may be more clinically relevant.

Some definitions of persistence may include competing outcomes such as mortality which can inflate discontinuation estimates. This is the case when using claims databases which rely exclusively on prescription refills for which failure to refill a script may not only encompass periods of 'immeasurable time' when patients are hospitalized,[38] but may be combined with patient death.[39,40]

Analytic considerations

Analyses of comparative studies should consider the impact of differential censoring between drugs that could lead to populations with differing probabilities for outcomes.[22] If patients are more prone to switch with one medication compared with another, one might appear to have fewer outcome events but be confounded by censoring of more vulnerable patients at the point of switching to another medication. Hence more advanced modelling techniques to consider time-varying confounders may be appropriate.[22] Issues such as these are mainly problematic when persistence measures are drug specific.

Finally, in order to define clinically relevant targets for improving persistence with an intervention, it is fundamental to establish the relationship between some magnitude of effect (i.e. change in persistence) to rates of clinically important outcomes such as stroke or mortality, and studies that report outcomes following discontinuation meet the first important step to establish if there is a relationship at all.[19,41,42]

Timing of assessment and duration of follow-up

Exploring medication persistence has an implicit requirement for establishing an effective period for which patients should remain on treatment. For guideline adherent OAC for AF patients, this is an indefinite period which requires clinical judgement to weigh the stroke prophylactic benefits of OACs against their inherent risks for bleeding[43] (which are dependent on evolving patient co-morbidities and characteristics that largely overlap with stroke risk factors). To understand the trajectory of treatment persistence over the disease course requires long-term follow-up to illustrate the complex relationships of patient characteristics, and drug effects over time yet some study designs offer only a cross-sectional description of patients with heterogeneous characteristics at diverse points following treatment initiation.[44]

One potential issue seen with adherence measurements, which has a related issue for persistence measurement is the potential for confounding by timing or duration of follow-up. Adherence to medication has been shown to be inversely associated with the total time of follow-up[45,46] [as the proportion of days covered (PDC) is a ratio of estimated total days on medication over the total number of follow-up days], and with a constant PDC, longer follow-up will dilute this ratio resulting in lower adherence estimates than those with shorter follow-up. This has further implications when comparing medications with differential timing for market availability in that these differences will favour the most recent medication introduced to the market if follow-up remains unadjusted.[46] Similarly, longer duration of follow-up time has been associated with lower mean persistence.[35]

The timing of persistence measurement relative to diagnosis may introduce additional variability that should be considered in the interpretation of findings. For example, in incident populations assessed soon after diagnosis and drug initiation (inception cohort[47]) patients may have higher inherent risk for discontinuation by virtue of starting measurement before sufficient time has transpired for detection of any important adverse drug reactions or drug interactions that drive discontinuation.[48] In contrast, starting assessment in patients on medication at a later point following diagnosis and drug initiation such as those with ≥2 prescriptions filled[46] may look more favourable as patients with certain characteristics reflective of those with higher discontinuation risk will have dropped treatment at an earlier time point (a concept referred to as 'depletion of susceptibles'[49]).

Following patients from the time of treatment initiation can also help characterize *when* patients may be most likely to discontinue, an aspect of high importance when considering how to maximize the

impact of interventions (especially those that come with high cost and/or resource burden) to optimize persistence.[30,41]

Inception cohort study designs measuring persistence from the time of diagnosis and treatment initiation to discontinuation, may be instrumental for differentiating drug and patient factors that contribute to discontinuation. A well-designed cohort study with enough follow-up time to evaluate long-term persistence using reliable, precise, and ecologically valid measurements of persistence could be informative to clinicians. Restricting enrolment to patients newly diagnosed with AF, with documented stroke risk and without prior long-term exposure to anticoagulants would reduce further risk of confounding. Non-persistence defined by stopping of all OAC medication for a period of 30 days or more, would reduce the impact of temporary discontinuations. In support of this, a minimum 30- to 90-day period of medication lapse has been associated with doubling of stroke risk in high-risk patients, with increased risk not evident with shorter gaps.[42] Sensitivity analyses examining different cut-points could further be conducted to confirm the optimal interval without medication for classification of discontinuation.

Patient and treatment factors

Factors such as patient sampling, treatment exposure, and disease characteristics may further affect the generalizability of results and will be addressed next.

Patient clinical predictors of discontinuation

In addition to considering the broad selection of patients included in studies of persistence, there are additional patient-level clinical characteristics that have been associated with OAC persistence which should be acknowledged, such as lower persistence reported in younger males,[6] those with higher bleeding risk[50] and lower stroke risk,[30,35,40] and higher persistence in patients with higher body mass index.[41] Other co-morbidities such as diabetes have been reported to be associated with a reduced risk for non-adherence, while hypertension and vascular disease was associated with a higher risk for non-adherence.[19] In contrast, certain AF characteristics which may be surrogate markers for disease severity such as asymptomatic or minimally symptomatic AF and permanent AF[30] have been associated with higher persistence. The groups identified as being most prone to be non-persistent are perhaps the groups to preferentially target to deliver interventions (*Figure 2*). A Supplementary data online, *Table S1* provides examples of factors which may be associated with anticoagulation persistence or adherence.

The reasons reported for discontinuing NOACs have not been primarily due to adverse events,[30] suggesting that other reasons based on patient risk, or patient or physician preference may have an important role in driving discontinuations. In support of this hypothesis is the attribution of warfarin discontinuations to patient-centric reasons such as patient preference or refusal to continue medication, patient frailty and frequent falls, high bleeding risk and inability to adhere to, or monitor their treatment.[48] The complexity of reasons for discontinuation, those made unilaterally by patients as well as those jointly made with treating physicians, has highlighted the need for a multi-level approach. An approach that incorporates both patients' treatment preferences as well as physicians' prescription and management determinants (including associated healthcare systems) that can be addressed in their interaction may better support overall adherence to anticoagulant treatments.[45]

Finally, awareness of other issues such as selection practices at the patient level may also affect results and potentially limit generalizability of findings. For example, studies that require patient consent to participate may naturally represent a patient subset more likely to persist with treatment. The act of providing consent itself could act as implicit agreement to improve patient commitment to persist with treatment. Furthermore, including chronic medication users only (defined by ≥2 prescriptions filled) could result in higher estimates of adherence and persistence than if 'non-chronic' users were also included.[46]

Treatment factors

As treatments evolve and new options become available, reported persistence rates may improve simply due to availability of better, more tolerable or easier to manage therapies. This appears to be the case with the introduction of NOACs which are recommended as the preferred OACs in newly diagnosed AF patients with guidelines highlighting the importance of treatment adherence.[43]

The availability and endorsement of NOACs for stroke prophylaxis[43] have diminished some of the challenges inherently seen with warfarin such as those associated with the drug's narrow therapeutic window, possible interactions with other drugs and diet, and highly varied individual patient dose responses requiring frequent drug monitoring.[51] There is growing evidence that patients remain on NOACs longer than warfarin[30,40,52] which is supported by recently published systematic reviews.[35,53]

The availability of different doses to manage bleeding risk, such as seen with some of the NOACs, as well as once a day formulations[54,55] may impact adverse drug reactions and overall likelihood to persist with drug regimens. Although once daily dosing of NOACs has not been shown to be associated with higher persistence compared with twice daily formulations,[35] less frequent dosing has generally been associated with better adherence in other chronic illnesses.[56] Similarly, fewer overall number of medications has generally been associated with better adherence in other conditions.[57,58] In AF patients, while polypharmacy and direct impact on persistence or adherence have not been reported, a higher number of co-morbidities have been associated with lower adherence suggesting this may potentially be an explanatory factor driving non-adherence and non-persistence.[59]

These associations between patient characteristics and persistence suggest there is room for enhancing clinician–patient decision-making to initiate and maintain treatment with selected anticoagulants.[60] Patient groups who are most susceptible to discontinue should be preferentially targeted with persistence interventions, such as those who are newly diagnosed, those with low stroke risk, and those with symptomatic AF (*Figure 2*). Interventions such as patient and physician education[61] or other patient management interventions such as instituting more frequent follow-up in high-risk patients, engagement of associated healthcare professionals such as nurses or pharmacists or technological interventions could be potential options to explore further.[62,63]

The next broad area to consider when examining persistence is related to external or environmental factors including the impact of different treating physicians, treatment settings, and country or regional considerations.

Other external factors

The settings in which persistence to anticoagulation is measured can vary by geography as well as the type (e.g. institutions, clinics, or private offices), or the infrastructure of the healthcare system itself. In addition, the type of healthcare provider such as specialists or general practitioners (GPs) may be associated with different observed rates of patient persistence to medication. These factors may be confounders if comparing persistence (e.g. between interventions or different drugs), without settings balanced between groups.

Healthcare infrastructure and treating physician

Differences in healthcare infrastructure have been noted as a potential factor which could impact treatment persistence.[60] Patient management through specialized anticoagulation clinics for warfarin dosing for instance showed lower rates of non-persistence compared with studies without anticoagulation clinics.[37,64] While there is no explicit requirement for monitoring of NOACs, there may still be differences between healthcare settings with some preliminary evidence showing a trend for patients followed in university hospital settings to have higher non-persistence than community hospitals.[30] This may be directly related to the predominant type of treating physicians in these settings (e.g. higher proportion of specialty care physicians associated with large academic institutions) and associated patient contact patterns for appropriate disease management. For example, cardiologists may not keep patients treated with NOACs under frequent and regular surveillance unless there are precipitating disease factors necessitating it, such as renal dysfunction. Thus, patients may not be seen by their cardiologist for longer intervals or until an outcome event or other complication arises.[65] Supporting this hypothesis is the higher persistence reported with a NOAC in AF patients followed by GPs compared with specialists[41] which has similarly been reported for other patient groups such as those taking bone sparing drugs.[66] There may be opportunities to improve persistence through encouragement of certain patient management practices such as cardiologist referral to GPs for follow-up after initial diagnosis is made, as one example.

Regional and country differences

Important regional differences in guideline adherent prescribing of anticoagulants have been reported with significantly lower rates of treatment initiation in regions such as Asia.[67] It has similarly been reported that relative to patients in Europe, Asian patients (and those in North America) had higher discontinuation, and patients from Latin America had lower discontinuation.[30,35] The explanations for these regional differences and in particular the lower persistence seen in Asia are complex and not fully understood, although they could relate to higher perceived risk for catastrophic outcomes such as intracerebral haemorrhage,[68] perceived lower stroke risk,[69,70] potential for interactions with more frequently used herbal remedies,[71] or simply issues related to access to care.

Regional differences have also been observed in OAC uptake and persistence within a country such as in Denmark.[17] Although the reasons for the observed differences were not clear, the authors suggested that variability in healthcare delivery and in 'attitude and attention' in AF patient management could have been contributing factors.

Cost of medications and coverage

While the availability of NOACs has introduced efficacious agents with greater convenience, they have come with an increased cost to patients and the healthcare system. Cost of medications may be an access barrier, and this has been reported as a reason for not persisting with anticoagulation (albeit in a minority of cases).[30,72] Coverage through private insurance compared with federal or statutory insurance has also been associated with higher non-persistence rates over time suggesting that those drugs without public reimbursement may be more prone to discontinuation.[41]

Assessing persistence studies and considerations for future research

In reviewing the variability of approaches in measuring persistence to OACs in AF patients, the utility of a framework to guide interpretation of current research as well as planning for future research becomes clear. The assessment domains proposed (*Table 1*), relate to strengths and limitations for patient selection (e.g. those newly initiating treatment), as well as definitions of persistence measurements. While studies blinded to the objectives of persistence measurement may have less motivated or inadvertently modified drug-taking or drug-monitoring behaviours, revealing study objectives in an open design may be more ethically sound and produce more precisely documented information.

In addition, reliable measurements with low degree of missing data and high precision (e.g. medication start and stop dates as opposed to surrogate measures such as prescription refill dates) are important considerations. While objective and reliable measures (e.g. retrospective chart abstraction) have value, these can be prone to limitations such as missing data or inaccuracies. Ecologically valid studies conducted in clinical practice settings rather than more contrived environments of RCTs have obvious strengths but also limitations if representativeness of settings or patients is not adequately demonstrated.

Measurements of persistence should have carefully considered definitions, and exclude the competing outcome of mortality from measures of non-persistence.[73] Outcomes should include follow-up beyond 6 months as the probability of non-persistence is observed to be non-linear over time,[41] and patient-important outcomes following discontinuation should be measured. Studies designed with these considerations may have higher utility and lend more confidence to draw conclusions.

Optional assessment domains related to analyses are further proposed. For example, comparative analyses of different drugs should adjust for important patient co-morbidities or other potential

confounders such as differences in follow-up time, settings or differences in drug formulation or dosing.

Scoring of classification scheme

In total, this proposed classification scheme includes 16 mandatory assessment domains and 3 optional ones for a total of 19 potential domains. For all applicable items, a simplified scoring schema would allocate one point for affirmative responses, and no points if not affirmative, unknown or not reported. The final percentage would be calculated by dividing the total number of affirmed responses over the total denominator of applicable items (to produce estimates ranging from 0% to 100%). Studies could thus be compared with assess in a comprehensive and consistent way, their methodological strengths and clinical utility. The scoring algorithm and application of the algorithm to some key recently published studies are included in Supplementary data online, *Table S2*. Further testing of this schema is warranted in further research.

Future directions

A recent systematic review has identified that >80% of 48 studies identified examining OAC persistence have been published from 2016 to June 2018.[35] This is an area of high clinical importance for patients and healthcare professionals. Additional factors associated with better or worse persistence may be further identified through systematic review and extraction of information from studies cited in this review.[35] Furthermore, validating the schema against this growing body of evidence will be useful for future researchers, for example by pooling estimates from studies with similar characteristics or preferentially pooling those with higher quality ratings. In this systematic review,[35] quality of studies could not be differentiated and all were rated as good quality despite their methodological differences.

While this review highlights important findings in the areas of OAC adherence, there are further system factors and knowledge gaps identified which result in failure to initiate OAC treatment. These factors and strategies for mitigation continue to be a focus of professional organizations.[74]

As suboptimal persistence with NOACs continues to be a challenge, intervention studies may be designed and should similarly consider these methodological aspects to measure and improve persistence in various settings. Without robust methods, the best interventions may fail to show clinical benefit. Studies which measure reasons for discontinuation will be pivotal for developing effective interventions. These may bring future innovative solutions such as technological aids aimed to both systematically measure and improve persistence.

Conclusions

Estimates of oral anticoagulation persistence may vary due to study methodology or design, patient, treatment, or other factors linked to higher or lower persistence estimates. We identified multiple factors and summarized them in a pragmatic diagram.

We also identified important methodological heterogeneity and to our knowledge, this is the first framework developed to assess, interpret, and design future OAC persistence research. The importance of selecting appropriate patients, outcomes with high reliability, objectivity, and validity is emphasized. Definitions of persistence and important aspects of the definition that impact outcomes are included in this framework.

Examining persistence in AF patients indicated for long-term anticoagulation has important implications for improving patient outcomes and allocating resources efficiently. Sound, reliable, and comprehensive measures of OAC persistence can form the basis for developing cost-effective interventions to improve persistence.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Pharmacotherapy* online.

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