Adherence to Oral Anticoagulant Therapy in Patients with Atrial Fibrillation:

Focus on Non-Vitamin K Antagonist Oral Anticoagulants

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ABSTRACT

Oral anticoagulation is pivotal in the management of thromboembolic risk in non-valvular atrial fibrillation (NVAF) patients. Effective anticoagulation is important to avoid major adverse events and medication adherence is central to achieve good anticoagulation control.

Non-vitamin K antagonist oral anticoagulants (NOACs) are as effective and safe as vitamin K antagonist (VKAs) in NVAF patients. Due to the absence of routine anticoagulation monitoring with NOACs treatment, concerns have been raised about patient's adherence to NOACs and real-life data demonstrates variability in adherence and persistence. A multi-level approach, including patients' preferences, factors determining physicians' prescribing habits and healthcare system infrastructure and support, is warranted to improve initiation and adherence of anticoagulants. Adherence to NOACs is paramount to achieve a clinical benefit. Implementation of educational programs and easy-to-use tools to identify patients most likely to be non-adherent to NOACs, are central issues in improving the quality of NVAF anticoagulation management.

Keywords: atrial fibrillation; oral anticoagulation; non-vitamin K antagonist oral anticoagulants; adherence; persistence.

INTRODUCTION

Oral anticoagulant (OAC) therapy is recommended for the prevention of thromboembolic events in non-valvular atrial fibrillation (NVAF) patients(1). One of the major challenges for stroke prevention with OAC, vitamin K antagonists (VKAs) and non-VKA oral anticoagulants (NOACs), is medication adherence and persistence, to ensure efficacy and safety.

Awareness of the importance of medication adherence as a pivotal issue in medical management has increased(2–4). The World Health Organisation (WHO) recommends that accurate assessment of medication adherence and strategies to counteract medication discontinuation are necessary for effective treatment in chronic diseases(5). *Adherence* implies that the patient chooses to appropriately follow prescriber's recommendations concerning medication intake (6). *Persistence* with medication, defined as the time from initiation to discontinuation, should be pursued to increase the success of any prescription(7–9). Therefore, evaluation of the factors affecting medication adherence, specifically related to OAC for stroke prevention in NVAF patients, and development of strategies to improve it, are warranted but remain challenging(10).

The aims of this review are: i) to discuss the relevant issues related to adherence and persistence for OAC therapy in the management of NVAF patients; ii) to summarise the available literature on adherence and persistence during treatment with NOACs in NVAF patients from both randomized clinical trials (RCTs) and observational studies; and iii) to review possible strategies to improve adherence and persistence with OAC therapy.

DETERMINANTS OF MEDICATION ADHERENCE FOR OAC IN NVAF PATIENTS: PATIENT PERSPECTIVES AND PHYSICIAN ADHERENCE TO GUIDELINES

Achieving optimal prevention of stroke in NVAF patients is multifactorial, incorporating numerous patient, physician and healthcare system factors (Table 1). It requires the availability of the medication, physicians to prescribe the most appropriate OAC drug to eligible patients and relies on patients taking their medications properly and continuously. Moreover, adequate infrastructure, resources and support from the local healthcare system are essential. These factors are often co-dependent and the determinants of medication adherence are complex and multifaceted [Figure 1].

Since NOACs are as effective and safer than warfarin, their use in clinical practice is expected to improve patient uptake and clinicians' inclination to prescribe OAC therapy according to current guidelines(9). The more convenient fixed-dose regimen, fewer drugs interactions and no known food or alcohol interactions might improve patients' uptake and adherence. Nevertheless, in a clinical setting where no laboratory monitoring of anticoagulation is required, poor medication adherence could be problematic(11). Due to scarcity of data about determinants of adherence to NOAC therapy, we will discuss factors related to non-adherence in relation to VKA therapy which may also be pertinent to NOACs, and where data is available, for NOACs.

Suboptimal adherence to OAC is potentially harmful for NVAF patients due to the increased risk of stroke and bleeding. Poor medication adherence to VKA involves approximately one third of NVAF patients, based on observational studies and RCTs(12,13).

Patient and physician concerns about OAC therapy may be responsible for the substantial proportion of AF patients who discontinue OAC therapy within 1 year, with a resulting increased embolic stroke risk(14).

The Patient's Perspective

Increasingly AF guidelines highlight the importance of discussing patients' preferences for treatment as an integral part of the decision-making process when prescribing OAC therapy(15–18), as patients' experiences of AF, their patients' values and preferences are likely to affect OAC uptake and adherence(15,16,19).

Real-world studies reveal that 1-year discontinuation rates for warfarin-naïve patients initiating VKAs are consistently high (26% -35%)(7,20,21). Moreover, between 40–50% of NVAF patients do not even start VKA therapy, often due to the fear of fatal complications(20).

Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) which assessed patterns of warfarin discontinuation over 1 year of follow-up found that the majority were classified as patient-related(14).

Demographics, Patients' Understanding and Behavioural Factors

Non-adherence to VKAs appears more prevalent among younger patients, those of lower social-economic status, and those less well-informed about their disease and medications(20–22). Attitudinal and behavioural patient-related factors also play a role in medication non-adherence. Thus, depressive symptoms or pessimistic attitude towards the future, psychiatric illness, impaired quality of life due to co-morbidities, lack of social support, alcohol and drug abuse, were also commonly reported reasons for non-adherence to VKAs(23–26). In addition, the perception of

taking too many pills, that taking OAC increases bleeding, as well as worries about worsening health outcomes all contribute to low VKA adherence(27), (28). Moreover, evidence indicates that medication adherence in chronic diseases is time-dependent and decreases consistently after the first 3 months of treatment(3).

One US survey showed that women were significantly less willing to switch from warfarin to a NOAC than men, while older patients were significantly more willing to switch to a NOAC than younger patients(29). Another US survey of Veterans from primary care and OAC clinics, found that most patients would prefer to actively participate in OAC decision-making(30). Qualitative research has shown that physicians tend to believe that shared decision-making occurs regularly when choosing OAC, while patients believe that the physician often chooses the medication for them(31,32).

Recently, a European survey(33) demonstrated that: i) most AF patients were aware of the need for OAC for stroke prevention; ii) patients were not concerned about renal function checks and around 20% of NOAC-treated patients ignored these checks; iii) OAC discontinuation was approximately 14.5% but around half of the patients did not know the reason for NOAC cessation and iv) discontinuation related to bleeding was evident in only 4%. Overall, these findings suggest the need to address the lack of knowledge and awareness of AF patients towards requirements and benefits of NOACs prescription.

Comorbidities and Concomitant Medications

Co-morbidities also play an important role in non-adherence. For example, severe cognitive impairment affects patients' knowledge of medications and ability to adhere(34). Moreover, the patient's comorbidity burden may indirectly influence medication adherence due to the increasing

complexity associated with a wide range of medications(35). The presence of polypharmacy, defined as the prescription of 5 or more drugs at the same time for several different conditions, has been suggested to influence adherence to treatments(36). Of note, polypharmacy was found to be highly prevalent among AF patients(37,38) and was associated with worst clinical outcomes(37,38).

The Physician's Perspective

Physicians' perspectives on OAC also have to be considered when accounting for non-optimal treatment. Specifically, physicians' often overestimate bleeding risk and this is the most commonly cited explanation for under-prescription of OACs(39). Indeed, data from the ORBIT AF registry reported that the most common reason for discontinuation was physician preference (47.7%), followed by patient refusal/preference (21.1%), then bleeding events (20.2%)(14).

Knowledge in Balancing Thromboembolic and Bleeding Risk

Prescription of OAC may be influenced by the presence of potential contraindications. The most frequently listed contraindications include prior bleed, high bleeding risk, patient refusal/preference, and frequent falls/frailty(40,41), although none is an absolute contraindication.

Recent systematic reviews emphasize the impact of physicians' apprehension about feeling responsible for a major bleed, which seemed to outweigh their concern about risk of stroke(41,42). Physicians were less likely to prescribe VKAs after a patient experienced a major bleed associated with OAC. Conversely the occurrence of an ischaemic stroke in an untreated AF

patient did not influence the odds that a physician would prescribe warfarin in subsequent patients(42).

Recent data from the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) Pilot General Registry showed that up to 40% of AF patients were sub-optimally anticoagulated(43) Clinical factors associated with physicians' non-adherence to guidelines were the presence of concomitant coronary artery disease, which predicted both under- and over-treatment. Persistent AF and symptomatic status also predicted over-treatment(43) whilst smoking, concomitant malignancy and previous pharmacological cardioversion were significantly associated with under-treatment. Both under-treatment and overtreatment were associated with worst clinical outcomes.(43)

Physicians' Concerns over Patient Adherence to NOACs

Many physicians have the perception that even minor deviations from strict adherence can significantly decrease the efficacy of NOACs, due to their shorter half-lives, and this may significantly affect the NOAC prescription rate(44). One study,(45) found that although the majority of physicians prescribed NOACs and considered NOACs to be equally safe or safer than VKAs, the proportion of patients receiving NOACs was relatively low (mostly <10%). Physician's perceived that adherence to VKAs and NOACs was similar, but 10.6% stated that they felt patient adherence was better with VKAs(45).

A European survey revealed that considerable time and resources are dedicated in daily clinical practice to inform AF patients about their risk profile and available OAC therapies(46). Communication of stroke and bleeding risk communication was given highest priority for

discussion with patients. Overall the strongest driver for AF patients choosing a NOAC over a VKA were the fixed dosing, without the need for routine laboratory monitoring of the anticoagulation effect. In the majority of centres, the proportion of patients who would refuse NOAC despite being informed about the benefits and risks of therapy was <10%; main reasons for NOAC refusal were patients' fear of bleeding with NOAC and under-appreciation of stroke risk despite adequate information(46).

Healthcare Systems and Settings

Systematic reviews suggest that specialized management by OAC clinics is associated with better anticoagulation control compared to community-based services(47,48). In addition, data from a large observational study demonstrated that hospitalization is associated with a significantly higher rate of both critically sub- and supra-optimal international normalized ratios (INR)(49).

Further, reimbursement could influence the OAC prescription. A recent analysis of AF patients with high thromboembolic risk from the US PINNACLE registry, found that insurance type granting greater prescription coverage substantially increased the use of both OAC and NOACs.(50).

ADHERENCE AND PERSISTENCE TO NOACs

Absence of INR monitoring and lifestyle restrictions with NOACs could potentially improve adherence, although from a pharmacokinetic standpoint, it is likely that non-adherence to NOACs will be less well tolerated than with VKAs. The long average half-life of warfarin ensures some residual anticoagulant effect up to 72 hours following ingestion of the last tablet. If AF patients report an occasional missed dose, due to the slow-offset of VKA, they might be at less risk of thromboembolic complications compared with NOACs users. However, an analysis from the UK

General Practice Research Database reported that persistence with VKA progressively decreased during a 5-year follow-up. One-year persistence was 70% among chronic AF patients, falling to 50% at 2 years and 35% at 5 years. Currently we have relatively limited data on NOAC adherence.

NOACs Persistence in Phase III Randomized Clinical Trials

Evaluation of adherence in patients treated with NOACs is challenging(10). The Phase III NOAC RCTs only reported discontinuation rates, rather than adherence per se; discontinuation rates ranged from 18% to 35% across studies (see Figure 2)(51–55). Of note, the occurrence of a serious adverse event was only a minor determinant of non-persistence (Figure 2). Nevertheless, data on discontinuation rates and persistence with NOACs seen in these RCTs cannot be translated automatically into clinical practice, since RCTs are likely to enhance adherence by frequent follow-up visits and pill-count procedures, in selected and highly motivated patients.

From Clinical Trials to Real-Life Observations in NOACs Use

Data on NOAC adherence from actual clinical practice are needed to provide a more reliable estimate of medication adherence and persistence rates(56–59).

Adherence and persistence rates to NOACs in observational studies vary dramatically, from 38.0%(60) to 99.7%%(61) (Table 2). In most studies adherence is defined as the proportion of patients with a proportion of days covered (PDC) (*i.e.* numbers of days on which medication was taken as prescribed) of ≥80%, while persistence refers to the percentage of patients who do not discontinue therapy. To date 22 studies have investigated adherence and/or persistence to NOACs.

Dabigatran

Six studies exploring adherence and persistence to dabigatran alone have been published so far(8,61–65). A small study reported high adherence (99.7%)(61), meanwhile a recent analysis from the Veterans Health Administration reported dabigatran adherence up to 74%, with huge variations related to site-level practices(62). The proportion of adherent patients was higher at sites performing appropriate selection, patients' education/monitoring and with specific pharmacist-based activities(62). More recently, an analysis of prescription reported an adherence of 75% during the first year.(63) Patients at high risk for stroke and patients with great co-morbidities showed better adherence. Similarly, data from another large administrative database found that lower thromboembolic risk and higher bleeding risk were the main factors associated with dabigatran discontinuation(8). Despite this, dabigatran users still reported higher persistence than patients treated with warfarin (63.3% vs. 38.8%)(8).

Similar data overall data about adherence and persistence for dabigatran have also been reported by Tsai et al(65). Interestingly, the authors reported that warfarin-naïve patients had consistently lower adherence and persistence rates compared to warfarin-experienced patients (both p<0.001) (Table 2)(65).

Consistently, a subgroup analysis, derived from the Dresden NOAC registry, reported a discontinuation rate of 36.4% for dabigatran with an overall incidence of 25.8 per 100 patient-years. Incidence rate for discontinuation was found to be higher in the first 6 months of treatment (46.6 per 100 patient-years)(64). The largest proportion of discontinuation was for non-bleeding side effects (32.3%) and due to physician choice (13.7%); this mirrors data from the RCTs. Only 8.9% patients discontinued NOAC due to adverse bleeding events(64).

Rivaroxaban

In US healthcare claims database of propensity-matched cohorts of AF patients newly initiated on rivaroxaban or warfarin, patients treated with rivaroxaban had significantly higher persistence rates compared to warfarin-treated patients(66,67). Results from the Dresden NOAC registry(68) reported a discontinuation rate of 13.6 per 100 patient-years. The most common reasons for discontinuation were bleeding complications (30%)(68). A further analysis of this registry reported high levels of adherence both at 360 (85% of patients) and 720 days (78.8%)(69). One large international multicentre study about rivaroxaban use in real-life reported that 20.1% discontinued rivaroxaban after 1-year follow-up, mainly due to adverse events(70).

Apixaban

Adherence to apixaban in NVAF patients has been investigated in an RCT; the "AEGEAN" study *(ClinicalTrials.Gov unique identifier: NCT01884350)*. Patients started on apixaban were randomized to receive 'usual care' or 'usual care plus additional education'. Adherence (88.5% vs. 88.3%) and persistence (90.5% vs. 91.1%) rates were not significantly different between the two groups after 6-months of treatment(71). The final results are still awaited.

Comparison of ≥1 NOAC

A recent meta-analysis demonstrated that NOAC discontinuation rates were not statistically different when compared to warfarin and aspirin for prevention of stroke in NVAF patients(72). Studies that have examined adherence to ≥1 NOAC report varying and inconsistent results. A population derived from a well-structured AF clinic showed that patients treated with apixaban had the lowest incidence of discontinuation after 367 median follow-up time compared to both dabigatran (11.5 vs. 30.0 per 100 patient-years, p<0.001) and rivaroxaban (11.5 vs. 23.9 per 100

patient-years, p=0.001)(73). Similar data were reported by an observational study from a Japanese anticoagulation clinic(74).

A retrospective analysis of a US healthcare claims database was performed to evaluate NOACs adherence(75). Significantly more patients were adherent to rivaroxaban (72.7%) than either dabigatran (67.2%) or apixaban (69.5%)(75).

Recently a flurry of studies reporting adherence and/or persistence data for NOAC versus VKAs have been published (Table 2)(60,76–80). A large prospective cohort reported that the unadjusted persistence in dabigatran users was lower when compared to rivaroxaban, apixaban and warfarin(76). Initiation with both warfarin and apixaban were associated with a better persistence at 1-year follow-up. Higher adherence rates were reported for rivaroxaban compared to dabigatran treatment (p<0.001), while no difference was found when compared to apixaban(76).

Evidence from a UK primary care database reported significantly higher persistence rates with all NOACs at both 180 and 365 days compared to VKA treatment (both p<0.0001)(77). Similar data were reported from a retrospective US insurance database, showing an overall higher adherence for NOACs when compared to warfarin (p<0.001). Another study reported overall adherence to NOACs (dabigatran, rivaroxaban, apixaban) of >70%.(80).

Another large "real-world" observational study found that patients with rivaroxaban where consistently more persistent and adherent both at 180 days and 360 days when compared to dabigatran and VKAs(78). Similar evidence was reported by US claim database, showing that adherence to rivaroxaban was consistently higher than dabigatran(60). Similarly, in the study by Alberts et al.(80), patients treated with once daily rivaroxaban were found to be more adherent

than those treated with twice daily NOACs (dabigatran and apixaban) (73.1% vs. 67.9% respectively, p<0.001).

Practical Considerations about NOACs Adherence and Persistence

All NOACs are rapidly absorbed and have half-lives below 24 hours; nevertheless, different dosing regimens have been selected, depending on the drug. Modelling analyses that combine patients' dosing history data and pharmacokinetic properties of the drugs, have demonstrated that a twice-daily dosing regimen maintains a better continuity of drug plasma levels than once-daily dosing for drugs with a half-life of 12 h(81).

Nevertheless, it is unknown whether any NOAC regimen is superior in guaranteeing the best net clinical benefit in terms of thromboembolic prevention efficacy and safety. In modelling data, a larger decrease in anticoagulant activity was computed with a single dose omitted from an OD regimen compared with a single or more pills omitted from a BID regimen(81). As the clinical relevance of anticoagulant activity fluctuations has not yet been clinically elucidated, it is essential to ensure that drugs are taken according to the prescribed regimen to obtain results resembling those seen in the RCTs(82).

The current perception is that peak plasma drug-concentrations are important determinants of bleeding, especially since a twice-daily regimen reduces peak plasma drug concentrations compared with once daily dosing, and this should, in theory, maximize safety. However, pharmacokinetic analyses from a Phase II study on edoxaban in AF patients reported less bleeding events with OD regimen rather than BID dosing, albeit with the same daily dose(83).

STRATEGIES TO IMPROVE PATIENT'S ADHERENCE TO ORAL ANTICOAGULATION

Identification of factors accounting for non-adherence to VKAs and NOACs in clinical subgroups is essential for targeting patient management and improving overall adherence to medication. The evaluation of the time in therapeutic range (TTR) represents one of the most reliable ways to evaluate treatment efficacy in patients undertaking VKA-based anticoagulant therapy[84]. In fact, TTR inversely related to both thromboembolic and bleeding events in patients treated with VKAs [85–87]. The ESC Working Group on Thrombosis recommends achieving a TTR of at least 70%[88].

A simple clinical-based tool to identify patients who may be less likely to achieve and maintain good anticoagulation control has been proposed in the setting of NVAF, the SAMe-TT_2R_2 score (Sex (female), Age (<60 years), Medical history, Treatment (VKA interacting drugs, *i.e.* amiodarone), Tobacco use, Race (non-Caucasian))[89]. The SAMe-TT_2R_2 score has been validated in several cohorts [90–93] and could be used to aid OAC decision-making[94].

Those patients with a SAMe-TT_2R_2 score>2 (hence with a high probability of ineffective anticoagulation), could be targeted with intensive educational strategies to improve patients' knowledge and awareness about AF and anticoagulant treatment, in order to achieve a better adherence[15]. Indeed, the "TREAT" study showed that warfarin-treated AF patients, who received a one-off educational group session, achieved better anticoagulant control, assessed by TTR, compared to patients treated with usual care[95]. Similar strategies, tailored to each NOAC and considering social, ethnic and cultural/geographical differences[5], could be developed to improve adherence to NOACs and consequently reduce adverse events.

Regular scheduled contact with healthcare professionals may improve adherence with NOACs. The European Heart Rhythm Association practical guide to NOACs provides a framework for structured

start-up and follow-up of patients receiving NOACs(96). Regular review of patient adherence by health care providers (HCPs) along with a patient card recording all relevant information, may be needed to improve patients' adherence(96). An active multidisciplinary approach involving professional HCPs such as nurses, general practitioners (GPs) and cardiologists has been also proposed(97).

An European Working Group convened to consider the challenges facing HCPs and healthcare systems in different countries and the educational gaps that hinder optimal patient management(82).

Education needs and responsibilities have been identified and should be implemented in clinical practice(82). Updates on available evidence on NOACs should be provided with role-appropriate levels of complexity to all HCPs. Simple flow charts, as well as software and e-support, should be made available for guiding treatment. HCPs should be responsible for reinforcement of key educational messages about the anticoagulant they are taking, assessment of patient understanding, periodic contact to follow-up and active interactions among all HCPs(82).

The long-term management of patients receiving anticoagulation could be efficiently handled by centralised anticoagulation clinics. As an alternative, GPs or specialist nurses could also take responsibility. The initial prescriber (or a member of his team) should be responsible for initial patient education and for educating and up-skilling other HCPs about NOACs(82).

Awareness of the importance of OAC for stroke prevention and practical information on the medication (when and how to take it, what dose etc.) through education seems to be a reliable

strategy to try to improve patient's adherence. This goal could be achieved through interdisciplinary AF-expert programs for management of AF patients(81,98,99). In this context, the central role of nurses in anticoagulation management is emerging(99,100). Nurse-led programmes have been shown to allow more systematic care and co-ordinated follow-up(98,101). Therefore, when compared to usual care, an integrated chronic care program including a nurse-led, guideline-based, software-supported AF clinic resulted in a significant reduction in the number of cardiovascular deaths or hospitalizations over one-year follow-up(99). Moreover, a nurse-based AF approach was tested in the SAFETY trial, finding a significant increase in the number of days being alive and free of hospital admissions, compared to hospital follow-ups(101).

Among HCPs, pharmacists may also play an important role in the monitoring patient adherence to NOACs(82). Pharmacists' daily practice is an ideal forum for checking that patients understand the dose and regimen and are adherent, as well as reinforcing general educational messages (82).

Finally, patients taking NOACs must be made aware of their condition and treatment. Information should be provided using appropriate language, in a variety of formats (verbally, booklets, apps, websites etc.), and confirmation of patients' understanding should be checked. It is important to utilise each patient visit to discuss the modalities of intake (once-daily vs. twice-daily; interactions with food and other medications), the importance of strict adherence to the prescribed dosing regimen to reduce the likelihood of serious adverse events and to convince patients that NOACs therapy should not be discontinued. With the gradual availability of antidotes to NOACs, it is even more important that the patient knows what drug they are taking, as the administration of the 'wrong' antidote in an acute bleeding event may have catastrophic consequences.

What else can we do? To improve medication adherence HCPs should assess (through discussion and pill counts) and record adherence; re-educate patients on the importance of the strict intake schedule; inform patients about adherence aids (medication boxes, smartphone applications, timers, etc.)(96). In a recent review, electronic monitoring (EM) feedback was the biggest adherence-influencing factor(102). Of the currently EM options, automatic compilation of dosing histories using electronic detection of package entry (smart packages) or direct detection of pills in the stomach (smart pills) seem to be promising reliable and sufficiently richly sampled methods to estimate patients' adherence(81).

CONCLUSIONS

In the context of NVAF patients' management, patient-, physician-, and healthcare-system factors have a significant impact on adherence to the prescribed anticoagulation regimen.

Although several papers about adherence and/or persistence with NOACs treatment in AF patients exist, the heterogeneity of setting, definition of adherence employed and results suggests that more robust research is needed to elucidate which of the available NOACs is associated with adherence and persistence, in combination with a reduction in major adverse events.

A multi-level approach, including patients' preferences for treatment and physicians' prescription determinants, as well as structured multidisciplinary healthcare systems, are warranted to improve uptake and adherence to anticoagulant therapy. This is particularly important in the era of greater use of NOACs where medication adherence would be paramount to avoid and/or reduce adverse events. Identification of simple practical tools to detect patients at risk of non-adherence, as well as implementation of patients and physician educational programs and

strategies to improve adherence, are central issues to be addressed in future studies for improving

the quality of anticoagulation management in NVAF patients.

AUTHORS' CONTRIBUTIONS

VR, MP and SB conceived the work. VR and MP collected the data. VR, MP, DAL and SB drafted the manuscript. RC and GYHL contributed substantially with critical revision of the manuscript at all the stages.

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FIGURE LEGENDS

Figure 1: Medication Adherence Main Determinants

Figure 2: Discontinuation Rates in Phase III NOACs trials

Legend: NOACs= non-vitamin K antagonist oral anticoagulants; SAE= serious adverse event; *data related only to bleeding episodes.

Table 1: Factors Influencing Medication Adherence in Chronic Disease

	MAIN CATEGORIES	EXAMPLES
PATIENT	1. Demographics	Age
		Ethnicity
		Educational Level
		Socioeconomic Status
		Presence of Caregivers
	2. Patient-Related Medical Conditions	Co-morbidities
		Disability
		Fragility
		Cognitive Impairment
		Tolerance and Side effects of Drugs
		Polypharmacy
	3. Behavioural Factors	Social Isolation
		Psychiatric Disorders
	4. Patient Understanding of the Medication Regimen	Awareness of the risk and benefit related to drug assumption and discontinuation
PHYSICIAN/HEALTH SYSTEM	1. Knowledge	Adherence to Guidelines
		Awareness of Recommendations and Risk Treatment
	2. Work Setting	Specialized Centres
		Structures of Health Care System
		Continuity in Patients-Doctor Relation
		Multidisciplinary approach
	3. Cost of the Care	Accessibility (Public vs. Private Services)
		Economic Concerns

Table 2: Adherence and Persistence Rates in Real-Life Studies on NOACs Use

Study	Year	Country	NOAC	Design	N	Adherence/Persistence	Primary Outcomes	Follow-Up
Dabigatran								
Schulman(61)	2013	Canada	Dabigatran	Observational Prospective	139	99.7%	Adherence Rate	3 months
Zalesak(8)	2013	United States	Dabigatran	Observational Retrospective	3,370	63.3%	Persistence Rate	1 year
Tsai(65)	2013	United States	Dabigatran	Observational Retrospective	17,691	56.5%# / 62.6%^ 67.4%# / 71.2%^	Adherence & Persistence Rate	6 months
Gorst-Rasmussen(63)	2015	Denmark	Dabigatran	Observational Retrospective	2,960	76.8%	Adherence Rate	1 year
Shore(62)	2015	United States	Dabigatran	Observational Retrospective	4,863	74%	Adherence Rate	30 days
Rivaroxaban								
Laliberté(66)	2014	Canada	Rivaroxaban	Observational Retrospective	3,654	82.5%	Major bleeding, ICH, GI bleeding, stroke/SE, VTE	6 months
Nelson(67)	2014	United States	Rivaroxaban	Observational Retrospective	7,259	77.1%	Persistence Rate	184 days
Beyer-Westendorf(68)	2015	Germany	Rivaroxaban	Observational Retrospective	1,204	81.5%	Persistence Rate	544 days
Camm(70)	2015	European Multinational	Rivaroxaban	Observational Prospective	6,784	79.8%	Major Bleeding, All-cause Death, All AEs and SAEs	1 year
Hecker(69)	2016	Germany	Rivaroxaban	Observational Prospective	1,204	78.8%	Stroke/TIA/SE ISTH Major Bleeding	796.2 days (mean)

Legend: AE= adverse event; GI= gastrointestinal; ICH= intracranial haemorrhage; NOAC= Non-vitamin K antagonist oral anticoagulant; SAE= serious adverse event; SE= systemic embolism; TIA= transient ischemic attack; VTE= venous thromboembolic event; *Dabigatran, Rivaroxaban, Apixaban; #warfarin naïve; ^warfarin experienced.

Table 2 (continued): Adherence and Persistence Rates in Real-Life Studies on NOACs Use

Study	Year	Country	NOAC	Design	N	Adherence/Persistence	Primary Outcomes	Follow-Up
Multiple NOACs								
Forslund(76)	2015	Sweden	Dabigatran Rivaroxaban	Observational Prospective	2,701 2,074	92.0% / 74.4% 95.7% / 77.4%	Adherence & Persistence Rate	1 year
Martinez(77)	2015	UK	Apixaban All NOACs*		1,352 914	93.5% / 85.9% 79.2%	Persistence Rate	1 year
McHorney(75)	2015	United States	Dabigatran Rivaroxaban	Observational Retrospective	6,548 11,095	67.2% 72.7%	Adherence Rate	1 year
Shiga(74)	2015	Japan	Apixaban All NOACs*		3,532 401	69.5% 70.0%	Discontinuation Rate	12 months
Alberts(80)	2016	United States	All NOACs*	Observational Retrospective	38,868	70.3%	Ischemic Stroke	12 months
Beyer-Westendorf(78)	2016	Germany	Dabigatran Rivaroxaban	Observational Retrospective	821 1,317	47.6% / 47.3% 62.6% / 53.1%	Adherence & Persistence Rate	360 days
Coleman(60)	2016	US	Dabigatran Rivaroxaban	Observational Retrospective	10,878 10,878	38.0% 49.0%	Adherence Rate	24 months
Yao(79)	2016	US	Dabigatran Rivaroxaban Apixaban	Observational Retrospective	10,235 12,336 3,900	38.5% 50.5% 61.9%	Stroke/TIA/SEE Major Bleeding	1.1 years (median)

Legend: AE= adverse event; GI= gastrointestinal; ICH= intracranial haemorrhage; NOAC= Non-vitamin K antagonist oral anticoagulant; SAE= serious adverse event; SE= systemic embolism; TIA= transient ischemic attack; VTE= venous thromboembolic event; *Dabigatran, Rivaroxaban, Apixaban; #warfarin naïve; ^warfarin experienced.