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How important it is for therapy adherence to be once a day?

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New oral anticoagulants (NOACs) or non-vitamin K antagonists (VKAs) do not possess the numerous negative properties of VKAs in the therapy of atrial fibrillation patients. NOACs have a more rapid onset of action, are less dependent on interactions, food intake, age and body weight, and there are fewer gene polymorphisms. The large Phase III trials have shown that all NOACs are not inferior to VKA therapy. Nevertheless, these results are certainly based on the adherence and persistence to NOAC therapy. A once-a-day strategy has been shown to increase the adherence to therapy. Therefore, this review provides an overview over adherence to NOAC therapy and tries to assess the impact of once-a-day treatment regiments on treatment adherence in anticoagulated patients with atrial fibrillation.

Introduction

New oral anticoagulants (NOACs) should ideally not possess the numerous negative properties of vitamin K antagonists (VKA) in the therapy of atrial fibrillation (AF) patients. Examples of these are variable oral bioavailability, dependence on food intake, slow onset of action, dependence of metabolism on numerous gene variants, and associated need for frequent measurements of effect. The currently available NOACs no longer have many of these negative properties. They have a more rapid onset of action, are less dependent on interactions, food intake, age and body weight, and there are fewer gene polymorphisms. The large Phase III trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, ENSURE AF) have shown that all NOACs are not inferior to VKA therapy.[1–3] Nevertheless, the results are certainly based on the correct intake of the various NOACs. Thus, adherence to therapy appears of major importance for adequate anticoagulation.[4–6]

Compliance, adherence, and persistence

Medication compliance

Medication compliance refers to the act of conforming into the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. Therefore, medication compliance may be defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen'. Compliance is measured over a period of time and reported as a percentage.[7–9]

Medication adherence

The word 'adherence' is preferred by many health care providers, because 'compliance' suggests that the patient is passively following the physician's orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the treating physician. Adherence to therapy is defined by the WHO as the extent to which a person's behaviour in taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider.[7–9]

Medication persistence

Medication compliance/adherence refers to the act of conforming to a recommendation of continuing treatment for

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the prescribed length of time. Therefore, medication persistence may be defined as 'the duration of time from initiation to discontinuation of therapy'. Continuing to take any amount of the medication is consistent with the definition of persistence. This definition can be operationalized in both prospective and retrospective assessments by determining the initiation of treatment, or a point in time during chronic treatment, to a point in time defined as the end of the observation period. By definition, persistence is reported as a continuous variable in terms of number of days for which therapy was available. Persistence may also be reported as a dichotomous variable measured at the end of a predefined time period (e.g. 12 months), considering patients as being 'persistent' or 'non-persistent'.[7-9]

Adherence to therapy

Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period.[6-14] Some studies have also used a definition of adherence to include data on dose taking (taking the prescribed number of pills each day) and the timing of doses (taking pills within a prescribed period).[7,8,13] Adherence is in general better among patients with acute medical diseases, as compared with chronic diseases. Adherence to therapy among patients with chronic conditions is disappointingly low, dropping most dramatically after the first 6 months of therapy.[8,9] Thus, adequate anticoagulation in long-term use of oral anticoagulants is based on adherence to therapy. The average rates of adherence in clinical studies were reported to be 43–78% among patients receiving treatment for chronic diseases.[9] There is no consensual standard for what constitutes adequate adherence. Rates >80% appear acceptable for adequate adherence.[6-9,13,14] However, it is unclear, what the adequate adherence rates for the use of NOACs need to be in order to achieve the full clinical benefit of anticoagulative therapy in AF patients.[6] So far, the exact rates of adherence have not been reported in the different NOAC trials. Although data on adherence are often reported as dichotomous variables (adherence vs. non-adherence), adherence can vary along a continuum from 0 to more than 100%, as patients sometimes take more than the prescribed amount of medication. The ability of physicians to recognize non-adherence is poor if there is no specific test to measure correct drug intake. The potential benefit of NOACs, which require no drug monitoring, might therefore appear as a disadvantage with regard to the assessment of treatment adherence. Predictors of poor adherence are the presence of psychological problems, presence of cognitive impairment, treatment of asymptomatic disease, inadequate follow-up or discharge planning, side effects of medication, patient's lack of belief in benefit of treatment, patient's lack of insight into the illness, poor provider–patient relationship, presence of barriers to care or medications, missed appointments, complexity of treatment, cost of medication, copayment, or both.[8] Thus, the live-long use of a complex therapy such as NOACs for primary prevention of stroke may have a particular trend to poor adherence if patients are not clearly educated about the benefits of therapy. Of note, rates of non-adherence have been reported in the range of 22–58% for VKAs.[15-20] In real-world practice, the proportion of anticoagulated patients who are commonly found within the therapeutic range is lower than 40%, this proportion increasing up to 60% in the framework of randomized clinical trials.[21]

Nevertheless, in long-term therapy cost may play a role in modulating adherence to therapy. A large retrospective study assessed the impact of generic drugs on therapy adherence.[13] The authors identified 327 629 new users of drug therapy. Proportion of individuals starting generic therapies ranged from 9% in hypothyroidism to 45% in hypertension. After 1 year of therapy, 66.2% of individuals with hypothyroidism achieved adequate adherence ≥80% compared with 53.4% with hypertension, 53.2% with hypercholesterolaemia, 52.0% with diabetes, and 42.2% with seizure disorders. Logistic regressions of adequate adherence showed generics were associated with higher adherence relative to brands in two conditions (hypercholesterolaemia odds ratio, OR 1.52, 95% confidence interval, CI: 1.44–1.60; diabetes OR 1.06, 95% CI: 1.01–1.12, $P<0.05$), with lower adherence in two conditions (hypertension OR 0.75, 95% CI: 0.73–0.77; hypothyroidism OR 0.86, 95% CI: 0.78–0.94, $P<0.05$), and no difference in seizure disorders.[13] In comparison, the likelihood of achieving adherence ≥80% with $0 copayments relative to $1–9 ranged from OR 1.32 for seizure disorders (95% CI: 1.41–1.43) to OR 1.45 for hypothyroidism (95% CI: 1.43–1.48). Thus, generic prescribing was associated with improved medication adherence in two of five study conditions, and the effect was modest.[13] Therefore, medication costs appear to have an impact on adherence, in particular in long-term treatment regiments. This might also occur in the case of NOAC therapy if drugs become available off-patent.

Adherence to new oral anticoagulant

So far, reports about adherence to NOAC therapy are limited.[6] Recently, Andrade *et al.*[14] published a study on self-reported adherence to various NOACs. In their study, a sample of AF patients on OACs for stroke prevention was surveyed between May and September 2014. Patients were recruited on a voluntary basis from (i) pharmacy dispensary counters (pharmacists were provided a blinded invitation to hand out to any person who filled a prescription for any of the target medications); (ii) a syndicated Canadian patient online panel (~4500 Canadians who self-identified as undergoing regular medical care, which was filtered for individuals who self-identified as receiving medical management for a heart condition. The panel owner provided blinded invitations to these individuals, and invited those currently taking one of the four target medications to participate); and (iii) referrals from physicians associated with stroke management clinics in geographic regions not sufficiently represented by participating pharmacies or the syndicated panel (these physicians were invited by e-mail to refer patients currently receiving one of the four target medications to the study). All patients were screened to

ensure that they were currently taking an OAC (apixaban, dabigatran, rivaroxaban, or warfarin; edoxaban) for stroke prevention in AF. Maximum quotas were set by medication use and geographic region. In total, 175 physicians who prescribed OAC therapy for AF were invited to participate in the survey by Andrade *et al*. A total of 266 patients were surveyed.[14] More than 80% of the patients were aged younger than 75 years. Apixaban and warfarin were used more frequently in younger patients (18–64 years; 61% and 70%, respectively), compared with rivaroxaban, which was used relatively more frequently in older patients (65 years of age and older; 60%). Dabigatran use did not differ between age groups (51% used in those 18–64 years, and 49% in those 65 years and older). Patients who were prescribed once-daily (q.d.) OACs reported better adherence with their prescribed OAC therapy than those who were prescribed twice-daily (b.i.d.) OACs (*Figure 1*). Compared with those who received apixaban or dabigatran, fewer patients who received rivaroxaban or warfarin reported a missed dose in the previous 7 days. The most common reason given for missing a dose was forgetting to take the medication (58% overall; 78% apixaban, 60% rivaroxaban, 53% dabigatran, 50% warfarin), or side effects (36%; no difference among agents). Patients were more likely to take the q.d. OACs at the recommended dosing regimen.[14]

Although a few registries and cross-sectional cohort studies have so far reported satisfactory real-life persistence with the use of NOACs in patients with AF, there are currently limited real-world data comparing adherence of the direct NOACs with standard therapy.[22–24] A cross-sectional cohort study of patients receiving dabigatran in a real-life setting showed that 30% of patients had missed their medication and 12% had inadequate adherence.[25] Non-adherence is likely to be a true problem and a reason for concern when prescribing NOACs for long-term anticoagulation. Depending on the type of treatment regimen, adherence may be even harder to achieve.

Once-a-day vs. twice-a-day

Simple dosing (one pill, q.d.) helps to maximize adherence, particularly when combined with frequent reinforcing visits, despite the fact that 10–40% of patients taking these simple regimens continue to have imperfect dosing. Eisen *et al*.[26] reported the medication adherence (called 'compliance' in that paper) of 105 patients receiving antihypertensive medications. Analysing data obtained from special pill containers that electronically record the date and time of medication removal, they could show that inaccurate adherence improved from 59.0% on a three-time daily regimen to 83.6% on a q.d. regimen.[26] Thus, the authors of that study concluded that adherence improves dramatically as prescribed dose frequency decreases. Furthermore, the authors stated 'probably the single most important action that health care providers can take to improve compliance (adherence) is to select medications that permit the lowest daily prescribed dose frequency'.[26] In a large systematic review of 76 trials in which electronic monitors were used, Claxton *et al*.[9] found that adherence was inversely proportional to frequency of dose (*Figure 1*), and patients taking

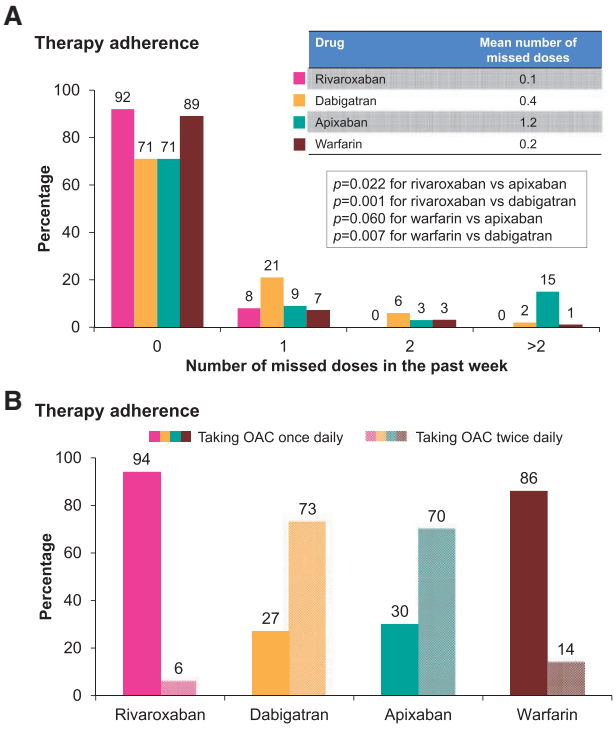

Figure 1 (*A*) Adherence to various new oral anticoagulants and number of missed doses in the past week (adopted from Ref. 14). (*B*) Adherence to therapy for once-daily vs. twice-daily application of new oral anticoagulants (adopted from Ref. 14).

medication on a schedule of four times daily achieved average adherence rates of about 50% (range, 31–71%). However, the analysis included antihypertensive drugs, and therefore, it needs to be determined whether patients with AF respond differently with regard to anticoagulative therapy. Nevertheless, a q.d. regiment appears to have the highest rate of adherence to therapy.

This concept is supported a Canadian Survey, which showed that patients were more likely to take the q.d. OACs at the recommended dosing regimen. Six per cent and 14% of patients who received rivaroxaban and warfarin reported taking their OAC b.i.d. instead of q.d., 27% and 30% of patients who received dabigatran and apixaban took their OAC q.d. instead of their recommended b.i.d. dosing regimens.[14] Patients who received rivaroxaban were less likely to consider stopping treatment compared with those taking other agents (8% for rivaroxaban vs. 18% for warfarin, 18% for dabigatran, and 27% for apixaban).[14]

Another study also postulated that multiple daily dosing may be negatively associated with patient medication adherence.[10] Thus, the authors compared adherence rates with q.d. vs. b.i.d. dosing regimen of chronic medications in patients with non-valvular AF. A total of 8256 q.d. and 2441 b.i.d. patients were identified.[10] The mean duration of exposure to therapy for q.d. and b.i.d. patients was 447 and 406 days, respectively. 75.3% of q.d. and 70.4% of b.i.d. patients were adherent. At 12 months, the proportion of adherent patients for the q.d. and b.i.d. groups was 56.5% and 49.6%, respectively.[10] This study demonstrated that non-valvular AF patients treated with q.d. dosing regimens for chronic medications were associated with

approximately a 26% higher likelihood of adherence compared with subjects on b.i.d. regimens.[10]

In another study, a large nationally representative US claims database was used to conduct a retrospective cohort analysis of patients with AF on rivaroxaban or dabigatran.[27] All patients had ≥6 months of data prior to the index date and were followed until the earliest of inpatient death, end of continuous enrolment, or end of the study period. Rivaroxaban patients were matched 1:1 with dabigatran patients using the propensity score matching technique. Persistence was defined as absence of a refill gap of ≥60 days. Discontinuation was defined as no additional refill for at least 90 days and until the end of follow-up. A total of 30 337 AF patients on rivaroxaban or dabigatran met the study criteria.[27] All 7259 rivaroxaban patients were matched 1:1 to dabigatran patients. Compared with dabigatran users, rivaroxaban patients were 11% less likely to become non-persistent with therapy (hazard ratio, HR: 0.89, 95% CI 0.84–0.95) and 29% less likely to discontinue therapy (HR: 0.71, 95% CI 0.66–0.77). This matched cohort analysis indicated that, compared with dabigatran, rivaroxaban was associated with better persistence and lower rates of discontinuation. However, the study could provide the exact medical reason of the observed differences.[27]

Another Canadian study aimed to assess the adherence to medication of patients who used the NOACs rivaroxaban, dabigatran, or apixaban in 2014 based on the Pharmacy Quality Alliance adherence measure.[5] Adult patients with ≥2 dispensings of NOAC agents in 2014, at least 180 days apart, with >60 days of supply and ≥180 days of continuous enrolment prior to the index NOAC were identified. A total of 11 095 rivaroxaban, 6548 dabigatran, and 3532 apixaban users were identified. A significantly higher proportion of rivaroxaban users (72.7%) was found to be adherent compared with dabigatran (67.2%: $P < 0.001$) and apixaban (69.5%: $P < 0.001$) users. Thus, rivaroxaban users were found to have significantly higher adherence compared with apixaban and dabigatran users.[5] A number of factors can account for these findings. For example, dabigatran may induce intolerable dyspepsia in up to 10% of patients.[28] In addition, dabigatran is cleared through the urinary tract to a remarkably higher extent than the inhibitors of factor Xa (80% vs. on average 30%), making it likely to switch patients to VKAs or an inhibitor of factor Xa whenever renal failure develops. Finally, it requires b.i.d. administration. Apixaban shares with dabigatran the need for b.i.d. administration. This is the most likely explanation for the higher adherence to therapy in users of rivaroxaban.[29] Indeed, in a comprehensive overview of studies conducted in patients with chronic diseases, adherence to the prescribed medications was found to be considerably lower for drugs requiring b.i.d. dosing than those requiring q.d. dosing. Similar results were found in a recent review addressing the treatment of cardiovascular disorders.[8,30]

The conclusions of these analyses are interesting and relevant to clinical practice, as they have the potential to have an impact on the prescription of NOAC agents. Although the choice of the proper NOAC has to take into account a number of considerations, including efficacy, risk of bleeding, patient's renal function, comorbidities, and preferences, the prescription of q.d. rivaroxaban is more likely to favourably impact a patient's adherence than that of b.i.d. dabigatran or apixaban.[6,14,30] Anyway, the adherence to long-term treatment does not seem to exceed that reported for most drugs used for prevention or treatment of cardiovascular disorders.

Adherence to new oral anticoagulant vs. warfarin

A large nationally representative US claims database was used to conduct a retrospective cohort analysis of patients with AF treated with rivaroxaban or warfarin.[31] All patients were followed until the earliest of inpatient death, end of continuous enrolment, or end of study period. Rivaroxaban patients were matched 1:1 by propensity scores. Medication persistence was defined as absence of refill gap of ≥60 days. Discontinuation was defined as no additional refill for at least 90 days and until the end of follow-up.[31] A total of 32 886 NVAF patients on rivaroxaban or warfarin met the study inclusion criteria. Each of the 7259 rivaroxaban patients identified was matched 1:1 to warfarin patients. Patients on rivaroxaban had a significantly better rate of persistence (HR: 0.63, 95% CI 0.59–0.68) and lower rate of discontinuation (HR: 0.54, 95% CI 0.49–0.58) compared with warfarin recipients. This matched cohort analysis indicated that rivaroxaban was associated with significantly higher medication persistence and lower discontinuation rates compared with warfarin.[31]

How can these NOAC adherence data be interpreted in relation to other therapies in medicine? A large retrospective study assessed drug adherence and persistence across six chronic medication classes.[32] The retrospective analysis of pharmacy claims in a database of more than 64 million members enrolled in 100 health plans. Patients were included in that study if they initiated a prescription drug of interest in any of six drug classes—prostaglandin analogues, statins, bisphosphonates, oral antidiabetics, angiotensin II receptor blockers (ARBs), and overactive bladder (OAB) medications—between 1 January and 31 December 2005.[32] A total of 167 907 patients were identified across six cohorts. Using the 60 day gap, 6 month persistence rates were prostaglandin analogues 47%, statins 56%, bisphosphonates 56%, oral antidiabetics 66%, ARBs 63%, and OAB medications 28%. After the first 90 days of therapy, relative persistence was stable across cohorts, and rates declined consistently from 6 months post-index to study end. Logistic regression models showed that oral antidiabetic users had a 59%, 36%, 37%, and 79% decreased risk of non-persistence in a 12 month follow-up period compared with patients taking prostaglandin analogues, statins, bisphosphonates, or OAB medications, respectively. Risk of non-persistence decreased with increasing age. Mean 12 month adherence rates were: prostaglandin analogues 37% (26%), statins 61% (33%), bisphosphonates 60% (34%), oral antidiabetics 72% (32%), ARBs 66% (32%), and OAB medications 35% (32%). This analysis of adherence and persistence across a sample of six chronic therapies found variable but uniformly suboptimal medication use.[32] Adherence to prostaglandin eye drops and OAB medications was lower than to cardiovascular, oral antidiabetic, and oral

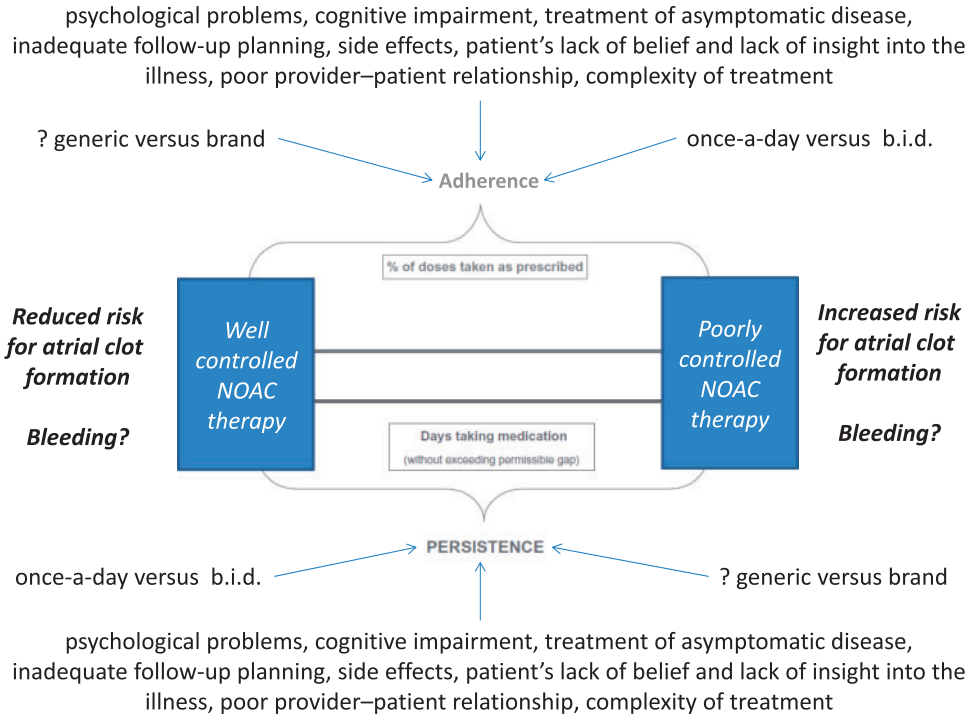

Figure 2 Illustration of adherence and persistence to new oral anticoagulants and potential confounders, which may affect the overall outcome of new oral anticoagulant therapy in patients with atrial fibrillation.

osteoporosis therapies.[32] Recently, data from 7265 patients from primary care practices were published.[33] The study assessed persistence with and adherence to anticoagulation in anticoagulant-naıve patients with AF newly treated with dabigatran, rivaroxaban, or VKA during follow-up periods of at least 180 days, respectively 360. Persistence after 180 days were 66.0% for rivaroxaban, 60.3% for dabigatran, and 58.1% for VKA. After 1 year of therapy, persistence probabilities were 53%, 47%, and 26%. Thus, in contrast to other therapies, NOAC adherence seems to be significantly better. One recent study has related the impact of adherence NOAC as well as VKA to clinical outcome.[34] In total, 64 661 US patients with AF who initiated warfarin, dabigatran, rivaroxaban, or apixaban were followed for 1 year. Overall adherence to NOACs was better compared with warfarin. They found that patients with CHA2DS2-VASc score $\geq$4 were at increased risk of stroke when they were not taking anticoagulation $\geq$1 month. Patients with CHA2DS2-VASc score 2 or 3 were at increased risk of stroke when they were not taking anticoagulation $\geq$6 months. In patients with CHA2DS2-VASc score $\geq$2, non-adherence was not associated with intracranial haemorrhage. Thus, the authors concluded that adherence to therapy appears to be most important in patients with CHA2DS2-VASc score $\geq$2.[34] However, further studies have to evaluate the impact of different NOACs on clinical outcomes.

Conclusion

A q.d. dosing schedule is associated with increased adherence and persistence to cardiovascular therapies. In addition, such feature appears to be responsible for the significantly lower discontinuation of q.d. NOACs compared with b.i.d. NOACs in large, real-world dataset of patients with AF. Although a cause–effect relationship between dosing schedule and adherence and persistence cannot be fully established at present, findings support nonetheless the preferential selection of NOACs with the easiest and most convenient regimen. Thus, maximal effort should be used in implementing measures to enhance patient's adherence to and persistence. Interestingly, simulation of drug exposures indicates that b.i.d. dosing of NOACs could be beneficial for maintaining continuity of drug action when there is variable drug exposure from suboptimal adherence.[6] The b.i.d. dosing regimen might be more forgiving for a missed dose or an extra dose than the q.d. dosing regimen for drugs with a half-life of 12 h. Therefore, q.d. dosing may require more vigilance for single missed or extra doses and thus more intensive management of patient adherence.[6] At this point, it remains unclear whether differences in patient adherence (better adherence in once-a-day vs. twice-a-day regiments) balance the effects on drug concentrations in the case of missed doses (*Figure 2*). It is also unclear whether the underlying pathology of the atria influences the effect of variable NOAC concentration if NOAC doses are missed.[35] Thus, the true effect on clinical outcome needs to be better assessed in once-a-day and twice-a-day regiments in AF patients treated with various NOACs. Nevertheless, several studies support once-a-day and even a single-pill approach, which appears to increase adherence to therapy even more.[36]

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