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Benefits of once-daily dosing with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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Atrial fibrillation (AF) is the most prevalent clinically relevant arrhythmia, affecting millions of individuals in Europe and the USA. Atrial fibrillation increases the risk of stroke; the long-term standard of care for prevention of AF-related stroke is anticoagulation. The use of anticoagulants should be based on the absolute risks of stroke and bleeding and the relative benefit–risk profile of the individual patient. Treatment options include vitamin K antagonists (VKAs) such as warfarin, whose use is long-established but associated with drawbacks, including regular coagulation monitoring requirements and many food and drug interactions. The non-VKA oral anticoagulants are gaining widespread use as alternatives to VKAs, and are supported in treatment guidelines for patients with AF at moderate to high risk of stroke. Adherence to medication is important for the long-term efficacy of any therapy; however, relatively low levels of medication adherence are to be expected in 'real-world' AF patients compared with clinical trials. Experience across several therapy areas, including cardiovascular disease, shows that poor adherence to chronic medication is common. However, simple dosing schedules may be advantageous in this respect, and because long-term outcomes in AF are likely to be influenced by adherence, once-daily dosing has the potential to improve rates of stroke prevention in patients with AF.

Introduction

Atrial fibrillation (AF), the most common of the clinically relevant arrhythmias, affects 1–2% of the general population[1,2]: according to figures for 2010, ~3–6 million people in the USA[3] and ~9 million people (>55 years) in the EU[4] were estimated to have AF. Atrial fibrillation becomes more common with age, affecting ~10% of individuals over the age of 80,[5] and leads to a substantial increase in the risk of stroke.[5–7] Because AF-related stroke is associated with a doubling in mortality rate and an increased risk of severe disability compared with non-AF-related stroke,[8,9] the long-term prevention of AF-related stroke is an important aspect of patient management.

Anticoagulation is the long-term standard of care for preventing AF-related stroke[1,2,10,11] and is highly effective. This article will highlight the advantages of non-vitamin K antagonist oral anticoagulant (NOAC) therapies in patients with AF, and discuss issues surrounding adherence, patient preference, and outcomes with once-daily vs. multiple-daily dosing.

Long-term stroke prevention in patients with atrial fibrillation: balancing benefit and risk

There is a wealth of evidence that anticoagulant therapy reduces the risk of stroke and all-cause mortality.[1,2,10,11] The major concern for clinicians when prescribing

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anticoagulants for patients with AF is the risk of bleeding.[12] Decisions regarding appropriate treatment involve balancing the benefit of preventing stroke against the risk of major bleeding,[12,13] including intracranial haemorrhage, which is difficult to manage and carries a high risk of death and disability. Many patients with AF may be elderly or frail, and these patients are at increased risk of bleeding.[14] A careful evaluation of bleeding risk for the individual patient is needed; in this regard, the HAS-BLED scoring system [which assigns 1 point for each of the following: uncontrolled hypertension (systolic blood pressure >160 mmHg), abnormal renal/liver function (1 point each), stroke history, bleeding history or predisposition, labile international normalized ratio (INR), elderly (age >65 years), drug/alcohol use (1 point each)][15] is a useful tool to assess bleeding risk that has been recommended by a range of AF guidelines, including the Canadian Cardiovascular Society,[16,17] the European Heart Rhythm Association, and the European Society of Cardiology.[2,10,18] A HAS-BLED score of ≥3 indicates high risk of bleeding, for which caution and regular follow-up of patients after the initiation of anticoagulant therapy are needed. It should be noted that, although a patient's risk of bleeding is increased significantly when anticoagulants are administered, the frequency of serious bleeding events is low, and, on balance, the benefit in numbers of AF-related strokes prevented outweighs the increased risk of major bleeding events.[2] Therefore, a score of ≥3 is not a contraindication to anticoagulation. Nevertheless, the selection of an anticoagulant agent should be based on the absolute risks of stroke and bleeding, and the relative benefit–risk for the specific patient.

Interestingly, a recent Japanese study showed considerable divergence of opinion between AF patients and physicians with regard to the relative importance of stroke and bleeding outcomes, and highlighted the need for close communication between physician and patient.[19] For patients, disabling stroke was reported to be 16-times more important than non-major clinically relevant bleeding, and 2.6-times more important than extracranial major bleeding. Conversely, among physicians, disabling stroke was considered to be 2.7-times more important than non-major clinically relevant bleeding, and just as important as major bleeding.

Treatment options

Over the past decades, the vitamin K antagonist (VKA) warfarin, usually taken once daily, has been the established therapy for long-term stroke prevention in patients with AF. Despite their effectiveness, VKAs have several limitations, including an unpredictable pharmacological profile and a narrow therapeutic window, leading to a substantial risk of under- or overtreatment.[20] For this reason, regular coagulation monitoring of the INR, and dose titration, are required to maintain patients within the therapeutic range (INR 2.0–3.0).[12,21] This monitoring is performed either at an anticoagulation clinic or through the use of a home monitoring system, but many patients find this requirement inconvenient,[22] and adherence to therapy can consequently be low. Interactions with food and other drugs are also common and can affect treatment adherence; these issues must be considered when VKAs are administered.[21,23]

Major new developments in therapeutic interventions to reduce the likelihood of an AF-related stroke have occurred in recent years. Non-vitamin K antagonist oral anticoagulants, including dabigatran, rivaroxaban, and apixaban, are alternatives to VKAs and have become widely approved and accessible for patients with non-valvular AF, following the availability of data from phase III clinical trials (RE-LY, ROCKET AF, and ARISTOTLE, respectively) showing these alternatives to be at least non-inferior to warfarin.[24–27] These agents have been shown to be highly effective for stroke prevention in patients with AF while also reducing the risk (compared with warfarin) of serious bleeding events, including intracranial haemorrhage, the risk of which increases linearly with INR levels >3.0.[28] However, it should also be borne in mind that there is increased risk of gastrointestinal bleeding events reported with dabigatran and rivaroxaban vs. standard of care.[29] Data from the ARISTOTLE trial indicated that apixaban had a risk of gastrointestinal bleeding comparable with the standard of care (hazard ratio 0.89, 95% confidence interval 0.70–1.15, $P = 0.37$).[27] Interestingly, results from a non-interventional, observational study of rivaroxaban in >6700 'real-world' patients with non-valvular AF (XANTUS) reported a major gastrointestinal bleeding rate of <1% per year.[30] This low gastrointestinal bleeding rate may reflect the lower risk profile of the XANTUS patient population compared with that in ROCKET AF, and XANTUS is discussed further in the accompanying article.[26,30] Current guidelines support NOACs as the optimal choice for patients with non-valvular AF at moderate to high risk of stroke [e.g. CHA_2DS_2-VASc (which assigns 1 or 2 points for each of the following: congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack (2 points), vascular disease history, age 65–74 years, female sex) score of ≥1].[10,16,17] The NOACs have the advantage that, unlike warfarin, they can be given in fixed doses without the need for routine coagulation monitoring. However, dosing regimens differ among the NOACs. Apart from variations in the actual doses used, rivaroxaban is given once daily, whereas apixaban and dabigatran are administered twice daily.[31–33]

Adherence to long-term therapy

Adherence to medication, defined as the extent to which patients take their medication as recommended by their healthcare provider,[34] is a crucial component of the efficacy of any therapy, especially one used with the aim of improving long-term health outcomes.[10,35,36] Unfortunately, a wealth of data shows that poor adherence is usual in patients on long-term cardiovascular medication, regardless of the type of therapy or population.[35] Even when patients fully appreciate the benefits of therapy, successful adherence is not guaranteed. Dosing frequency, pill size, and forgetfulness are among the reasons for poor adherence, and typical adherence rates for medications can be

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<50%.[36] Although effective within the recommended INR, poor control with warfarin is evident from real-world data, showing that more than two-thirds of patients with high-risk AF on warfarin were outside the therapeutic INR range (i.e. suboptimally anticoagulated) at the time of an acute stroke.[20] For patients taking warfarin, the requirement for clinic visits and INR monitoring is often seen as relatively advantageous for adherence,[35] but many find the need for regular coagulation monitoring inconvenient, and some outpatients fail to attend clinic visits.[37] In addition, INR values can be affected by factors such as food or drug interactions, independent of adherence to the daily dosing regimen.[2]

Although patients in clinical trials of NOACs are generally highly motivated and encouraged to adhere to medication, adherence rates in the real-world setting may be substantially lower.[38,39] In patients with AF who have not experienced symptoms of cerebral ischaemia or a major bleeding episode, and who require anticoagulation indefinitely, ongoing adherence to NOAC therapy will be extremely important to attain good clinical outcomes. Patient preference in treatment and monitoring is an important consideration for success.[40] European Society of Cardiology guidelines from 2012 recommend that, prior to initiating treatment, medication preferences should be discussed with patients with AF who are eligible for anticoagulation therapy.[10] Because long-term outcomes in AF are likely to be influenced by differences in adherence to the different oral anticoagulant (OAC) regimens, it is important to assess preference for, and likely impact on outcomes of, once-daily vs. twice-daily dosing schedules. On this point, recent data from a real-world study suggest that differences in adherence to OACs can be pronounced, even within the bounds of once-daily single-dose schedules: patients with AF taking rivaroxaban had a significantly higher persistence rate (i.e. frequency of requesting repeat medication) over 3- and 6-month periods compared with those on warfarin (84.5 vs. 75.6 and 81.5 vs. 68.3%, respectively; both $P < 0.0001$).[41] In a US retrospective cohort analysis of >32 000 patients with AF treated with rivaroxaban or warfarin, rivaroxaban was also associated with better rate of persistence (i.e. no refill gap of ≥60 days) and a lower rate of discontinuation (i.e. no additional refill for ≥90 days and until end of the follow-up) compared with warfarin.[42] A recent US study has also found that in the first 200 days of OAC therapy in patients with AF ($n = 17\,356$), discontinuation rates with NOACs were lower than with warfarin, and that apixaban demonstrated better continuation rates than either rivaroxaban or dabigatran over this time period.[43]

Once-daily vs. twice- or multiple-daily dosing

As well as patients' appreciation of the risks of inappropriate medication use, a fundamental requirement for adherence to any treatment regimen is an understanding of dosing instructions. Results from a study of patients' interpretation of medication label instructions show that understanding is often flawed; as expected, the highest degree of patient understanding was associated with the simplest regimens.[44] This degree of understanding decreased with the increasing number of doses per day and with the number of medications being taken. In addition, patients tend not to take twice-daily medications at standard intervals, such that the time interval between oral doses can range from 1 to 18 h.[45] For anticoagulation therapy, this has the implication that plasma concentrations may vary considerably over a 24-h period, with many patients having higher peak and lower trough plasma concentrations than those adhering to a standard 12-h interval.[46]

In general, data across many therapeutic areas show that simpler, less-frequent dosing regimens result in better adherence.[47–51] Data from a systematic review of the literature on medication adherence across various disorders found that once-daily dosing showed the highest adherence rates for both 'taking the dose' and 'timing of dosing' compared with multiple dosing (*Table 1*).[47] Overall adherence rates for oral tablets were broadly similar across all therapy areas examined. In a large evaluation of adherence to medications commonly used by patients with cardiovascular disease, a study found that, overall, a once-daily dosing regimen was associated with a significant 16% higher rate of adherence vs. a twice-daily regimen[48] (*Figure 1*). In another similar study, once-daily dosing was shown to result in significantly better adherence than twice-daily dosing across multiple therapies ($P < 0.01$),

Table 1 Medication adherence rate of dose-taking and dose-timing (i.e. taken within the correct time frame over a 24-hour period) across 85 studies in various disorders, by frequency of dosing regimen[47]

Dose frequency	Mean (±SD) dose-taking adherence rate, %	Timing frequency	Mean (±SD) dose-timing adherence rate, %
Once daily	79 (14)[a†‡]	1 dose/24 h	74 (31)
Twice daily	69 (15)[§]	1 dose/12 h	58 (23)
Three-times daily	65 (16)[a]	1 dose/8 h	46 (8)
Four-times daily	51 (20)[§]	1 dose/6 h	40 (–)
Overall	71 (17)		59 (24)

SD, standard deviation.
[a]Differences between once-daily vs. twice-daily, and twice-daily vs. three-times daily regimens were not significant.
[†]$P = 0.008$ vs. three-times daily regimen.
[‡]$P < 0.001$ vs. four-times daily regimen.
[§]$P = 0.001$ for twice-daily vs. four-times daily regimen.

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including antidiabetic, antihyperlipidemic, and antiplatelet agents.[49] This significantly improved adherence to once-daily medication seems to apply regardless of how adherence is calculated; i.e. by 'taking' adherence (bottle cap openings/prescribed doses), regimen adherence (percentage of days with the appropriate number of doses taken), or timing adherence (percentage of near-optimal inter-administration intervals), the latter parameter being the most stringent definition of adherence commonly used.[49] These findings were echoed in another study in which adherence to chronic medication for diabetes mellitus or hypertension in patients with venous thromboembolism was analysed, finding a significant advantage ($P < 0.001$) for adherence to once-daily vs. twice-daily medication over 1 year.[51] Whether assessed by 'medication possession' ratio (number of days for which medication was supplied divided by the total period of treatment exposure) or proportion of days covered, once-daily dosing was associated with an ~39–61% higher likelihood of adherence compared with twice-daily dosing regimens.[51]

Patient preference is an important consideration in the association between improved adherence and less-frequent dosing. The number of medications taken by a patient is known to affect adherence;[52] with regard to AF-specific studies, one patient survey of >1000 patients

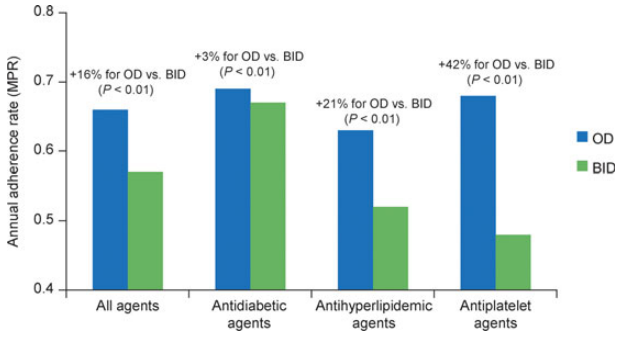

Figure 1 Results from a US study of >1 million cardiovascular patients in 2007, in which 1 440 254 medication claims [once-daily (OD) dosing = 1 384 226; twice-daily (BID) dosing = 56 028] were assessed,[48] showing improved adherence to once-daily vs. twice-daily therapy. MPR, medication possession ratio (no. of days for which medication supplied/365).

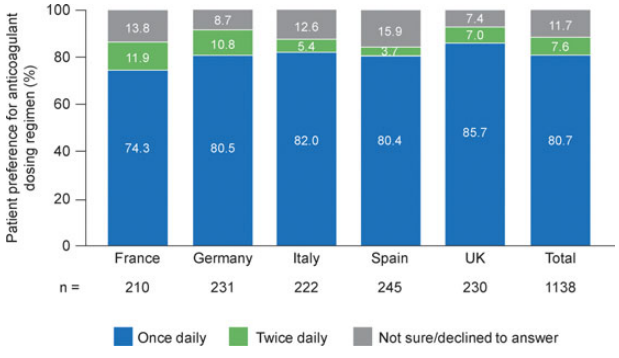

Figure 2 Preference for anticoagulant dosing regimen among respondents receiving medication for atrial fibrillation in the European Patient Survey in Atrial Fibrillation. Overall, the study included 1507 patients (mean age 70.1 years) who were taking a mean of 5.7 medications each.[53]

with AF in five European countries (France, Germany, Italy, Spain, and the UK) who were taking a mean of six prescribed medications each were questioned on their level of satisfaction with their AF management.[40] In Italy, Spain, and the UK, patients were largely in favour of reduced coagulation monitoring (range, 63.8–77.9%), although the proportion in favour of reduced monitoring was not as high in Germany (47.5%) or France (49.0%). A large majority (~81%) expressed a preference for taking anticoagulation medication once daily, compared with only 7.6% who preferred a twice-daily regimen, with some patients reporting that the once-daily regimen made it easier to follow their physician's instructions. This preference for once-daily medication was evident across all of the countries included in the study (*Figure 2*).[53]

German registry data for patients with AF have shown that NOAC therapy is effective and well tolerated, with low rates of cardiovascular or major bleeding events.[54] In this ongoing, prospective registry study, 1665 patients with AF were registered, of whom 967 received rivaroxaban once daily (52% male, mean age 74 years, mean $CHADS_2$ score 2.4, 62% newly anticoagulated) for stroke prevention. The data showed that adherence to once-daily rivaroxaban at 9 months was high (~91%).[54] A subsequent analysis from the same registry reported that 18.5% of 1204 patients with AF had stopped rivaroxaban during a median follow-up period of 544 days, giving a discontinuation rate of only 13.6% (95% confidence interval 11.8–15.4%) per year.[55] The prospective XANTUS study reported a discontinuation rate of 20.1% with rivaroxaban once daily at 1 year of follow-up.[30] However, it should be noted that, in general, adherence to oral medication decreases as the number of daily doses increases,[47] and this, as with the other factors, needs to be taken into consideration when prescribing. Discontinuation of treatment is also a concern because long-term management of stroke risk is dependent on adherence to OAC therapy.[43]

Conclusions

Strict adherence to anticoagulant therapy, including therapy with NOACs, is critical to avoid stroke in patients with AF.[10] Adherence to chronic medication across different therapy areas, including cardiovascular disease, has been found to be improved with once-daily dosing, compared with regimens that require more frequent daily dosing. There are many additional strategies to improve adherence, including patient education and improved communication between healthcare providers and patients, but simple dosing schedules are advantageous for chronic conditions and in polydrug regimens. It is anticipated that, compared with twice-daily dosing, once-daily dosing has the potential to improve adherence to stroke prevention medication in patients with AF. Patient education regarding adherence to treatment needs to be reinforced.

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