New atrial fibrillation guidelines: implementation in the clinic

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Practice Points

- Oral anticoagulant therapy (OAT) is underused in atrial fibrillation (AF) patients, even though an increase has occurred in recent years.
- OAT is not prescribed in accordance with thromboembolic risk AF patients.
- OAT quality is suboptimal, with intensity often outside the target range (International Normalized Ratio: 2.0–3.0).
- OAT discontinuation after starting warfarin for AF is substantial.
- The choice between rhythm control and rate control strategies is not driven by AF symptoms.
- Adherence to guidelines for AF substrate catheter ablation is moderate.

SUMMARY The adherence to guidelines in atrial fibrillation (AF) management is not satisfactory. In particular, oral anticoagulant therapy is underused in AF patients and is not prescribed in accordance with thromboembolic risk. Moreover, the quality of oral anticoagulant therapy is suboptimal, with intensity often outside the target range (International Normalized Ratio: 2.0–3.0) and discontinuation after starting warfarin is substantial. Regarding therapeutic strategies, the choice between rhythm control and rate control is not driven by AF symptoms and the adherence to guidelines for AF substrate catheter ablation is moderate. AF patients are different from AF trial patients, in particular for age and comorbidities. Therefore, it is not surprising that relevant gaps exist between the results of research and their application in clinical practice. Database, registries, comparison among different medical centers and an active involvement of practicing clinicians may play a pivotal role for the assessment of guidelines adherence.

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. The lifetime risk of developing AF in individuals aged 40 years and older is one in four [1] and is associated with substantial mortality and morbidity from stroke and systemic thromboembolism. The prevalence of AF in the USA is approximately 2.2 million individuals; 56–59% for women with a median age of 75 years [2]. In Europe, the prevalence of arrhythmia is approximately 2.8 million cases. As the population aged over 80 years is expected to quadruple over the next few years, the number of subjects with AF will increase exponentially, giving rise to a real pandemic [3].

A recent update of guidelines from the European Society of Cardiology [4] and from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [5] provided recommendations for the management of AF. The guidelines emphasize that AF is a multifaceted disorder with many causes and different clinical manifestations, therefore the treatment target is not straightforward. Treatment strategies for patients with AF are rhythm control and rate control, but regardless of the therapeutic strategy, the first evaluation to be performed is the stratification of patient's thromboembolic risk in order to select appropriate thromboprophylaxis.

In the present paper, we will review the adherence to guidelines in AF management and possible strategies for their implementation in clinical practice.

Adherence to guidelines in AF management

■ Pattern of use of oral anticoagulants

AF is associated with high annual risk of stroke and systemic embolism (4.5%), and it can be paroxysmal, persistent or permanent [6]. Thromboembolic risk is not homogeneous and it is increased by the presence of additional risk factors including prior stroke, or systemic embolism, hypertension, diabetes and increasing age [7]. Notably, annual thromboembolic risk arises in 23.5% of patients aged between 80 and 89 years [8].

Oral anticoagulant therapy (OAT) with dose-adjusted warfarin (International Normalized Ratio [INR] range: 2.0–3.0) is the treatment able to significantly reduce AF thromboembolic risk [9]. Aspirin treatment is associated with a modest reduction of AF stroke risk, predominantly of noncardioembolic stroke.

In the most recent European guidelines, OAT is recommended not only in patients at high risk of stroke (CHA_2DS_2–VASc score ≥2), but also in patients at intermediate risk of stroke (CHA_2DS_2–VASc score = 1) [4].

Despite efficacious OAT [10], AF patients at high risk of stroke are often undertreated and in clinical practice an underutilization of OAT is reported [11]. In particular, only a half of patients affected by AF are effectively treated with OAT, and underuse in the elderly is even higher. In a meta-analysis, which included five studies conducted between 2005 and 2008, only 48% of patients eligible for OAT were treated with warfarin [12]. In the 'real world', the use of warfarin in AF patients decreases with increasing age, demonstrating an 'anticoagulation paradox', because the risk of stroke increases in the elderly [13]. In addition to older age, a history of falls, hemorrhage and cerebrovascular disease have been reported to influence OAT prescribing practices. In such patients, physicians do not generally prescribe OAT, even when no contraindications to anticoagulation therapy are present and even when the patient's risk profile suggests potential benefit from OAT [14]. There is much debate regarding which comorbid conditions should be considered valid contraindications to the use of OAT. Fall-related subdural hematomas and intracranial hemorrhages are extremely rare events. In addition, it has been calculated that patients taking OAT must fall almost daily (~295-times in 1 year) in order to lose the net clinical benefit of OAT [15]. A similar argument can be made about a history of upper gastrointestinal bleeding, which is a relative contraindication that can be eliminated by eradicating *Helicobacter pylori* or prescribing a proton-pump inhibitor. For other possible contraindications, such as alcoholism, bleeding diathesis and noncompliance with monitoring, there is conflicting evidence [16].

In the literature, a lack of correlation between AF patients' thromboembolic risk and OAT prescription is reported. Similar proportions of patients with low, moderate and high stroke risk received warfarin, confirming OAT is underused among patients with high stroke risk, while overused in those with low stroke risk [17]. A recent study reported 53.1% of AF patients with or at high risk of atherothrombosis were treated

with OAT. Even with high $CHADS_2$ scores, anticoagulant use did not exceed 59%. Use of anticoagulants, whether alone or in combination with antiplatelet agents, increased with higher $CHADS_2$ scoring, from 44.7% in $CHADS_2$ score 0 to 60.0% in $CHADS_2$ score 4 patients. Approximately 15% of patients with AF were receiving a combination of antiplatelet and anticoagulant agents, and the proportion was similar across all $CHADS_2$ categories [18].

In a recent Italian study (Antithrombotic Agents in Atrial Fibrillation [ATA-AF]), 7148 patients, referred to 164 cardiology and 196 internal medicine departments for AF, received OAT in 58.8% of cases and antiplatelet therapy in 34.1% of cases, in the absence of correlation with the CHA_2DS_2–VASc score. In this study, the prescription of OAT is influenced by age (66.2% patients aged ≤75 years vs 53.1% patients aged >75 years; $p < 0.0001$), the type of AF (64.3% permanent AF; 69.6% persistent AF and only 37.4% paroxysmal AF; $p < 0.0001$), the therapeutic strategy adopted (63.2% in case of rate–control strategy vs 59.7% in the case of rhythm–control strategy; $p < 0.0001$) and sex (60.7 vs 56.6% males vs females; $p = 0.0003$) [19].

In contrast to guideline recommendations, the literature demonstrates an inadequate quality of anticoagulation in many patients. In addition, implementing monitoring and frequent dose adjustment, patients treated with OAT are outside the therapeutic range for more than a third of the time [20]. An increase of 10% of time outside the therapeutic range results in an increase in mortality by 29%, stroke by 12% and a higher frequency of hospitalizations [21]. Anticoagulation can be considered satisfactory if the time spent in therapeutic range (TTR) is at least 60%, and a recent study has identified predictors of stability of the INR in the therapeutic range include male gender and absence of heart failure and chronic diseases [22]. A recent meta-analysis of efficacy and safety outcomes in patients with AF treated with warfarin for stroke prevention in contemporary randomized controlled trials, showed that overall TTR was 55–68% [9]. Compared with a previous meta-analysis [12], there has been significant improvement in the proportion of TTR, with a resultant decline in observed stroke rates.

In a recent Italian survey, only 47.9 and 56.3% of INR determinations in vitamin K antagonists (VKA) of naive and established patients, respectively, resulted in the recommended range (INR: 2.0–3.0) [23]. Moreover, the percentage of INR determinations below the recommended range was higher than the percentage of INR determinations above the range for both naive and established patients. In addition, in patients with the highest adherence to VKA treatment, only additionally 60% of INR determinations were in the recommended range.

These findings could be attributed to the effects of VKA underdosing owing to an overestimated risk of hemorrhage: physicians estimate intracranial bleeding rate related to the use of warfarin to be ten-times higher than that reported in the literature [24]. A recent systematic review found a strong association between anticoagulation intensity and outcomes. The hemorrhagic risk significantly increased when the INR exceeded three, while the thromboembolic risk was greatest when the INR was below two [25]. When both hemorrhagic and thromboembolic events are considered, the data show that patients were safer with a ratio slightly above, rather than below, the therapeutic range of 2.0–3.0.

Risks of stroke and mortality associated with suboptimal anticoagulation in AF patients is recently reviewed in an English study including 27,458 warfarin-treated patients. Overall, TTR was 63% and this percentage did not vary substantially by age, sex or CHA_2DS_2–VASc score. Patients who spent at least 70% of the time within the therapeutic range had a 79% reduced risk of stroke compared with patients with ≤30% of the time in range. Mortality rates were also significantly lower when at least 70% of the time was spent within the therapeutic range [26].

At a glance, the anticoagulation control in clinical practice settings is still unsatisfactory and it is necessary to evaluate interventions to increase the amount of time at which patients' INR are within the recommended range, because good anticoagulation control is associated with a reduction in the risk of stroke and mortality.

Furthermore, OAT is often interrupted, mostly within 3 months after its initiation. Anticoagulation interruption seems to be correlated with the absence of recurrent AF within 12 months after the first prescription of warfarin [27]. In a recent study, 26% of OAT suspension within 1 year from initiation has been documented, which was independent from bleeding events, observed only in 2.3% of cases.

OAT interruption occurs mainly in patients aged <65 years compared with those aged ≥85 years, patients with poorer anticoagulation control and patients with lower stroke risk according to the $CHADS_2$ score [28]. Few studies have examined factors associated with long-term antithrombotic therapy use in AF patients at high thromboembolic risk (previous stroke/transient ischemic attack). Results of the AVAIL Registry, aimed at the evaluation of persistence of medications in the year after hospital discharge for stroke/transient ischemic attack, have demonstrated a decrease in the rate of warfarin use in AF patients with a $CHADS_2$ score of >3. Notably, 17.8% of patients using warfarin at discharge were taken off warfarin for unknown reasons at 12 months [29]. There are several possible explanations for warfarin discontinuation, initially related to transition of care from hospital admission to discharge, such as clinical inertia, difficulty with INR monitoring or bleeding complications.

New oral anticoagulants

Warfarin management remains problematic due to its complex pharmacokinetic and pharmacodynamic properties and the narrow therapeutic range. VKA's limitations are slow onset and offset of action, multiple drug and food interactions and the requirement of monitoring to maintain the therapeutic range.

The development of new oral anticoagulants have been pursued with the aim of finding effective and safer therapies. Many of the new agents attempt to meet the goals of an ideal anticoagulant by targeting a specific step or factor in the coagulation pathway. Advantages of new oral anticoagulants are rapid onset and offset of action, predictable therapeutic effect with fixed dosing, no food or drug interactions and no monitoring required.

The direct thrombin inhibitor, dabigatran etexilate, and direct factor Xa inhibitors, rivaroxaban and apixaban, have recently been studied in randomized clinical trials and are rapidly becoming approved for AF thromboembolism [30].

The RE-LY trial compared two doses of dabigatran with warfarin in AF patients with one or more stroke risk factors and reported that dabigatran 110 mg two-times a day (b.i.d,) was noninferior to warfarin fro the primary end point of stroke and systemic embolism, with 20% fewer major bleeding events. Dabigatran 150 mg b.i.d. was superior to warfarin for the primary end point of stroke and systemic embolism, with a similar rate of major bleeding [31,32].

The ROCKET-AF trial studied a high-risk population of AF patients and discovered rivaroxaban 20 mg once-daily (15 mg for patients with moderate renal impairment) was noninferior to warfarin for stroke and systemic embolism, with a similar rate of major bleeding [33].

The ARISTOTLE trial reported that apixaban 5 mg b.i.d. (2.5 mg b.i.d. for patients with two of the following criteria: aged >80 years, BMI <60 kg/m^2 and serum creatinine <133 µmol/l) was superior to warfarin by 21% for reducing stroke and systemic embolism, with 31% fewer major bleeding events [34]. A common property of new oral anticoagulants is significantly reduced intracranial bleeding.

Both dabigatran and rivaroxaban already have regulatory approval and a license for stroke prevention in some countries.

In 2012, focused updates of the European Society of Cardiology guidelines in AF patients with a CHA_2DS_2–VASc score of ≥2, OAT with new oral anticoagulants (dabigatran etexilate, rivaroxaban and apixaban) is recommended (class I, level A) as an alternative to dose-adjusted VKA (INR: 2.0–3.0) [4].

Choice between rhythm control & rate control

The AFFIRM [35] and RACE [36] studies showed no clear survival advantage for rhythm control (restoration and maintenance of sinus rhythm) versus rate control (adjustment to a physiological ventricular rate while allowing AF to continue) strategy in AF patients, but the optimal management strategy for AF is still a matter of debate.

Current guidelines recommend rate control as the initial strategy and rhythm control for patients who remain symptomatic [4]. Rhythm control strategy is also reasonable in patients with infrequent and well-tolerated recurrence of AF in the absence of heart disease. Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. In patients with AF rhythm, a control strategy can be useful to prevent tachycardia-induced cardiomyopathy. However, in the real world, there is a significant use of antiarrhythmic drugs despite long-term

safety and tolerability concerns, suggesting that clinical practice does not adhere to current guidelines [37].

In the Euro Heart Survey on AF, a rhythm control strategy was applied to 67% of patients with AF symptoms and to 44% patients without AF symptoms [38]. The German AFNET Registry reported rhythm control therapy in 53% patients with AF symptoms and in 48% patients without AF symptoms [39]. A recent retrospective multicenter study regarding the management of new-onset AF in the emergency department, reported a substantial adherence to the current AF guidelines, but with important differences between different cohorts and multiple hospitals. Rhythm control was used in different proportions ranging from 41 to 60% of AF patients. Despite this strategy, decisions were made considering the symptoms onset (within 48 h) and the type of symptoms [40]. The presence of palpitations and syncope was associated with a rhythm control choice, while dyspnea was associated with a rate control strategy.

AF treatment appeared to be heterogeneous. In particular, the choice between rhythm control and rate control strategies is not driven by AF symptoms.

Recently, antiarrhythmic therapy was reported to have superior efficacy in reducing unplanned cardiovascular (CV) hospitalization, CV mortality and stroke. In addition, there is a growing perception that atrial remodeling could be better prevented by early rhythm control.

Although antiarrhythmic drugs use is associated with a greater incidence of adverse events and treatment discontinuation, a recent meta-analysis confirms their efficacy in preventing AF recurrence [41]. In the meantime, physicians' preference seems to favor the rhythm control strategy.

Use of nonpharmacological treatment

Substrate catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no left atrial enlargement. It is recommended in the presence of paroxysmal/persistent AF, in relatively young patients (age <70 years) with relevant symptoms refractory to pharmacological treatment.

A recent Expert Consensus Statement reported that in symptomatic AF patients refractory or intolerant to at least one class 1 or 3 antiarrhythmic medication, catheter ablation is recommended provided that AF is paroxysmal and reasonable if AF is persistent [42].

In a prospective multicenter Italian survey according to AF guidelines, recommendations for substrate catheter ablation was indicated in approximately 14% of AF patients, but was correctly offered by the attending cardiologist in only 57% cases. Ablation centers prescribed this procedure more frequently than nonablation centers and with a better accordance with guideline indications [43].

The success of AF ablation is variable and there is evidence that it is operator dependent. High success rates and low complication rates are achieved in high-volume, experienced centers [44]. However, the long-term efficacy of this procedure requires further study; this is especially true in patients with persistent, long-standing AF and enlarged atria. In addition, the durability of maintenance of sinus rhythm after ablation in the long term is unknown. Preliminary data suggest that the recurrence rate after the first year is 6–9% per year [45].

A recent meta-analysis indicated that catheter ablation had a better effect in inhibiting recurrence of AF versus medical treatment, but there were no differences in mortality, fatal and nonfatal embolic complications or death from thromboembolic events [46]. There is limited evidence that catheter ablation may be a better treatment option compared with medical therapy in the management of AF.

Strategies for guideline implementation

AF is a very frequent and complex disease, often associated with other medical conditions. Not only the arrhythmia itself, but also the underlying comorbidities determine the patient's long-term prognosis. Physicians' focus on the arrhythmia frequently distracts their attention from the true problems AF patients face, leading to a lack of anticoagulation and heart failure treatment, and futile installment of rhythm control in asymptomatic patients. The Euro Heart Survey on AF demonstrated that adherence to guidelines may reduce morbidity and mortality in AF patients and may also reduce costs [47–49].

Frequently, medical doctors perceive guidelines and recommendations as requirements with scarce knowledge of their scientific background and sometimes suspect involvment of conflicts

of interest. Therefore, it is not surprising that relevant gaps exist between the results of research and their application in practice.

The primary goal remains optimization of the global therapeutic approach to the disease with respect to quality, which in medicine can be defined as how much health services increase the likelihood of desired health outcomes and how closely they adhere to professional knowledge [50].

Randomized clinical trials and outcome studies have provided a basis for informed decisions regarding the use of medical technologies. However, clinical trials cannot answer all questions and many decisions in clinical practice are based on the physician's experience and the individual patient characteristics. Therefore, registries are performed in order to collect data of real-world patients. Multiple practice registries can provide feedback on the performance of individual practices, while also validating the relationship between greater adherence to guidelines and improved patient outcomes. The direct involvement of physicians in the collection of data and the coordinated discussion of results, positive and negative, clear-cut or controversial, are also the most effective and accepted educational tools [51].

International guidelines should be localized in the local reality, as their application also relies on healthcare resource availability. Regarding OAT, for example, in the presence of dedicated centers, such as anticoagulation clinics, the quality of anticoagulation is better than patient self-management [52].

To provide the best care for patients, a model for a basic approach to CV medicine was provided. This model integrates quantitative measurements of quality and performance into the development cycle of existing and future therapeutics [53]. There are six main 'stops' along the cycle, each representing a chance to apply quantitative strategies to integrate quality (Figure 1). In an ideal clinical world, for every clinical decision there would be an indicator based on guidelines based on evidence from randomized trials, such that a standard of care could be defined for each situation.

Conclusion

The adherence to guidelines in AF management is far from being optimal. Although the practice guidelines may provide cultural support for translating the results of clinical research into patient care, their implementation in the clinical arena is a long-lasting process involving practicing physicians, national medical associations and

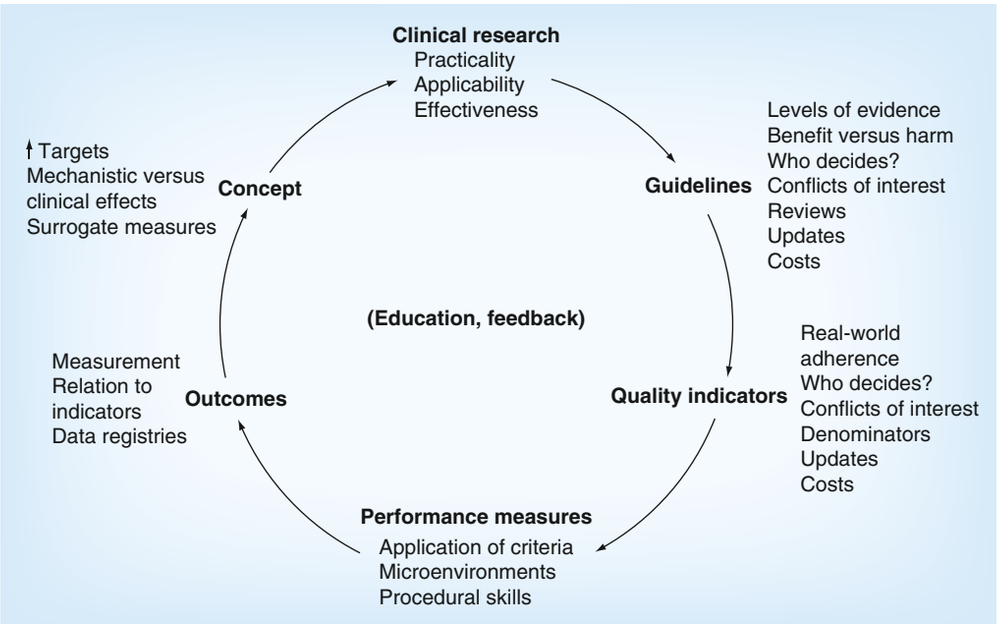

Figure 1. Model for the integration of quality into the therapeutic development cycle.
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healthcare authorities. Database, registries, comparison among different medical centers and an active involvement of practicing clinicians may play a pivotal role for the assessment of guidelines adherence.

Future perspective

With the development and the introduction into clinical practice of new oral anticoagulants warfarin will finally be replaced in a near future, but more importantly anticoagulant undertreatment of atrial fibrillation will be partially overcome and guidelines' adherence will improve.

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■■ **Improves guideline adherence.**