Contemporary Management of Stroke Prevention in Atrial Fibrillation Following the European Society of Cardiology Guidelines

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Abstract

The recent publication of the European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation provides a timely update at a time when the rapid uptake of non-vitamin K antagonist oral anticoagulants has changed the landscape of clinical practice. Several key changes have been highlighted, including better identification of those deemed to be low risk for thromboembolic complications and a more standardised approach to patients with atrial fibrillation who require concomitant antiplatelet therapy following either percutaneous coronary intervention or an acute coronary syndrome. This article distils the key messages from the ESC guidelines and draws the reader's attention to both gaps and advances in our knowledge.

Keywords

Atrial fibrillation, stroke prevention, non-vitamin K antagonist oral anticoagulants, risk-stratification, bleeding risk

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Prevention of ischaemic stroke has long been central to the management of patients with atrial fibrillation (AF), historically relying on the use of vitamin K antagonists (VKAs) or antiplatelet agents depending on the risk of thromboembolism. Difficulties associated with maintaining VKAs in therapeutic range and the perceived risk of bleeding have been highlighted as reasons to withhold oral anticoagulation (OAC) and these issues have partly been addressed by the introduction of non-vitamin K antagonist oral anticoagulants (NOACs). These agents require less intensive monitoring and are generally better tolerated by patients. The 2016 iteration of the European Society of Cardiology (ESC) guidelines for the management of AF provide a contemporary update on stroke prevention in the era of NOAC therapy and present important new recommendations with respect to those deemed to be at low risk of thromboembolic events and also those who require antiplatelet therapy following percutaneous coronary intervention (PCI).¹ At the same time it is important to acknowledge that there are some gaps in our knowledge that are not covered by the guidelines. This brief review presents an assessment of the main recommendations and also highlights areas where further work is needed.

Identifying Those at Risk of Stroke

The guidelines continue to recommend use of the CHA₂DS₂-VASc score as the main risk stratification tool, but the blanket recommendation to initiate OAC in all patients with a score of 2 or more is no longer advocated. Equally, those deemed to be low risk (no clinical risk factors for stroke) should not receive antithrombotic therapy. This therefore recognises that antiplatelet therapy has no role in the prevention of stroke and its use as monotherapy should be actively discouraged. Female gender alone is not deemed to be a risk factor for stroke in the absence of another risk factor. The guidelines acknowledge the relative over-representation of patients at high risk of stroke in the major trials of OAC and stroke prevention. Accordingly, guidance on how to manage patients with one clinical risk factor (i.e. men with a

score of 1 and women with a score of 2) is given more nuance. The ESC commissioned an analysis of stroke risk in this group to inform their recommendations and identified the importance of age as a risk factor. Age (>65 years) conveys a relatively high and continuously increasing stroke risk that also potentiates other risk factors (such as heart failure and sex). It is therefore recommended that risk in this group should entail an individualised weighing of risk as well as patient preference. Looking to the future, newer risk scoring systems may provide better identification of the truly low-risk group (who do not require anticoagulation). Data from nearly 40,000 patients enrolled in the Global Anticoagulant Registry In The Field-Atrial Fibrillation (GARFIELD-AF) registry has been used to develop risk models and the resulting GARFIELD-AF score appears to offer better discrimination in predicting all-cause mortality, ischaemic stroke/systemic embolism, or haemorrhagic stroke/major bleed in low-risk patients and may provide more detailed risk estimation pending external validation.²

Addressing Bleeding Risk

Another important aspect of clinical care described in the guidelines is bleeding risk. Several bleeding risk scores have been proposed, including the HAS-BLED (hypertension, abnormal renal/liver function [1 point each] stroke, bleeding history or predisposition, labile international normalised ratio, elderly [>65 years], drugs/alcohol concomitantly [1 point each]), ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), or the more recent ABC (age, biomarkers, clinical history) bleeding scores. No single scoring system is favoured over the others, but the emphasis is now to generally refrain from withholding OAC, rather bleeding risk factors should be identified and treatable factors corrected. This is an important point, as the perceived risk of bleeding can often be erroneously elevated and is in fact often outweighed by the risk of ischaemic stroke in most cases.

VKA or NOAC?

VKAs are effective but efficacy depends on adequate time in therapeutic range. Clearly, VKAs are the only option for AF patients with mechanical valve prostheses or rheumatic mitral stenosis that is more than mild in severity. Outside this specific group, the need for intensive monitoring makes them slightly cumbersome for patients and clinicians alike. Data from the GARFIELD-AF registry indicate that there has been an increase in newly diagnosed patients with AF receiving guideline-recommended therapy since NOACs were introduced.³ This is predominantly driven by the increased use of NOACs and reduced use of VKAs. This is not a universal phenomenon, and the second phase of the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation (GLORIA-AF) demonstrates that a large proportion of patients remain undertreated, particularly in Asia and north America.⁴

There is also a safety argument for the use of NOACs over VKAs as there appears to be less haemorrhagic stroke with NOACs and this is reflected in the guideline recommendation that NOACs should be the first-choice agent in most patients. At the current time, there is not enough evidence to recommend one particular NOAC over the others and the decision on which agent to use is best taken after accounting for individual patient characteristics. Specific attention should be paid to patients with chronic kidney disease (CKD). Both VKAs and NOACs are effective in patients with mild–moderate CKD (creatinine clearance >30 mL/min) but none of the major NOAC trials included patients with severe CKD. If used, NOACs should be subject to dose adjustment (reduction) when administered to patients with mild–moderate CKD and dabigatran should not be used in patients with creatinine clearance <30 mL/min. The benefit of OAC in dialysis-dependent patients is debatable, with conflicting evidence from large observational studies. The association of AF with higher mortality in these patients is important and randomised trials of OACs versus placebo are urgently required.

OACs in Combination with Antiplatelet Agents

It is estimated that 5–15 % of AF patients will require PCI at some point in their lives. The accompanying need to administer antiplatelet therapy and the recognition that so-called triple therapy (VKA plus dual anti-platelet therapy) is associated with high rates of bleeding complications has led to widespread variation of practice. This most often manifests as eligible AF patients being less likely to receive OACs following PCI. The introduction of NOACs has further complicated the issue. A meta-analysis involving more than 30,000 patients with recent acute coronary syndrome (ACS) evaluated the effects of adding NOAC therapy to single or dual antiplatelet therapy. Bleeding risk increased

by 79–134 % with only a marginal decrease in ischaemic events in patients without AF.⁵ The guidelines adopt a pragmatic approach and place the emphasis on limiting the duration of triple therapy (OAC, aspirin, clopidogrel). In general, a short period of triple therapy is recommended, followed by a period of dual therapy (OAC plus single antiplatelet). A key recommendation is that most AF patients with stable coronary artery disease who are >1 year post PCI or ACS should continue OAC as monotherapy (without any antiplatelet agent). The guidelines expressly advise against using dual antiplatelets (aspirin and clopidogrel) with a low dose of the NOAC rivaroxaban (2.5 mg twice daily) as there are concerns that this does not offer sufficient stroke prevention. Recent publication of the Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose Adjusted Oral Vitamin K Antagonist Treatment Strategy in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) has demonstrated that triple therapy with VKA, aspirin and clopidogrel is associated with significantly higher rates of bleeding when compared with reduced-dose rivaroxaban (15 mg once daily) with a single antiplatelet agent or low-dose rivaroxaban (2.5 mg twice daily) with aspirin and clopidogrel. Crucially, there was no difference in ischaemic or thromboembolic events between the three arms.⁶ The study was powered for safety (bleeding risk) and not efficacy but it represents the best data available given the fact that an appropriately powered efficacy study would require an unfeasible 30,000 patients to be recruited. There is a move towards adopting the low-dose rivaroxaban plus a dual antiplatelet regimen for a limited period (3–6 months) before stepping down to an OAC and single antiplatelet and then finally OAC monotherapy at 1 year. Similar studies involving the other NOACs are on-going and will provide further information in this area.

Conclusion

The updated ESC guidelines for AF management provide contemporary guidance in the NOAC era. There are still gaps in our knowledge, particularly when trying to identify the truly low-risk groups who do not require anticoagulation. Large-scale ‘real-world’ initiatives such as the GARFIELD-AF registry will provide more detailed scoring systems that are likely to supersede the widely recommended CHA₂DS₂-VASC risk stratification tool and these should help better identify these patients. Similarly, determining the optimal stroke prevention strategy in patients with severe kidney disease should be a priority as there is a compelling association between AF and morbidity in these patients. Finally, the evidence base has begun to overtake the recommendations (as we have seen with the PIONEER AF-PCI study) and it is important that clinicians acknowledge the fluid nature of clinical medicine and do not treat the guidelines as dogma. ■

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