Guidelines—Special issue: Atrial Fibrillation

Summary of the 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: Prepared by the Czech Society of Cardiology

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Introduction

Guidelines summarise and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition. Since August 2010, when ESC guidelines for the management of atrial fibrillation (AF) were published, European regulatory approvals of several new drugs were announced, reports from major clinical trials of the novel oral anticoagulants revealed, and one antiarrhythmic drug study was early discontinued. Therefore, an update of the ESC guidelines was prepared. It is not intended as a comprehensive new guideline. This article is the summary of an update to the 2010 ESC Guidelines.

The prevalence of (AF) in developed countries is now estimated to be 1.5–2% of the general population. Many episodes of AF are silent. Diagnosis of AF before the complications occur is important. Recent data collected in patients with implanted devices reinforced the assumption that even short episodes of silent AF convey an increased risk of stroke. Therefore it is recommended that in patients aged 65 years or over, screening for AF by pulse palpation, followed by recording of an ECG to verify diagnosis, should be considered.

2. Stroke and bleeding risk assessment

The term valvar AF is used to imply that AF is related to rheumatic valvar disease (predominantly mitral stenosis) or prosthetic heart valves. Stroke risk stratification proposed in that guideline is more focused on the identification of ‘truly low-risk’ patients who do not need any antithrombotic therapy, and more evidence on the use of novel oral anticoagulants (NOACs; see below) as alternatives to dose-adjusted vitamin K antagonist (VKA) therapy [e.g. warfarin, international normalised ratio (INR) 2.0–3.0].

Given the availability of NOACs, the use of antiplatelet therapy (such as aspirin–clopidogrel combination therapy, or – less effectively – aspirin monotherapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC. There is no evidence for the decrease in total or cardiovascular mortality with aspirin (or antiplatelet drugs) in the AF population. Patients with AF who have stroke risk factor(s) ≥1 are recommended to receive effective stroke prevention therapy, which is essentially OAC with either well-controlled VKA therapy [INR 2–3, with a high percentage of time in the therapeutic range (TTR), for example, at least 70%] or one of the NOACs.

Whilst the CHADS2 [Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)] score is simple, most now agree that it does not include many common stroke risk factors and its limitations have been highlighted. For example, vascular disease (not included in the CHADS2 score) is an independent risk factor for stroke in AF and significantly improves the predictive ability of CHADS2. Many patients classified as ‘low-risk’ using CHADS2 (score=0) have stroke rates 1.5%/year, and a CHADS2 score of 0 does not reliably identify AF patients who are ‘truly-low-risk’.

The 2010 ESC Guidelines on AF de-emphasised the use of the artificial low-, moderate-, and high-risk strata and recommended a risk factor-based approach defining ‘major’ and ‘clinically relevant non-major’ risk factors, which can be expressed as an acronym, CHA2DS2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled]—Vascular disease, Age 65–74, and Sex category [female]).

Antithrombotic therapy is not recommended in patients with AF (irrespective of gender) who are ‘aged <65 and lone AF’ (i.e. truly ‘low-risk’), as the latter have very low absolute event rates.

The CHA2DS2\textsubscript{VASc} score is inclusive of the most common stroke risk factors in everyday clinical practice. Contrary to older, conflicting (and weak) data, thyroid disease (or hyperthyroidism) is not considered to be an independent stroke risk factor on multivariable analysis. A history of ‘any heart failure’ per se is not consistently defined as a risk factor, and the ‘C’ in CHA2\textsubscript{DS2-VASc} refers to documented moderate-to-severe systolic dysfunction [i.e. heart failure with reduced ejection fraction (HF-REF)] or patients with recent decompensated heart failure requiring hospitalisation, irrespective of ejection fraction [i.e. both HF-REF and heart failure with preserved ejection fraction (HF-PEF)].

Female gender independently increases the risk of stroke overall, unless the criterion of ‘age <65 and lone AF’ is clearly fulfilled, whereby female gender does not independently increase stroke risk. Stroke rates in patients with the criterion of ‘age <65 and lone AF’ are so low in both males and females that antithrombotic therapy is not recommended. Thus, female patients with gender alone as a single risk factor would not need anticoagulation. CHA2\textsubscript{DS2-VASc} refines stroke risk assessment in ‘low-risk’ AF patients after ablation.
AF patients with severe renal failure are at high risk for stroke, but are also at increased risk for death, coronary events and serious bleeding. These patients have not been adequately studied and have been excluded from clinical trials, and their risk assessment is complex.

Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially ICH, which is the most feared complication of anticoagulation therapy and confers a high risk of death and disability. The 2010 ESC Guidelines on AF recommended use of the simple bleeding risk assessment score, HAS-BLED. The HAS-BLED score highlights risk factors that can be actively managed to reduce the bleeding risk. The HAS-BLED score has been validated in several independent cohorts, and correlates well with ICH risk. It is noteworthy that the ICH (and major bleeding) rate in patients on aspirin, for a given HAS-BLED score, was similar to that for those taking warfarin.

Thus, a formal bleeding risk assessment is recommended for all patients with AF, and in patients with a HAS-BLED score ≥ 3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding. The HAS-BLED score per se should not be used to exclude patients from OAC therapy but allows clinicians to make an informed assessment of bleeding risk (rather than relying on guesswork) and, importantly, makes them think of the correctable risk factors for bleeding: for example, uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory factors for bleeding: for example, uncontrolled blood pressure, and, importantly, makes them think of the correctable risk assessment of bleeding risk (rather than relying on guesswork) from OAC therapy but allows clinicians to make an informed HAS-BLED score per se should not be used to exclude patients caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding. The HAS-BLED score per se should not be used to exclude patients from OAC therapy but allows clinicians to make an informed assessment of bleeding risk (rather than relying on guesswork) and, importantly, makes them think of the correctable risk factors for bleeding: for example, uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), labile INRs, etc. Use of the CHA2DS2-VASc and HAS-BLED scores to aid practical decision-making for thromboprophylaxis in non-valvular AF has recently been reviewed.

In the net clinical benefit analysis-balancing ischaemic stroke against intracranial bleeding-by Olesen et al. those patients with a high HAS-BLED score had an even greater net clinical benefit with warfarin, given that the higher-risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events.

Additional evidence emphasises that stroke prevention with a VKA is effective where the individual mean time in therapeutic range (TTR) is good; for example 70%. Thus, where a VKA is used, efforts to improve quality of INR control are needed in order to achieve high TTRs.

3. Novel oral anticoagulants

The NOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (e.g. dabigatran) and oral direct factor Xa inhibitors (e.g. rivaroxaban, apixaban, etc.). In contrast to VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in coagulation. Another oral factor Xa inhibitor with an ongoing, large phase III trial is edoxaban; this will probably be reported in 2013.

3.1. Practical considerations

The NOACs so far tested in clinical trials have all shown noninferiority compared with VKAs, with better safety, consistently limiting the number of ICH. On this basis, this guideline now recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF, when used as studied in the clinical trials performed so far. Since there is still limited experience with these agents, strict adherence to approved indications and careful post-marketing surveillance are strongly recommended.

In the absence of head-to-head trials, it is inappropriate to be definitive on which of the NOACs is best, given the heterogeneity of the different trials. Indirect comparison analyses do not suggest profound differences in efficacy endpoints between the NOACs, but major bleeding appears lower with dabigatran 110 mg b.i.d. and apixaban. Patient characteristics, drug tolerability, and cost may be important considerations. Some costeffectiveness data for dabigatran have been published in various healthcare settings, and dabigatran appears to be cost-effective for most patients, except in those with very well-controlled INRs. None of the novel OACs has a specific antidote.

The net clinical benefit of VKAs, balancing ischaemic stroke against ICH in patients with non-valvular AF, has been modelled on to stroke and bleeding rates from the Danish nationwide cohort study for dabigatran, rivaroxaban, and apixaban, on the basis of recent clinical trial outcome data for these NOACs. At a CHA2DS2-VASc score of 1, apixaban and both doses of dabigatran (110 mg b.i.d. and 150 mg b.i.d.) had a positive net clinical benefit while, in patients with CHA2DS2-VASc score ≥ 2, all three NOACs were superior to warfarin, with a positive net clinical benefit, irrespective of bleeding risk. When switching from a VKA to a NOAC, the INR should be allowed to fall to about 2.0 before starting the NOAC, all of which have rapid onset of anticoagulation effect. When changing from a NOAC to a VKA, overlap with VKA for 2–3 days is necessary, as VKAs would take a few days to achieve therapeutic anticoagulation.

Compliance and adherence to treatment is crucial, especially since these drugs have a relatively short half-life, such that patients would be left without any anticoagulation protection if more than one dose were missed. Renal function should be assessed annually in patients with normal (CrCl ≥ 80 mL/min) or mild (CrCl 50–79 mL/min) renal impairment, and perhaps 2–3 times per year in patients with moderate (i.e. creatinine clearance 30–49 mL/min) renal impairment. Dabigatran may also cause dyspepsia, which may perhaps be ameliorated by taking the drug with food or the use of a proton pump inhibitor.

The NOACs do not require dose adjustment on the basis of a specific coagulation test (in contrast to the INR for VKAs). There are non-specific coagulation tests that can be used to check for the presence of an anticoagulation effect (rather than anticoagulation intensity per se). These should not be used for dose adjustment. For dabigatran, the ecarin clotting time and thrombin clotting time are useful tests, and directly reflect thrombin inhibition however, an activated partial thromboplastin time (aPTT) can also be used (especially in an emergency setting), although the correlation is not linear, particularly at higher concentrations. Rivaroxaban prolongs the prothrombin time (PT) and this might be used as a rough estimate of an anticoagulation effect. A better estimate for an anticoagulant effect for the oral Factor Xa inhibitors is an anti-Xa assay.
<table>
<thead>
<tr>
<th>Recommendations for prevention of thromboembolism in non-valvular AF—general</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged &lt;65 years and lone AF), or with contraindications.</td>
<td>I</td>
<td>A</td>
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<tr>
<td>The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>The CHA₂DS₂-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with a CHA₂DS₂-VASc score of 0 (i.e., aged &lt;65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with a CHA₂DS₂-VASc score ≥2, OAC therapy with:</td>
<td>I</td>
<td>A</td>
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<tr>
<td>• adjusted-dose VKA (INR 2–3); or</td>
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<tr>
<td>• a direct thrombin inhibitor (dabigatran); or</td>
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<tr>
<td>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)*</td>
<td></td>
<td></td>
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<tr>
<td>… is recommended, unless contraindicated.</td>
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<tr>
<td>In patients with a CHA₂DS₂-VASc score of 1, OAC therapy with</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>• adjusted-dose VKA (INR 2–3); or</td>
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<tr>
<td>• a direct thrombin inhibitor (dabigatran); or</td>
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<tr>
<td>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)*</td>
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<tr>
<td>… should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.</td>
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<tr>
<td>Female patients who are aged &lt;65 and have lone AF (but still have a CHA₂DS₂-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively— aspirin 75–125 mg daily.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations for prevention of thromboembolism in non-valvular AF—NOACs</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:</td>
<td>I</td>
<td>B</td>
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<tr>
<td>• a direct thrombin inhibitor (dabigatran); or</td>
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<tr>
<td>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)*</td>
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<tr>
<td>… is recommended.</td>
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<tr>
<td>Where OAC is recommended, one of the NOACs, either:</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>• a direct thrombin inhibitor (dabigatran);</td>
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<tr>
<td>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)*</td>
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<tr>
<td>… should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.</td>
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<tr>
<td>Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in:</td>
<td>IIa</td>
<td>B</td>
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<tr>
<td>• elderly patients, age ≥ 80</td>
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<tr>
<td>• concomitant use of interacting drugs (e.g. verapamil)</td>
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<tr>
<td>• high bleeding risk (HAS-BLED score ≥3)</td>
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<td></td>
</tr>
<tr>
<td>• moderate renal impairment (CrCl 30–49 mL/min).</td>
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<tr>
<td>Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in:</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>• high bleeding risk (HAS-BLED score ≥3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• moderate renal impairment (CrCl 30–49 mL/min).</td>
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<tr>
<td>Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl &lt;30 mL/min).</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
These novel drugs do not have specific antidotes and management of bleeding is thus largely supportive, given that these drugs have a relatively short (5–17 h) half-life. One small study suggested normalisation of coagulation tests with nonactivated prothrombin complex concentrate COFACT (Sanquin Blood Supply, Amsterdam, the Netherlands) administered to healthy and relatively young individuals taking rivaroxaban, but no effect was seen with dabigatran. Another study found that low-dose FEIBA (Baxter AG, Vienna, Austria) reversed the anticoagulant activity of rivaroxaban and dabigatran.

Perioperative management is another important consideration. Given the rapid onset and offset of action of dabigatran etexilate, no bridging therapy with low molecular weight heparin (LMWH) is required for the majority of interventions. Following surgery, NOACs can be restarted as soon as effective haemostasis has been achieved. The available data suggest that elective cardioversion can be safely performed on dabigatran, with the requirement for 3 weeks of therapeutic anticoagulation pre-cardioversion and 4 weeks post-cardioversion. Drug compliance is crucial for the anticoagulation period peri-cardioversion as, unlike the INR for VKAs, there is no easy means to assess therapeutic anticoagulation. No published data on cardioversion with rivaroxaban or apixaban are yet available.

Data from limited case series suggest that appropriate post-ablation management with dabigatran is associated with a low risk of embolic or bleeding complications, although brief interruption of dabigatran use is associated with more thromboembolic and bleeding complications. Patients taking the NOACs may present with an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). Concomitant use of antiplatelet therapy with the NOACs significantly increases bleeding risk, as is the case with combining any OAC with antiplatelet therapy.

The only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited. Patients with AF and stable vascular disease (i.e., no acute events or revascularization for >12 month whether coronary or peripheral artery disease) can be managed with NOAC alone, whether as adjusted dose VKA therapy, or probably a NOAC. In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious haemorrhage, including intracranial haemorrhage.

Patients taking the NOACs may also present with an acute ischaemic stroke. If the aPTT is prolonged in a patient taking dabigatran (or the PT with rivaroxaban), it should be assumed that the patient is anticoagulated, and thrombolysis should not be administered. Given that dabigatran 150 mg b.i.d. did result in a significant reduction in both ischaemic and haemorrhagic stroke, should the acute ischaemic stroke occur whilst the patient is taking rivaroxaban or apixaban (neither of which significantly reduced ischaemic stroke, compared with warfarin, in their respective trials), the clinician may consider the use of dabigatran 150 mg b.i.d. instead. Algorithms illustrating the choice of antithrombotic therapy and the management of bleeding in patients on NOACs in patients with AF are shown in Figs. 1 and 2. Although NOACs may be preferred on the basis of clinical trial data clinicians should remain aware that clinical experience with these agents is still limited and that care, vigilance and further information on their effectiveness in clinical practice are needed.

Key points

- The efficacy of stroke prevention with aspirin is weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.
- The use of antiplatelet therapy (aspirin–clopidogrel combination therapy or – less effectively – aspirin monotherapy for those who cannot tolerate aspirin—clopidogrel

<table>
<thead>
<tr>
<th>Recommendations for prevention of thromboembolism in non-valvular AF—bleeding</th>
<th>Class</th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates high risk and same caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A).</td>
<td>IIa</td>
<td>A B</td>
</tr>
<tr>
<td>Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, stable INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B).</td>
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<tr>
<td>Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, and should not be used on its own to exclude patients from OAC therapy (LoE = B).</td>
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</tr>
<tr>
<td>The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.</td>
<td>IIa</td>
<td>B</td>
</tr>
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<thead>
<tr>
<th>Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion</th>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td>For patients with AF of ≤48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/ i.v. pharmacological).</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.</td>
<td>I</td>
<td>B</td>
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</table>
combination therapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.

- The CHA2DS2-VASc score is better at identifying ‘truly low-risk’ patients with AF and as good as – and possibly better than – scores such as CHADS2 in identifying patients who develop stroke and thromboembolism.

- The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk and, importantly, makes them think of the correctable risk factors for bleeding. In patients with a HAS-BLED score ≥3, caution and regular review are recommended, as well as efforts to correct the potentially reversible risk factors for bleeding. A high HAS-BLED score per se should not be used to exclude patients from OAC therapy.

4. **Left atrial appendage closure**

The left atrial appendage (LAA) is considered the main (but not the only) site of thrombus formation inducing ischaemic stroke in patients suffering from AF. Trans-oesophageal echocardiography detects most thrombi in the LAA and low stroke rates are reported in patients in whom the LAA has been surgically removed. Surgical exciton or stapling of the...
LAA is widely performed as a concomitant procedure during open heart surgery. More recently, minimally invasive epicardial techniques and interventional trans-septal or also epicardial techniques have been developed for occlusion of the LAA orifice to reduce the stroke risk.

Although clinically applied for decades, there is no conclusive evidence that surgical LAA excision or occlusion reduces stroke risk in AF patients. There are no large, controlled trials with systematic follow-up. Furthermore, some data to suggest that not all strokes in AF patients are cardio-embolic or due to AF, and the LAA is probably not the only left atrial region where thrombi can potentially originate. This suggests that there may be a need for antithrombotic therapy in AF patients, even after removal or closure of the LAA.

Data from retrospective or observational studies in different patient populations have shown inconsistent results of surgical LAA excision or occlusion. In addition, no conclusive data are available on the best surgical technique for performing LAA closure. Risks of surgical LAA excision include major bleeding and incomplete LAA occlusion with residual stroke risk. Non-randomized observational studies, involving relatively small numbers of patients, have shown the feasibility of percutaneous LAA occlusion. Currently, two self-expanding devices, the WATCHMAN (Boston Scientific, Natick, MA, USA) and the Amplatzer Cardiac Plug (St. Jude Medical, St. Paul, MN, USA), are available for clinical use in Europe.

The WATCHMAN LAA system for embolic PROTECTION in patients with Atrial Fibrillation (PROTECT AF) trial randomized 707 eligible patients either to percutaneous closure of the LAA, using the WATCHMAN device, or to OAC (INR range 2–3). The primary efficacy event rate (composite endpoint of stroke, cardiovascular death, and systemic embolism) in the LAA occlusion group was non-inferior to patients treated with OAC. There was a high rate of adverse events in the intervention group, mainly due to peri-procedural complications. Many of the adverse events in the intervention group occurred early in the trial, indicative of an learning curve. A second randomized trial, PREVAIL, is currently enrolling patients. In a feasibility and safety study, LAA occlusion with the Amplatzer Cardiac Plug was attempted in 137 of 143 patients, and was successfully performed in 96% of patients. A randomized prospective study with the device is currently under way (Amplatzer Cardiac Plug Trial).

Although the concept of LAA closure seems reasonable, the evidence of efficacy and safety is currently insufficient to recommend these approaches for any patients other than those in whom long-term OAC is ineffective or contraindicated. At present, LAA closure is not indicated simply as an alternative to OAC therapy to reduce stroke risk. If the efficiency of LAA closure will be conclusively shown in the future, it could potentially replace long-term OAC. However, other studies comparing interventional/percutaneous/surgical LAA closure with NOAC drugs will be needed.

### 5. Cardioversion with pharmacological agents

Since the last ESC guidelines, a new intravenous antiarrhythmic agent, vernakalant, has been approved for pharmacological cardioversion.

Vernakalant acts preferentially in the atria by blocking several ion channels, resulting in prolongation of atrial refractoriness and rate-dependent slowing of atrial conduction, but has little impact on currents involved in ventricular depolarisation. Vernakalant has rapid onset of action and mean elimination half-life of 3–5 h.

**Key points:**

- Vernakalant is effective in cardioversion of patients with AF≤7 days or ≤3 days after cardiac surgery and provides a rapid antiarrhythmic effect with approximately 50% of patients converting within 90 min after the start of treatment and median time to conversion of 8–14 min.
- Vernakalant is administered as a 10 min infusion of 3 mg/kg and, if AF persists after 15 min, a second infusion of 2 mg/kg can be given.
- Vernakalant has a satisfactory safety profile in patients with minimal to moderate heart disease, including ischaemic heart disease, but should be used with caution in haemodynamically stable patients with NYHA class I and II heart failure, because of increased risk of hypotension and non-sustained ventricular arrhythmias in these patients.
- Vernakalant is contraindicated in patients with hypotension <100 mmHg, recent acute coronary syndrome (<30 days), NYHA class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (QT >440 ms).

The integration of vernakalant into the general schema for pharmacological and electrical cardioversion is shown in Fig. 3.

### 6. Oral antiarrhythmic drug therapy

#### 6.1. Upstream therapy

All of the recent placebo-controlled, double blind trials with angiotensin-receptors blockers (ARBs) and the majority of trials with polyunsaturated fatty acids failed to show convincing results. There is very little reason to consider the use of such therapy for the prevention of AF in patients with little or no underlying heart disease. It may be justified to co-prescribe an ARB or an angiotensin-converting enzyme inhibitor with an antiarrhythmic drug to increase the likelihood of maintaining sinus rhythm after cardioversion.

#### 6.2. Principles of antiarrhythmic drug therapy

Oral antiarrhythmic drug therapy can be considered for the treatment of recurrent AF. It is important to emphasise that antiarrhythmic drug therapy should only be offered to control resistant symptoms due to recurrent AF and that a safety-first principle should prevail.

Antiarrhythmic drug therapy for AF has generally been given as long-term therapy. The short-term antiarrhythmic drug therapy (4 weeks) after cardioversion should not be the default type of treatment and should not be considered with amiodarone, but may be useful in patients who are either at
high risk for drug-induced adverse effects or for patients with infrequent recurrences of AF.

6.3. Update on dronedarone

As a consequence of the PALLAS (Permanent Atrial fibrillation outcome Study) trial (prematurely stopped due to an increase in cardiovascular events including cardiovascular mortality in the dronedarone arm), patients with permanent AF should not be treated with dronedarone, particularly those with a significant cardiovascular disease burden. The drug can still be used in patients with paroxysmal or persistent AF and less severe heart failure (NYHA class I–II) if there is no suitable alternative.

There was a signal in the PALLAS trial that dronedarone was associated with increased sudden mortality in patients on concomitant digoxin therapy, hence the combined use of these two drugs is discouraged. Dronedarone has also been associated with severe hepatotoxicity in a few instances. Hence, monitoring of liver function tests is advisable in patients on long term dronedarone treatment. Since dronedarone is a P-glycoprotein inhibitor, it increases plasma concentrations of dabigatran; therefore concomitant use of the two drugs has to be avoided.

Key points:

- Rhythm-control therapy is indicated to relieve symptoms associated with AF.
- Antiarrhythmic drugs should not be used for rate control in patients with permanent AF, unless appropriate rate control agents fail.
- In selected patients, limiting antiarrhythmic drug therapy to 4 weeks after cardioversion may help to improve safety.
- The choice of an antiarrhythmic drug should be driven by perceived safety of the drug, this is more important than perceived efficacy.
- Dronedarone is appropriate for maintaining sinus rhythm in patients with paroxysmal or persistent AF.
- Dronedarone should not be given to patients with moderate or severe heart failure, and should be avoided in patients with less-severe heart failure, if appropriate alternatives exist.

The current choice of antiarrhythmic drugs related to underlying pathophysiology is illustrated in Fig. 4.
7. Catheter ablation of atrial fibrillation

7.1. New evidence for catheter ablation

Since the publication of the ESC AF Guidelines in 2010, several new sets of data have become available.

These data further support the 2010 recommendation that it is reasonable to recommend catheter ablation as first-line therapy for AF rhythm control in selected patients, i.e. those with paroxysmal AF preferring interventional treatment with a low risk profile. Other reports also report that catheter ablation is more effective than antiarrhythmic drug therapy for the maintenance of sinus rhythm in patients with AF, mostly in patients without marked structural heart disease. While catheter ablation is more effective than antiarrhythmic drugs, the number of AF recurrences during the long-term follow-up seems to be significant. The most important predictor for such late recurrence appears to be early recurrence of AF after the ablation procedure. A low rate of recurrences, which may be due to progression of atrial damage, continues to add up to relevant, long-term recurrence rates.

Catheter ablation of AF conveys a relevant risk of major complications. This is illustrated by the recent publication of the pilot survey of AF ablation within the EURObservational Research Programme, which included also five Czech centers.

In this survey, which reported the outcome of more than 1000 ablation procedures carried out in high-volume centres throughout Europe, acute severe complication rates were 0.6% for stroke, 1.3% for tamponade, 1.3% for peripheral vascular complications, and around 2% for pericarditis. In a very recent medical database analysis in 4156 patients who underwent their initial ablation between 2005 and 2008, the complication rate was 5% and the rate of all-cause hospitalisation in the first year after catheter ablation was 38.5%. Furthermore, some reports suggest that silent cerebral infarctions, detectable by cerebral magnetic resonance imaging, may be induced by catheter ablation procedures. The clinical significance of this silent cerebral infarction is unclear, but these risks need to be carefully considered, when selecting an ablation tool or technology.

7.2. Catheter ablation in patients with heart failure

The recommendations for antiarrhythmic drug therapy leave amiodarone as the only available antiarrhythmic agent in patients with severe heart failure. In patients who suffer from symptomatic AF recurrences on amiodarone therapy, catheter ablation remains as the sole choice for escalated rhythm control therapy.

The likelihood of maintaining sinus rhythm after ablation is lower and the procedure-related risks may be higher in heart failure patients.
7.3. **Anticoagulant therapy peri-ablation**

There is consensus that OAC is helpful to prevent thromboembolic complications around ablation procedures. Several reports suggest that catheter ablation of AF may be performed with fewer complications when OAC therapy is continued (usually VKA). These reports also conclude that continuous OAC is safe during ablation. At present, for patients on OAC with VKA, we therefore recommend undertaking catheter ablation of AF on continuous anticoagulation. Anticoagulant therapy should be kept at low therapeutic levels (such as an INR of 2 to 2.5) throughout ablation.

Experience with NOACs is limited. Initial reports suggest that the stroke risk may be slightly increased.

Exact relative risk of uninterrupted OAC with NOACs peri-ablation is not known. For patients taken off OAC before the ablation procedure, initiation of anticoagulation with NOAC shortly after the ablation procedure seems to be reasonable.

7.4. **Safety first**

Improving safety of catheter ablation should be a primary goal in the further development of this therapy.

However, pathophysiological considerations suggest that rhythm control therapy may be best performed early after the initial diagnosis, as this time period may provide a ‘window of opportunity’ for effective rhythm control therapy.

7.5. **New considerations for AF catheter ablation**

Considering the results of randomized studies on catheter ablation of AF vs. antiarrhythmic drug therapy and recent publications from randomized and non-randomized trials, it is reasonable to upgrade this recommendation to class I. For patients with highly symptomatic paroxysmal AF with a low-risk profile for catheter ablation, primary catheter ablation should be considered (Fig. 5). These recommendations are restricted to: (i) highly experienced centres/investigators; (ii) appropriate patient selection; (iii) careful evaluation of treatment alternatives and (iv) patient preference. For patients with drug-refractory persistent and long-standing persistent AF, there is no change in recommendations. Currently there is no evidence to recommend catheter ablation of AF in asymptomatic patients.

**Key points**

- Catheter ablation is recommended as an alternative to antiarrhythmic drug therapy for patients with symptomatic recurrent paroxysmal AF on antiarrhythmic drug therapy, provided the procedure is performed by an experienced operator.
- Continuation of oral VKA therapy can be considered throughout the ablation procedure but robust data for NOACs are lacking.
- In selected patients with paroxysmal AF and no structural heart disease left atrial ablation is reasonable as first-line therapy.
REFERENCES*


* All references supporting the recommendations in this document can be found in the original full text.