that is active in the market of drug packaging and electronic adherence recording. Moreover, we have to wait for validation of whatever approach. In the absence of any available validated data, we had to restrict ourselves to a summary of the potential approaches to optimize adherence. Definitely, we ask for ‘vigilance’ among prescribers to tailor adherence approaches to their individual patients. Moreover, this required vigilance goes far beyond monitoring adherence, as we have highlighted important issues related to plasma levels and pharmacodynamic interactions in the Guide too. Inappropriate use of the correct drug, or with an inappropriate dose, carries a potential for harm. We agree that reliance on patient information like (last) drug intake is weak; in the section on cardioversion, for instance, we stated that if any incorrect information is suspected, it may be safer to proceed with a transoesophageal echocardiography, rather than rely naïvely on only patient information. Physicians, be vigilant, indeed!

Only on-going randomized trials on adherence measures and large registries will be able to tell how well the results of controlled clinical trials are translated to the real world. In modern clinical NOAC trials, adherence was still measured in the old-fashioned way of pill counting, but we agree that the uncertainty of when a new drug package was delivered to the patient and opened for the first time, severely limits its usefulness in daily practice. We take that suggestion at heart time, severely limits its usefulness in daily practice. We take that suggestion at heart.

We do object to the assertion of the authors that we stated in the Guide that once-daily NOAC dosing is preferable to twice-daily dosing. Exactly for the reasons spelled out by Vrijens and Urquhart, we suggested that ‘it is unknown whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and the safety profile as seen in the clinical trials’. Also, in this respect, more data are required. Again, registries will have to tell us to what extent the Phase 3 study results can be replicated in the overall population for different drugs and dosing schemes.

The NOACs marketed come in calendered blister packages or calendered boxes (containing the blisters), although the former do not all spell out the days of the week and the latter are not rated to be very practical by patients. Calendered pill boxes (also containing other medication) unfortunately cannot be used for dabigatran, which needs to be preserved in its original packaging. Electronic means certainly have high potential value concerning traceability and information sharing, and we look forward to studies on their use in the NOAC field. However, patients may also develop some wariness concerning such electronic surveillance. Again, we will need proof that the benefits outweigh the disadvantages in the field, and that such measures really translate into a clinically meaningful effect. Therefore, we all have to work on making patients adherent to their treatment to guarantee the intended safety and effectiveness. We certainly feel as partners of Vrijens and Urquhart on this issue.

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References

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Should catheter atrial fibrillation ablation be considered as a ‘high bleeding risk’ intervention?

We read with interest the last EHRA practical guide on the use of new oral anticoagulants (NOAC) in patients with non-valvular atrial fibrillation (AF) reported by Heidbuchel et al.,

and the problematic issue of NOAC during catheter AF ablation (CAFA). Several studies have confirmed the reduction of both bleeding and thromboembolic (TE) complications when performing CAFA during uninterrupted vitamin K antagonist therapy in comparison with a bridging strategy. Recent non-randomized studies with NOAC continued during CAFA showed similar safety profiles while still considering TE and bleeding events.

In the absence of a specific classification including CAFA procedures, the present guideline concerning the NOAC strategy was based on the exact definition of the bleeding risk associated which CAFA, which can be ambiguous.

Careful reading of the text appears confusing in our opinion. In the text, the authors suggest NOAC interruption 48 h before a procedure that carries a ‘risk for major bleeding’ (p. 640), whereas in the corresponding Table 10, CAFA is classified within the group of ‘high bleeding risk’ interventions. The table itself refers to a study reported in 2003 by Torn M et al., in which CAFA was completely absent from that classification. Should we consider CAFA as a procedure with ‘frequent’ bleeding complications?

There is a dissociation between these two concepts. On the one hand, the ‘risk of major bleeding’—this complication can be either frequent or exceptional—is defined by the gravity and/or consequence of per-or post-procedural bleeding. On the other hand, ‘high bleeding risk’ procedures refer to the rate of bleeding complications—the consequence of which going from mild to fatal. This concerns both the rate of bleeding complications, and their severity. Low bleeding risk procedures designate procedures with clinical bleeding rates of 1.5% or less in the classification from the American Society for Gastrointestinal Endoscopy. The worldwide survey on CAFA from Cappato et al. reports total bleeding rate events of 2.8% when adding tamponade, hemothorax, and groin complications. Then, according to the above-mentioned classification, CAFA can be defined as a procedure associated with a bleeding risk which is not low. But then, does this imply that it is a ‘high bleeding risk’ procedure?

In fact, CAFA is a procedure associated with major bleeding risk, because it can be complicated with transfusions, permanent disability (e.g. bleeding-induced stroke or myocardial infarction), and even death. Procedures that may result in intra-thoracic or pericardial bleeding are classified as major.

The other confusion concerns the distinction—even though this may appear elementary—in the same table, between single-(associated with low bleeding risk) and double-transseptal puncture procedures. No reference is provided to support this proposal.

To conclude, in the absence of specific validated bleeding risk classification, CAFA can...
be defined as a major bleed risk procedure, and is not a low bleeding risk procedure.

Despite these remarks, we would like to sincerely thank Heidbuchel and his collaborators for this courageous practical guide which offers elements of answers in our daily practice.

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References

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Author reply
As mentioned in the Practical Guide manuscript, its authors welcome feedback and comments, and therefore appreciate the considerations of Dr Bun and colleagues. By nature, the Practical Guide aimed to cover areas without clear-cut evidence, and we contend with Bun et al. that anticoagulation around catheter ablation is such an area. Especially ablation for atrial fibrillation (AF) is a ‘special procedure’ as it conveys a relevant bleeding risk and a specific risk for left atrial (LA) thrombus formation and stroke. A specific characteristic of AF ablation is the formation of lesions and hence creating prothrombotic surfaces in the LA, in an already prothrombotic milieu due to AF itself.

We agree with the argument that the Practical Guide was confusing in the wording of ‘risk of major bleeding’ and ‘high bleeding risk’, which may be interpreted in a different way. However, the intent of the guidance for both wordings was similar, i.e. to adapt the new oral anticoagulant (NOAC) dosing for procedures that carry a risk for major or potentially life-threatening bleedings. As Bun et al. pointed out, such bleedings also do occur at a relevant rate during complex ablations such as for AF.

Most electrophysiologists will contend that nowadays a transseptal puncture by itself is associated with a low risk of perforation/tamponade in well-trained hands, especially if online echo-imaging is used. In that respect, the difference between procedures with a ‘single’ transseptal puncture on the one hand, and ablations for AF or ventricular tachycardia on the other hand (as in Table 10 of the Practical Guide), is not related to one or two transseptal punctures, but to the much more complex catheter manipulation and more extensive ablation lesion deployment in the latter which carry a recognized risk for perforation/tamponade.

Much debate is ongoing about the most appropriate approach to anticoagulation during AF ablation in patients on NOAC therapy. For patients on vitamin K antagonist (VKA), consistent findings such as most recently in the COMPARE trial, point to less thromboembolic and bleeding events when ablation is performed under uninterrupted anticoagulation, avoiding bridging. There is no prospective data, however, in patients on NOACs. According to the ESC Guidelines for the treatment of AF patients, anticoagulation can be interrupted by up to a few days peri-procedurally for general procedures in patients with a low thrombo-embolic profile (CHA₂DS₂-VASC = 0 or 1). How far that applies to AF ablation remains uncertain given the direct catheter manipulation in the LA (which may dislodge small clots) and the risk for major bleeding. A recent HRS/EHRA/ECAS consensus statement recommended performing AF ablation during uninterrupted VKA therapy. Of note, the rate of tamponade/haemothorax (1.33%) was higher than the rate of stroke and transient ischaemic attack (0.94%) in the worldwide AF ablation survey, although this ratio was inverse in the COMPARE group with bridged VKA therapy.

Recent meta-analyses of different observational trials (and one small randomized study) in dabigatran-treated patients referred for AF ablation showed no difference concerning thrombo-embolic events, and major and minor bleeds compared with VKA-treated patients (mostly under continuous anticoagulation). However, there was marked heterogeneity among the different trials, with dabigatran therapy ranging from being continued without interruption to being withheld for ≥24 h in line with Table 9 from the Practical Guide.

Activated clotting time (ACT)-titrated heparin should and can be used throughout the ablation procedure as soon as transseptal access has been assured, also in NOAC-treated patients. Shorter pre-procedural cessation of NOAC will even result in more rapid achievement of target ACT values between 250 and 350 s. The fact that timely cessation of anticoagulation can be titrated much better with NOACs than with VKA, and also that resumption of full anticoagulation is rapid and highly predictable, may make a temporary interruption strategy with NOACs preferable over uninterrupted administration. It is also relevant that no rapid reversal agents for NOACs are available if a major peri-procedural bleeding occurs. Prospective studies with different NOACs (dabigatran and also FXa inhibitors) are now underway or in the planning stage, some with timed cessation and others with uninterrupted NOAC administration. These trials will ultimately show in which direction the balance tilts. For the time being, we would like to maintain the recommendation to stop NOAC for at least 24 h before an AF ablation (depending on renal function), except in patients with a very high thromboembolic risk. We are not sure whether we can provide better guidance in the absence of reasonably well-collected datasets.

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References