Quick, easy, and safe? On the use of low-molecular-weight heparins in cardioversion of atrial fibrillation

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This editorial refers to "The use of enoxaparin compared with unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion: Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) II randomized multicenter study" by A.L. Klein et al., on page 2858

Low-molecular-weight heparins (LMWHs) are gradually replacing unfractionated heparin (UFH) in several settings in cardiology and internal medicine. In most studies, LMWHs were either as effective as UFH or superior and had the additional advantage of the greater ease of subcutaneous application. Although earlier studies focused on the use of LMWHs in the venous vasculature, more recent studies have demonstrated some clinical advantages compared with UFH also in the arterial bed, e.g. in patients with unstable angina pectoris. Another clinical entity with the risk of arterial thrombo-embolism is atrial fibrillation (AF), an arrhythmia which not only shows a rising prevalence in recent years but is also associated with increased morbidity and mortality mainly due to thrombo-embolic events. Several studies in the late 1980s and early 1990s have demonstrated that inhibition of plasmatic coagulation is more effective than antiplatelet drugs in preventing thrombo-embolic events in patients with chronic AF. This has been underscored by more recent data showing that even combined antiplatelet therapy with acetylic salicylic acid plus clopidogrel is less effective than oral anticoagulation in this setting. Mainly because of their mode of application (intravenous or subcutaneous route), the role of heparins in AF is confined to short-term anticoagulation, such as the initiation of anticoagulation before the full effect of oral anticoagulants is reached, e.g. before cardioversion of AF. The results of the ACUTE II trial have demonstrated that the use of UFH, combined with exclusion of a left atrial thrombus by transoesophageal echocardiography (TEE), allows earlier cardioversion which may lead to a higher cardioversion success rate with similar safety compared with prolonged pre-treatment with oral anticoagulants. However, the use of UFH has the disadvantage that reliable plasma levels are only achieved by intravenous infusion, which may necessitate an unnecessary prolongation of hospitalization. Therefore, the use of LMWHs is not only likely to be as effective as UFH in the setting of AF cardioversion but may actually be cost-saving due to the reduction of hospitalization days, despite the higher cost of these compounds when compared with UFH.

The ACUTE II trial compared the use of the LMWH enoxaparin with UFH in the setting of AF cardioversion in a prospective randomized trial. The study demonstrates that enoxaparin administered for initiation of anticoagulation before cardioversion appears to have the same safety and efficacy as UFH for the prevention of embolic events, major bleeding, and death. Thus, the findings of this study are in accordance with those of the ACE trial, which found very similar results in patients undergoing cardioversion either with or without TEE guidance. The fact that in the ACE trial, the majority of patients underwent TEE-guided cardioversion and in the ACUTE II study, only TEE-guided cardioversion was investigated points to a tendency among many cardiologists to prefer this approach over pre-treatment with oral anticoagulation, probably because of the earlier chance to restore sinus rhythm. Because the observed data from both studies pertain primarily to TEE-guided cardioversion, it is not proved whether the same would apply if prolonged anticoagulation before cardioversion without TEE-guidance is used. It is at least reassuring that in the ACE trial, even prolonged treatment with enoxaparin after cardioversion did not lead to an increase in bleeding complications. In contrast to ACUTE II, enoxaparin was not only used during the initiation phase of anticoagulation in this study but continued at a lower dose (40 mg twice daily for patients <65 kg body weight and 60 mg twice daily for heavier patients) until 4 weeks after cardioversion. Keeping in mind that high-risk AF patients usually require long-term anticoagulation after AF cardioversion because of the high relapse rate of AF, the approach used in ACUTE II may be more practical for these patients, whereas for younger patients with a low long-term embolic risk, the continuation of...
subcutaneous LMWH administration for 4 weeks after the restoration of sinus rhythm may be preferable.

Nevertheless, both the ACE and the ACUTE trials were unable to show a reduction of adverse events with LMWH in AF cardioversion. The main reason for this is the overall low event rate in cardioversion studies with any type of anticoagulation, thus requiring a very large patient number to show superiority of a novel therapeutic approach. The fact that the ACUTE II study was stopped because of a low enrolment rate suggests that such a large trial will probably never be performed. If LMWHs are only equally safe and effective in preventing adverse events during AF cardioversion, it is mandatory to prove that this approach is cost-effective in order to convince government agencies to accept this indication for LMWHs. It is unfortunate that the authors do not provide this essential piece of information in their manuscript, which would clearly strengthen the message of the study. A cost-effectiveness analysis, however, was part of the ACUTE II protocol, and full publication of these results is eagerly awaited. Health-economic analysis of the ACE data set seems to indicate that the use of LMWH is indeed cost-effective at least under the rules of the German healthcare system.7

One more unanswered question is whether the results from the ACE and ACUTE II trials which used enoxaparin apply for all LMWHs. In fact, there are only few data with other LMWHs for the prevention of arterial thrombo-embolism, and due to distinct differences in pharmacokinetics and antithrombotic effects, similar studies with other LMWHs would be desirable. Evidence from some small observational studies at least suggests that the use of other LMWHs may also portend a favourable outcome.8 However, a note of caution is necessary for elderly patients with impaired renal function9 in whom bleeding complications are more common with LMWH, which may offset the potential benefit of these compounds.

Finally, the role of the new oral thrombin antagonists, e.g. ximelagatran, in the setting of AF cardioversion is yet unclear. These agents may have the potential to replace other anticoagulants for the prevention of embolic complications of AF. However, due to unclear hepatotoxic side effects, ximelagatran will not be market-released for anticoagulation in AF and thus it is likely that LMWH will remain an interesting option in this clinical scenario for the next years to come.

In summary, the use of LMWHs in the setting of cardioversion appears safe and effective according to the available evidence. The updated ACC/AHA/ESC guidelines already recommend the use of LMWHs as an alternative to UFH in TEE-guided cardioversion with a class Ila indication.10 With now two randomized prospective trials available, I believe the level of evidence for this recommendation should, however, be increased from 'C' (i.e. expert consensus) to 'A' (i.e. supported by several prospective randomized trials).

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References