Atrial Fibrillation: Is There a Role for Low-Molecular-Weight Heparin?

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Summary: Atrial fibrillation (AF) is the most common form of tachyarrhythmia and carries a significant risk of serious thromboembolic complications. Anticoagulation is used for long-term thromboprophylaxis and for short-term management in a number of clinical situations, among which is the medical or electrical cardioversion of AF to sinus rhythm. Current guidelines recommend prompt cardioversion with heparin cover for AF of < 48 h duration, and several weeks of warfarin therapy prior to cardioversion when the duration of disease is longer. Recent animal and human studies, however, have shown that swifter cardioversion is likely to be more successful in achieving sinus rhythm and in reducing the risk of recurrence of AF. Other observations have demonstrated that thrombi can develop within a few hours of the development of AF. These considerations suggest that cardioversion should be carried out as early as possible in all cases, and that the most sensitive means of detecting atrial thrombi, currently transesophageal echocardiography (TEE), should be used to screen all patients prior to cardioversion. Within this context, there is growing interest in the use of low-molecular-weight heparin (LMWH) as an anticoagulant therapy in AF. Compared with unfractionated heparin, LMWH therapy does not involve prolonged intravenous administration, hospitalization, or laboratory monitoring; LMWH therefore has the potential to greatly simplify anticoagulation therapy for AF, especially pericardioversion. Recent studies have demonstrated that LMWH can be used safely and effectively in place of unfractionated heparin for acute treatment at the onset of AF and during early cardioversion. For example, in patients with AF, a strategy of immediate administration of dalteparin (100 IU/kg s.c. twice daily) continued for 11 days, combined with early TEE and

immediate cardioversion in patients with no thrombus, resulted in sinus rhythm in 74% of patients after a median of 7 days. Low-molecular-weight heparin therapy may also find a role perioperatively and in selected patients, notably those with warfarin intolerance, as a replacement for warfarin following cardioversion. Controlled clinical studies are still required, however, to establish a firm, evidence-based foundation for the use of LMWHs in AF.

Key words: atrial fibrillation, cardioversion, anticoagulation, low-molecular-weight heparin, warfarin, transesophageal echocardiography

Introduction

Atrial fibrillation (AF) is the most common form of tachyarrhythmia.¹ Although seldom directly life threatening, it can cause troublesome symptoms and carries the risk of potentially fatal thromboembolic complications. The risk of systemic thromboembolism during chronic AF has been estimated at five-fold the risk of similar patients in sinus rhythm and up to 18-fold when rheumatic mitral stenosis is the cause of the arrhythmia.² Thromboembolism is more common in the elderly and in those with underlying heart disease, especially left ventricular systolic or diastolic dysfunction. The risk of thromboembolism is greatest early after the onset of AF and when an attempt is made to cardiovert AF to sinus rhythm, no matter whether electrical or pharmaceutical techniques are used.

Atrial fibrillation can be treated according to two fundamentally distinct strategies. The first and most important is cardioversion, the restoration of a healthy sinus rhythm, by pharmacologic or electrical means.^{1,3} Following cardioversion there is a risk of recurrence of AF if the cause of the disease cannot be eliminated. Antiarrhythmic drugs are often used to reduce this risk. Recurrent AF continues to pose a threat of thromboembolism, and anticoagulation is often essential for patients treated in this manner. The second clinical algorithm is to control the ventricular rate but to allow the atria to continue to fibrillate.¹ Ventricular rate control can be achieved by the use of atrioventricular (AV) nodal blocking drugs such as digitalis, beta blockers, or calcium antagonists,

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TABLE I Advantages of low-molecular weight heparins

Rapid anticoagulation by inhibiting Factor Xa in < 4 h
Single or double subcutaneous daily doses on a weight-by-weight basis
INR and/or aPPT measurements are not necessary
Few bleeding complications
Good patient compliance and reduced need for hospitalizations
Few if any problems with coadministered medications
No long-term intravenous line is needed
Ambulant self-administration is possible

Abbreviations: INR = International Normalized Ratio, aPPT = activated partial thromboplastin time.

or by AV nodal ablation and pacemaker implantation. Since the atria continue to fibrillate, anticoagulant therapy is prescribed to high-risk patients according to accepted guidelines.

Traditionally, anticoagulation for AF has been based on warfarin, with unfractionated heparin (UFH) used to provide stronger anticoagulation at the onset and cardioversion of the arrhythmia. However, although long-term treatment with warfarin has been estimated to decrease the risk of an embolism by about two-thirds, chronic anticoagulation remains underused in patients with AF,⁴ largely because of the associated bleeding risk and the inconvenience of therapy.

In the treatment of deep vein thrombosis, the low-molecular-weight heparins (LMWHs) have greatly simplified clinical management compared with UFH-based management protocols. Unlike UFH, LMWHs have considerable advantages (Table I) such as not requiring laboratory monitoring, long-term intravenous infusions, or extended hospitalization: LMWHs therefore substantially reduce the overall burden on healthcare resources.⁵ There has been growing interest in the possibility of using LMWHs as thromboprophylaxis for AF, primarily as a replacement for UFH but also as a potential replacement for warfarin in selected patients (Table II).

Current Approaches to Thromboprophylaxis

Currently, the management of AF, including the use of thromboprophylaxis, is inadequate. Several sets of guidelines are currently available to assist physicians in the management of AF and the use of anticoagulants.^{6,7} Not only are these poorly adhered to, but in the light of current evidence they are likely to be intrinsically suboptimal in several important respects.

There are specific guidelines for anticoagulation pericardioversion, published by the American College of Chest Physicians (ACCP) and updated in 1995 (Fig. 1). These guidelines are probably the most influential set currently available, although they are based on anecdotal consensus rather than systematic clinical evidence.⁶ Of importance is the fact that these guidelines have certainly reduced dramatically the incidence of cardioversion-related stroke, but they are probably less than optimal with respect to minimizing the bleeding risk. These guidelines recommend prompt cardioversion supported by

TABLE II Potential roles for low-molecular weight heparin in the management of atrial fibrillation

Instead of unfractionated heparin
Perioperatively
Postembolic stroke
Pericardioversion
Awaiting formal anticoagulation
Instead of warfarin, etc.
Pre- and post cardioversion
Patients intolerant of warfarin and other dicoumarols
New clinical algorithms

UFH cover for cases of AF of <48 h duration. For AF of longer duration, they recommend 3 weeks of warfarin treatment prior to cardioversion, then a further 4 weeks of warfarin, with UFH given during cardioversion. In practice, clinical inefficiencies mean that such precise schedules for anticoagulation therapy are seldom achieved. In both Europe and the United States, warfarin is often given for up to 8–12 weeks before cardioversion, and afterward for periods varying from 24 h to indefinitely. Patient exposure to warfarin is often unnecessarily prolonged and the bleeding risk is therefore higher than is warranted.

Our current knowledge of AF now suggests that even when correctly followed, clinical management based on the ACCP guidelines has important shortcomings. First, with regard to the use of immediate cardioversion in AF of <48 h duration, the risks of thromboembolism during this period appear to be greater than were originally estimated. Thromboembolism is typically associated with the permanent and recurrent, persistent forms of AF, and is less common with the recurrent paroxysmal form that spontaneously converts to a sinus rhythm, usually within 24 h. However, left atrial thrombus may develop within just 4 h of the onset of AF. Black *et al.*⁸ found at least

FIG. 1 Current standards of care for atrial fibrillation (AF): The American College of Chest Physicians guidelines for anticoagulation and current medical practice.⁶ For AF of >48 h duration, ACCP guidelines recommend 3 weeks of warfarin therapy prior to and 4 weeks following cardioversion (see R). However, current medical practice frequently involves 8–12 weeks of anticoagulation prior to cardioversion and highly variable treatment duration afterward (see P). This model for AF management now requires substantial revision. DCC = direct current cardioversion.

21 cases of thromboembolism after cardioversion in patients in whom there was no prior evidence of thrombus on transesophageal echocardiography (TEE). Since thrombus may develop so early after the onset of AF, great care should be taken to identify possible thrombus even in patients with new-onset AF prior to cardioversion. Moreover, antithrombotic therapies using a heparin should be considered mandatory for all cases of AF, as early as possible after AF onset and at cardioversion.

Second, there are also serious doubts over the wisdom of delaying cardioversion for several weeks in patients in whom AF has been established for >48 h, merely to establish adequate anticoagulation with warfarin. There is now clear evidence, both from animal models and clinical studies, that the development of AF renders the atrium more vulnerable to more persistent and perhaps recurrent forms of AF, whereas prompt establishment of a sinus rhythm renders the atrium electrophysiologically more stable against recurrence.^{9,10} Thus, according to this concept, patients with AF should, in general, be cardioverted as quickly as possible after diagnosis to prevent electrophysiologic remodeling in favor of persistence or recurrence, provided there is no evidence of thrombus prior to cardioversion and effective anticoagulation therapy is given.

Toward New Management Models

Clearly, the existing guidelines for AF management are far from ideal and will have to be replaced by more precise, evidence-based, and clinically effective management algorithms. One of the most important problems such algorithms will have to address is the difficulty of identifying whether or not a thrombus is present, since this is critical in deciding whether to proceed to cardioversion. In this context, TEE provides a highly sensitive means of assessing the presence of a thrombus.¹¹ Unfortunately, systematic evidence for the incorporation of TEE into management protocols for AF has taken some time to accumulate. The first major study to investigate TEE in this

context was the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) pilot study.¹² In this study, patients were randomized to receive either a TEE-based approach, with cardioversion when no thrombus was present, or conventional warfarin therapy for 3 weeks followed by cardioversion. The pilot for the ACUTE study gave promising results (Fig. 2), with a mean time to cardioversion of 0.6 weeks in the thrombus-free subgroup of the TEE arm and no emboli observed following TEE. This compared favorably with a time to cardioversion of 4.8 weeks in the conventional arm, with one peripheral thromboembolus reported. In the larger definitive study, however, the TEE arm was not associated with any clinical benefits, and the entire study was discontinued for futility after only 1,222 of the projected 2,900 patients had been enrolled. Unfortunately, the intent behind the study design was not realized in that patient enrollment took place an average of 13 days after the onset of AF. By this time, significant electrocardiographic remodeling of the atrium toward a state of permanent fibrillation would have been expected to occur, and hence the goal of using TEE to promote early cardioversion was defeated by the trial protocol.

Low-Molecular-Weight Heparins for Atrial Fibrillation: Clinical Studies

Several studies involving LMWHs are now in progress. In addition to assessing the role of LMWHs in AF, they are more fully addressing the use of TEE in the selection of suitable candidates for early cardioversion.

Roijer *et al.*² recently described a study of 242 patients who had suffered from AF for >48 h, all of whom were subjected to TEE-based screening (Fig. 3). Following TEE, patients without a thrombus were given immediate cardioversion, while the

Fig. 2 The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) pilot study flow chart showing the reduced time needed to achieve cardioversion in the patients investigated by transesophageal echocardiography (TEE) (0.6 weeks) compared with those anticoagulated with warfarin (4.8 weeks). Abbreviation as in Figure 1.

Fig. 3 In a study by Roijer *et al.*,² transesophageal echocardiography (TEE) allowed patients with no thrombogenic heart disease (no thrombus, no spontaneous echo contrast [SEC] and a left atrial appendage [LAA] emptying velocity >0.25 m/s) to be cardioverted within 24 h compared with an average of 86 days if pretreated conventionally with warfarin. Although the long-term success of cardioversion (CV) was greater in the group treated with dalteparin, the effect appeared to be due to the absence of heart disease in that group rather than the shorter AF to cardioversion period. AF = atrial fibrillation, SR = sinus rhythm, OHD = organic heart disease, 1m = 1-month follow-up.

Fig. 4 Dalteparin and transesophageal echocardiography (TEE)-driven strategy for early cardioversion in patients without thrombus. In this management strategy, anticoagulation was provided by dalteparin, and patients without thrombus, identified by TEE, were selected for cardioversion. Sinus rhythm (SR) was established in 74% of patients after a median of 7 days. AF = atrial fibrillation, CV = cardioversion, AADs = antiarrhythmic drugs, DCC = direct current cardioversion, Spont = spontaneous.

procedure was delayed in those with evidence of thrombus. When indicated, cardioversion was carried out within 5–8 h of TEE, and adjunctive dalteparin was given at a dose of 200 IU/kg once daily subcutaneously. In the group in which TEE results supported prompt cardioversion, sinus rhythm was established in 75% of patients at 1 month, whereas only 45% of patients in the delayed cardioversion group had an established sinus rhythm by this time. The mean time from onset to cardioversion was 42 days in the early cardioversion group, compared with 157 days in the non-early cardioversion group. This study therefore underlined the ability of TEE to reduce the duration of necessary anticoagulation significantly, but it did not permit early cardioversion because patients were enrolled on average at 42 days in the TEE / LMWH group and at 71 days in the conventionally treated group. However, the study provided preliminary support for the use of dalteparin therapy in AF.

A second study involving dalteparin was recently reported by Bechtold *et al.*¹³ (Fig. 4). In this study of 100 consecutively screened patients with AF, 36 with AF of durations varying from 24 h to over 1 year suitable for cardioversion were investigated by TEE to exclude left atrial thrombi. Of these, 31 patients had no signs of thrombus, and 23 were subsequently cardioverted using pharmacologic or subsequent electrical methods. All patients received dalteparin-based anticoagulation therapy at a dose of 100 IU/kg twice daily at entry into the study. Cardioversion was performed 2 days after the start of dalteparin therapy and the LMWH was administered for a total of 11 days. Sinus rhythm was established after a median of 7 days, and there were no thromboembolic events.

Although a trial comparing TEE-driven early cardioversion with conventional therapy has yet to be conducted, the evidence emerging from clinical studies clearly supports both the use of TEE-based protocols and the introduction of LMWHs as anticoagulants in AF. The small studies reported to date have given preliminary support to the use of LMWHs both in early acute management and as adjunctive therapy during cardioversion. It is likely that further evidence to support these uses, in which LMWH is used as a straightforward replacement for UFH, will be generated by trials currently in progress. As in other indications, the primary advantages of

LMWH over UFH may not be in terms of clinical efficacy, but by virtue of their ease of use, rendering intravenous administration, prolonged hospitalization, and regular monitoring unnecessary. Indeed, these features of LMWHs may also offer advantages in relation to warfarin in some clinical contexts, both in warfarin-intolerant patients and more generally.

Conclusions

The management of AF is currently in a period of transition, as the recommendations in published guidelines are undermined by the findings of more recent investigations. There is now good evidence that prompt cardioversion is likely to prevent or delay recurrence of AF, and that the presence of thrombus should be ruled out using TEE before proceeding to cardioversion in all patients with AF, including those with new-onset disease. At the same time, LMWHs are now set to challenge the traditional role of UFH in the management of AF and may also play a role in place of warfarin in selected patients. Promising results have been obtained with a strategy of dalteparin treatment pre- and post cardioversion, combined with early TEE, and further studies are warranted. The rationale for the use of LMWH pericardioversion is summarized in Table III. The current guidelines for anticoagulation pericar-

TABLE III Low-molecular-weight heparins for pericardioversion anticoagulation

Very prompt cardioversion reduces the likelihood of cardioversion failure and probably prevents or delays recurrence of AF
Present guidelines for anticoagulation for cardioversion are not evidence based, and while effective and moderately safe, probably delay cardioversion
Clinical practice inefficiencies delay cardioversion even further
The use of LMWHs could quicken effective anticoagulation and clot dissolution
Postcardioversion anticoagulation with LMWHs could be more efficient and safer than the use of warfarin

Abbreviations: AF = atrial fibrillation, LMWHs = low-molecular-weight heparins.

A necessary trial: TEE + LMWH versus conventional

FIG. 5 A suggested trial design for patients who have had atrial fibrillation for between 48 h and 7 days, to evaluate the role of low-molecular-weight heparin (LMWH) treatment prior to and immediately after cardioversion. TEE = transesophageal echocardiography, DC cardioversion = direct current cardioversion, INR = International Normalized Ratio.

dioversion are based on long experiences and observational databases. No large systematic trials have explored the many variables that could have been considered. A trial similar to that outlined in Figure 5 is recommended to evaluate the role of LMWH treatment prior to and immediately after cardioversion. Any new algorithm for the management of anticoagulation pericardioversion will need explicit and carefully designed trials to supplant a scheme that certainly works as far as reducing the risk of thromboembolism, but may be less successful at minimizing bleeding risks and hopeless as far as expediting the cardioversion of AF. For all these potential developments, however, controlled clinical studies are required to place the management of AF on a more clinically effective, evidence-based foundation.

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