High Intensity Anticoagulation for Cardioversion of Atrial Arrhythmias? The Shocking Truth*

Brian Olshansky, MD, FACC
Iowa City, Iowa

Direct current (DC) cardioversion is now a common, accepted, outpatient procedure that treats a growing number of patients with symptomatic atrial flutter and atrial fibrillation (AF), but complications can occur. Stroke following cardioversion is the most feared consequence of this beneficial and effective therapy.

Thromboemboli are a known complication of chronic AF, and acute reversion of AF to sinus rhythm (SR) (by a drug or an electric shock) can increase the risk 10-fold. Most embolic episodes occur within 10 days of cardioversion (1). The cause for this increased risk is only postulated. The incidence of clinically apparent thromboemboli is only the tip of the iceberg because many thrombi that become lodged in blood vessels throughout the body may go undetected (Fig. 1) (2).

The use of anticoagulants to protect patients with AF from thromboemboli is not new (3). Data from placebo-controlled randomized trials demonstrate the clear benefit of long-term anticoagulation in high-risk patients with AF. A compilation of data from five major multicenter trials shows a 67% average risk reduction with warfarin given long term based on an intention-to-treat analysis, but the benefits may really be greater than that. The safety and efficacy of warfarin anticoagulation for chronic AF in high-risk patients are indisputable, notwithstanding the few students of the literature who have attempted to cast doubt on its utility (4).

Persuasive data demonstrate unequivocally that warfarin anticoagulation offsets the augmented risk of thromboemboli after DC cardioversion, but several important questions remain: 1) Is it safe for a patient with AF to undergo cardioversion in the first 48 h without anticoagulation? 2) Is it safe to cardiovert atrial flutter without anticoagulation? 3) What is the level of anticoagulation needed to ensure safety during and after cardioversion? 4) Is heparin or low molecular weight heparin as safe and effective as warfarin anticoagulation to protect against thromboemboli? 5) What is the proper anticoagulation regimen required for those whose cardioversion attempt is guided by transesophageal echocardiography (TEE)?

In this issue of the Journal, Gallagher et al. (5) address, in part, these important challenging issues. Their article underscores the crucial importance of “proper” anticoagulation for cardioversion of atrial arrhythmias and amplifies key issues. As such, proper anticoagulation is now in better focus.

Is it safe for a patient with AF to undergo cardioversion in the first 48 h (or even 7 days) without anticoagulation? It appears safe for patients with <48 h of AF to undergo cardioversion even without anticoagulation. Several trials demonstrated a low risk for thromboemboli even when a patient with short-term AF did not undergo anticoagulation at the time of cardioversion or soon thereafter. Weigner et al. (6) showed that, of 1,822 patients with AF, 375 episodes lasted <48 h and, of these, only three (0.8%), converting spontaneously to SR, had thromboembolic events. Arguably, this represents a moderate risk for an elective procedure. Gallagher et al. (5) even more strongly support the concept that cardioversion of short-term AF is associated with a low risk of thromboemboli. Only one event occurred in 443 patients (0.22% or 0.28% for those not receiving prolonged anticoagulation) who had an atrial arrhythmia lasting 2 days or less. Unfortunately, the data in this ≤48-h group are difficult to assess in the report of Gallagher et al. (5) because the use of anticoagulation and the number with atrial flutter are not clear. This issue is even more cloudy in patients with atrial arrhythmias lasting up to 7 days; policies varied among hospitals.

It appears acceptable to withhold anticoagulation in patients undergoing cardioversion for an atrial arrhythmia lasting 2 days or less, as is already recommended (7). The concern remains: how certain is the arrhythmia onset? Risks may also increase if there are “sputtering,” self-terminating AF episodes before cardioversion. Even so, atrial arrhythmias of short duration can be cardioverted safely without anticoagulation.

Is it safe to cardiovert atrial flutter without anticoagulation? Apparently it is not. Until recently, few long-term studies indicated a benefit of warfarin in preventing thromboemboli in atrial flutter, but concern was raised several years ago (8). Data from our laboratory (9) and others (10) have shown that chronic atrial flutter is associated with long-term risk of thromboemboli, similar to AF, and that the risk is reduced by maintaining effective warfarin anticoagulation. Biblo et al. (11) reviewed 8 years of retrospective Medicare population data and showed that the risks of stroke are substantial in patients with an atrial flutter diagnosis, although perhaps not at the level of AF.

Thromboemboli can occur from cardioversion of atrial flutter (12). Thrombi and spontaneous echo contrast have been observed by TEE in atrial flutter (13–15). Left atrial stunning can occur after ablation or cardioversion of atrial flutter with return to SR (16,17). In our laboratory (18), TEE, before cardioversion of atrial flutter, revealed abnor-

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From the Division of Cardiology, Department of Internal Medicine, University of Iowa Hospital, Iowa City, Iowa.
AF and that the risk of an atrial thrombus was “thromboemboli in atrial mal left atrial transport. The mechanism responsible for thromboemboli in atrial flutter, and its conversion to SR, may differ from that for atrial fibrillation, but the risks are nevertheless noteworthy.

Gallagher et al. (5) confirm that thromboemboli can occur with cardioversion of atrial flutter. The actual risk is difficult to determine, because the policies regarding anticoagulation, the time to enrollment in the study, the length of episode, the underlying cardiac diagnoses, and other undetermined factors were not controlled. Only 21.6% with atrial flutter lasting longer than 2 days had an international normalized ratio (INR) ≥2.5 at the time of cardioversion. Those with INR values ≥2.5 had no embolic complications compared with those not receiving anticoagulation (0.9% risk) or those taking ineffective anticoagulation (0.5% risk; p = nonsignificant).

The FLASIEC multicenter study (19) suggested that the risk for cardioversion of atrial flutter might be lower than for AF and that the risk of an atrial thrombus was “small” (left atrial appendage thrombus in 1.6% and right atrial thrombus in 1%). An embolic event occurred after cardioversion in 2 of 93 (2.2%) patients (1 month follow-up in 78 and restoration of SR in 62 patients). Thirty-four percent underwent anticoagulation with warfarin or heparin.

Elhendy et al. (20) showed that the 30-day risk of thromboemboli after cardioversion of atrial flutter may be “acceptable” at 1%. It is 0%, however, for those receiving therapeutic anticoagulation. Which risk would you rather have?

Data from the study of Gallagher et al. (5) confirm the apparent risk of stroke in the cardioversion of atrial flutter. The risk may actually be higher than that for cardioversion of AF even though the two groups are not completely comparable owing to differences in level of anticoagulation and other risk factors. Based on these data, it is clearly desirable for patients with atrial flutter (as with AF) to undergo anticoagulation before cardioversion.

**What is the level of anticoagulation needed to ensure safety during and after cardioversion?** The INR values that ensure safety from thromboembolism in patients with chronic atrial fibrillation may not apply to those undergoing cardioversion. An INR between 2.0 and 3.0 has been considered generally safer and effective (7). Based on available data and reasonable evidence, clinical guidelines now state: “Administer anticoagulation therapy regardless of the method (electrical or pharmacological) used to restore sinus rhythm in patients with AF lasting >48 hours or of unknown duration for at least 3 to 4 weeks before and after cardioversion (INR: 2 to 3)” (7). There is a rapid fall-off in efficacy as the INR drops below 2.0, and there is increased risk of bleeding as the INR exceeds 3.0. Gallagher et al. (5) challenge this common wisdom and posit that the acceptable INR floor is 2.5. The data from the study of Gallagher et al. (5) call into question an INR of 2.0 as an acceptable lower limit to prevent stroke from cardioversion of AF.

Data from our laboratory on 532 consecutive patients undergoing outpatient DC cardioversion of atrial flutter and AF confirm that these recommendations are effective as long as there is scrupulous attention to the INR value (measured at least weekly for 3 weeks with INR values ≥ 2.0 at each measurement) (21). No embolic events occurred in those so anticoagulated. Some risk of stroke may always be present with elective DC cardioversion of AF, but that risk, far less than 1%, is now achievable.

An INR of 2.5 at the time of cardioversion may ensure that recent INR values before cardioversion have remained over 2.0, considering daily fluctuations. It is difficult to ascertain what the INR values were in the 3 weeks before cardioversion in the study of Gallagher et al. (5). Little information is provided regarding the nine patients who had thromboembolic events other than that their INR values were 1.4 to 2.4. Two of these patients had no INR values available, and of the nine patients with thromboembolic events, some of the remaining seven may have had an INR F.C. <2.0. It is surprising that the investigators used this wide INR range, because it is well known that an INR <2.0 places patients at risk. It is not clear how many patients in the study of Gallagher et al. (5) had an INR between 2.0 and 2.4 and had a thromboembolic event. In only five patients was the INR known at the time of the thromboembolic event (INR: 1.7 to 2.5; mean, 2.1). No median value is presented. The entire case recommending an INR of 2.5 or more as a condition for stroke prevention could hinge on two people with an INR >2.0, with the remainder having an INR <2.0. Basing sweeping recommendations on such a small subset is fraught with error. These few patients may not be enough to mount a case to maintain an INR at the level of 2.5. Is it safe for a patient to undergo cardioversion with an INR measured at 2.1 for four consecutive
weeks? This study does not answer that situation, but based on data from our laboratory (21), it is safe.

Is heparin or low-molecular-weight heparin as safe and as effective as warfarin for protection against thromboemboli? Historically, heparin has been considered a surrogate for warfarin for AF. The two are not the same. The risk/benefit ratio of heparin has not been carefully explored. Despite recent guidelines that advocate its use (7), the efficacy and safety of heparin anticoagulation are not well established for AF. Interest in the use of low-molecular-weight heparin is growing, and although it may be as effective as warfarin, more information is needed before it can be recommended without restraint.

What is the proper approach to anticoagulation for patients and who have cardioversion guided by TEE? Experience and studies supporting the use of TEE-guided cardioversion (22) make anticoagulation issues even more complex. It appears safe to cardiovert a patient with AF who has no left atrial clot on TEE as long as anticoagulation is undertaken at the time of cardioversion and thereafter.

Prospective, randomized data can be powerful, but as Gallagher et al. (5) point out, their retrospective data are more persuasive; they did not purposely exclude patients undergoing cardioversion who do not fit into the trial. Further, these data do conform to present clinical management of patients with AF. It is unlikely that a prospective, placebo-controlled, randomized clinical trial, testing effective anticoagulation schemes for cardioversion of atrial arrhythmias, will materialize any time soon.

Cardioversion can be performed safely, but a high enough level of anticoagulation must be assured, especially if AF or atrial flutter lasts >48 h. It may be prudent to attempt to raise the acceptable INR floor to 2.5 before cardioversion. On the other hand, if careful, weekly assessments demonstrate that the INR exceeds 2.0 consistently, then it is safe to cardiovert (21). Data from Gallagher et al. (5) and others highlight the importance of patients with atrial flutter and AF undergoing anticoagulation before cardioversion (23). The risk involved in cardioversion is improving. The risks may improve further with better use of anticoagulation regimens for AF and atrial flutter.

Reprint requests and correspondence: Dr. Brian Olshansky, Professor of Medicine, Director Cardiac Electrophysiology, University of Iowa Hospital, 200 Hawkins Drive, Iowa City, Iowa 52242. E-mail: brian-olshansky@uiowa.edu.

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