Ablation of Atrial Fibrillation Under Therapeutic Warfarin Reduces Periprocedural Complications
Evidence From a Meta-Analysis

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Background—Observational data suggest that performing radiofrequency catheter ablation of atrial fibrillation (AF) under therapeutic warfarin (continuous warfarin [CW]) may reduce the periprocedural risk of complications, such as thromboembolic events, compared to warfarin discontinuation (DW) with periprocedural bridging with heparin. We systematically reviewed the available evidence on the impact of CW compared with DW on periprocedural complications of AF catheter ablation.

Methods and Results—We searched major Web databases for studies on radiofrequency catheter ablation of AF under CW versus DW with periprocedural bridging with heparin. Data on periprocedural complications were extracted. We identified 9 studies (1 large case series indirectly compared with the latest Worldwide Survey). A total of 27 402 patients were included in the analysis (6400 undergoing ablation with CW). CW was associated with a striking decrease of thromboembolic complications (OR, 0.10; 95% CI, 0.05–0.23; P<0.001) and minor bleeding complications (OR, 0.38; 95% CI, 0.21–0.71; P=0.002) compared with DW. CW also did not increase the risk of major bleeding (OR, 0.67; 95% CI, 0.31–1.43; P=0.30), including cardiac tamponade (OR, 0.69; 95% CI, 0.19–2.47; P=0.57).

Conclusions—There is highly consistent evidence from observational studies that a CW strategy during radiofrequency catheter ablation of AF reduces the risk of thromboembolic complications without increasing the risk of bleeding. (Circ Arrhythm Electrophysiol. 2012;5:302-311.)

Key Words: atrial fibrillation • catheter ablation • anticoagulants • complications

Periprocedural thromboembolic events are among the most important and insidious complications of radiofrequency catheter ablation of atrial fibrillation (AF).1–3 Proper periprocedural anticoagulation management is mandatory to minimize the thromboembolic risk,1,3 although the optimal anticoagulation strategy is still undefined.5–10 Current guidelines suggest warfarin discontinuation (DW) 3 to 5 days before ablation, with periprocedural bridging with low-molecular-weight heparin.1,3 In recent years, it has been increasingly reported that radiofrequency catheter ablation can be safely performed without warfarin interruption (continuous warfarin [CW]),4–11 and recent data suggest that this strategy may decrease the risk of periprocedural thromboembolic complications compared to DW with heparin bridging.4 In this article, we provide a systematic review of the available evidence comparing AF catheter ablation under CW with the currently suggested strategy of DW with heparin bridging1,3 to better evaluate the benefits and risks of different periprocedural anticoagulation strategies.

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Methods

Data Sources and Selection
Two investigators (P.S., L.D.B.) independently searched Pubmed, CENTRAL, BioMedCentral, Cardiosource, ClinicalTrials.gov, and ISI Web of Science (January 1980–April 2011). Search key words were atrial fibrillation AND radiofrequency catheter ablation, ablation, catheter ablation, stroke, transient ischemic attack, thromboembolism, thromboembol*, bleeding, pericardial effusion, anticoagulation, warfarin, oral anticoagulation, heparin, and anticoag* (where * denotes a wildcard). No language restriction was used. Proceedings from the annual American Heart Association, American College of Cardiology, European Society of Cardiology, Heart Rhythm Society, and Europace meetings for the past 5 years and scientific society Web sites were manually searched.
Study Selection

Two investigators (P.S., L.D.B.) independently performed study selection. Studies were included if they enrolled patients undergoing AF ablation (population) and reported periprocedural complications (outcome) comparing CW (intervention) with DW plus periprocedural bridging with heparin (comparator). Studies specifically evaluating the safety of catheter ablation with CW were also included, and periprocedural complications were compared with that reported in the latest Worldwide Survey on AF ablation,2 in which DW was the strategy consistently adopted in participating centers. We chose the Worldwide Survey as the reference comparator study because it is the largest to date to assess the safety of AF ablation with DW, with internationally recognized reliability of information on the standards of methodology, efficacy, and safety of AF ablation.1,3

Data Extraction

Reviewers extracted the data with regard to inclusion criteria: total number of patients; ablation strategy; number of patients in the CW group; number of patients in the DW group; and periprocedural complications in each group, including thromboembolic complications (ie, stroke, transient ischemic attack [TIA]), major and minor bleeding complications, and cardiac tamponade. In the case of missing data, the senior authors of the included studies were contacted to retrieve unpublished data.

Statistical Analysis

Outcomes from individual studies were analyzed according to the Mantel-Haenszel method to compute individual and pooled odds ratios (ORs) with pertinent 95% CIs.12 Heterogeneity among studies was evaluated with the Cochran Q test, and I², which describes the percentage of the variability in effect estimates that is due to heterogeneity, was used to evaluate inconsistency (I² >50% denotes substantial heterogeneity).13 A fixed-effects model of analysis was adopted in the absence of statistical heterogeneity, whereas a random-effects model was preferred in cases of substantial heterogeneity. Sensitivity analyses were conducted as follows: withdrawing 1 study at a time, withdrawing studies in which preprocedural bridging with low-molecular-weight heparin in the DW group was not required,6,11,14 withdrawing low-quality studies,6,8,11,14 and withdrawing the study in which an indirect comparison analysis with the Worldwide Survey population was performed.2,7

Subgroup analyses were carried out to appraise the impact of baseline patient characteristics (age, sex, average CHADS2 [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA] score, type of AF, and left atrial diameter), procedural data and different intraprocedural anticoagulation strategies (ie, use of open-irrigation catheters, ablation techniques, administering unfractionated heparin bolus before or after the transseptal puncture, different heparin doses or target activated clotting times), and of intracardiac echography (ICE) monitoring on periprocedural complications. For dichotomous variables, a direct test of statistical significance among the results obtained at subgroup analyses was performed using the Bland-Altman test for interaction (the ratio of the difference between the treatment effect estimates of 2 subgroups to the SE of this difference).14 For continuous variables, a meta-regression analysis using inverse-variance weighting was carried out. Publication bias was explored using the Egger test16 and by visual estimation of the funnel plot of precision (SE of log OR) against the treatment effect (displayed as OR on a logarithmic scale). Study quality was evaluated by 2 blinded reviewers according to established methods of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group using GRADE Profiler software version 3.5 (2004–2007).12,17 The GRADE score defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. Quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.12,17 In case of disagreement between the reviewers, a third reviewer reevaluated the studies and assigned the score.

The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.18 Statistical level of significance was defined as a P < 0.05 (2 tailed). Analyses were performed using the STATA version 11.1 statistical software.

Results

Qualitative Findings

A flow diagram of the selection process is shown in Figure 1. We identified 9 studies that met the inclusion criteria (Tables 1–3).

Six studies had a prospective observational design,4,7–10 2 were retrospective analyses,5,6 and 1 did not report the design.14 Study quality assessment is reported in Table 3. The target international normalized ratio in the CW group was between 2.0 and 3.5 in all the studies,4–6,8–11,14 with the exception of the study by Hussein et al,7 which allowed a target international normalized ratio of ≥1.8. In the DW group, preprocedural bridging with heparin was necessary in 5 studies8,9,8–10 and consisted of variable doses of low-molecular-weight heparin.

Procedural data differed among studies. Intravenous unfractionated heparin was administered in all patients, although with different doses and at different stages of the procedure (Table 2). ICE was used in 5 studies,4,5,7,10,14 and irrigated ablation catheters were used in all but 2 studies.6,10

The definition of thromboembolic complication was quite consistent among the included studies and basically was the composite of ischemic stroke and TIA. Definitions of hemorrhagic complications differed slightly among studies (Table 1), although any bleeding requiring intervention or transfusion was classified as a major complication in all the studies.

Overall, 27,402 patients were included in the analysis. Of these, the 6400 CW patients included 3052 (48%) from a large prospective case series evaluating CW safety,7 2618 (41%) from a large comparative cohort study of CW and DW,4 and 730 (11%) from 7 smaller comparative studies.5,6,8–11,14 The 21,002
Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Patients CW</th>
<th>DW</th>
<th>Target INR (CW)</th>
<th>Doses of LMWH for Bridging (DW)</th>
<th>Thromboembolic Events Definition</th>
<th>Major Bleeding Definition</th>
<th>Minor Bleeding Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazni et al10</td>
<td>2007</td>
<td>355</td>
<td>150</td>
<td>205</td>
<td>2.0–3.5</td>
<td>Ischemic stroke</td>
<td>Cardiac tamponade, hematoma needing intervention or transfusion</td>
<td>Hematoma not requiring intervention</td>
</tr>
<tr>
<td>Hussein et al14</td>
<td>2009</td>
<td>3052</td>
<td>3052</td>
<td>16309*</td>
<td>≥1.8</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade, &gt;2 g/L decrease in Hb level, need for transfusion or rehospitalization, hemoptysis, hemothorax, retroperitoneal bleeding</td>
<td>Hematoma not requiring intervention</td>
</tr>
<tr>
<td>Schmidt et al14</td>
<td>2009</td>
<td>194</td>
<td>87</td>
<td>107</td>
<td>2.0–3.5</td>
<td>Ischemic stroke</td>
<td>Cardiac tamponade requiring intervention or transfusion</td>
<td>Hematoma not requiring intervention</td>
</tr>
<tr>
<td>Di Biase et al4</td>
<td>2010</td>
<td>6454</td>
<td>2618</td>
<td>3836</td>
<td>2.0–3.5</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade, need for transfusion or intervention, hemothorax, retroperitoneal bleeding</td>
<td>Groin hematoma not requiring intervention</td>
</tr>
<tr>
<td>Gautam et al5</td>
<td>2010</td>
<td>427</td>
<td>181</td>
<td>246</td>
<td>2.0–3.5</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade, &gt;2 g/dL decrease in Hb level, need for transfusion or intervention, retroperitoneal bleeding</td>
<td>Bleeding not requiring intervention</td>
</tr>
<tr>
<td>Hayes et al6</td>
<td>2010</td>
<td>81</td>
<td>49</td>
<td>32</td>
<td>2.0–3.5</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade or bleeding requiring intervention</td>
<td>Gastrointestinal bleeding not requiring intervention</td>
</tr>
<tr>
<td>Kwak et al8</td>
<td>2010</td>
<td>104</td>
<td>49</td>
<td>55</td>
<td>2.0–3.0</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade, ≥4 g/dL decrease in Hb level, need for transfusion</td>
<td>&lt;4 g/dL decrease in Hb level</td>
</tr>
<tr>
<td>Page et al9</td>
<td>2010</td>
<td>198</td>
<td>89</td>
<td>109</td>
<td>2.0–3.5</td>
<td>Ischemic stroke or TIA</td>
<td>Cardiac tamponade, need for transfusion or intervention</td>
<td>Gastrointestinal bleeding not requiring intervention</td>
</tr>
<tr>
<td>Hakalahti et al11</td>
<td>2011</td>
<td>228</td>
<td>125</td>
<td>103</td>
<td>2.0–3.5</td>
<td>Ischemic stroke</td>
<td>Cardiac tamponade, intracranial bleeding, need for transfusion or intervention</td>
<td>Hematoma not requiring intervention</td>
</tr>
</tbody>
</table>

CW indicates continuous warfarin; DW, warfarin discontinuation; INR, international normalized ratio; LMWH, low-molecular-weight heparin; TIA, transient ischemic attack; NR, not reported; Hb, hemoglobin.

*Rates of complications in the DW group derived from the Worldwide Survey by Cappato et al.2

DW patients with whom CW patients were compared correspondingly included 16309 (78%) from the Worldwide Survey, 3836 (18%) from the large comparative study, and 857 (4%) from the smaller comparative studies (Table 3). Procedure-related mortality occurred in 26 patients (0.09%) (25 reported in the Worldwide Survey, and 1 reported in the DW group of the study by Schmidt et al14).

Analysis of Complications

Thromboembolic Events

The pooled rate of thromboembolic events in the CW group was 0.06% versus 0.94% in the DW group. This resulted in a significant decrease of periprocedural ischemic stroke or TIA in the CW group (OR, 0.10; 95% CI, 0.05–0.23; P<0.001; I²=32%) (Figure 2A). The same results were obtained in an analysis of only studies in which DW was associated with preprocedural low-molecular-weight heparin bridging (OR, 0.06; 95% CI, 0.01–0.24; P<0.001; I²=10%). The benefit of CW compared with DW was also confirmed in a secondary analysis of the separate end points of stroke (OR, 0.22; 95% CI, 0.10–0.50; P<0.001) and TIA (OR, 0.04; 95% CI, 0.01–0.22; P<0.001) (Figure 2B). All other prespecified sensitivity analyses provided results similar in direction and statistical significance. In particular, results were not affected after withdrawing
the study in which an indirect comparison analysis with the Worldwide Survey population was performed. Publication bias was absent (bias coefficient, 0.92; \( P = 0.47 \)).

**Major Bleeding Complications and Cardiac Tamponade**
Major bleeding complications occurred in 0.55% of patients in the CW group and in 1.25% of patients in the DW group (OR, 0.67; 95% CI, 0.31–1.43; \( P = 0.30; \ F^2 = 54\% \) (Figure 3A). The majority of major bleeding complications was due to cardiac tamponade, which occurred in 0.29% of patients in the CW group and in 18.6% of patients undergoing DW with or without bridging with low-molecular-weight heparin, which accounted for a significant reduction in the CW group (OR, 0.38; 95% CI, 0.21–0.71; \( P = 0.002; \ F^2 = 76\% \) (Figure 4). Sensitivity analyses showed that the benefit associated with CW was driven by an increased risk of minor bleeding due to preprocedural bridging with low-molecular-weight heparin because it was not confirmed after repeated analyses that included only studies in which preprocedural bridging was not required (OR, 1.02; 95% CI, 0.52–1.99; \( P = 0.97; \ F^2 = 0\% \)).

**Subgroup Analyses**
A CW strategy was associated with a significant reduction of major bleeding complications in studies adopting ICE (OR, 0.39; 95% CI, 0.20–0.75; \( P = 0.005 \)), which was driven by a reduction of cardiac tamponade (Figure 5A). Notably, CW tended to increase the risk of major bleeding compared with
DW when ICE monitoring was not adopted (OR, 2.69; 95% CI, 0.87–8.33; \( P \approx 0.086 \)). The interaction between use of ICE and the effect of CW on major bleeding complications was highly significant (ratio of OR, 0.14; \( P \approx 0.003 \)).

As mentioned, the reduction in minor bleeding complications associated with CW was due to an excess of such complications in the DW group adopting preprocedural bridging with low-molecular-weight heparin (Figure 5B). The interaction was highly significant (ratio of OR, 0.22; \( P < 0.001 \)). All other clinical and procedural variables of interest failed to show a statistically significant interaction with treatment effects in the meta-regression analysis.

### Table 3. Quality of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Centers Involved</th>
<th>Design</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Large Treatment Effect</th>
<th>Confounding and Other Considerations</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazni et al(^10)</td>
<td>2</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>Very large</td>
<td>Two LMWH doses directly compared with warfarin continuation.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Hussein et al(^7)</td>
<td>2</td>
<td>Prospective cohort</td>
<td>No</td>
<td>High</td>
<td>No</td>
<td>Very large</td>
<td>Indirect comparison with Worldwide Survey population. One stroke in warfarin group occurred because of subtherapeutic INR. Elimination of such event increases the treatment effect.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Schmidt et al(^14)</td>
<td>2</td>
<td>Unclear</td>
<td>High risk</td>
<td>No</td>
<td>High</td>
<td>No</td>
<td>Study design unclear. No bridging required for patients with subtherapeutic INR. Unclear definition and reporting of outcomes. Statistical inconsistency driven by the inclusion of this study.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Di Biase et al(^4)</td>
<td>10</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Very large</td>
<td>Appropriate study design. Clear explanation of anticoagulation protocols. Results adjusted for baseline confounders and covariates.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Gautam et al(^5)</td>
<td>2</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>Very large</td>
<td>Clear definition and reporting of outcomes. Results adjusted for baseline confounders and covariates.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Hayes et al(^9)</td>
<td>1</td>
<td>Retrospective cohort</td>
<td>High risk</td>
<td>No</td>
<td>High</td>
<td>No</td>
<td>No bridging required for patients with subtherapeutic INR. Significant baseline differences between groups and lack of adjustment for baseline confounders and covariates.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Kwak et al(^8)</td>
<td>3</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>No</td>
<td>Clear definition and reporting of outcomes. Lack of adjustment for baseline confounders and covariates. Adjustment would likely increase the treatment effect.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Hakalahti et al(^11)</td>
<td>2</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>Large</td>
<td>No bridging required for patients with subtherapeutic INR. Unclear definition and reporting of outcomes. The only stroke in warfarin group occurred because of subtherapeutic INR.</td>
<td>+ ++</td>
</tr>
<tr>
<td>Page et al(^9)</td>
<td>1</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Clear definition and reporting of outcomes. No significant baseline differences between compared groups.</td>
<td>+ ++</td>
</tr>
</tbody>
</table>

Quality scores are as follow: high quality, +++++; moderate quality, +++; low quality, ++; very-low quality, +. All included studies had an initial quality score of +2 (observational design). The quality of the evidence was upgraded in the case of large magnitude of treatment effect (+1 point if OR for thromboembolic complications [CW vs DW] < 0.5 or +2 points if OR < 0.2) or the presence of confounding factors that would decrease the treatment effect (Confounding and Other Considerations column; also see Discussion section) (+1 point). The quality of the evidence was downgraded in the case of limitation in study design (−1 or −2 points), inconsistency (−1 or −2 points), indirectness (−1 or −2 points), imprecision (−1 or −2 points), and publication bias (−1 or −2 points). No evidence of publication bias was detected.

Design indicates limitations in study design (retrospective vs prospective or unclear); inconsistency, qualitative or statistical inconsistency detected; indirectness, indirect comparison with another study population; imprecision, wide CI for the treatment effect estimate; LMWH, low-molecular-weight heparin; INR, international normalized ratio; CW, continuous warfarin; DW, warfarin discontinuation.
Discussion

This review evaluated the benefits of periprocedural CW compared with DW in patients undergoing radiofrequency catheter ablation of AF. To our knowledge, the study includes the largest population to date, with >27,000 patients, in which these 2 different periprocedural anticoagulation strategies have been compared. It mainly shows that CW reduces the risk of periprocedural stroke without increasing the risk of bleeding.

For years, DW with low-molecular-weight heparin bridging has been the recommended and most widely adopted anticoagulation protocol in patients undergoing catheter ablation of AF. However, such an approach is not supported by adequate evidence and has been derived from methodologically limited uncontrolled studies and expert consensus opinions. Notably, the risk of periprocedural stroke/TIA with DW and heparin bridging is nonnegligible and varies from 1% to 5%.
The results of the present study provide consistent evidence that CW is superior to DW in terms of periprocedural thromboembolic protection. The findings were robust because they were not affected by all the prespecified sensitivity analyses. Overall, a total of 4 strokes in the CW group were reported in 2 studies. Three of these events occurred in the study by Hussein et al, which considered acceptable an international normalized ratio of $\leq 1.8$ (1 patient with stroke had an international normalized ratio of $\leq 1.8$), and 1 was reported by Schmidt et al, who allowed patients to begin therapy with warfarin only 3 days before the scheduled procedure. Although all other studies required long-term therapy with warfarin in the CW group, it is important to emphasize that the antithrombotic effect of warfarin is not present until approximately the fifth day of therapy because of the long half-life of prothrombin ($\approx 50$ hours). Moreover, in the first few days of therapy, warfarin may also paradoxically increase the risk of thrombosis because of the rapid decline in the concentration of protein C.

The present results may even underestimate the real benefit of CW in preventing periprocedural thromboembolism if a standardized anticoagulation protocol with long-term therapeutic warfarin were adopted in all studies. Notably, the baseline thromboembolic risk of patients undergoing AF ablation with CW was consistently higher than that of patients in the DW group (Table 2), which further supports the benefit of CW versus DW. The impact of CW on top of other strategies capable of reducing the risk of periprocedural thromboembolism, such as withdrawal of the transseptal sheaths in the right atrium, merits further investigation.

With regard to bleeding events, the primary analysis did not show a significant difference in the rates of major bleeding complications between CW and DW. Most of these events were cardiac tamponades, and a separate analysis for
this outcome provided similar results. A careful appraisal of event rates within included studies, however, showed significant heterogeneity. The pooled CI of the risk of major bleeding was wide (0.31–1.56), and the upper CI limit did not allow safe exclusion of an increased bleeding risk with CW across all patients in the included studies.

Subgroup analyses showed that intraprocedural monitoring with ICE was an important modulator of the bleeding risk associated with CW. Pooled analysis of studies adopting ICE showed a statistically significant reduction of major bleeding complications driven by a reduction of cardiac tamponade in the CW group. On the other hand, CW tended to increase the risk of major bleeding events when ICE monitoring was not adopted. Although the results of these subgroup analyses should be interpreted with caution, the findings support that major bleeding complications due to cardiac tamponade are not increased by CW when ICE is used (upper CI limit, 0.81; range of upper CI limits excluding each study in turn, 0.55–1.10). In this regard, the use of ICE may be of significant value in less-experienced centers, especially when a CW strategy is implemented, although it necessitates additional expertise and increases the cost of the procedure.

With regard to the management of major bleeding complications, most studies adopted therapeutic warfarin reversal with either fresh frozen plasma or infusion of prothrombin complex concentrate on top of heparin reversal with protamine. The need for fresh frozen plasma and prothrombin complex concentrate, although a potential disadvantage, is greatly mitigated by the reduced risk of stroke/TIA.

Minor bleeding complications were also reduced by CW. However, in this case the benefit was driven by a considerable increase of minor bleeding events in the DW arm of studies adopting preoperative bridging with low-molecular-weight heparin. On the other hand, the latter finding further argues against the convenience of DW versus CW.

**Strength of the Evidence**

The main issue that arises from the present analysis is whether it provides sufficient evidence to change the current practice.1–3 A key objection is that the findings are based on nonrandomized studies. To the best of our knowledge, however, no randomized study has demonstrated the effectiveness of DW with heparin bridging in the setting of catheter ablation of AF, yet this strategy is recommended and widely accepted.

Another point is whether a randomized trial to demonstrate thromboembolic protection with CW compared with DW is feasible. When the risks of events are small, as is the case for periprocedural thromboembolism, large observational studies may provide relevant findings difficult to replicate in randomized trials. The pooled event rate in the DW group was 0.94%, and a randomized trial with an adequate power (90%, α=0.05) to demonstrate a thromboembolic protection of CW would need to enroll 3130 patients. In our view, such a trial
Table 4. Major Bleeding Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Major Bleeding Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazni et al^10</td>
<td>Blood transfusion in large hematomas (9 in DW), 2 pericardiocentesis (DW), and thrombin injection in the femoral pseudoaneurysm (3 in DW, 2 in CW).</td>
</tr>
<tr>
<td>Hussein et al^7</td>
<td>Routine type and cross-match for packed red blood cells and FFP. Five pericardiocentesis and FFP, 1 surgery for refractory effusion, and 3 blood transfusions (1 for retroperitoneal bleeding, 1 for ( &gt;2 \text{ g/L decrease in Hb level}, 1 ) for vascular laceration).</td>
</tr>
<tr>
<td>Schmidt et al^14</td>
<td>Routine type and cross-match for packed red blood cells and FFP. Ultrasound guidance for venous access at the discretion of the operator. Four surgery for refractory pericardial effusion (3 in DW, 1 in CW).</td>
</tr>
<tr>
<td>Di Biase et al^4</td>
<td>Routine type and cross-match for packed red blood cells and FFP. Ultrasound guidance for venous accesses at the discretion of the operator.</td>
</tr>
<tr>
<td>Gautam et al^5</td>
<td>Three patients required surgical intervention (all in the DW group: 1 for retroperitoneal bleeding, 1 for large arteriovenous fistula, 1 for femoral pseudoaneurysm). Pericardial effusion managed with drainage using echocardiographic and fluoroscopic guidance and protamine for reversal. No patient required surgery for pericardial effusion.</td>
</tr>
<tr>
<td>Hayes et al^6</td>
<td>One patient with pericardial tamponade (CW) received prothrombin complex concentrate and pericardiocentesis.</td>
</tr>
<tr>
<td>Kwak et al^8</td>
<td>Blood transfusion for 1 hemopericardium (CW).</td>
</tr>
<tr>
<td>Hakalahti et al^11</td>
<td>Two femoral hematomas (1 in DW, 1 in CW) requiring surgery because of damage to the femoral artery.</td>
</tr>
<tr>
<td>Page et al^9</td>
<td>Two pericardiocentesis (CW), with 1 patient receiving protamine and protrombin complex, and 1 receiving only protamine. One large hematoma requiring surgery (DW).</td>
</tr>
</tbody>
</table>

DW indicates warfarin discontinuation; CW, continuous warfarin; FFP, fresh frozen plasma; Hb, hemoglobin.

is very unlikely to be feasible, unless patients at higher risk of thromboembolic events (ie, CHADS\(_2\) score \( \geq 2 \)) and a higher event rate of periprocedural thromboembolism were considered to reduce the sample size. On these premises, we should rely on available evidence from observational studies to steer guideline recommendations, and a meta-analytic approach is the best way to appraise such evidence.

Other methods of interpretation of available studies, as is the case for expert consensus opinions,\(^1,3\) have several disadvantages that meta-analyses may overcome. Expert opinions are subjective and, therefore, prone to bias and error. Without guidance by formal rules, experts can disagree about what types of studies are appropriate to include and how to balance the quantitative evidence they provide; selective inclusion of studies that support the experts’ views is also common. This approach to evidence-based medicine is clearly unsound because it ignores sample size, effect size, and research design. However, the current meta-analysis incorporates one such judgment by a priori substitution of safety results of the Worldwide Survey for those of all other published DW case series. We base this on expert consensus that the Worldwide Survey, which is the largest study assessing the safety of AF ablation (with DW as the periprocedural anticoagulation strategy) in multiple AF ablation centers, tracks the current standards of care to the extent that results have been incorporated in the international guidelines on catheter ablation of AF. Although the survey was potentially subject to selection bias in that only 85 centers responded, single-institution case series publications are also self-selected, and other case series on safety of AF ablation with DW and periprocedural bridging with heparin have consistently reported risks of stroke/TIA consistent with the Worldwide Survey and higher than that reported by Hussein et al\(^7\) (range, 1%–5%\(^19,21-24\)). Moreover, removal of the Hussein et al case series and the Worldwide Survey did not materially change our results.

Although randomized controlled trials remain the gold standard to derive high-quality evidence, meta-analyses (including that of observational studies) provide an objective appraisal of all the available evidence, which is relevant to steer recommendations in the absence of properly designed randomized trials. On the basis of the available evidence, experts should not continue to recommend DW because CW has been consistently shown to be a superior periprocedural anticoagulation strategy. On the other hand, it should also be emphasized that the studies included in the present analysis were conducted in highly experienced AF ablation centers, with the majority of the patients deriving from 2 large multicenter series. Whether the benefit and safety of CW also extend to low-volume centers merits further investigation.

Conclusions

Compared with DW, CW reduces periprocedural thromboembolic complications without increasing the risk of major bleeding events, including cardiac tamponade, at least when ICE monitoring is adopted.

Disclosures

Dr Natale has received consultant fees or honoraria from Biosense Webster, Boston Scientific, Medtronic, Biotronik, and LifeWatch.

References


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Periprocedural thromboembolic and hemorrhagic events represent potential complications of radiofrequency catheter ablation of atrial fibrillation. Proper anticoagulation management is important to minimize the risk of such complications. For years, periprocedural warfarin discontinuation with bridging with low-molecular-weight heparin has been the recommended and most widely adopted anticoagulation protocol in patients undergoing atrial fibrillation ablation. The risk of periprocedural thromboembolism with such an anticoagulation strategy is also nonnegligible, ranging from 1% to 5%. Recent observational data suggest that performing catheter ablation of atrial fibrillation under therapeutic warfarin may reduce the periprocedural risk of complications, such as thromboembolic events. The present review systematically evaluated the benefits of periprocedural maintenance of therapeutic warfarin compared to warfarin discontinuation with heparin bridging. With >27 000 patients undergoing atrial fibrillation ablation in different institutions, the present analysis includes the largest population to date in which different periprocedural anticoagulation strategies have been compared and mainly shows that performing ablation procedures without discontinuing therapeutic warfarin reduces the risk of periprocedural thromboembolism without increasing the risk of bleeding. Because of the relatively low incidence of such events, a randomized trial with an adequate power to address these issues is unlikely to be feasible. The results of this analysis provide the strongest evidence to date that periprocedural maintenance of therapeutic warfarin should be considered the best available periprocedural anticoagulation strategy in patients undergoing catheter ablation of atrial fibrillation.

Ablation of Atrial Fibrillation Under Therapeutic Warfarin Reduces Periprocedural Complications: Evidence From a Meta-Analysis
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