The Optimal Range of International Normalized Ratio for Radiofrequency Catheter Ablation of Atrial Fibrillation during Therapeutic Anticoagulation with Warfarin

Running title: Kim et al.; INR Levels and Complications

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Abstract:

**Background** - Uninterrupted anticoagulation with warfarin during radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) is associated with a lower risk of periprocedural complications than when warfarin is temporarily discontinued. However, the optimal international normalized ratio (INR) levels during RFA have not been defined.

**Methods and Results** - In this retrospective analysis, RFA was performed in 1133 consecutive patients (mean age: 61±10 years) with paroxysmal (550) or persistent AF (583). Patients were grouped based on the INR on the day of RFA. There was a quadratic relationship between the INR and bleeding and vascular complications (P<0.001). Complications were less prevalent when INR was ≥2.0 and ≤3.0 (5% [31/572]), than when INR was <2.0 (10% [49/485], P=0.004) and >3.0 (12% [9/76], P=0.03). The prevalence of pericardial tamponade (1%) was similar at all INRs. From the quadratic model, the optimal range of INR was calculated as 2.1 to 2.5, INRs <2.0 and >3.0 were associated with a >2-fold increase in complications, with a further steep rise beyond an INR >3.5. Concomitant clopidogrel use was associated with a significant increase in complications at all INRs (OR=3.1, ±95% CI: 1.4-7.4). Unfractionated heparin requirements to maintain a therapeutic ACT during RFA was reduced by 50% in patients with an INR >2.0.

**Conclusions** - The optimal INR range during uninterrupted periprocedural anticoagulation using warfarin is narrow. Therefore INR levels should be carefully monitored in preparation for radiofrequency catheter ablation of AF.

**Key words**: ablation; atrial fibrillation; complication; warfarin; bleeding
Recent studies have demonstrated that uninterrupted therapeutic anticoagulation with warfarin during radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) is associated with a lower risk of thromboembolic and bleeding complications compared to interrupted warfarin and bridging with fractionated and/or unfractionated heparin.\textsuperscript{1-4} However, the optimal range of international normalized ratios (INRs) has not been well-defined. The purpose of this study was to determine the relationship between INR and the risk of thromboembolic and bleeding complications in patients undergoing RFA of AF.

**Methods**

**Study Subjects**

The subjects of this study were 1133 consecutive patients who underwent RFA to eliminate AF with uninterrupted anticoagulation using warfarin between January 2010 and December 2011. There were 832 men and 301 women. The mean age was 61±10 years. AF was paroxysmal in 550 and persistent in 583. The mean left atrial size and left ventricular ejection fraction were 44±7 mm and 0.56±0.11, respectively. The clinical characteristics of patients are shown in Table 1.

**Anticoagulation Protocol**

All patients were scheduled to undergo RFA of AF without discontinuing warfarin. Warfarin therapy was started ≥4 weeks before the procedure with an INR goal of 2.0-3.0. A transesophageal echocardiogram (TEE) was performed in all patients who had persistent AF, a prior thromboembolic event or left atrial appendage (LAA) thrombus, or who had been in AF for >48 hours without adequate anticoagulation prior to the procedure. The INR was measured within 60 minutes before the RFA procedure. Unfractionated heparin was administered as a bolus (50-100 U/kg) after the transeptal puncture and then continuously infused to maintain an ACT of 300-350 seconds. The sheaths were removed once the ACT returned to baseline values. In all patients, the
regular maintenance dose of warfarin was continued. In patients with an INR ≥2.0 on the day of the procedure, no additional heparin was administered after the procedure. In patients with an INR <2.0 on the day of the procedure intravenous heparin was infused 3 hours after vascular hemostasis was achieved and maintained during an overnight hospital stay. If the INR was still <2.0 the morning after the procedure, the patient was discharged home on LMWH (0.5 mg/kg SQ, bid) until the INR was ≥2.0. Anticoagulation with warfarin was continued for ≥3 months after the RFA.

**Electrophysiologic Study and Radiofrequency Catheter Ablation**

All patients provided informed written consent. The procedures were performed in the fasting state under moderate or deep sedation using propofol, fentanyl sodium and midazolam at the direction of an anesthesiologist. Among the 1133 patients, 505 (45%) presented in sinus rhythm and 628 (45%) presented in AF. Vascular access was obtained through a femoral vein using the modified Seldinger technique. A 7 Fr short sheath, and two 8.5 Fr SL 0 sheaths (St. Jude Medical) were placed into the same vein. A steerable decapolar catheter (Biosense Webster, Diamond Bar, CA) was positioned in the coronary sinus for recording electrograms and atrial pacing. Bipolar electrograms were displayed and recorded at filter settings of 30 to 500 Hz (EPMed Systems, West Berlin, NJ, USA). After the transeptal puncture, antral pulmonary vein (PV) isolation was performed in all patients using a 3-dimensional electroanatomical mapping system (Carto 3, Biosense Webster). All PVs were mapped with a circular deca- or duo-decapolar catheter (Lasso, Biosense Webster). Ablation of complex fractionated atrial electrograms or linear ablation was performed at the discretion of the operator. A 3.5-mm, open-irrigation-tip catheter (Thermocool, Biosense Webster) was used for mapping and radiofrequency energy delivery at a power of 20-35 W, and a flow rate of 17-30 mL/min, and a maximum temperature of 48 °C.
Postprocedural Management and Follow-Up

All patients had electrocardiographic monitoring during an overnight hospital stay after the RFA. All patients were seen in an outpatient clinic 3 months after the procedure or sooner as necessary. Long-term follow-up was performed by clinic visits or telephone and mail.

Study Protocol

The study protocol of this retrospective analysis was approved by the Institutional Review Board. With a perspective on clinic utility, patients were categorized a priori, based on the preprocedural INR as follows: INR<1.5, 1.5 to <2.0, 2.0 to ≤2.5, 2.5 to ≤3.0, 3.0 to ≤3.5, and >3.5. However, regression analysis was performed incorporating INR as a continuous variable to identify a predictive model.

Complications were analyzed in 4 categories: 1) major bleeding complications; 2) minor bleeding complications; 3) thromboembolic complications; and 4) other complications. Major bleeding complications were defined as: 1) pericardial tamponade that required percutaneous or surgical drainage; 2) vascular complications such as arteriovenous (AV) fistula, pseudoaneurysm, or hematoma that required percutaneous/surgical intervention, rehospitalization, a longer hospital stay, or a blood transfusion. Minor bleeding complications were defined as groin hematoma or any bleeding that did not require an intervention or prolonged hospitalization such as self-limited hematuria, or epistaxis. Groin hematoma was defined as a symptomatic swelling at the vascular access site with an obvious collection of blood. Thromboembolic complications included ischemic stroke, peripheral thromboembolic events, and deep vein thrombosis (DVT). Although not reported in this study, potential complications include pulmonary vein stenosis, atrioesophageal fistula, and phrenic nerve palsy.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD). Continuous variables
were compared by one-way analysis of variance (ANOVA) with post-hoc analysis using Tukey’s HSD (Honestly Significant Difference) test. Kruskal-Wallis’ test was used for analysis of continuous variables that did not have equal variance (baseline ACT, mean and maximum ACT, and unfractionated heparin per body weight). Categorical variables were reported as counts and percentages, and compared using $\chi^2$ test or Fisher’s exact test as appropriate. Confounding variables affecting both INR and bleeding complications were evaluated using Pearson’s correlation test or Spearman’s rank correlation test. A multivariate logistic regression analysis was performed to determine the relationship between INR and complications. All potential parameters suggestive of an association with complications including the square of INR (based on the distribution pattern of complications according to INR), were included in a stepwise regression analysis as the variable-selection process. From the regression analysis, a quadratic model was developed and applied for the binary outcomes of bleeding complications as follows: Logit ($\Pr[Y=1]$) = $\alpha + \beta X + \gamma X^2 + \delta C$, where $Y$ is the dichotomous outcomes of bleeding complications, $X$ is the continuous INR value, and $C$ is the binary indicator of a covariant such as clopidogrel use.

Then the goodness-of-fit of the data across different polynomial logistic regression models, were assessed using the AIC (Akaike Information Criterion) under 1) the null model ($\beta=0, \gamma=0$), 2) the linear model ($\gamma=0$), 3) the quadratic model, and 4) the cubic model with the additional parameter, $X^3$. From the quadratic logistic regression curve, it is possible to define an INR value at which the lowest likelihood of bleeding complications can be estimated. The value of $x$-coordinate of the angular point can be calculated as $-\beta/2\gamma$. Confidence intervals of those angular points are determined using parametric bootstrapping; 100,000 sets of parameters ($\alpha, \beta, \gamma, \delta$) are sampled from the multivariate normal distribution with mean and covariance of the estimated parameters, under the generalized linear model (GLM) described in equation; Logit ($\Pr[Y=1]$) = $\alpha + \beta X + \gamma X^2 + \delta C$. The safety range of INR levels for complications can be considered within 95% of the
confidence intervals of \(-\beta/2\gamma\). All data were analyzed using SPSS statistical software (SPSS, Chicago, IL, USA). A \(P < 0.05\) indicated statistical significance.

Results

Procedural INR Levels

Among the 1133 patients, 485 (43\%) had an INR < 2.0, 572 (50\%) had an INR ≥ 2.0 and ≤ 3.0, and 76 (7\%) had an INR > 3.0. The INR range was 0.9 to 4.2, and 13 patients (1\%) had an INR > 3.5. The clinical characteristics and distribution of INRs are shown in detail in Table 1. The mean CHADS\(_2\) scores were similar among all groups. Aspirin was used less frequently when the INR was > 3.0 (26\%) than ≥ 2.0 and ≤ 3.0 (38\%) and < 2.0 (43\%, \(P = 0.02\)). Clopidogrel use was similar at all INRs. There was no significant difference in plasma hemoglobin, hematocrit, and platelet counts (Table 1). There were not any clinical or laboratory predictors of INR levels.

INR Levels and Intraprocedural ACT and Heparin Requirements

There was a direct correlation between INR and baseline ACT (\(r = 0.64, P < 0.001\)), mean ACT (\(r = 0.44, P < 0.001\)), and maximum ACT during RFA (\(r = 0.25, P < 0.001\), Figure 1A, 1B, and 1C, respectively). There was a negative correlation between the INR and the total heparin dose adjusted for body weight during the RFA procedure (\(r = -0.61, P < 0.001\), Figure 1D). The mean baseline ACT was 153 ± 31s in patients with INRs < 2.0, 189 ± 23s in patients with INRs of 2-3, and 211 ± 25s in patients with INRs > 3.0 (\(P < 0.001\) for all comparisons). The mean ACT during the procedure was 323 ± 19s when the INR was < 2.0, and was significantly lower than when the INR was 2.0-3.0 (339 ± 19s, \(P < 0.001\)) and when INR was > 3.0 (342 ± 20s, \(P < 0.001\)). The maximum ACT during the procedure in patients with an INR < 2.0, 360 ± 15s, was also significantly lower than in patients with an INR 2-3, 368 ± 19s (\(P < 0.001\)), and in patients with an INR > 3.0, 370 ± 18s (\(P < 0.001\)).
The mean total heparin dosage needed to maintain a therapeutic ACT during RFA was lower in patients with an INR of 2-3 (133±55 U/kg) and >3.0 (103±41 U/kg) than in patients with an INR <2.0 (235±101 U/kg, P<0.001). There was no further decrease in total heparin requirements once the INR was >2 (Table 1).

**Procedural Complications**

Bleeding complications occurred in 89/1133 patients (8%) and included minor bleeding in 56 (5%), vascular complications in 19 (2%); and pericardial tamponade in 14 (1%, Table 2).

Thromboembolic complications occurred in 3 patients (0.3%) after RFA, and included a transient ischemic attack (TIA) in 2 (0.2%) and DVT of a lower extremity in 1 (0.1%). Except in 3 patients, all bleeding complications occurred during or shortly after the RFA while the patient was monitored as an inpatient. A delayed groin hematoma developed in 3 patients 4.0±2.6 days after the RFA and prompted a readmission. All of these patients were receiving LMWH for an INR <2.0. Hematoma resolved without intervention in these 3 patients.

A TIA occurred in 2 patients within few hours after the RFA and completely resolved within 6-12 hours. Both of these patients had persistent AF and there was no evidence of intracardiac thrombus on TEE prior to the procedure. Their CHA$_2$DS$_2$-VASc scores were 2 and 1. At the time of TIA, they both were in sinus rhythm and had an INR of 1.1 and 1.5. They were receiving heparin. On neurologic imaging (CT and MRI) there was no evidence of an intracerebral thromboembolic event.

One patient had an acute DVT in right iliofemoral vein just after the procedure and the patient was in sinus rhythm. His CHA$_2$DS$_2$-VASc score was 2 and INR was 1.3. This patient received an inferior vena cava (IVC) filter and heparin bridging to warfarin. All patients with thromboembolic complications had an INR <2.0. Among the 1133 patients, only 1 experienced more than one complication, an arteriovenous fistula and a DVT. There were no other
complications.

**INR and Complications**

Patients with an INR <1.5 had more bleeding complications than patients with an INR ≥2.0 and <2.5 (12% vs. 4%; P<0.001, Figure 3). Patients with an INR <1.5 also had more vascular complications and groin hematomas than patients with an INR >2 and <2.5 (3% vs. 1%, P = 0.02; and 8% vs. 3%; P = 0.006, respectively). The prevalence of total bleeding complications was not significantly different in patients with INRs of 2.0 to 3.5 (Figure 2), however significantly increased in patients with an INR >3.5 (31%) compared to patients with lower INRs of ≥2.0 and <2.5 (4%, P=0.003), ≥2.5 and <3.0 (8%, P=0.02) and ≥3.0 and <3.5 (8%, P=0.04, Figure 2).

**Procedural ACT Levels, Heparin Requirements and Complications**

The baseline ACT did not correlate with major or minor bleeding complications. The mean and maximum ACT during the procedure had a positive correlation with pericardial tamponade (r=0.09, P=0.004; and r=0.09, P=0.002, respectively). There was a direct relationship between the total heparin requirements and vascular complications (r=0.06, P=0.04) and groin hematomas (r=0.08, P=0.01). On multivariate analysis, however, there was no association between ACT levels or heparin requirements and bleeding or vascular complications.

In patients with an INR <2.0, the prevalence of bleeding complications was 35/433 (8%) when heparin was used, 28/373 (8%) when LMWH was used, and 3/12 (25%) when clopidogrel was used.

**The INR and Risk of Complications**

Because the distribution of bleeding complications based on INR was U-shaped, a quadratic logistic regression model was utilized to analyze the relationship between the bleeding complications and INR. Although clopidogrel use had a weak correlation with INR (r=0.06, P=0.04) and with both total bleeding complications (r=0.08, P=0.006) and groin hematomas
(r=0.09, P=0.004), clopidogrel use was a significant explanatory variable for the quadratic INR function determined by the variable selection procedure (P=0.01). Therefore, logistic regression analysis was adjusted according to clopidogrel use. There were no other clinical predictors of complications.

On logistic regression analysis of the INR vs. bleeding complications, the quadratic model had a better goodness-of-fit (AIC=606, P<0.001, Figure 3) than the null (AIC=622) and linear models (AIC=622). There was no relationship between pericardial tamponade and INR either by the linear or quadratic models. There was a significant relationship between the INR and vascular complications (P=0.03) and groin hematomas (P<0.001).

Clopidogrel use was associated with a higher probability of developing overall bleeding complications (OR=3.1; ±95% CI: 1.4-7.4; P=0.006) and groin hematomas (OR=3.7; ±95% CI: 1.4-9.4; P=0.007), but not with pericardial tamponade (P=0.4) or vascular complications (P=0.6).

From the x-coordinate of vertex (angular point; -\(\beta/2\gamma\)) in the quadratic equation and its 95% confidence interval (CI), optimal range of INR associated with the lowest risk of an adverse event was estimated as, 2.3 (±95% CI: 2.1-2.5) for total bleeding complications, 2.5 (±95% CI: 0.6-5.4) for vascular complications, and 2.2 (±95% CI: 2.0-2.5) for groin hematomas (Figure 3 and Table 3).

Discussion

Main Findings

The main findings of this study are: 1) there is a quadratic relationship between the preprocedural INR and the risk of hemorrhagic or thromboembolic complications during RFA of AF; 2) the risk of bleeding and thromboembolic complications is higher when the INR is subtherapeutic (<2) and the risk of bleeding complications is higher when the INR is >3, with a further steep increase in
risk at INRs >3.5; 3) there is no relationship between the INR and risk of pericardial tamponade; 4) intraprocedural heparin requirements to maintain an ACT between 300-350 seconds are reduced by 50% when the INR is >2. However when the INR is >2, there is no relationship between INR and heparin requirements; 5) there is a weak but significant direct relationship between the ACT during RFA and the risk of pericardial tamponade; and 6) concomitant clopidogrel use appears to be associated with a 3-fold increase in bleeding complications.

**Procedural INRs, Heparin Requirements and ACT Levels**

The optimal range of INRs for RFA of AF has not been described. INR levels often vary prior to a scheduled procedure due to changes in diet, travel and NPO status. Therefore the INR may be outside of the typical 2-3 range immediately prior to the procedure. In this study INR was within the range of 2-3 in only 50% of patients.³

Despite therapeutic anticoagulation with warfarin, it has been recommended to maintain the ACT at >300 seconds during RFA of AF.⁶ In patients with an INR of 1, unfractionated heparin at initial doses of 100-120U/kg usually is required to achieve such ACT levels with subsequent intermittent boluses or continuous infusion during RFA. A prior study demonstrated that baseline ACT levels were higher in patients with an INR ≥2 than <2.⁷ In this study, baseline ACT levels were elevated by ~25% and ~40% in patients with INRs >2 and >3, respectively. Total intraprocedural heparin dose was reduced by ~50%. However, there was no further decrease in heparin requirements at INRs >2.0.

Warfarin and heparin interfere with different components of the coagulation cascade. Warfarin has a facilitatory role on the anticoagulant effects of heparin,⁸ which is likely to become saturated at INRs >2. The findings of this study suggest that unfractionated heparin should be administered at half of the regular dose, i.e., 50-60 U/kg in patients with an INR >2. This is likely to prevent overshooting of the target ACT range, which was shown to correlate with the risk of
pericardial tamponade in this study. The optimal dose of heparin during RFA in patients with a therapeutic INR remains to be determined.

**Complications**

The prevalence of major and minor complications was 8% in this study, and included minor bleeding in 5%, vascular complications in 2%, pericardial tamponade in 1% and thromboembolic events in 0.3%. The prevalence of bleeding and vascular complications has been reported to vary between 0.8 to 13% previously. In a worldwide survey of RFA for AF, major complications including AV fistula and pseudoaneurysm, and pericardial tamponade were reported in 1.5% and 1.3% of the patients, respectively. A number of variables such as the rigor with which complications, particularly the minor ones are recorded, the technique and technology used for vascular access and RFA, anticoagulation regimen, patient characteristics, operator experience and RFA settings can each affect the risk of complications.

In this study, a U-shaped relationship between INR and bleeding complications was observed. INRs <2 and >3 were associated with a ~2 fold increase in the risk of bleeding complications. In patients with a subtherapeutic INR, total heparin requirements during RFA and the need for LMWH after the procedure are greater than in patients who have a therapeutic INR. Prior studies have demonstrated that uninterrupted anticoagulation with warfarin at INRs >2 is associated with fewer bleeding complications compared to interrupted warfarin. In this study there was a direct relationship between the total dose of heparin and the risk of complications. LMWH has been recognized to increase the risk of vascular and bleeding complications, even at reduced doses. Large doses of heparin and LMWH lead to wide variations in anticoagulant activity and lead to an increase in the risk of bleeding complications, particularly groin hematomas and vascular complications. On the other hand, a consistent and therapeutic anticoagulant milieu during RFA can be achieved with uninterrupted anticoagulation using warfarin and lower doses of
Therefore, use of heparin products particularly LMWH as a bridge to therapeutic anticoagulation with warfarin in patients who present with a subtherapeutic INR prior to the procedure is likely to increase the risk of bleeding complications and should be minimized whenever possible.

A new finding of this study is that the risk of bleeding complications increased by 2-fold in patients who had an INR >3, with a further 6-fold increase when the INR exceeded 3.5. Patients who had an INR >3 or >3.5 received lower total doses of heparin. Therefore, the increase in bleeding complications during or shortly after the procedure at INRs >3 most likely is due to the incremental anticoagulant effects of warfarin, further augmented by a synergistic effect of heparin.

**Clopidogrel use was an independent predictor of bleeding complications and was associated with a significant 3-fold increase in the risk of bleeding complications at all INRs.** An association between the clopidogrel use and the risk of bleeding complications after RFA, independent of concomitant warfarin use, was reported previously. Therefore, although the number of patients on clopidogrel in this study was small, it seems to be advisable to discontinue clopidogrel prior to RFA whenever possible.

**Pericardial Tamponade, INR and ACT Levels**

The prevalence of pericardial tamponade during RFA of AF appears to be independent of the anticoagulation regimen, suggesting that mechanical or RF-energy-related perforation is the key factor. A recent study demonstrated that outcomes of patients who had pericardial tamponade during RFA were similar regardless of the intensity of anticoagulation. In this study, there was no relationship between the INR and pericardial tamponade. Because the procedure was terminated prematurely, the total heparin dosage was lower in patients who had pericardial tamponade than those who did not. On the other hand, there was a direct correlation between the risk of pericardial tamponade and both the mean and maximum ACT during RFA. Therefore, it is
plausible that in patients with a therapeutic INR, high ACT levels may facilitate progression of a small puncture to tamponade. Although ACT levels $\geq$400 seconds are targeted at some centers, it is possible that this increases the risk of tamponade.

**Study Limitations**

A limitation of this retrospective analysis is the small number of patients who had INR values $>$3.5. However, this did not negate the ability to detect a strong association with an increased risk of bleeding complications.

**Clinical Implications**

The optimal INR during uninterrupted therapy with warfarin for RFA of AF falls into a rather narrow range of 2.1 – 2.5. To minimize the risk of bleeding complications, it may be helpful to start monitoring INR earlier and more frequently before the procedure to achieve steady-state, stable INR values within the desired range. High ACT levels ($>$350 seconds) during RFA may be associated with a higher risk of pericardial tamponade. Total heparin dose should be reduced by 50% in patients with an INR $>$2. Concomitant clopidogrel use with warfarin appears to be associated with almost a 3-fold increase in the risk of bleeding complications and should be avoided when possible. Whether the use of new anticoagulants such as dabigatran or rivaroxaban will prove to be safer than uninterrupted warfarin during RFA of AF remains to be determined.

**Conflict of Interest Disclosures:** None.

**References:**


Table 1. Clinical Characteristics of Study Subjects

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<th></th>
<th>INR&lt;1.5</th>
<th>INR 1.5-1.9</th>
<th>INR 2.0-2.5</th>
<th>INR 2.6-3.0</th>
<th>INR 3.1-3.5</th>
<th>INR &gt; 3.5</th>
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<td>Age (years)</td>
<td>61 ± 11</td>
<td>62 ± 9</td>
<td>61 ± 9</td>
<td>60 ± 10</td>
<td>61 ± 9</td>
<td>60 ± 9</td>
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<td>Female</td>
<td>77 (26%)</td>
<td>58 (31%)</td>
<td>94 (25%)</td>
<td>52 (26%)</td>
<td>16 (25%)</td>
<td>4 (31%)</td>
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<td>Non-paroxysmal AF</td>
<td>149 (51%)</td>
<td>94 (50%)</td>
<td>195 (52%)</td>
<td>101 (51%)</td>
<td>35 (56%)</td>
<td>9 (69%)</td>
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<tr>
<td>Previous ablation</td>
<td>144 (49%)</td>
<td>93 (49%)</td>
<td>181 (52%)</td>
<td>101 (41%)</td>
<td>33 (56%)</td>
<td>8 (62%)</td>
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<td>BMI (kg/m²)</td>
<td>30 ± 6</td>
<td>31 ± 6</td>
<td>32 ± 6</td>
<td>31 ± 7</td>
<td>31 ± 6</td>
<td>29 ± 7</td>
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<td>CHADS² score</td>
<td>0.86 ± 0.89</td>
<td>1.09 ± 1.0</td>
<td>0.97 ± 0.96</td>
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<td>LA (mm)</td>
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<td>45 ± 7</td>
<td>44 ± 8</td>
<td>44 ± 8</td>
<td>45 ± 6</td>
<td>42 ± 10</td>
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<td>LVEF (%)</td>
<td>56 ± 11</td>
<td>55 ± 12</td>
<td>57 ± 11</td>
<td>58 ± 9</td>
<td>56 ± 10</td>
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<td>Aspirin</td>
<td>134 (45.4%)</td>
<td>74 (38.9%)</td>
<td>136 (36.6%)</td>
<td>84 (42.0%)</td>
<td>16 (25.4%)</td>
<td>4 (30.8%)</td>
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<td>Clopidogrel</td>
<td>7 (2.4%)</td>
<td>5 (2.6%)</td>
<td>14 (3.8%)</td>
<td>13 (6.5%)</td>
<td>2 (3.2%)</td>
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<td>Hemoglobin (g/dL)</td>
<td>14.3 ± 1.4</td>
<td>14.2 ± 1.5</td>
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<td>14.3 ± 1.4</td>
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<td>Hematocrit (%)</td>
<td>41.8 ± 3.8</td>
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<td>42.0 ± 3.9</td>
<td>42.4 ± 3.9</td>
<td>41.7 ± 3.8</td>
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<td>Platelet (x 10^3)</td>
<td>202 ± 53</td>
<td>201 ± 53</td>
<td>201 ± 51</td>
<td>204 ± 60</td>
<td>189 ± 55</td>
<td>188 ± 58</td>
<td>0.46</td>
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<td>Baseline ACT (s)</td>
<td>137 ± 31^a</td>
<td>165 ± 25^b</td>
<td>183 ± 20^c</td>
<td>200 ± 23^d</td>
<td>212 ± 25^d</td>
<td>207 ± 21^d</td>
<td>&lt;0.001*</td>
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<td>Maximum ACT (s)</td>
<td>358 ± 15^a</td>
<td>363 ± 15^ab</td>
<td>368 ± 18^b</td>
<td>368 ± 21^b</td>
<td>370 ± 19^b</td>
<td>370 ± 14^b</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean ACT (s)</td>
<td>317 ± 18^a</td>
<td>332 ± 18^b</td>
<td>337 ± 19^bc</td>
<td>341 ± 18^bc</td>
<td>342 ± 21^bc</td>
<td>344 ± 19^c</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UFH/kg body weight</td>
<td>271 ± 87^a</td>
<td>179 ± 96^b</td>
<td>140 ± 53^c</td>
<td>121 ± 56^ed</td>
<td>100 ± 37^d</td>
<td>115 ± 59^d</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

^a,b,c,d: same letters indicate no significant difference based on Tukey’s HSD test.

BMI = body mass index; AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; ACT = activated clotting time; UFH = unfractionated heparin; RF = radiofrequency.
Table 2. Complications

<table>
<thead>
<tr>
<th></th>
<th>INR &lt; 1.5</th>
<th>INR 1.5-1.9</th>
<th>INR 2.0-2.5</th>
<th>INR 2.6-3.0</th>
<th>INR 3.1-3.5</th>
<th>INR &gt; 3.5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=295</td>
<td>N=190</td>
<td>N=372</td>
<td>N=200</td>
<td>N=63</td>
<td>N=13</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (4.7%)</td>
<td>5 (2.6%)</td>
<td>6 (1.6%)</td>
<td>6 (3.0%)</td>
<td>1 (1.6%)</td>
<td>0</td>
<td>0.20</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>4 (1.4%)</td>
<td>2 (1.1%)</td>
<td>3 (0.8%)</td>
<td>4 (2.0%)</td>
<td>1 (1.6%)</td>
<td>0</td>
<td>0.87</td>
</tr>
<tr>
<td>Vascular</td>
<td>10 (3.4%)</td>
<td>3 (1.6%)</td>
<td>3 (0.8%)</td>
<td>2 (1.0%)</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>22 (7.5%)</td>
<td>8 (4.2%)</td>
<td>10 (2.7%)</td>
<td>9 (4.5%)</td>
<td>4 (6.3%)</td>
<td>3 (23.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1 (0.3%)</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.57</td>
</tr>
<tr>
<td>DVT</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.58</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; TIA = transient ischemic attack; DVT = deep vein thrombosis.

Table 3. Quadratic Model for INR and the Risk of Complications

Logit (Pr[Y=1]) = α + βX + γX² + δC

Y: binary outcomes of bleeding complications, X: INR as a continuous variable, C: binary covariant of clopidogrel use

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Cardiac tamponade</th>
<th>Vascular complications</th>
<th>Groin hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B ± S.E.</td>
<td>P-value</td>
<td>B ± S.E.</td>
</tr>
<tr>
<td>α</td>
<td>0.79 ± 0.72</td>
<td>0.27</td>
<td>-3.70 ± 1.91</td>
</tr>
<tr>
<td>β</td>
<td>-3.38 ± 0.73</td>
<td>&lt;0.001</td>
<td>-0.92 ± 1.83</td>
</tr>
<tr>
<td>γ</td>
<td>0.75 ± 0.17</td>
<td>&lt;0.001</td>
<td>0.25 ± 0.41</td>
</tr>
<tr>
<td>δ</td>
<td>1.15 ± 0.42</td>
<td>0.007</td>
<td>0.67 ± 1.06</td>
</tr>
<tr>
<td>-β/2γ</td>
<td>2.3 (95% CI: 2.1 – 2.5)</td>
<td>1.8 (95% CI: 1.4 – 4.2)</td>
<td>2.5 (95% CI: 0.6 – 5.4)</td>
</tr>
</tbody>
</table>

*: x-coordinate of the vertex on a quadratic equation. This point indicates the INR value associated with the lowest risk of bleeding complication.

B = regression coefficient; INR = international normalized ratio; S.E.= standard error.
Figure Legends:

**Figure 1.** Correlation between the INR and ACT levels (baseline, mean, and maximum ACT in seconds) and heparin requirements during RFA (Panels A, B, C, and D, respectively). ACT: activated clotting time, UFH: unfractionated heparin, INR: international normalized ratio.

**Figure 2.** Complications and INR levels. Shown are all complications according to the INR levels. Abbreviations as in Figure 1.

**Figure 3.** Quadratic logistic regression model explaining the relationship between all bleeding complications and INR. INR corresponding to the vertex of the quadratic equation (-\(\beta/2\gamma\); Table 3) is 2.3 with ±95% confidence intervals of 2.1 and 2.5.
Figure 2

Complications (%)

INR

- <1.5
- 1.5-1.9
- 2.0-2.5
- 2.6-3.0
- 3.1-3.5
- >3.5

INR < 2.0: N=485
433 received postprocedural heparin
373 received postprocedural enoxaparin

* : P = 0.02
** : P = 0.006

P = 0.003
P = 0.02
P = 0.04

Cardiac tamponade
Vascular complications
Groin hematoma
Figure 3

- $\beta/2\gamma$

Complications (%)

INR

Cardiac tamponade
Vascular complications
Groin hematoma

without clopidogrel
with clopidogrel
95% confidence limits
The Optimal Range of International Normalized Ratio for Radiofrequency Catheter Ablation of Atrial Fibrillation during Therapeutic Anticoagulation with Warfarin

Jin-Seok Kim, Krit Jongnarangs, Rakesh Latchamsetty, Aman Chugh, Hamid Ghanbari, Thomas Crawford, Miki Yokokawa, Eric Good, Frank Bogun, Frank Pelosi, Jr., Fred Morady and Hakan Oral

Circ Arrhythm Electrophysiol. published online February 26, 2013;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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