# Unreliability of International Normalized Ratio for Monitoring Warfarin Therapy in Patients with Lupus Anticoagulant

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**Study Objective.** To compare the international normalized ratios (INRs) of patients positive for lupus anticoagulant and the INRs of control patients receiving warfarin therapy with equivalent therapeutic chromogenic factor X levels.

**Design.** Prospective case series.

**Setting.** A 625-bed, adult, private, tertiary care teaching hospital.

**Patients.** Sixty-eight outpatients positive for lupus anticoagulant and 57 control patients receiving long-term warfarin therapy.

**Measurements and Main Results.** Concomitant INR and chromogenic factor X activity were measured in all patients. In 44 control patients (77%) and 46 patients with lupus anticoagulant (68%), chromogenic factor X activity was 22–40% of normal, which is therapeutic. Of the 44 control patients, 4 (9%) had an INR above 3.0, and none had an INR above 4.0. In contrast, 18 (39%) of the 46 patients with lupus anticoagulant had an INR above 3.0, and 5 (11%) had an INR above 4.0.

**Conclusion.** At least 10% of patients with lupus anticoagulant receiving long-term warfarin therapy may have falsely high INR values, which could lead to inappropriate warfarin dosage reduction. Monitoring warfarin therapy by chromogenic factor X activity in patients with lupus anticoagulant avoids this INR artifact.

**Key Words:** international normalized ratio, INR, warfarin therapy, lupus anticoagulant, chromogenic factor X activity.

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The lupus anticoagulant is an antiphospholipid antibody associated with a variety of venous and arterial thrombotic events, yet it is detected in the laboratory as a paradoxical prolongation of various clotting tests.[1] However, this prolongation is an in vitro phenomenon and does not reflect in vivo anticoagulation in patients with lupus anticoagulant. The lupus anticoagulant even may prolong the international normalized ratio (INR) in some patients who are not receiving warfarin therapy.[2–5]

Some laboratories report that patients with lupus anticoagulant treated with warfarin may have excessively elevated INR values unreflective of the true state of anticoagulation.[5–8] Other laboratories have not detected this artifactual INR elevation.[9, 10] Accordingly, controversy exists regarding the appropriate INR target for warfarin therapy in patients with lupus anticoagulant.[11–13]

An independent measure of warfarin effect that avoids the lupus anticoagulant clotting test artifact is the chromogenic factor X assay, an enzymatic measure of the activity of factor X, a vitamin K–dependent clotting factor. This assay has been the gold standard by which to assess anticoagulation status in patients with lupus

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anticoagulant.[5, 7, 9, 10] The results of the assay are reported as a percentage of normal activity: the lower the chromogenic factor X activity, the greater the warfarin effect. An INR of 2.0 in control patients treated with warfarin corresponds to a factor X activity of approximately 40% of normal, whereas an INR of 3.0 corresponds to a factor X activity of approximately 20%.[5, 7, 9, 14]

We have used the chromogenic factor X assay for monitoring warfarin-treated patients with lupus anticoagulant since 1999. The objective of this study was to describe the distribution of INR values in patients with lupus anticoagulant compared with warfarin-treated control patients who had the same therapeutic activity of factor X.

## Methods

### Patients

We measured concomitant INR and chromogenic factor X values in two groups of patients. The first group consisted of 57 consecutive warfarin-treated outpatients whose INRs had been measured during a 12-day period in one of our clinics. For the purposes of this study only, chromogenic factor X activity was measured at the same time. Of this group, 24 (42%) were women; median age was 74 years (range 41–90 yrs). This group was presumed to contain a low percentage of undiagnosed patients with lupus anticoagulant, since in this clinic physicians routinely test for lupus anticoagulant in patients with thrombosis.

The second patient group consisted of 68 consecutive outpatients from a number of clinics. From these patients, samples for chromogenic factor X testing had been sent to our reference laboratory over a 2-month period. Patients in this group had been diagnosed as positive for lupus anticoagulant by our laboratory sometime during the previous 4 years. Again, for study purposes only, INR values were obtained concomitantly. Of this group, 39 (57%) were women; median age was 50 years (range 24–90 yrs).

The lupus anticoagulant group was different from the control group in age, sex, and indication for anticoagulation, since all patients with lupus anticoagulant had experienced a thrombotic event. In contrast, the control group contained patients receiving prophylactic anticoagulation for atrial fibrillation or artificial heart valves. However, these differences should not affect the relationship between a patient's INR and factor X activity.

The patients with lupus anticoagulant were not retested for lupus anticoagulant for this study. Thus, some patients could have reverted to a negative lupus anticoagulant state. However, most physicians had monitored these patients with chromogenic factor X activity regularly since information about the stability of lupus anticoagulant status was lacking.

The study was reviewed by the institutional review board and met the criteria for exemption.

### Laboratory Assays

Blood samples were collected directly into 0.105-mol/L (3.2%) sodium citrate coagulation tubes (BD Vacutainer, Becton Dickinson Co., Franklin Lakes, NJ), which were centrifuged at 3000 x g for 10 minutes. Plasma was sampled in the coagulation analyzer directly from the centrifuged tubes to minimize platelet activation.

The INR was measured on Stago Compact and STA-R instruments using Neoplastine CI Plus reagent (Diagnostica Stago, Asnières-sur-Seine, France). This combination of reagent and instruments was carefully calibrated in 1998 using a series of fresh-frozen plasmas (Precision BioLogic, Dartmouth, Nova Scotia, Canada). These plasmas had known INR values determined in two internationally calibrated laboratories. Subsequently, each new lot of INR reagent was calibrated back to the original international standard.

Chromogenic factor X was measured on the Stago Compact using the DiaPharma Factor X Kit that uses the amidolytic substrate S-2765 and Russell's Viper venom as an activator (DiaPharma, West Chester, OH). Results were reported as a percentage of normal activity. The factor X assay is automated and available daily without delay in our laboratory.

The presence of lupus anticoagulant was confirmed using the Staclot LA assay (Diagnostica Stago) and the LA SURE dRVVT assay (Precision BioLogic) on the Stago Compact instrument (Diagnostica Stago). If either of these test results was positive, a patient was considered positive for lupus anticoagulant.

### Statistical Analysis

Descriptive statistics and group comparisons were performed with JMP 5 (SAS Institute, Cary, NC). Descriptive statistics are reported as medians and ranges; group comparisons of variables were made using the nonparametric Wilcoxon rank sum test. A p value of 0.05 or less was considered to indicate a statistically significant difference.

**Table 1. Chromogenic Factor X Activity and International Normalized Ratios in Controls and Patients with Lupus Anticoagulant**

| Measure of Warfarin Effect | Control Patients (n=44) | Patients with Lupus Anticoagulant (n=46) | p Value[a] |
|---|---|---|---|
| Chromogenic factor X activity | | | |
| Range (%) | 22–40 | 22–40 | |
| Median (%) | 32 | 30 | 0.1 |
| INR value | | | |
| Range | 1.9–3.9 | 1.7–5.5 | |
| Median | 2.4 | 2.8 | 0.02 |
| No. (%) of patients | | | |
| > 3.0 | 4 (9) | 18 (39) | |
| > 4.0 | 0 | 5 (11) | |

[a]Wilcoxon rank sum test.

## Results

Of the 57 patients in the control group, 44 (77%) had chromogenic factor X values in the therapeutic range (20–40%; Table 1). The median chromogenic factor X activity was 32% (range 22–40%). From the 68 patients with lupus anticoagulant, we identified 46 (68%) whose chromogenic factor X activity values were within the same 22–40% range to be sure that this group was comparable with the control group. The median chromogenic factor X activity in the lupus anticoagulant patient group was 30% (p=0.1 for the difference in factor X activity values between groups).

In the 44 control patients with chromogenic factor X values in the therapeutic range, the median INR was 2.4 (range 1.9–3.9) compared with the median INR in the lupus anticoagulant group was 2.8 (range 1.7–5.5; p=0.02 for the difference between the groups).

Four (9%) of the 44 control patients with therapeutic chromogenic factor X activity levels had an INR above 3.0; none had an INR above 4.0. In contrast, 18 (39%) of 46 patients with lupus anticoagulant and therapeutic chromogenic factor X activity levels had an INR above 3.0; 5 (11%) had an INR above 4.0.

Figure 1 shows the relationship between the chromogenic factor X activity and INR values in the control patients and those with lupus anticoagulant. Although most patients with lupus anticoagulant had the same relationship between chromogenic factor X activity and INR values as the controls, a subgroup of patients with lupus anticoagulant and disproportionately high INR values can be seen.

## Discussion

The target INR range for patients with lupus anticoagulant receiving warfarin therapy for thrombosis is often higher than that recommended for other patients.[1, 11, 12] It is not clear if this target was recommended because patients with lupus anticoagulant are more thrombogenic than others, or because the INR values of patients with lupus anticoagulant may overstate their true anticoagulation status.

The controversy about the validity of INR values in patients with lupus anticoagulant seems related to variability both in patients and in laboratory methods. Studies have suggested that

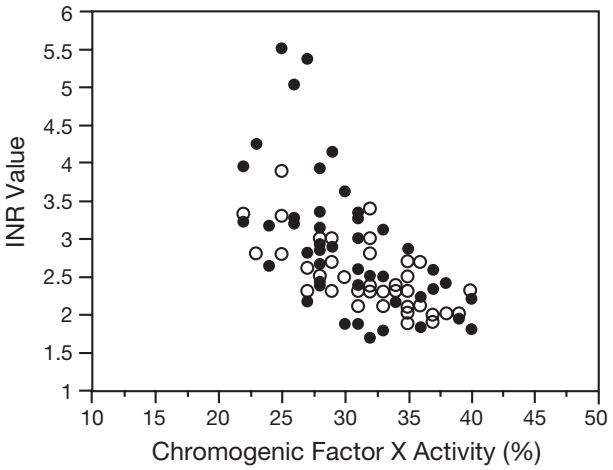


**Figure 1.** International normalized ratio (INR) versus chromogenic factor X activity values in control patients (❍) and patients with lupus anticoagulant (●). Factor X activity values are expressed as percentage of normal activity.

the INR variability problem may occur predominantly with recombinant human thromboplastins.[6–8] Of note, four studies reporting INR variability in patients with lupus anticoagulant involved 10, 34, 43, and 58 patients.[5–8] Two studies reporting a lack of variability involved 11 and 14 patients with lupus anticoagulant.[9, 10] Our study involved 46 patients with lupus anticoagulant. To decrease potential sources of bias, our INR assay was calibrated to international standards and did not use a recombinant human thromboplastin.

The INR artifact did not affect most of our patients. The lupus anticoagulant status of some of our patients may have reverted to a negative state since we did not reconfirm their status by retesting them at the time of the study. Also, it may be that only some patients have enough lupus anticoagulant, or the right type, to falsely elevate their INR.

Despite having therapeutic chromogenic factor X activity (20–40%), a noteworthy proportion (11%) of our patients had INR values above 4. If these patients had been monitored only with the INR, their warfarin dosage likely would have been reduced to a subtherapeutic level, leaving them at risk for thrombosis.

In many warfarin-treated patients with lupus anticoagulant, the INR may be a valid measure of anticoagulation, but it seems prudent to validate this with a concomitant chromogenic factor X activity assessed at steady state. If the INR is 2–3 at steady state and is associated with chromogenic factor X activity of 20–40%, it seems reasonable to continue monitoring the INR. However, if a therapeutic INR is associated with a chromogenic factor X activity clearly above 40%, it may be better to monitor the chromogenic factor X activity. The safety and reliability of this assay may be worth the additional cost in this high-risk group of patients.

Of importance, this study pertains only to patients positive for lupus anticoagulant and does not indicate that patients with other antiphospholipid antibodies need to have their INR validated with chromogenic factor X assays. Patients who have other antiphospholipid antibodies but are negative for lupus anticoagulant should have no risk of an INR artifact and can be reliably monitored with the INR.

Some of the uncertainty about the appropriate INR target range for warfarin treatment in patients with antiphospholipid antibodies may have been introduced by clinical treatment studies that involved patients who were positive or negative for lupus anticoagulant.[13] The greater the proportion of patients with lupus anticoagulant in any group of patients with antiphospholipid antibody, the greater the chance that an INR therapeutic range of 2–3 could result in undertreatment of some patients. However, if patients with lupus anticoagulant are in the minority, then the INR artifact would affect only a small number of patients, and INR ranges of 2–3 would seem appropriate.

## Conclusion

This study shows that a subgroup (at least 10%) of patients with lupus anticoagulant receiving warfarin therapy may have clinically important false elevations of their INR values. This false elevation could lead to potential undertreatment with warfarin if a standard INR range of 2–3 were used. To deal with this artifact, some specialists have recommended maintenance of a higher INR range in all patients with lupus anticoagulant. However, since many patients with lupus anticoagulant seem free of this artifact, it may be unreasonable to overtreat the majority in an effort to treat the minority appropriately. The chromogenic factor X activity assay is an independent measure of warfarin effect and can avoid overtreatment and undertreatment with warfarin in patients with lupus anticoagulant.

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