Correlation of Point-of-Care International Normalized Ratio to Laboratory International Normalized Ratio in Hemodialysis Patients Taking Warfarin

Robert W. Hoel,*† Robert C. Albright,‡ Lisa K. Beyer,§ Paula J. Santrach,‖ Donna L. Magtibay,‖ Stephanie L. Everson,‖ and Robert D. McBane¶

‡Division of Nephrology, §Department of Laboratory Medicine/Pathology, ‡Division of Cardiovascular Medicine, *Department of Pharmacy Services, ‖Department of Nursing, and ¶College of Medicine, Mayo Clinic, Rochester, Minnesota

Background and objectives: To determine whether point-of-care (POC) International Normalized Ratio (INR) test results correlate with plasma INR measures in intermittent hemodialysis (IHD) patients on warfarin. Anemia is thought to reduce the accuracy of POC INR assay results. Whether POC INR testing could be implemented for hemodialysis patients on chronic warfarin, who are often anemic despite hematopoietic therapy, has not been established.

Design, setting, participants, & measurements: Thirty-seven chronic hemodialysis patients on warfarin contributed sets of three consecutive blood samples for INR comparison immediately before hemodialysis: one finger stick, two from hemodialysis access (arteriovenous graft, fistula, or catheter). POC INR testing was performed using CoaguChek S device. Anemia was defined as hematocrit < 32%.

Results: Pairwise comparison and correlation of 258 INR results showed high correlation for POC versus laboratory INR (r = 0.94; P < 0.001). Of these, 16 (6%) differed by >0.6 INR units, four (1.6%) differed by >0.8 INR units, and one differed by >1.0 INR units. Resulting pairwise correlation analyses between samples were: for anemic patients (0.96; P < 0.001), nonanemic patients (0.93; P < 0.001), and for those obtained from arteriovenous grafts (0.94; P < 0.001). POC INR samples from dialysis catheters correlated poorly with laboratory INR results.

Conclusions: POC INR correlates well with plasma INR measures in IHD patients requiring chronic warfarin, and anemia did not influence this reliability. Blood sampling from finger stick or arteriovenous graft or fistula showed excellent correlation with laboratory INR, whereas sampling from dialysis catheters was unsatisfactory, likely from heparin contamination.


Microfluidics technology for point-of-care (POC) International Normalized Ratio (INR) measurement is an established, reliable, and efficient means of monitoring patients requiring chronic warfarin therapy (1–5). Minimizing both the amount of blood sampled and the turnaround time for test results, POC testing has become the standard of care for chronic warfarin management strategies. Many ESRD patients on chronic intermittent hemodialysis (IHD) are anticoagulated with warfarin, which necessitates close INR monitoring. Delayed laboratory INR result availability complicates the logistics of warfarin dose management in these patients. Manufacturers of POC INR devices have specified anemia (hematocrit < 32%) as a condition in which test accuracy using this technology may suffer (6). Most IHD patients are intermittently anemic despite the routine use of hematopoietic therapy. It is therefore not clear whether POC INR testing would be suitable in the management of IHD patients on chronic warfarin therapy. To our knowledge, POC testing has not been validated in a chronic IHD population.

On the basis of the existing literature, we hypothesized that POC INR testing would correlate well with plasma INR in IHD patients who are on chronic warfarin. The three main objectives of this study were: (1) to determine the correlation between POC INR and standard plasma INR (Lab INR) values in hemodialysis patients receiving chronic warfarin therapy, (2) to determine the influence of anemia on the accuracy of POC INR test results in these patients, and (3) to compare practical sites for POC INR blood sampling to confirm which were feasible and which were inappropriate. For this purpose, finger-stick blood samples for POC INR were compared with the hemodialysis access sources [indwelling central venous catheter, arteriovenous (AV) fistula, or graft] to standard dialysis INR blood sampling. Blood samples obtained from dialysis access sites that have been subject to heparin exposure including instillation to prevent catheter clotting when not in use are invalid according to technical specifications.
Materials and Methods

All chronic IHD patients receiving warfarin anticoagulation to a therapeutic goal of 2 to 3 or higher for at least 1 mo were approached for study participation. Mayo Foundation has two hemodialysis centers that are staffed by nurses, physicians, and practitioners working within the division of Nephrology at Mayo Clinic, Rochester. The Mayo Clinic Institutional Review Board approved this study.

In this prospective comparison of paired patient data, blood samples were collected serially within 10 min immediately before hemodialysis circuit access and heparin initiation. Each patient provided at least six sets of blood samples for INR, including the standard laboratory draw as well as POC INR samples from finger stick and from their IHD access. Serial blood samples obtained by standard finger stick and dialysis access site were analyzed immediately using the CoaguChek S device (Roche Diagnostics, Indianapolis, Indiana) (6). Dialysis access included either a central venous catheter (typically an Ash-split catheter), AV fistula, or graft. Whole blood samples (5 ml) for plasma INR assessment were collected into 3.8% sodium citrate (1:9 dilutions). Plasma INR were processed using the MDA 180 analyzer (BioMerieux, Durham, North Carolina). The thromboplastin used for INR measurements was Innovin reagent (Dade Behring Inc, Deerfield, Illinois), which has an International Sensitivity Index of 1.0. During the study, warfarin dose adjustments were based on the plasma INR results.

Complete blood counts were obtained at least weekly and the results of those hematocrit data were each recorded coinciding with the INR samples tested. Anemia was defined as a hematocrit <32%. Most of the patients were intermittently treated by protocol with an erythropoietic agent and some patients required blood transfusions.

Statistical Analyses. Bland–Altman methodology was used to assess the limits of agreement and inter-reliability between POC and plasma INR values (7). Paired t tests were used to assess for significant bias between measures, and correlation coefficients were calculated. Descriptive statistics are reported as mean ± SD, frequency (percentage), and 95% confidence intervals. Two sample t tests were used to compare anemic and nonanemic measurements with respect to the paired differences between methods. Similar methods were utilized comparing the sample obtained from AV graft, fistula, or dialysis catheter for POC INR to plasma sample for Lab INR.

For the purposes of confirming clinical applicability, we specified that an INR outside of the therapeutic goal range ±0.2 in previously INR-stable patients would result in a warfarin dosage change. Therefore, we established that a POC INR difference ≥0.2 when one of the INR was outside therapeutic range would result in a discrepant dosage adjustment (2). Statistical analyses were performed on JMP version 6.0 (SAS Institute Inc. Cary, North Carolina) P values <0.05 were considered statistically significant.

Results

All 39 chronically anticoagulated patients receiving hemodialysis were approached for study participation. The 37 study patients provided 258 blood sample triplicates over the time period of the study. The demographic information for these study participants is provided in Table 1. The mean age of patients participating was 73 yr and nearly half were women. The indications for warfarin anticoagulation were venous thrombosis, pulmonary emboli, chronic atrial fibrillation, antiphospholipid syndrome, artificial (heart) valve, or a combination. There were none taking lower-dose warfarin for dialysis access patency. Seven patients did not fulfill the planned six samples because of medical complications in their dialysis schedules, but all were results were included.

The correlation between POC and plasma INR values was quite high (Figure 1). Of the 258 data pairs, POC INR results were in agreement with Lab INR by ±0.2 INR 67% of the time and ±0.4 INR 89.2% of the time. There was a single occurrence of an observed difference of >1.0 INR (0.38%). Observed dif-

Table 1. Baseline clinical characteristics of dialysis patients receiving warfarin therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dialysis Patients (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr; mean ± SD)</td>
<td>73.5 ± 9.9 yrs</td>
</tr>
<tr>
<td>Sex (percent women)</td>
<td>20 (54%)</td>
</tr>
<tr>
<td>Warfarin indication (n)</td>
<td></td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>13</td>
</tr>
<tr>
<td>venous thromboembolism</td>
<td>17</td>
</tr>
<tr>
<td>mechanical heart valve</td>
<td>2</td>
</tr>
<tr>
<td>cerebrovascular accident (non-Afib)</td>
<td>2</td>
</tr>
<tr>
<td>pulmonary embolus (non-Afib)</td>
<td>1</td>
</tr>
<tr>
<td>antiphospholipid antibody</td>
<td>2</td>
</tr>
<tr>
<td>Anticoagulation duration (mo; mean ± SD)</td>
<td>14.4 ± 16.5</td>
</tr>
<tr>
<td>INR goal range</td>
<td></td>
</tr>
<tr>
<td>2.0 to 3.0</td>
<td>36</td>
</tr>
<tr>
<td>3.5 to 4.5</td>
<td>1</td>
</tr>
<tr>
<td>Dialysis access (n)</td>
<td></td>
</tr>
<tr>
<td>AV graft</td>
<td>4</td>
</tr>
<tr>
<td>AV fistula</td>
<td>11</td>
</tr>
<tr>
<td>Ash-split catheter</td>
<td>22</td>
</tr>
<tr>
<td>Hemodialysis duration (mo ± SD)</td>
<td>28.2 ± 30.6</td>
</tr>
<tr>
<td>Hemodialysis run duration (h ± SD)</td>
<td>3.6 ± 0.4</td>
</tr>
</tbody>
</table>

Afib, atrial fibrillation; INR, International Normalized Ratio; AV, arteriovenous.
ferences of 0.7 or more occurred in 12 of the 259 (4.6%), of which seven occurred when the INR was elevated to 4.0 or higher. There is a known low bias for INR results exceeding 5 with the device that we used.

To address the second objective regarding the effect of anemia on the absolute difference between Lab INR and POC INR, paired INR measures were compared separately for both anemic and nonanemic patients using the accepted hematocrit cutoff of 32%. Anemia status did not appear to have a clinically important effect on the magnitude of the difference between POC and Lab INR (Figure 2, A and B). Table 2 presents the number of differences for INR of $>1$, $>0.8$, and $>0.6$, comparing both anemic and nonanemic patients. Anemic patients showed a small likelihood to have a slightly lower POC INR in 60% of the measurements (Figure 2, A and B). This tendency to have a slightly lower POC INR measurement was reflected in the overall $t$ test, which revealed the statistical bias. Despite this bias, the magnitude of the differences shown was small but did not appear important in the vast majority.

Our third objective was to compare POC INR measures from blood sampled by finger stick and the patient's dialysis access (central venous catheter, AV fistula, or dialysis graft) each to the standard plasma INR. A strong correlation was noted between INR measures obtained from finger stick and either AV fistula or dialysis graft and plasma INR (Figure 3A). In contrast, blood obtained from a central venous catheter did not correlate well with standard phlebotomy plasma INR values that we knew had heparin contamination (Figure 3B).

Discussion

The principal finding of this study is that POC INR measures using the Roche CoaguChek S device compare quite favorably with plasma INR values in hemodialysis patients on chronic warfarin therapy. With the availability of new technology that
is more convenient, efficient, and potentially cost-effective, the
general applicability to particular patient populations requires
validation. POC testing provides expedient INR results that
enable health care providers to perform prompt warfarin dos-
ing adjustment decision-making and face-to-face education
with the patient. This management paradigm improves com-
pliance and provider and patient satisfaction while reducing
both bleeding and thrombotic complications (8). Despite com-
plex hematologic and electrolyte derangements associated with
ESRD and intermittent dialytic therapy, POC INR testing did
not show impairment relative to plasma INR determinations.
This finding is anticipated to ease the management of these
complicated patients requiring chronic warfarin therapy. Our
results showed a high degree of correlation between the POC
INR method and standard Lab INR (Figure 1) shown in our
data (Table 2) in our 258 paired samples. We searched several
INR magnitudes within our POC INR results for any break-
down in agreement with Lab INR and found that 67% of results
were within ±0.2 INR and ±0.4 INR 89.2% of the time. The
mean difference of 0.08 with a SD of 0.31 met our goal for
concordance of POC testing. Similar studies have found accep-
table mean differences (±SD) of between 0.2 (±0.31) and 0.8
(±0.68) to establish an INR concordance between POC methods
and Lab INR (2). Our data showed 16 instances (6%) in which
the difference between Lab INR and POC INR was >0.6, only
four (1.5%) when the difference was >0.8, and just one (0.38%) in
which the difference exceeded 1.0 INR unit, which could be
data outlier and arguably excludable.

The second major finding of this study is that POC INR-mea-
ured results were not necessarily impaired by low hematocrit
counts. Most POC INR testing device manufacturers list anemia as
a potential limiting factor in INR measurement accuracy with their
device (6). Anemia is a common complication in hemodialysis
patients, but did not appear to clinically impair our test accuracy.
We analyzed our data for discernible differences between the two
INR methods specifically in comparing those with anemia versus
nonanemic and found them lacking. The 16 paired results show-
ing an INR difference of >0.6 occurred similarly in both anemic
and nonanemic patients. Additionally, result differences of >0.8
INR all occurred in patients who were proven not anemic (Table
2). Correlation results remained high in our anemic patients com-
pared with those nonanemic as shown in the plot of the INR
difference (Figure 2B). However, there was noted bias in the
anemic group for a slightly lower POC INR measurement as
depicted in the box plot (Figure 2A) and difference in calculated
SD. Figure 2B depicts the slight difference graphically over our

<table>
<thead>
<tr>
<th>INR Differences</th>
<th>Overall</th>
<th>Hematocrit &lt; 32%</th>
<th>Hematocrit ≥ 32%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab INR − POC INR</td>
<td>(n = 258)</td>
<td>(n = 84)</td>
<td>(n = 174)</td>
</tr>
<tr>
<td>Difference &gt; 1.0 (%)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Difference &gt; 0.8 (%)</td>
<td>4 (1.6%)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Difference &gt; 0.6 (%)</td>
<td>16 (6%)</td>
<td>6 (7%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Mean paired difference (SD)</td>
<td>0.08 (0.31)</td>
<td>0.17 (0.25)</td>
<td>0.04 (0.33)</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>0.04 to 0.12</td>
<td>0.11 to 0.22</td>
<td>−0.01 to 0.09</td>
</tr>
<tr>
<td>Pairwise correlation (r)</td>
<td>0.94 (P &lt; 0.001)</td>
<td>0.96 (P &lt; 0.001)</td>
<td>0.93 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

Figure 3. Sampling source and POC INR accuracy. (A) Scatterplot of Lab INR versus POC INR samples taken from dialysis arteriovenous (AV) fistula or graft with the line of equality (n = 96). Lab INR graft-obtained POC INR analysis: Mean 0.0573, SD 0.253, 95% confidence interval 0.006 to 0.109. (B) Scatterplot of Lab INR versus POC INR. Both samples taken from dialysis catheter (usually an Ash-split catheter) with the line of equality (n = 139). Catheter-obtained POC INR results showed poor agreement with Lab INR results.
entire hematocrit range. Although samples drawn in anemia \( (n = 83) \) showed this slight statistical bias, it did not appear to have a clinically significant effect on the magnitude of the difference between POC and Lab INR. In other words, the finding of a small but significant tendency for anemic patients to have a slightly lower POC INR result compared with Lab INR results did not tend to affect the clinical utility of the method of POC INR.

The third major finding of this study is that blood sampling from a finger stick, AV graft, or fistula provide similarly acceptable blood source for accurate INR assessment. In contrast, blood sampling from a central venous catheter did not compare well with plasma INR data, likely because of heparin contamination. Central catheters for dialysis are routinely utilized for practically obtaining laboratory blood samples, but are instilled with a heparin solution to prevent them from clotting. Heparin-exposed blood samples for POC INR are known to invalidate testing with this device. The correlation of POC INR data for blood samples obtained from these heparin-exposed catheters was terrible despite repeated attempts at thorough catheter flushing techniques (Figure 3). In contrast, the blood sample for POC INR obtained from the patients’ dialysis AV fistula or grafts showed excellent correlation to both the POC INR from finger stick and the standard Lab INR measurement. Dialysis fistulas and grafts are not subjected to heparin as the dialysis flushing techniques (Figure 3). In contrast, the blood sample for POC INR obtained from the patients’ dialysis AV fistula or grafts showed excellent correlation to both the POC INR from finger stick and the standard Lab INR measurement. Dialysis fistulas and grafts are not subjected to heparin as the dialysis catheters are to prevent clotting. We confirmed that blood for POC INR sampled from a central dialysis catheter was confirmed invalid, as stated by the device manufacturer.

Even with our good statistical correlation of POC INR methodology, the applicability of POC INR to clinical practice was a priority. For the purposes of defining clinical applicability we established that an INR outside of the goal range \( \pm 0.2 \) would result in a warfarin dosage adjustment (2). For dosing purposes, discordance between the POC INR and Lab INR occurred when one of the two results indicated a dose change and its corresponding pair INR suggested no change (within our defined goal of 2 to 3 \( \pm 0.2 \) INR units). We counted the absolute number of inappropriate dosing decisions that would have occurred using the POC device in our dialysis practice (Table 3). There were no instances where one INR result indicated a dose alteration in the opposing direction from its paired INR. Agreement between dosing decisions occurred in 212 (82%) instances in which both the POC and Lab INR results suggested no change or a change of warfarin dose in the same direction; that left 46 (17.8%) instances in which either the POC INR or the Lab INR was suggesting a change, but not both. Of note, discrepant dosing decisions were not any more likely to occur in anemic patients than nonanemic. Had we broadened the allowable INR 2- to 3-goal range from \( \pm 0.2 \) to \( \pm 0.3 \), there would be only 18 (7%) instances in which dosing discordance occurred between the POC and Lab INR.

Limitations in our conclusions include the fact that most of our anemic patients were modestly so at hematocrit 28 to 32% with relatively few INR results to compare in patients with more significant anemia. The issue of POC INR reliability in anemia should be examined in a larger study. Another limitation may be that we obtained our paired samples from 37 chronic dialysis patients and some of those contributed more results than others. Lastly, venipuncture sampling for Lab INR would have been the most ideal comparator; however, dialysis patients with viable access object to venipuncture. In our dialysis centers, blood sampling from a dialysis access whenever possible is the routine preference for the comfort of our patients.

In summary, this POC INR method appears to correlate well with standard Lab INR in our dialysis patients taking warfarin. Although we compared only 84 POC INR results, the concern with using the POC INR method in our anemic dialysis patients was not confirmed. In our anemic patients, other than a modest bias, POC INR methodology compared favorably with the standard Lab INR method despite the caution in doing so from the manufacturer of POC devices. We confirmed that blood obtained for INR from a heparin-exposed catheter cannot be utilized on this POC device; however, a drop of whole blood taken from an AV fistula (graft) before introducing heparin and dialysis worked well. Lastly, therapeutic decisions based on POC INR results in our dialysis population appear valid, with few discrepant decisions made, and the proper use of this technology makes anticoagulation management expedient.

### Acknowledgments

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Trials registry name and number: Correlation of Point-of-Care INR to Laboratory INR in Hemodialysis Patients Taking Warfarin, NCT00660946.

### Disclosures

None of the authors has any conflicts of interest, sponsorships, or relationships potentially influencing any part of this study.

### References


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**Table 3. Incidence of dose concurrence comparisons between POC INR and Lab INR (n = 258)**

<table>
<thead>
<tr>
<th>POC INR</th>
<th>Standard Laboratory INR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose Change</td>
</tr>
<tr>
<td>Dose change</td>
<td>95</td>
</tr>
<tr>
<td>No dose change</td>
<td>18</td>
</tr>
</tbody>
</table>

*AChange indicated if outside goal by \( \pm 0.2 \) INR.*


6. Roche Diagnostics. Technical information on CoaguChek S, Indianapolis, Roche Diagnostics, 2004
