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Information for Providers

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**Point-of-Care INR Testing: Limitations that Impact Clinical Performance and Utility**

Many physicians, advance practice nurses, and other clinicians are surprised to learn that point-of-care (POC) INR testing is a “different beast” than standard PT/INR testing on a lab coagulation analyzer. Understandably, the laboratory receives frequent questions and concerns from clinicians and staff when a POC INR result does not “match” the laboratory analyzer result. It isn’t obvious that the accuracy and utility of POC INR testing is very limited. To help clinicians understand these limitations and their impact on clinical practice, this article provides background information and answers to “frequently asked questions.”

Although it’s reasonable to expect the POC INR to be as reliable as any other POC test, this is unfortunately not true:

- None of the currently available POC INR tests are as accurate or reliable as other common POC tests such as glucose or creatinine.
- The nature of coagulation testing is very different than measuring glucose or creatinine.
- Ideally, the POC INR reaction should be dependent purely on the coagulation factor levels in a specimen, but in fact, this is not true.
- There are several factors inherent to the POC methods that affect the POC INR result, independent of coagulation status, and these include: hematocrit, platelets, testing prior to steady-state, and proteins-induced-by-vitamin-K-absence (PIVKA).
- All of these factors tend to falsely increase the INR.
- The effects are variable between patients and are nonlinear, so it is not possible to apply a mathematical factor to correct for false elevations of the POC INR.
Frequently Asked Questions about Point-of-Care INR testing

Can the POC INR test be generally substituted for a prothrombin time (PT), for example, in bleeding patients or preoperative patients?

POC INR testing is FDA-approved only for monitoring stable patients on warfarin (Coumadin) within the therapeutic range. The POC INR test is not approved as a test for coagulation deficiencies and may not be used in other patient groups under any circumstances for reasons explained later in this article.

What is the difference between the International Normalized Ratio (INR) and Prothrombin Time (PT)?

Recall that the prothrombin time (PT) is the amount of time, in seconds, for a sample to clot after adding a standard amount of thromboplastin reagent. The PT reaction is complex and depends on the concentrations of multiple coagulation factors in the specimen. The INR is not a test, but simply a metric calculated from the PT and has utility only in steady-state warfarin monitoring and allows comparison of PT results between different laboratories. The INR metric does not have any clinical relevance for other patient groups.

What is meant by steady state?

It takes 5-10 days or longer to reach steady state on warfarin. INR results are not reliable before steady-state, due to unstable biochemical changes in early therapy. If PT/INR testing of any type is done before 5-10 days, the PT in seconds should be followed to assure trending in the right direction, not the INR.

| Inherent Factors that Tend to Falsely Elevate POC INR Values vs. Standard INR testing |
|---------------------------------|---------------------------------|---------------------------------|
| Specimen type                    | POC INR (any vendor) | Standard INR (lab analyzer)     |
| Whole blood                      | Platelet-poor plasma       |

<table>
<thead>
<tr>
<th>Interferences</th>
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<tbody>
<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>False elevations of INR in anemic patients</td>
</tr>
<tr>
<td>No effect</td>
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<tr>
<td>Platelets</td>
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<tr>
<td>Potential to activate coagulation/consume factors prior to test reaction, raising the INR</td>
</tr>
<tr>
<td>No effect</td>
</tr>
<tr>
<td>Proteins-induced-by-vitamin-K-absence (PIVKA)</td>
</tr>
<tr>
<td>Potential to increase INR (thromboplastin required to drive the POC reaction is also sensitive to PIVKA)</td>
</tr>
<tr>
<td>No effect (thromboplastin used is not sensitive to PIVKA)</td>
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If the INR is not relevant for every patient, why is the INR reported for every PT?

Because the laboratory does not know which patients are taking warfarin.

Is the POC INR as accurate as a PT/INR performed on a laboratory coagulation instrument?

No, the POC INR is inherently limited and tends to over-estimate the INR as explained later in this article. Still, POC INR results are accurate enough within the therapeutic range (2-3) to be useful for monitoring many patients who are stable on warfarin. At INRs above 3, the POC INR is much less accurate and often cannot be used.

Internal correlation studies of POC INR results compared to laboratory analyzer results show similar results to peer-reviewed published studies. As these graphs show, there is good correlation when the INR is below 3. Above an INR of 3, the POC method consistently over-estimates the INR.

Correlation data is shown in the graphs below.
Published Correlation Data (Ref. 1)

![Graph showing International Normalized Ratio (INR) values from two point-of-care devices and reference laboratory instrumentation.](image)

Internal Correlation Data, n=118

![Graph showing INR results for POC (iSTAT) and Lab (STAGO).](image)
Why isn’t the POC INR as accurate as a PT/INR performed on a laboratory instrument?

The POC test is performed on fingerstick whole blood vs. platelet-poor plasma from a spun sample on the laboratory instrument. Whole blood INR testing is inherently less accurate.

Why would whole blood give a less accurate INR result than plasma?

Only plasma contains coagulation factors, but a whole blood sample has a variable amount of red cells mixed in, depending on the patient’s hematocrit. These red cells are just “junk” that take up space in the test cartridge. The reactants, the coagulation factors that are being tested, are all in the liquid part of blood – the plasma.

Because patients have different hematocrits, each patient sample adds a different amount of liquid plasma to the cartridge – but, the amount of thromboplastin in the test cartridge is fixed. In fact, the POC test system is configured for a hematocrit of 40%.

So how does hematocrit impact the POC INR result?

Consider two patients on warfarin with the same INR, but different hematocrits. Patient 1 has a hct of 40% (60% plasma) and Patient 2 has a hct of 25% (75% plasma). On the POC device, patient 2 will show a higher INR result than patient 1, because the amount of plasma is too high for the amount of thromboplastin in the cartridge. Why? The excess plasma volume dilutes the thromboplastin and slows clot formation even though the true INR is the same as Patient 1. This is one of the reasons that a patient can have an INR of 4.2 on the POC device that comes back as 3.1 from the laboratory instrument.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>True INR = 3</td>
<td>True INR = 3</td>
</tr>
<tr>
<td>Hct = 40%</td>
<td>Hct = 25%</td>
</tr>
<tr>
<td>POC INR ~ 3</td>
<td>POC INR &gt;4</td>
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Larger amount of plasma = more dilute reaction = slower clotting = longer INR

Same amount of blood, same amount of thromboplastin in the cartridge, but different volumes of plasma.
If this is true, how can the POC test be useful for any patients when they all have different hematocrits?

Because you can get away with it most of the time when the INR is less than 3. The PT/INR reaction is much less sensitive to differences in plasma volume at lower INRs. Since most patients on warfarin have an INR target of 2-3, and testing is performed only for routine monitoring, this is the population where the POC test performs best. The POC INR performs much worse when the INR target is above 3, for example, in valve replacement patients who are often also anemic. These are the patients who usually have significant false elevations of the INR on the POC device and require monitoring with a venous sample tested in the main laboratory.

Is there a numerical factor that could be used to correct the POC INR results for different hematocrits?

There is no numerical correction factor that works because the effects of hematocrit as well as other factors that influence POC INR testing are unpredictable and nonlinear.

To avoid the problems with whole blood, can plasma be tested on the POC device?

Results would be erroneous and invalid due to the anticoagulant in the blood collection tube. The POC cartridge does not contain reagents to neutralize anticoagulants. The device, cartridges, and software are calibrated for fingerstick whole blood only.

We collected a PT/INR to send to the main lab for testing. Can we run the whole blood from the tube on the POC device to get a preview of the lab result and make immediate dosing decisions?

The blood collection tube used for coagulation testing contains citrate as anticoagulant and will give erroneous and invalid results. There is nothing in the POC cartridge to counteract citrate. Blood collected in plain tubes (without anticoagulant) also cannot be used in the device because coagulation activates immediately, consuming coagulation factors in vitro. The INR would be falsely elevated. Only fresh flowing fingerstick blood can be added to the test cartridge.

Why can’t we use the POC INR device to monitor patients who are starting or restarting warfarin?

Results may be misleading. There are biochemical changes that occur during warfarin initiation that cause the POC INR to be unreliable. Until the patient is at steady state, the prothrombin time from a laboratory analyzer should be followed to assure trending in the right direction.
**What physiologic changes occur during warfarin initiation?**

Warfarin works by inhibiting vitamin K. It should be remembered that vitamin K only controls the final conversion step of precursor coagulation proteins into active factors. When this final conversion step is blocked by warfarin, the body responds by making more coagulation precursors, known as “Proteins Induced by Vitamin K Absence” or PIVKA. PIVKA increase in early therapy then stabilize at steady state, typically 5-10 days, but sometimes as long as a month.

**How do PIVKA interfere with POC INR testing?**

PIVKA are inert and do not inhibit clotting in the body, but they do inhibit the thromboplastin reagent used in the POC INR test. In other words, PIVKA can make the INR appear higher when the patient isn’t protected from clotting. The test system is calibrated to correct for some of this effect, but it only works if the PIVKA level is stable in your patient. Unstable PIVKA levels during warfarin starts or restarts can cause unstable or erroneous INR results.

**Do PIVKA interfere with the PT/INR on the laboratory analyzer?**

The thromboplastin used in the laboratory analyzers at Allina Health is not inhibited by PIVKA.

**Why can’t the POC INR device be used to monitor a-fib patients who are scheduled for cardioversion?**

This is a clinical context where a highly accurate INR (>2) is essential to prevent serious patient harm (stroke) during cardioversion. This is not a pure monitoring situation. Remember that the POC INR tends to over-estimate the INR. This over-estimation is usually not significant for routine monitoring in the 2-3 range, but in a patient scheduled for cardioversion, it means that POC INR may be greater than 2 when the true result is actually below 2. This may not be discovered until the patient arrives for the procedure and has an INR performed in the hospital lab – and means that the procedure will be cancelled at the last minute.

**What do I tell my patient who wants a fingerstick INR in the clinic, but doesn’t get accurate results with the POC test? The POC results are always greater than 4, but the lab results are always under 3.5. The patient doesn’t understand and wants an explanation.**

This frequently happens with patients who have valve replacements and INR targets above 3, where the POC accuracy is much worse. When patients enter the INR program, they should receive anticipatory guidance that the fingerstick method doesn’t work in some people with certain medical conditions. In this case, the POC test says they are taking too much blood thinner and should decrease their medication, when they are actually taking the right amount to protect their heart and brain. To ensure that they stay protected, and to avoid unnecessary confusion and alarm from inaccurate results, it’s safest in their particular case to have testing performed on the laboratory instrument.
Can we use the POC INR to test patients who are not taking warfarin?

Not under any circumstances.

What risk could there be from using the POC INR test in patients who are not on warfarin?

There is a patient safety risk because results from POC INR testing are not accurate enough for purposes other than stable warfarin monitoring. Clinicians could feel compelled to act on results that are potentially inaccurate and misleading. There is also a regulatory compliance risk, even if the POC test is performed at no charge or as a preliminary test; again, these regulations were established for patient safety.

Unlike medications, diagnostic tests, including waived tests, may not be used outside of FDA-approved indications without first performing a mandatory rigorous internal validation study to meet FDA requirements that is beyond the scope of this organization. “Off-label” use of an FDA-approved test carries a risk of inspection deficiencies, lookbacks, and CMS sanctions. Some organizations have already been cited for non-approved use of POC INR devices and were required to cease testing and document corrective action, including patient lookbacks.

References


For questions, comments, or suggestions about this newsletter or other laboratory issues, please contact Lauren Anthony, MD, Medical Director of Allina Health Laboratory, (612) 863-0409 or Lauren.Anthony@allina.com