

Precision of INR (International Normalized Ratio) Measurement using Laboratory and Point-of-Care Assays: Understanding the Impact of System Influence on Patient Management.

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BACKGROUND

- Oral anticoagulant therapy (OAT) requires the use of drugs known to have a “narrow therapeutic index” and thus require close monitoring to be effective.
- The International Normalized Ratio, which is the world-wide accepted method of reporting the prothrombin time test for OAT management, suffers from variability associated with assignment of ISI and method differences.
- Providing optimal oral anticoagulation management requires knowledge of INR differences attributable to the assay system and development of useful dose adjustment algorithms.

OBJECTIVES

Quantify the degree of INR compatibility among laboratory (Lab) and point of care (POC) assays and measure differences which influence clinical decisions

Study Demographics

- 9 normal donors
- 91 OAT patients (Multiple indications for OAT)
 - 69 with INR target of 2.0-3.0
 - 20 with target INR of 2.5-3.5
 - 2 patients with target INR of 3.0-4.0.

INR Systems Analyzed

ISI of all systems ~ 1.0

Reference	Instrument	Reagent	Reference	Device	Sample
Lab A	MLA	Innovin	POC1	ProTime	venous
Lab B	BCS	Innovin	POC2	ProTime	fingerstick
Lab C	BCS	Recombiplastin	POC3	ProTime3	venous
Lab D	STA-R	Innovin	POC4	ProTime3	fingerstick
Lab E	STA-R	Recombiplastin			

MLA – Medical Laboratory Automation
 BCS – Beckman Coulter Systems
 STA-R – Diagnostica Stago
 Innovin – Dade Behring
 Recombiplastin – Ortho Diagnostics
 ProTime – International Technidyne Corp

Methodology – Two separate fingerstick specimens are collected to perform the POC tests. A venous sample is collected and (a) used without treatment in the POC systems and (b) added to 3.2% sodium citrate, from which plasma is collected and assayed in a local laboratory (MLA; ITC, Edison, NJ) and a reference lab (BCS & STA-R; Midwest Hemostasis and Thrombosis Laboratory, Muncie IN, USA).

Analytical Comparisons – For each system linear correlation statistics and mean vs difference plots are generated, with the slope, offset and correlation coefficient used to describe the relationship among the systems. For each patient and donor specimen clinical decision agreement is defined based upon sample INR differences.

POC lot to lot variability

Changes in laboratory PT/INR reagent lots require the recalculation of normal range and verification of therapeutic values. POC lot numbers are changed more frequently than laboratory reagents so that verification of ranges for each lot of POC reagent is impractical. A clinical analysis was performed to establish lot to lot identity of the POC system, employed in these analyses.

RESULTS

Comparison of Lab Systems:

Linear Regression Analysis: $x = \text{Lab A}; y = \text{Lab B, C, D, E}$

	Low value	High value	Average
Slope	0.817	1.034	0.933
Intercept	0.020	0.228	0.096
Correlation	0.980	0.995	0.987
Bias	-0.2	0.1	-0.1

Bias is defined as the average difference of paired samples

Comparison of POC Systems to Lab Systems:

Linear Regression Analysis: $x = \text{Lab A, B, C, D, E}; y = \text{POC1, 2, 3, 4}$

	Low value	High value	Average
Slope	0.736	1.013	0.852
Intercept	0.100	0.452	0.326
Correlation	0.916	0.963	0.945
Bias	-0.2	0.1	0.0

Bias is defined as the average difference of paired samples

Comparison of POC Systems: Linear Regression Analysis of POC1,2,3,4

	Low value	High value	Average
Slope	0.913	1.099	0.996
Intercept	0.043	0.172	0.112
Correlation	0.913	0.964	0.943
Bias	0.01	0.04	0.01

Bias is defined as the average difference of paired samples

Clinical Decision Impact

Out-of-range (OOR) INR analysis – quantify the percent of INR which would influence patient management and generate a dose adjustment.

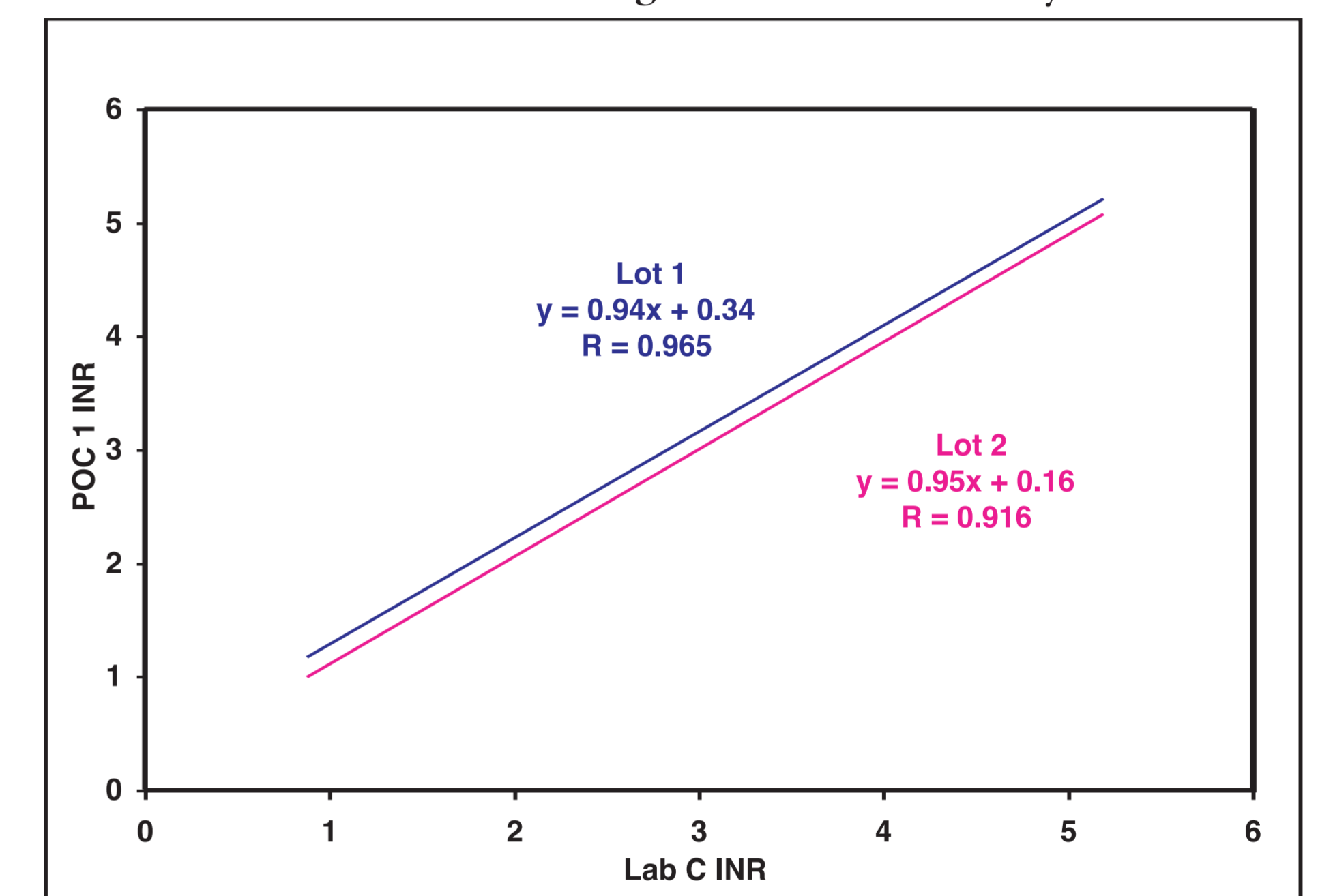
- Total Agreement Among all Lab and POC Systems
51% of all system values either within range or OOR.
- Single INR Disagreement – incidence in which a single Lab or POC value is OOR while other values are in-range:
Lab Systems 60% ; POC Systems = 57%
- Pair Analysis - percentage of INR pairs that were within 0.4 and 0.7 INR:

(values shown are ranges)	Pairs within 0.4 INR	Pairs within 0.7 INR
Lab to Lab	85.4 – 97.9 %	94.8 – 99.0 %
POC to Lab	74.7 – 89.9 %	87.9 – 99.0 %
POC to POC	89.9 – 94.9 %	97.0 – 99.5 %



POC lot to lot variability

- Every lot of POC reagents is subjected to testing against specific limits prior to release for sale.
- Lots were chosen for clinical analysis which represented the absolute ends of the allowable specification: Lot 1 – high end, Lot 2 – low end.
- Correlation of the data obtained to a single laboratory system shows the maximum deviation between reagent lots for the POC system.



These data, with nearly identical slopes, and an intercept difference of less than 0.2 INR, show that the lot to lot variability allowed in these reagents is clinically insignificant.

DISCUSSION

INR Variability

- Confirms prior reports of INR variability depending upon PT analysis system
- Correlation and regression differences are observed for all comparisons
 - Lab to Lab, POC to Lab, POC to POC
- Despite correlation and regression differences, there was a general INR agreement between the lab and POC systems

Clinical Agreement

- Complete agreement was only found in one-half (51%) of the cases.
- Clinical agreement of paired results suggests approximately 90% of pairs are within 0.4 INR units and 95% of pairs are within 0.7 INR – these values are similar to published reports of INR comparisons.
- Clinical agreement of the POC system to the Lab System is similar to the agreement among Lab Systems
- There is no need to reestablish ranges when reagent lots change for the systems evaluated in this study.

Application to OAT Management

- Anticoagulation management guided by patient-individualized INR target range and appropriate monitoring may lead to less frequent dose changes as spurious OOR results are re-evaluated before instituting a dose change.