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## ORIGINAL ARTICLE

# Comparison of Two HbA1c Measurement Methods and Their Analytical Performance: TINIA vs. Boronate Affinity HPLC

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## ABSTRACT

***Background:*** **Hemoglobin A1c (HbA1c) measurement is essential for the assessment of long-term glycemic control in patients with diabetes mellitus, as it reflects the average blood glucose concentration over the preceding 8 - 12 weeks. Global diabetes mellitus prevalence has increased dramatically, and HbA1c testing is critical for diagnosis, monitoring treatment efficacy, evaluating diabetes care quality, and predicting the risk of diabetic complications. Although HbA1c has become the standard method for assessing long-term glycemic control in diabetic patients, various measurement methods exist with different analytical characteristics and potential interferences. This study aimed to evaluate and compare the analytical performance of the Roche turbidimetric inhibition Immunological assay (TINIA) method with the Premier boronate affinity high-performance liquid chromatography (HPLC) method for HbA1c measurement.**

***Methods:*** **Blood samples were randomly selected from 75 diabetic and non-diabetic patients (48 females [64%], 27 males [36%], median age 55 years). HbA1c levels were measured using both Roche TINIA (cobas c501 analyzer) and Premier Hb9210 boronate affinity HPLC methods. Analytical performance was evaluated through precision studies, linearity analysis, bias estimation, and comparison studies using Passing-Bablok regression and Bland-Altman analyses according to CLSI EP-5 protocol.**

***Results:*** **Both methods demonstrated acceptable precision with coefficient of variation (CV%) values below 2.0%, meeting the IFCC-recommended criteria of < 2.8%. The correlation between the two methods was strong ($r = 0.986$, $p < 0.0001$), with mean HbA1c values of 7.16 ± 2.14% for Roche TINIA and 6.99 ± 1.94% for Premier Hb9210. Despite excellent correlation, a statistically significant difference was found between methods ($p = 0.0005$). The Bland-Altman analysis showed a mean difference of -0.17% (95% CI: -1.9 to 1.5%) between methods, with mean relative bias of 0.17%, which was well below the IFCC-defined total allowable error criterion of 0.46% at 6.7% HbA1c levels.**

***Conclusions:*** **Both Roche TINIA and Premier Hb9210 boronate affinity HPLC methods demonstrated acceptable analytical performance and excellent agreement for HbA1c measurement. The TINIA method showed good concordance with the reference boronate affinity chromatography method, supporting its clinical utility for diabetes management. However, clinicians should be aware of the small but consistent bias between methods when monitoring patients over time or when switching analytical platforms.**

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## INTRODUCTION

Hemoglobin comprises 97% of adult red blood cells, primarily as hemoglobin A (HbA) [1]. In 1958, Allen and colleagues first identified HbA1 components using ion-exchange chromatography, describing HbA1a, HbA1b, and HbA1c fractions [1]. Rahbar's landmark observation in 1968 demonstrated that diabetic patients, particularly those with poor glycemic control, exhibited increased levels of these minor fractions, notably HbA1c [1]. This discovery established the foundation for using glycosylated hemoglobin as a marker of glycemic control [2].

Hemoglobin A1c (HbA1c) is formed through non-enzymatic glycation, a post-translational modification where glucose binds to the N-terminal valine of the β-globin chain of hemoglobin molecules [3-5]. Unlike enzymatic processes, glycation is a time-dependent, concentration-dependent, and hemoglobin-dependent mechanism where glucose molecules gradually bind to amino groups of hemoglobin through a multi-step process beginning with Schiff base formation and progressing to stable Amadori products [3-6]. The Maillard reaction involved in this process eventually leads to the formation of advanced glycation end products (AGEs), which modify proteins throughout body tissues and contribute to inflammatory reactions and diabetic complications [6,7]. Red blood cells circulate with approximately ± 20% variation for approximately 120 days, thus HbA1c reflects the mean glucose concentration to which hemoglobin has been exposed over the preceding 8 - 12 weeks [3,4,8]. This temporal relationship makes HbA1c an ideal marker for long-term glycemic assessment.

The global prevalence of diabetes mellitus has risen dramatically and continues to escalate [1,9,10]. Glycosylated hemoglobin measurement, particularly HbA1c, is essential for the comprehensive management of diabetic patients [1,9,10]. HbA1c serves multiple critical clinical functions: monitoring long-term glycemic control, guiding therapeutic adjustments, evaluating diabetes care quality, and predicting the risk of developing diabetic complications [1,9]. The Diabetes Control and Complications Trial (DCCT) research group demonstrated that each 1% reduction in HbA1c level corresponds to approximately a 30% reduction in the risk of developing diabetic complications [11]. This landmark finding established the critical importance of tight glycemic control and standardized HbA1c measurement [10].

Although HbA1c has become the standard method for assessing long-term glycemic control in diabetic patients, more than 100 different HbA1c measurement methods are currently available in the clinical laboratory market [3]. These methods employ two fundamental principles: separation based on charge differences and separation based on structural differences resulting from glucose attachment to hemoglobin [3]. Methods utilizing charge-based separation include cation-exchange chromatography and capillary electrophoresis [2]. Methods based on structural differences include immunological assays, boronate affinity chromatography, and enzymatic approaches [3,8].

Immunological assays recognize specific anti-HbA1c antibodies that bind to the first 3 - 5 amino acids of the N-terminus of the hemoglobin β-chain, where glucose is attached [3]. Total hemoglobin is measured using bichromatic analysis, and the ratio of these two components is calculated to determine HbA1c percentage [3]. Test designs vary from immunoturbidimetric methods to latex agglutination inhibition approaches employing monoclonal antibodies [3]. Boronate affinity separation is based on the specific covalent binding of cis-diol glucose groups in HbA1c to a boronate matrix, where only glycosylated hemoglobin is retained while non-glycosylated hemoglobin passes directly through the column [3,5]. HbA1c is initially bound to the column and released when buffers with higher affinity for boronate binding sites are applied, producing two peaks representing glycosylated and non-glycosylated hemoglobin fractions [3].

HbA1c measurement is only clinically valuable when standardized and reliable [1]. In 2002, the International Federation of Clinical Chemistry (IFCC) established the Certified Reference Material and defined the reference measurement procedure, establishing HPLC-electrospray ionization mass spectrometry (HPLC-ESI/MS) and HPLC-capillary electrophoresis (HPLC-CE) as reference methods [3,4]. The IFCC Reference Laboratory Network, comprising 21 laboratories worldwide, was established to ensure standardization, with the responsibility of preparing secondary reference materials and ensuring that measurement devices and External Quality Assurance Services (EQAS) organizations maintain traceability to the IFCC Reference Measurement Procedure (PRMP) [3,4]. This process maintains an unbroken chain between patient results and primary reference material, ensuring that patients receive accurate results that are universally comparable according to clinical targets and large-scale study data [3,12,13].

The analytical performance of different methods has improved substantially, and international HbA1c measurement standards have aided quality evaluation [3]. The IFCC has established global performance criteria for HbA1c standardization implementation [3]. Using the concept of total allowable error that combines the effects of both bias and uncertainty into a single measure, a total error limit of no more than 0.46% at the 6.7% HbA1c level has been established [3,11]. Several recent studies have also emphasized the clinical importance of hemoglobin variants and their potential interference with various HbA1c measurement methods,

particularly immunoassays that may fail to detect variants that affect measurement accuracy [9,12,14,15].
This study aimed to evaluate and compare the analytical performance of the Roche third-generation turbidimetric inhibition immunological assay (TINIA) method operated on the cobas c501 analyzer with the Trinity Biotech Premier Hb9210 new-generation boronate affinity HPLC method, assessing precision, accuracy, bias estimation, and the interchangeability of these two commonly used clinical methods for HbA1c measurement.

## MATERIALS AND METHODS

### Study design and sample selection

This analytical cross-sectional study included 75 whole blood samples randomly selected from diabetic and non-diabetic patients aged 18 - 82 years (median age 55; 48 females, 27 males) [9,16]. All patients had HbA1c tests ordered for clinical purposes. Samples were collected into 2.0 mL $K_2$EDTA tubes (BD Vacutainer®, Hemogard, Becton Dickinson, Plymouth, UK), stored at 4°C, and analyzed within 24 hours [9].

### Ethical approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (approval no.: 144; 07. 02.2025).

### Roche TINIA method (Tina-quant hemoglobin A1c gen. 3)

The Roche TINIA method is based on a turbidimetric inhibition immunoassay (TINIA) performed on hemolyzed whole blood using the Roche cobas c501 analyzer [14,17,18]. HbA1c reacts with anti-HbA1c antibodies to form soluble antigen–antibody complexes, while remaining free antibodies are agglutinated by a synthetic polymer. The resulting turbidity is measured photometrically, and results are expressed as %HbA1c or mmol/mol HbA1c [14].
Recent studies on the Roche Cobas c513 system, which applies the same principle, have demonstrated excellent analytical precision (CV < 1.7%) and accuracy comparable to NGSP-certified reference HPLC methods [18, 19].

### Premier Hb9210 boronate affinity HPLC

The Premier Hb9210 analyzer (Trinity Biotech, Ireland) determines glycated hemoglobin (GHb) using boronate affinity high-performance liquid chromatography (HPLC) [2,5]. The method separates glycated and non-glycated fractions based on reversible binding of cis-diol groups on glycated hemoglobin to boronate residues in the column matrix [2]. Absorbance is measured at 413 ± 2 nm, and %HbA1c is calculated as (Peak 2/[Peak 1 + Peak 2]) × 100 [2].
Results are traceable to both NGSP and IFCC reference systems through two-point calibration [5]. The method is unaffected by hemoglobin variants, labile intermediates, and storage-related artifacts, offering high accuracy and reproducibility across clinical laboratories [1, 16].

### Analytical performance evaluation

Analytical precision and accuracy were assessed according to the CLSI EP5 protocol [9,18]. Within-run and between-run precision were determined using commercial control materials at high and low HbA1c levels, expressed as coefficient of variation (%CV) [9]. All samples were analyzed in duplicate on both systems, and mean values were used for comparison. Analytical performance was evaluated through linearity, bias estimation, and method comparison [9].
Statistical analyses included paired-sample *t*-test, Pearson´s correlation, Passing-Bablok regression, and Bland-Altman analysis to assess agreement and systematic bias between methods [9,18].

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics v22 (IBM, Turkey). The significance of differences between the two methods was assessed using paired-sample *t*-test ($p < 0.05$ considered significant). Correlation between methods was determined using Pearson´s correlation and Passing-Bablok regression analyses. Bland-Altman plots were used to visualize agreement, proportional error, and systematic bias [9, 18].

## RESULTS

### Precision study results

Precision studies were conducted on both Premier Hb9210 boronate affinity HPLC and Roche TINIA methods using control specimens at two concentration levels (low and high) [9,11]. The IFCC recommends CV% values below 2.8% for HbA1c measurement precision [5,6]. In our study, all CV% values were below 2.0%, performing better than the IFCC recommendations (Table 1) [5,6]. Both within-run precision and intermediate (between-run) precision demonstrated excellent performance, indicating reliable analytical stability across multiple measurement conditions [9].

### Descriptive statistics and method comparison results

Mean ± standard deviation (SD) HbA1c values were 7.16 ± 2.14% for Roche TINIA method and 6.99 ± 1.94% for Premier Hb9210 boronate affinity chromatography method [9,11]. Despite strong positive correlation between results obtained by both methods (Pearson $r = 0.986$, $p < 0.0001$), a statistically significant difference was found between the two methods ($p = 0.0005$) (Figure 1) [9,11]. This finding demonstrates excellent correlation despite a small but consistent bias between

**Table 1. Method precision evaluation.**

| Category | Level | Roche TINIA mean | Roche TINIA SD | Roche TINIA % CV | Premier Hb9210 mean | Premier Hb9210 SD | Premier Hb9210 % CV |
|---|---|---|---|---|---|---|---|
| Repeatability | 1 | 5.7 | 0.15 | 2.71 | 5.6 | 0.10 | 2.06 |
| | 2 | 10.8 | 0.26 | 2.47 | 11.3 | 0.21 | 2.03 |
| Intermediate precision | 1 | 5.6 | 0.13 | 2.31 | 5.6 | 0.09 | 2.03 |
| | 2 | 10.7 | 0.22 | 2.14 | 10.9 | 0.18 | 2.08 |

**Repeatability = within-run precision.**
**Intermediate precision = total precision/between-run precision.**
**Both methods demonstrated excellent precision with % CV values meeting IFCC criteria of < 2.8% [5,6,11].**

**Table 2. Method comparison regarding statistical analysis.**

| Statistical parameter | Results | IFCC/Clinical reference |
|---|---|---|
| Mean ± SD (Roche TINIA) (%) | 7.16 ± 2.14 | variable |
| Mean ± SD (Premier Hb9210) (%) | 6.99 ± 1.94 | variable |
| Median Roche TINIA (%) | 6.31 | variable |
| Median Premier Hb9210 (%) | 6.25 | variable |
| Paired samples *t*-test | 0.16 (0.07 - 0.26) (p = 0.0005) | > 0.95 acceptable |
| Pearson´s correlation (r) | 0.986 (0.977 - 0.991) (p < 0.0001) | > 0.95 acceptable |
| Passing-Bablok regression | y = -0.4201 + 1.0885x | slope 1.0 ± 0.05 |
| Bland-Altman mean difference | -0.17% (95% CI: -1.9 to 1.5%) | < 0.46% at 6.7% |

**Values show a strong correlation and excellent agreement between methods within clinically acceptable limits established by IFCC standardization criteria [11-13,16].**

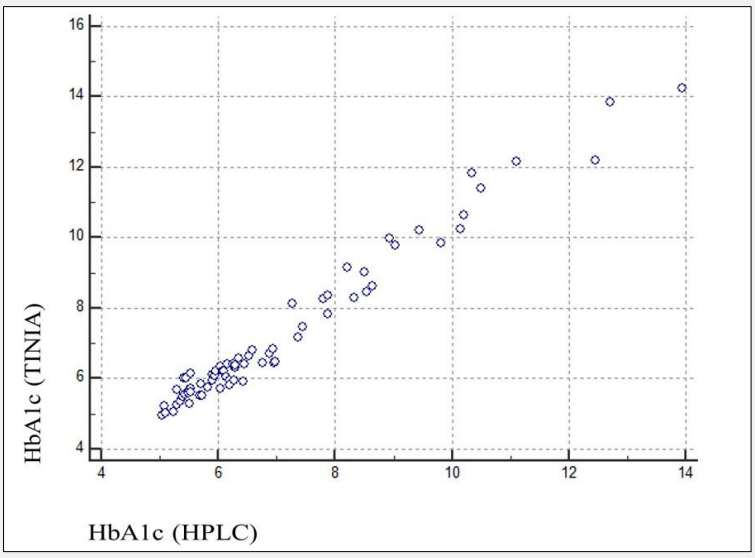



**Figure 1. Explanation graph of the two methods.**

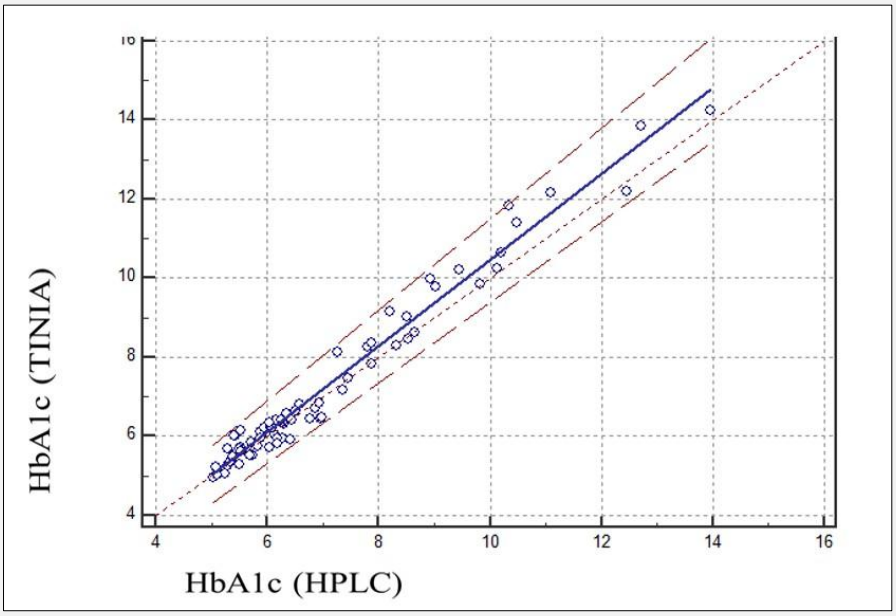



**Figure 2. Regression analysis of two methods by Passing-Bablok.**

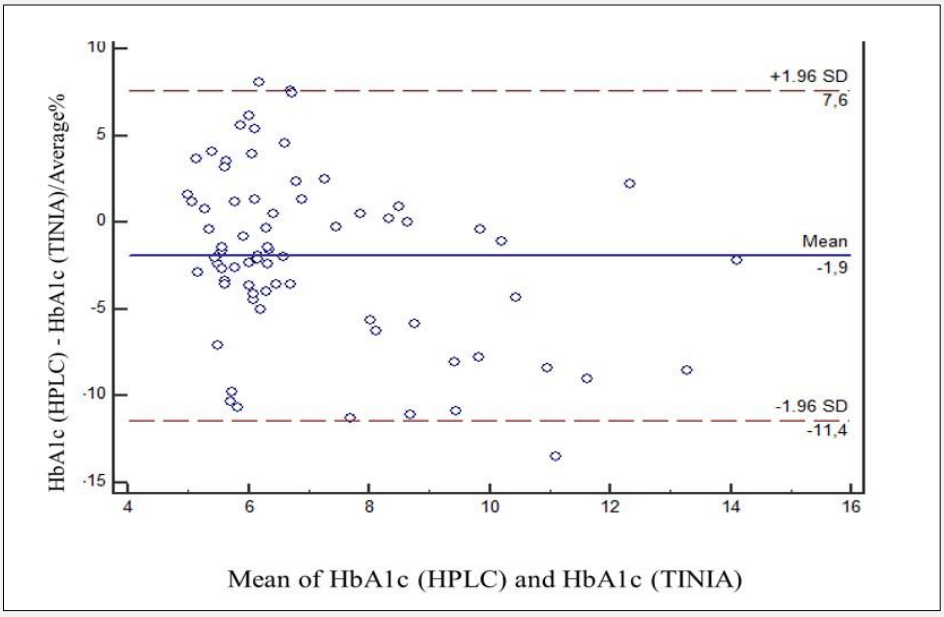



**Figure 3. Bland-Altman plot analysis of the two methods.**

methods, necessitating calibration verification when switching between analytical platforms [9,11,16].

Passing-Bablok regression analysis demonstrated both linear relationship and concordance between the two methods [9,11,16]. The regression equation was y = -0.4201 + 1.0885x, with 95% confidence intervals for slope and intercept of (1.0211 - 1.1528) and (-0.8121 to -0.0088), respectively, indicating minimal systematic bias (Figure 2) [9,11]. Bland-Altman analysis revealed a mean difference of -0.17% with standard deviation of ± 0.86% (95% limits of agreement: -1.9 to 1.5%) [9,11]. This analysis showed that Roche TINIA method measured slightly higher HbA1c levels compared to Premier Hb9210 boronate affinity chromatography method (Figure 3) [9,11].

The mean relative bias between the two methods was 0.17%, which was substantially below the IFCC-defined total allowable error criterion of 0.46% at the 6.7% HbA1c level [9,11]. This value meets stringent international standardization requirements and indicates that both methods can be considered clinically interchangeable for most applications, although the small systematic difference should be acknowledged when interpreting longitudinal patient data or when switching between methods (Table 2) [11,14,16,18].

## DISCUSSION

Our study demonstrated that both Roche TINIA and Premier Hb9210 boronate affinity HPLC methods exhibited acceptable analytical performance and demonstrated excellent agreement for HbA1c measurement [9,11]. The coefficient of variation values of both methods were consistently below 2.0%, exceeding IFCC recommendations of < 2.8%, indicating superior precision performance [5,6,11]. These results align with recent evaluations of the Cobas c513 analyzer using TINIA methodology, which also reported CV values below 1.7% across different HbA1c concentration levels [18,19]. The strong Pearson correlation (r = 0.986) between methods supports the reliability of both analytical approaches and their suitability for clinical diabetes management [9,11,16].

Despite the excellent correlation and narrow limits of agreement, a statistically significant difference was observed between the methods (p = 0.0005), with Roche TINIA producing mean values approximately 0.17% higher than Premier Hb9210 boronate affinity HPLC [9,11]. This finding, while statistically significant due to the sample size and low variability of both methods, remains clinically negligible as the bias is well below the IFCC total allowable error criterion of 0.46% [11,14, 16]. Such small systematic differences between analytical methods using different physical principles are commonly observed in the literature and reflect inherent methodological characteristics rather than analytical deficiency [16,20]. A comparative study by Wu et al. comparing four HbA1c analyzers including Roche c501 and Premier Hb9210 similarly documented small systematic biases between different methodologies with mean differences ranging from 0.04% to 0.13% [21].

The excellent analytical performance of both methods in our study is consistent with the rapid improvements in HbA1c assay technology over the past decade, driven largely by global standardization efforts and manufacturer innovations [3,18]. The IFCC standardization program and ongoing manufacturer improvements have resulted in continuous enhancement of new analyzer performance characteristics [2]. The Premier Hb9210 boronate affinity HPLC system has been evaluated in multiple centers and consistently demonstrated good correlation with routine methods and IFCC reference procedures, supporting its clinical utility and reliability [1,2, 16].

Previous literature comparing HbA1c measurement methods has provided valuable insights into method-specific characteristics and potential interferences. John and colleagues conducted a multicenter evaluation of Premier Hb9210 comparing it with Trinity Ultra 2 (boronate affinity), Tosoh G8 (ion-exchange HPLC), and Roche Tina-quant Gen2 HbA1c on Integra 800 (immunoassay), documenting that Premier Hb9210 demonstrated excellent correlation with routine methods and IFCC reference procedure performance [1,2]. Similarly, recent 2024 evaluations demonstrated that both immunoassay and HPLC-based methods can achieve satisfactory precision and accuracy when properly maintained and calibrated, provided they meet IFCC and NGSP certification criteria [12,18,19].

Genc and colleagues compared four contemporary HbA1c methods and documented that both TINIA and boronate affinity methods showed good agreement with capillary electrophoresis (CE), while cation-exchange HPLC showed linear relationship with CE but with statistically significant differences [11]. This demonstrates that both methodological approaches employed in our study represent valid, reliable analytical options for clinical use, though each has characteristic analytical profiles [11].

Arzuhal and colleagues evaluated Agilent 1100 ion-exchange HPLC performance compared with Premier Hb9210 boronate affinity HPLC across four different patient groups and demonstrated that both systems met clinical requirements and produced suitable HbA1c measurements [16,20]. This body of literature supports the clinical interchangeability of these methods within acceptable standardization parameters [16,20].

An important consideration in modern HbA1c testing is the potential for interference from hemoglobin variants and conditions affecting red cell lifespan [8,9,12,14,15]. Boronate affinity chromatography, like that employed in the Premier Hb9210 system, demonstrates resistance to interference from common hemoglobin variants (HbS, HbE, HbC, HbD) because separation is based on glycation status rather than charge differences [5,15]. In contrast, immunoassay methods may demonstrate variant-specific interference depending on whether variants

involve the N-terminal region of the β-chain [8,15]. Recent comprehensive evaluations emphasize the need for laboratories to understand their method's limitations regarding hemoglobin variants, especially when HbA1c results appear discordant with clinical glucose measurements or when HbA1c levels exceed 15% [9,12,15].

The standardization framework established by IFCC and NGSP has been instrumental in improving HbA1c result comparability globally [13,22-25]. The establishment of master equations relating IFCC and NGSP units (NGSP = [0.09148 × IFCC] + 2.152) enables seamless conversion between reporting systems while ensuring that results remain traceable to clinical outcome data from landmark trials like DCCT and UKPDS [13,22, 24]. Contemporary point-of-care testing devices must also meet these certification criteria, with recent 2024 evaluations revealing that only 5 out of 19 evaluated HbA1c POC devices met both IFCC and NGSP certification criteria, highlighting the importance of method validation [12,26].

Clinically, the importance of accurate HbA1c measurement is underscored by its multiple roles: 1) diagnosis of diabetes mellitus (HbA1c ≥ 6.5%/≥ 48 mmol/mol); 2) identification of prediabetes (HbA1c 5.7 - 6.4%/39 - 47 mmol/mol); 3) monitoring glycemic control in diabetic patients (target typically < 7.0%/< 53 mmol/mol); 4) assessment of complication risk; and 5) therapeutic decision-making [6,10,23,27,28]. The hemoglobin glycation index (HGI), representing the deviation between measured HbA1c and HbA1c predicted from continuous glucose monitoring data, has emerged as an important complementary parameter for individualized diabetes management, identifying patients with discordance between HbA1c and average glucose exposure [29-32]. This emphasizes the need for precise, standardized HbA1c measurement across clinical practice.

The accelerating global diabetes pandemic and progression toward HbA1c-based diagnosis necessitate error-free HbA1c measurement across all laboratory settings [8,24]. Ongoing standardization efforts by IFCC and NGSP, combined with continuous manufacturer improvements, have resulted in progressive enhancement of HbA1c analyzer performance characteristics and reduced interlaboratory variability [2,33]. Both immunoassay and boronate affinity HPLC approaches have demonstrated their value in routine clinical practice when properly standardized and regularly validated [2, 16,18,20].

Limitations of our study include the relatively modest sample size (n = 75) and single-site design. Future studies with larger patient populations, diverse geographic locations, and systematic evaluation of potential interferences (hemoglobin variants, hematologic conditions, medications) would provide additional validation. Additionally, cost-effectiveness analysis and high-throughput capacity comparisons between these methods would inform laboratory implementation decisions. However, our findings are consistent with the published literature and support the clinical reliability of both analytical approaches.

## CONCLUSION

This study demonstrates that both Roche TINIA and Premier Hb9210 boronate affinity HPLC methods exhibited acceptable analytical performance, excellent precision, and strong agreement for HbA1c measurement [9,11]. The Roche TINIA method demonstrated good concordance with the Premier Hb9210 boronate affinity HPLC reference method, with analytical performance meeting or exceeding IFCC standardization criteria [11,14]. Both methods are suitable for clinical diabetes management. While a small but consistent bias of 0.17% was observed, this remained well below clinically significant thresholds and IFCC-defined total allowable error limits [11,14]. The results support the clinical utility of both analytical approaches for routine HbA1c measurement in diverse laboratory settings. Laboratories should recognize the modest systematic difference between methods and ensure appropriate patient communication and medical provider notification if transitioning between analytical platforms. Continued standardization efforts and manufacturer innovations will likely further enhance the analytical performance and clinical utility of HbA1c measurement methodologies.

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The authors declare that generative AI was not used for this work.

**Declaration of Interest:**
The authors declare that there are no conflicts of interest regarding this work.

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