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Verifying measurements on Siemens Atellica® instruments using clinically acceptable analytical performance specifications

short title: Siemens Atellica® verified against *CAAPS*

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Abstract

Measurements on clinical chemistry analysers must be verified to demonstrate applicability to their intended clinical use. We verified the performance of measurements on the Siemens Atellica® Solution chemistry analysers against the clinically acceptable analytical performance specifications, *CAAPS*, including the component of intra-individual biological variation, CV_I. The relative standard uncertainty of measurement, i.e., analytical variation, CV_A, was estimated for six example measurands, haemoglobin A_{1c} in whole blood (B-HbA_{1c}), albumin in urine (U-Alb), and the following measurands in plasma: sodium (P-Na), pancreatic amylase (P-AmylP), low-density lipoprotein cholesterol (P-LDL-C), and creatinine (P-Crea). Experimental CV_A was calculated from single-instrument imprecision using control samples, variation between measurements on parallel instruments, and estimation of bias with pooled patient specimens. Each obtained CV_A was compared with previously developed *CAAPS*. The calculated CV_A was 1.4% for B-HbA_{1c} (*CAAPS* 1.9% for single diagnostic testing, *CAAPS* 2.0% for monitoring after duplicate tests; IFCC units), 10.9% for U-Alb (*CAAPS* 44.9%), 1.2% for P-Na (*CAAPS* 0.6%, after triplicate testing 1.5%), 8.2% for P-AmylP (*CAAPS* 22.9%). The CV_A was 4.9% for P-LDL-C (*CAAPS* for cardiovascular risk stratification 4.9% after four replicates), and 4.2% for P-Crea (*CAAPS* 8.0%). Three of the six measurands fulfilled the estimated clinical need. Results from P-Na measurements indicate a general need for improving the P-Na assays for emergency patients. It is necessary to consider CV_I when creating diagnostic targets for laboratory tests, as emphasized by the *CAAPS* estimates of B-HbA_{1c} and P-LDL-C.

List of Abbreviations

Alb,	albumin;
AmylP,	pancreatic amylase;
CAAPS,	clinically acceptable analytical performance specification;
CD,	clinically significant difference;
Crea,	creatinine;
CV_A,	(coefficient of) analytical variation;
CV_D,	(coefficient of) diagnostic variation;
CV_I,	(coefficient of) biological intra-individual variation;
CV_{INST},	imprecision of a single instrument (intermediate reproducibility);
$CV_{INST\text{-}WD}$	within-day imprecision of a single instrument
CV_{PAR},	(coefficient of) variation between parallel instruments;
$CV_{PAR\text{-}CORR}$	corrected variation between parallel instruments;
CV_{PRE},	(coefficient of) preanalytical (technical) variation;
CV_{REP}	(coefficient of) diagnostic variation for repeated measurements;
D,	difference of the new (Atellica®) result against the mean result of the new and the replaced (Architect™) measurement procedure;
D_{PAR},	difference of a result on parallel instrument against that of index instrument;
HbA_{1c},	haemoglobin A_{1c};
IFCC,	International Federation of Clinical Chemistry and Laboratory Medicine;
LDL-C,	low-density lipoprotein cholesterol;
MU	measurement uncertainty;
Na,	sodium;
NGSP,	National Glycohemoglobin Standardization Program;
RCV	reference change value;
RMS_D,	root mean square of differences D;
z,	Gaussian statistic;
α,	probability of type I error, false positives;
β,	probability of type II error, false negatives;
$1\text{-}\beta$,	statistical power, sensitivity.

Keywords

automation, laboratory; biological variation, individual; clinical chemistry tests; clinical decision making; diagnostic test approval; measurement uncertainty (non-MESH term); medical informatics applications; performance, analytical (non-MESH term)

Introduction

The EFLM Milan Strategic Conference in 2014 has recommended clinical outcomes (Model 1) and biological variation (Model 2) as preferred strategies to set analytical performance specifications (*APS*) for clinical chemistry measurements, leaving the state-of-the-art, Model 3, or combinations of all three as possibilities, if justified [1]. Performance specifications based on clinical need may derive directly from clinical outcome studies, Model 1a, or indirectly from defined use of laboratory results, Model 1b [2]. Consequently, the Milan models have been adapted to a list of the most common clinical chemistry measurands [3].

We have developed a model to estimate clinically acceptable analytical performance specification (*CAAPS*), starting from clinically significant differences (*CD*) between two measurements [4]. The formula of reference change value (*RCV*) was used to calculate the maximum allowable coefficient of diagnostic variation (CV_D) of patient measurements to detect the required *CD* [5]. In clinical laboratory practice, the CV_D includes intra-individual biological variation, CV_I [6], preanalytical technical variation, $CV_{PRE,}$ and analytical variation, CV_A [7, 8]. The *CAAPS* = maximum allowable analytical variation, also representing maximum allowable measurement uncertainty (*MU*) was obtained by subtracting the other components from the CV_D. The calculated *CAAPS* were developed for end-user verification of chemical measurements before the intended clinical use, as required by the ISO 15189:2022 standard, chapter 7.3 [9], and the CLSI guideline EP15-A3, chapter 1.6 [10].

The *CAAPS* approach was applied to verify the analytical performance of measurements on Siemens Atellica® platform at a multiple laboratory organisation (HUS Diagnostic Center in the Helsinki and Uusimaa Hospital District, Finland) against *CAAPS*. We now describe outcomes of this verification using six example measurands, i.e., haemoglobin A_{1c} in blood, B-HbA_{1c}, albumin in urine, U-Alb, sodium in plasma, P-Na, pancreatic amylase in plasma, P-AmylP (the primary test for pancreatitis at HUS Diagnostic

Center), low density lipoprotein cholesterol in plasma, P-LDL-C, and creatinine in plasma, P-Crea, as obtained in that verification.

Material and methods

Determining clinically significant differences (CD), and clinically acceptable analytical performance specifications (CAAPS)

The clinical need was modelled as a clinically significant difference (*CD*) in a measurand concentration that needs to be detected between two diagnostic or prognostic categories (diagnostic testing), or between two consecutive measurements (follow-up monitoring). These limits were sought from international clinical guidelines, as described in the previous publication [4]. The equation used to derive the needed CV_D was:

$$CD = z * \sqrt{2} * CV_D, \text{ converted into } CV_D = CD / (z * \sqrt{2}) \quad (1)$$

where z is the used Gaussian statistic, modified to improve the sensitivity of detection, CV_D = coefficient of diagnostic variation, and $\sqrt{2}$ assumes two identical distributions in the compared measurements.

The consequent equation to calculate the coefficient of maximum allowable analytical variation CV_A , representing maximum allowable measurement uncertainty, *MU*, was:

$$CV_D^2 = CV_I^2 + CV_{PRE}^2 + CV_A^2 \quad (2)$$

where CV_I = intra-individual biological variation, CV_{PRE} = preanalytical technical variation, and CV_A = allowable analytical variation.

From the equation (2), the allowable CV_A or *MU* was left over after subtracting variances of the other components from the variance of CV_D:

$$CV_A^2 \leq CV_D^2 - (CV_I^2 + CV_{PRE}^2) \quad (3)$$

The allowable CV_A, now called clinically acceptable analytical performance specification, $CAAPS = \sqrt{CV_A^2}$, is maximally allowed to detect the clinically significant difference *CD* of the model [4].

The coefficient of diagnostic variation acceptable for repeated measurements, CV_{REP}, was calculated as follows [11]:

$$CV_D = CV_{REP} / \sqrt{n}, \text{ where } n = \text{number of replicates} \quad (4)$$

Inversely, an acceptable $CV_{REP} = CV_D * \sqrt{n}$. After n repeats, a clinically significant difference may be detected according to the formula:

$$CD = z * \sqrt{2} * CV_D = z * \sqrt{2} * CV_{REP} / \sqrt{n}. \quad (5)$$

Empirical calculation of components in analytical variation

Compliance of the performance of measurements on the Siemens Atellica® Solution platform (Siemens Healthineers, Germany) with the estimated *CAAPS* budgets was assessed during a half-year verification project in 2019 at the Department of Clinical Chemistry at HUS Diagnostic Center, including a central laboratory and eight regional sites, with a combined production of about 19 million tests annually. The following components of analytical variation were included in the calculation of *MU*:

(1) intermediate reproducibility of the index instrument of the central laboratory using commercial control materials, expressed as coefficient of variation, CV_{INST};

(2) variation between the parallel instruments, comparing each parallel instrument pairwise against the index instrument of the central site using pools of patient samples, expressed as coefficient of variation between parallel instruments, CV_{PAR};

(3) bias of the new measurement procedures, assessed on the index instrument of the Siemens platform against measurements on the previous index Abbott™ Architect™ c16000 or c8000 platforms with pooled patient samples, calculated from the individual relative differences *D* (%) of Atellica® results against the mean between

the two measurement procedures, and combined into root mean square of differences RMS_D.

Reproducibility of the measurement procedures on the index Siemens Atellica® instrument was estimated as imprecision, CV_{INST}, according to the CLSI EP05-A3 guideline, with a modified 2x2 in 10 days protocol instead of 20 days [12], because of multiplicity of routine chemistry and immunochemistry assays and parallel instruments in different laboratories.. The details of the assays and calibrators of the Siemens Atellica® measurement procedures and those of the compared Abbott™ Architect™ measurement procedures for the example measurands are shown in **Table 1**. Third-party control materials at three different concentration levels were measured in duplicates twice a day during ten consecutive days. The following control materials from Bio-Rad were used: Liquichek Diabetes Control (catalogue no. 171, 172 and 173) for B-HbA_{1c}, Liquichek Urine Chemistry Control (catalogue no. 12004329 and 12004330) for U-Alb, and InteliQ Assayed Multiqual Control (catalogue no. 12008256, 12008257 and 12008258) for P-Na, P-Amyl-P, P-LDL-C and P-Crea. The results from the control concentration that was closest to the assessed clinical decision interval was chosen to represent the imprecision of a single instrument.

Relative differences between all 6-12 parallel Siemens Atellica® instruments were determined by comparing results from single measurements on them pairwise against those on the index instrument, using 11-44 pools of patient samples with different concentrations. The Dahlberg equation was used to calculate the coefficients of parallel variation, CV_{PAR} (%), including both imprecision and bias in the estimated variation [13,14]:

$$CV_{PAR} = (\sum D_{PARi}{}^2/2n)^{0.5} \quad (6)$$

where n = number of paired measurements, and $D_{PARi} = D_{PAR1} \ldots D_{PARn}$ represent individual differences in single results on each parallel instrument against those on the index instrument.

Coefficients of parallel variation, CV_{PAR}, were corrected for double inclusion of within-day imprecision of instruments already included in the CV_{INST} imprecision, by using the following formula:

$$CV_{PAR\text{-}CORR} = (CV_{PAR}^2 - CV_{INST\text{-}WD}^2)^{0.5} \quad (7)$$

where $CV_{INST\text{-}WD}$ = within-day imprecision of a single instrument.

Systematic difference (bias) of the measurement procedures on the new Siemens Atellica® platform was estimated against the mean of the new and the replaced procedure at the Abbott™ Architect™ platform, assuming the mean as the best estimate of the "true value". A total of 20-44 pooled patient samples were measured once on the designated index instruments of both platforms. The differences in Atellica® results against the mean between the two measurement procedures were labelled as D to separate them from D_{PAR} of parallel instrument comparisons. Each single relative difference D_i (%) of Atellica® assay to the mean was calculated using the equation:

$$D_i\ (\%) = [Atellica_i - (Atellica_i + Architect_i)/2]/\ [(Atellica_i + Architect_i)/2] \quad (8)$$

Squares of individual differences D_i were combined into a root mean square, RMS_D, to obtain an estimate for relative standard uncertainty of the assay including both bias and imprecision [13]:

$$RMS_D = (\sum D_i^2/n)^{0.5} \quad (9)$$

The RMS_D results from pooled patient samples were corrected for two example measurands: The differences in the Atellica® B-HbA_{1c} assay against the means were improved by correction of the bias of Abbott™ Architect™ results with an IFCC-traceable

reference procedure for B-HbA_{1c}, available through the ISO/EN 17043 accredited EQA scheme for Haemoglobin A_{1c} provided by Labquality's External Quality Assessment (PT02/FINAS). The combined standard uncertainty of calibration of the Siemens Atellica® assay for P-Na was documented by Siemens Healthineers to be 0.73% (k=1). The calibration of the P-Na measurement was confirmed with the certified reference material, NIST SRM 956d, level 2, with a target value of 139.3 and a u_{SRM} = 0.32%.

Data analysis

Method verification data from the instruments were stored for assessment and reporting purposes using the Validation Manager™ software (Finbiosoft Oy, Espoo, Finland). Otherwise, Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA) with Analyse-It module (Analyse-it Software, Ltd, The Tannery, 91 Kirkstall Road, Leeds, LS3 1HS, United Kingdom) were used for statistical calculations.

Results

CAAPS, and sources of intraindividual biological and technical preanalytical variation

The modelled clinically acceptable analytical performance specifications, *CAAPS*, and the collected preanalytical sources of variation were compiled in **Table 2,** as calculated in our previous work [4]. For B-HbA_{1c}, we modelled both a 10% change in disease monitoring and a 14% change for the use in diagnosing, expressed in the standardised IFCC units. The corresponding changes in the American NGSP units were 7% and 9%, respectively, using the difference of 0.5 haemoglobin % (Hgb%) as the critical difference [15]. Estimates of the CV_I were obtained from the EFLM database [6], except for that of B-HbA_{1c} taken from diabetic patients [15] and that of albuminuria taken from patients with chronic kidney disease [16]. The coefficients of technical preanalytical variation, CV_{PRE}, were estimated from the Finnish experience with regional transportation [7] (**Table 2**).

Components of analytical variation on Siemens Atellica® analysers

The calculated *CAAPS* were used to assess the performance of the new assays on Siemens Atellica® chemistry analysers. First, the intermediate overall reproducibility, CV_{INST}, of the chosen Siemens Atellica® index instrument was assessed during a modified two-week protocol (**Table 3**). Each single result obtained with a tested parallel instrument was compared to that with the index instrument, using selectively collected pooled patient samples to provide parallel instrument reproducibility (CV_{PAR}). The CV_{PAR} was calculated from individual differences according to the equation (6). The corrected $CV_{PAR\text{-}CORR}$ was obtained by removing the within-day imprecision $CV_{INST\text{-}WD}$ from the total CV_{PAR} according to the equation (7). The corrected $CV_{PAR\text{-}CORR}$ reduced the obtained *MU* with 0.2%, except for that of P-AmylP where 0.1% reduction was seen. We defined a *clinically important interval*

for each measurand when calculating CV_{PAR}, to avoid increased variation outside the common diagnostic intervals, as shown in the figures (**Figure 1, A-F)** and compiled into **Table 3**.

Biases of the Siemens Atellica® assays were estimated by comparing the two field procedures with each other, because no external quality assessment (EQA) data were available for most of the new Siemens Atellica® procedures at the time of the verification. The differences *D* of the new Atellica® assays were calculated against means between Siemens Atellica® and Abbott™ Architect™ procedures, using the equation (8). Concentrations above the lower limit of the chosen clinically important intervals were used, to focus accuracy estimates on the major range of clinical significance (**Figure 2, A-F**). The uncertainties of the assay biases were expressed as RMS_D, according to the equation (9), and compiled into **Table 3**. The means of differences *D* remained within the RMS_D estimates.

Two measurands needed corrections to their RMS_D estimates. Since the Siemens Atellica® procedure had a mean difference of -2.02% against the Abbott™ Architect™ in blood HbA_{1c} measurements (**Figure 2A**), we looked for the bias of the Architect™ procedure against a reference procedure at a higher level. Indeed, a bias of +5.0% was noted in B-HbA_{1c} results (using IFCC units) of the Architect™ assay against a value in the Labquality's EQA scheme, traceable to an IFCC reference procedure. After correcting this bias, the mean difference between Atellica® and Architect™ HbA_{1c} measurements was 0.42%, with an RMS_D = 0.76% (uncertainty of the EQA target value was considered negligible) (**Figure 2A, Table 3**). For P-Na, the obtained mean of differences of Siemens Atellica® results against means between the two field procedures was 1.49% (**Figure 2C**). The bias was replaced with a mean of 0.70% against the NIST SRM 956d using the index instrument, with an uncertainty of 0.32% at 139 mmol/L. After correction of the bias at the instrument, the combined standard uncertainty of calibrator 0.73% (k=1) for P-Na assay (Table 1) was used in the calculations, available for the Siemens Atellica® procedure (**Figure 2C**). All individual

results in Figures 2A-F are shown uncorrected despite the corrections shown in the explanatory boxes.

Comparison of analytical variation to the CAAPS

The variances of a single instrument, those of parallel instruments, and those obtained from measurement comparisons were summarized as the experimental analytical variation, CV_A , or relative standard uncertainty of measurement, *MU* (**Table 3**). *MU* results from three of the obtained six example measurands fell within the desirable *CAAPS* from clinical differences, using z= 3 to get a sensitivity $1\text{-}\beta$ = 85% (**Table 3)**. B-HbA_{1c} assay performed satisfactorily in diagnostic testing, when using the IFCC units (mmol/mol) to express the results but monitoring required duplicate testing (IFCC units), essentially due to the CV_I that consumed most of the allowable CV_A budget (**Table 2**). B-HbA_{1c} assay had a reduced performance when using NGSP units (Hgb%). The *CAAPS* estimate for P-Na were reached after triplicate follow-up measurements only, by using the obtained CV_A = 1.2%. *CAAPS* for P-LDL-C could be modelled with quadruplicate testing according to the equation (5) only (**Table 3**), due to a high CV_I of plasma LDL-C (**Table 2**).

Discussion

Applicability of the current CAAPS approach for test verification

This study describes a practical exercise of assessing applicability of our clinically acceptable analytical performance specifications (*CAAPS*) into a verification project of Siemens Atellica® automated platforms at a regional laboratory service of HUS Diagnostic Center [4]. *CAAPS* is an indirect outcome-based model of analytical performance specifications, *APS*. Detecting clinically significant differences, *CD*, provides a practical and easily understandable basis for end-user verification of laboratory measurements for intended clinical use, as required by the ISO15189 accreditation standard. The indirect clinical outcomes go further from models based on health-related biological variation, or state-of-the-art without clinical connections. The *CAAPS* model maximum allowable measurement uncertainties in detection of typical guideline-based *CD* between two patient results, also including the clinically relevant CV_I and CV_{PRE} components. They add a new way of indirect modelling of *APS*, previously estimated with diagnostic misclassifications [17].

Guideline-based modelling obviates opinion-based clinical specifications, but it has a risk of repeating the state-of-the-art level of performance inherent in clinical consensus guidelines [1]. In addition to the chosen *CD* targets, Gaussian modelling of the components of diagnostic variation CV_D, and a perception on the required Gaussian sensitivity to detect a difference, $1\text{-}\beta$, also create some uncertainty to the calculated *CAAPS* specifications.

The primary applicability question regarding the modelled *CAAPS* is whether they improve the assessment of analytical performance of clinical chemistry measurements. Because of the used equations (1-3), our estimates of *CAAPS* were mostly wider than those derived traditionally from biological variation of healthy individuals [18], but similar to those

calculated by Rigo-Bonnin and coworkers who studied reference change values with all components of analytical and extra-analytical variability [19]. A large or even moderate CV_I of some measurands [6] has not always been considered when creating clinical guidelines to the diagnosis or follow-up of different diseases. In our example measurands, monitoring of blood HbA_{1c}, or follow-up of plasma LDL-C is not possible with the existing CV_I by using single comparisons (Table 2). Thus, the *CAAPS* model pointed out a weakness in clinical guidelines where the CV_I was not considered. Including the CV_I in the assessment of patient measurements, as applied in the *CAAPS*, seems to increase their clinical validity.

Experimental components of analytical variation from Siemens Atellica® measurements

The intermediate reproducibility (CV_{INST}) of the Siemens Atellica® index instrument was studied with control solutions over 10 working days, with expectable results (Table 3). Measurements of controls of the P-Na procedure showed an imprecision = 0.80%, also repeated with measurements of the NIST SRM 956d (data not shown).

To see the reproducibility of 6-12 parallel Atellica® instrument modules at all regional laboratories, results from single measurements of 11-44 pools of selected patient specimen pools were compared to those on the Atellica® index instrument (Figure 1, A-F). The CV_{PAR} was estimated within the chosen clinically important intervals for diagnostic classifications, being the usual targets for optimization of automated platforms as well, as shown best in Figures 1B (U-Alb) and 1F (P-Crea). The results from 43 to 224 pooled samples remained within these intervals, allowing estimation of parallel instrument variation, i.e., within-laboratory reproducibility (Table 3). Subtraction of the within-day single instrument repeatability ($CV_{INST\text{-}WD}$) to get the corrected estimate $CV_{PAR\text{-}CORR}$ reduced the final estimate of analytical variation CV_A with 0.1 – 0.2% (data not shown).

The assay principle is an independent, and potentially a major source of bias in a clinical chemistry measurement. In the verification of an end-user laboratory, an extensive assessment of systematic errors with traceability chains is not possible. We modelled the bias of the new Siemens Atellica® procedure by comparing the difference of each individual measurement to the mean of measurements on both Atellica® and Architect™ index instruments, as the best estimate of the non-biased value (Figure 2, A-F). The mean of the 18-26 single relative differences ($mean_D$) within the clinically important interval represented the estimated bias of each Atellica® measurement procedure. Separate improved estimates of bias were used for B-HbA_{1c} and P-Na (Figure 2). Mean empirical estimates of bias were not directly used in the final calculations of *MU*, since the estimates fell within the calculated variation expressed as corrected or uncorrected RMS_D for each measurand, including both (undefined) bias and its variation (Table 3). The RMS_D estimates from two different measurement procedures using patient specimens were considered independent from the single instrument reproducibility CV_{INST} measured with control solutions. Since the size of the differences D was highly variable, and the distributions over the measured concentration were uneven, our RMS_D estimates are probably rather too high than too low, i.e., they may contain some extra uncertainty in the estimated bias and its variation.

Acceptability of performance of the Siemens Atellica® measurements

By using the *CAAPS* assessment tool, defects in the optimal analytical performance were observed with some measurands. Insufficient performance against the calculated *CAAPS* created further considerations. The components of analytical variation of the example measurands were summarised into the observed relative standard measurement uncertainty for each measurand (Table 3). The multi-laboratory CV_A of B-HbA_{1c} measurement on Siemens Atellica® was estimated to be 1.4% (the IFCC mmol/mol units, as used at HUS

Diagnostic Center) (Table 3). It satisfies the clinical need of diabetes classification, 1.9% with IFCC units derived from Table 2. The reduction of *CAAPS* to 0.8% with NGSP units (Hgb%) is related to the less accurate diagnostic target of *CD* = 0.5 Hgb%, or 9% (instead of 14% in IFCC units), and the measurement principle (Table 2). Monitoring of the proposed 10% (IFCC) or 7% (NGSP) changes in B-HbA_{1c} is not possible with a single comparison because of the CV_I of blood HbA_{1c}. The impact of CV_I view has not been considered when discussing the "clinically important differences" to be detected in monitoring of diabetes [20]. In practice, the borderline performance of B-HbA_{1c} measurements for glycaemic control of diabetes patients is alleviated by repeated visits and is also supported by continuous glucose monitoring by patients' devices to reduce the risk of hypoglycaemia [21].

Analytical performance to detect a change of 5 mmol/L for P-Na is critically needed to avoid cerebral edema in a range of 120-130 mmol/L, despite the small relative difference [22]. The estimated within-laboratory analytical variation of P-Na measurements on Atellica® platform was 1.2% (Table 3). Thus, the required *CAAPS* of 0.6% was achieved after triplicate measurements that broaden the modelled *CAAPS* into 1.5% (Table 2). This inaccuracy is shown in current practice that uses repeated monitoring of P-Na with point-of-care devices at intensive care units. In various clinical emergencies, an analytical performance specification, *APS*, of 0.6% remains a challenge of manufacturing for the future [23].

Plasma concentration of the low-density lipoprotein cholesterol (P-LDL-C) is a major biomarker of cardiovascular risk, and a target of treatment of the disease in those patients [24]. The prognostic grouping derives from cross-sectional epidemiology, not from actual follow-ups of individual patient measurements. Because of the high CV_I, nothing was left to the CV_A budget of LDL-C measurements if the cardiovascular risk assessment from a single measurement should success within 20% differences. After quadruplicate pairs of

measurements, the approximated target *CAAPS* = 4.9% in P-LDL-C was reached with a CV_A = 4.9% (Table 3). An alternate *APS* for P-LDL-C from biological variation 4% provides a similar challenge, using a desirable $CV_A \leq 0.5\ CV_I$ [3]. Our comparison detected no mean bias between Atellica® and Abbott™ measurements of P-LDL-C (Figure 2E). This is not the case when comparing LDL-C measurements between all commercial platforms. It is probable that a remarkable reduction of -50% or more from the baseline high concentration of plasma LDL-C is detectable with the observed analytical performance, e.g., as expected after statin treatment [24] with similar measurement technology of LDL-C, but the calculated *CAAPS* for the risk targets with given LDL-C concentrations was not possible. The role of CV_I should be included in dyslipidaemia recommendations in the future. Since the statin treatment is usually lifelong with low risk of overdosing, current repeated measurements of LDL-C mitigate the accuracy problem of LDL-C in practice. However, single measurements of LDL-C are used by the Social Security Insurance Institution in Finland to determine whether newer PCSK9 inhibitor are compensated by the national insurance showing that a single LDL-C result can have a large impact if the clinician is unaware of magnitude of analytical and biological variation.

The observed relative standard measurement uncertainties of U-Alb, P-AmylP and P-Crea satisfied clearly the modelled *CAAPS* (Table 3). An essential factor for this clear clinical performance is the remarkable increase in these measurand concentrations in disease, creating the wide diagnostic intervals between health and disease (Table 2). In some patient groups, such as chronic pancreatitis, borderline elevations as compared to health-related values may require better accuracy of measurements, or confirmations before starting the intended treatments.

The *CAAPS*-based frames for maximum allowable analytical variation, representing maximum allowable measurement uncertainty provide a general frame of acceptability

assessment of clinical laboratory measurements. In establishing the various analytical platforms, more stringent limits are needed for rules set for internal quality control, to be able to stay within the limits of the given CV_A in various practical conditions, including service needs of instruments.

Conclusions

Clinical acceptability-based analytical performance specifications, *CAAPS*, were valuable in the verification of measurement uncertainties on Siemens Atellica® Solution chemistry platforms of chemical measurands at a regional laboratory level. Three from the six example measurands fulfilled clearly the estimated clinical need. The verification of plasma sodium measurements demonstrated a measurement uncertainty comparable to that of other automated chemistry analysers and indicated a generally known challenge for further development in sodium assays to satisfy clinical hyponatraemia diagnostics, supporting validity of the *CAAPS* approach. *CAAPS* estimates of two measurands (haemoglobin A_{1c} and low-density lipoprotein cholesterol) reminded of the need to understand the role of intra-individual biological variation when creating diagnostic targets for laboratory tests.

Disclosure statement

Siemens Healthineers did not influence in the design or the interpretation of this study.

No external funding was obtained to this verification that was a part of a developmental process at HUS Diagnostic Center laboratories. The authors have no competing interests to declare.

Table 1. Measurement procedures on Siemens Atellica® and Abbott™ Architect™ analysers [a]

Measurand	*Siemens Atellica®*			*Abbott™ Architect™*	
	Assay application and reagent	***Calibrator***	***Standard uncertainty of calibrator (k=1)***	***Assay application and reagent***	***Calibrator***
Haemoglobin A_{1c} in whole blood (B-HbA_{1c})	A1c_3 Atellica® CH Enzymatic Hemoglobin A1c	Atellica CH A1c_E CAL	1.02%, IFCC units, at 102 mmol/mol	HbA1cWB (IFCC) Hemoglobin A1c	Hemoglobin A1c Calibrators
Albumin in urine (U-Alb)	µALB_2 Atellica® CH Microalbumin_2	Atellica CH µALB_2 CAL	2.35%, at 100 mg/L	uAlb MULTIGENT Microalbumin	MULTIGENT Microalbumin Calibrators
Sodium in plasma (P-Na)	Na (serum/plasma) A-LYTE® Integrated Multisensor, A-LYTE IMT Diluent	A-LYTE IMT Standard A and B	0.73%, at 14 mmol/L (diluted concentration)	Na-C ARCHITECT c Systems ICT, ICT (Na^+, K^+, Cl^-) Sample Diluent	ICT Serum calibrator
Pancreatic amylase in plasma (P-AmylP)	PAmy Atellica® CH Pancreatic Amylase	Atellica CH Diluent	3.44% at 425 U/L	AmyP MULTIGENT PANCREATIC AMYLASE	MULTIGENT Clin Chem Cal
LDL Cholesterol in plasma (P-LDL-C)	DLDL Atellica® CH LDL Cholesterol Direct	Atellica CH HDL/LDL CAL	1.34% at 3.52 mmol/L	DLDL MULTIGENT Direct LDL	LIPID MULTICONSTITUENT CALIBRATOR
Creatinine in plasma (P-Crea)	ECre_2 Atellica® CH Enzymatic Creatinine_2	Atellica CH CHEM CAL	0.22% at 787 µmol/L	CrEnz MULTIGENT Creatinine (Enzymatic)	MULTIGENT Clin Chem Cal

[a] Abbreviations in the names of reagents and calibrators represent commercial names of those products.

Table 2. Clinically acceptable analytical performance specifications (*CAAPS*) from clinically significant differences

Measurand	***Significant difference for medical decision***	***Clinically significant difference, %***	***Clinically acceptable diagnostic variation*** [a]	***Biological intra-individual variation*** [b] ***%***	***Preanalytical variation, estimated***	***CAAPS*** [c] ***based on clinical difference,*** [a] ***%***	***CAAPS with replicate testing,*** [a] ***%***
		CD [c]	$CV_D = CD / (3*\sqrt{2})$	CV_I	CV_{PRE}	$CAAPS = \sqrt{CV_A^2}$ α = 2.5%, *1-*β = 85%	***CAAPS*** (*n* = number of repeats)
Blood HbA_{1c}	Diagnostic testing:						
	42 -> 48 mmol/mol (IFCC)	14%	3.3%	2.5%	1%	1.9% (IFCC)	
	6.0 -> 6.5 Hgb% (NGSP)	9%	2.1%	1.7% [15]	1%	0.8% (NGSP)	
Blood HbA_{1c} [a]	**Monitoring:**						
	at 53 mmol/mol (IFCC)	10%	**2.4%**	**2.5%**	1%	**(<0%) (IFCC)**	2.0% (*n*=2; IFCC)
	at 7.0 Hgb% (NGSP)	7%	**1.6%**	**1.7%** [15]	1%	**(<0%) (NGSP)**	2.1% (*n*=3; NGSP)
Urine Alb	30 -> 100 mg/L	230%	54.2%	30% [16]	5%	44.9%	
Plasma Na	125 -> 130 mmol/L	4%	0.9%	0.5% [6]	0.5%	0.6%	1.5% (*n*=3)
Plasma AmylP	URL -> 2 x URL	100%	23.6%	4.0% [6]	4%	22.9%	
Plasma LDL-C [a]	1.8 -> 1.4 mmol/L	20%	**4.7%**	**8.0%** [6]	1%	**(<0%)**	4.9% (*n*=4)
Plasma Crea	72 -> 101 µmol/L	40%	9.4%	4.9% [6]	1%	8.0%	

[a] The maximum allowable coefficient of diagnostic variation CV_D was calculated using the formula: $CV_D = CD / (z*\sqrt{2})$, equation (1); the $z = 3$ for a significant difference was used to reach a sensitivity *1-*β = 85%. The variance remaining for allowable analytical variation CV_A was calculated with equation (3). For prognostic grouping with plasma LDL-C and monitoring of blood HbA_{1c}, detection of a *CD* between two individual measurements was not possible (marked **bold**), indicating a need for replicate testing using the equation (5). For a more detailed explanation, see the reference [4].

[b] References used for the estimates of intra-individual biological variation were the following:
[15] Biological variation of diabetics, derived from Carlsen S, et al. Clin Chem Lab Med 2011;
[16] Albuminuria in chronic kidney disease taken from Waikar SS et al. Am J Kidney Dis 2018; and
[6] Health-related biological intraindividual variation from Aarsand AK, et al, EFLM Biological Variation Database, 2022.

[c] Abbreviations used: Blood HbA_{1c}, blood haemoglobin A_{1c}; *CAAPS*, clinically acceptable analytical performance specification; *CD*, clinically significant difference; CV_A = coefficient of analytical variation; CV_D = coefficient of diagnostic variation; CV_I, coefficient of biological intra-individual variation; CV_{PRE}, coefficient of preanalytical (technical) variation; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine, mmol/mol unit; NGSP, National Glycohemoglobin Standardization Program, haemoglobin (Hgb) % unit; Plasma AmylP, plasma pancreatic amylase; Plasma Crea, plasma

creatinine; Plasma LDL-C, plasma low-density lipoprotein cholesterol; Plasma Na, plasma sodium; Urine Alb, urine albumin; *z*, Gaussian statistic; α, type I error of statistical testing (false positives); β, type II error of testing (false negatives); $1\text{-}\beta$, statistical power, sensitivity to detect a change (opposite probability to β).

Table 3. Measurement uncertainty at the HUS Diagnostic Center verification compared to the modelled *CAAPS* [a]

Measurand	***Single instrument reproducibility, %***	*CV_{INST} , squared*	***Variation between parallel instruments, corrected %***	*CV_{PAR}, corrected, squared*	***Uncertainty of the Atellica® procedure from differences D, [b] %***	*RMS_D, squared*	***Sum of variance components CV_A^2***	***Relative standard uncertainty of measurement, %***	***CAAPS, [a] %***
	CV_{INST}	***CV_{INST}^2***	***$CV_{PAR\text{-}CORR}$ [c]***	***$CV_{PAR\text{-}CORR}^2$***	***RMS_D***	***RMS_D^2***	***$= CV_{INST}^2 + CV_{PAR\text{-}CORR}^2 + RMS_D^2$***	***$MU = CV_A = \sqrt{CV_A^2}$***	***CAAPS, z=3*** α = 2.5%, *1-*β = 85%
B-HbA_{1c}, DT [c]	0.9%	0.000081	0.84%	0.000070	0.76%	0.000058	0.000245	1.4% (IFCC)	1.9% (IFCC); 0.8% (NGSP)
B-HbA_{1c}, Mon									**2.0% (*n*=2, IFCC); 2.1% (*n*=3; NGSP)**
U-Alb	2.7%	0.000729	3.27%	0.001071	10.0%	0.010000	0.012329	10.9%	44.9%
P -Na	0.8%	0.000064	0.46%	0.000021	0.73%	0.000053	0.000185	1.2%	**1.5% (*n*=3)**
P-AmylP	1.7%	0.000289	1.81%	0.000328	7.82%	0.006115	0.006854	8.2%	22.9%
P-LDL-C	2.0%	0.000400	4.09%	0.001676	1.80 %	0.000324	0.002625	4.9%	**4.9% (*n*=4)**
P-Crea	3.7%	0.001369	1.54%	0.000237	1.15%	0.000132	0.001934	4.2%	8.0%

[a] The *CAAPS* by using replicate measurements are shown **bold**, *n* = number of needed replicates (Table 2).

[b] Single differences *D* of the Atellica® procedure were calculated against the mean of the new Siemens Atellica® and the replaced Abbott™ Architect™ procedure. A root mean square (*RMS*) of the single differences, RMS_D, represented the estimate of bias with its variation, except for shaded figures that were based on separate reference measurements (B-HbA_{1c}) or traceability data (P-Na).

[c] Abbreviations used: B-HbA_{1c}, haemoglobin A_{1c} in blood; *CAAPS*, clinically acceptable analytical performance specification; CV_A, coefficient of analytical variation = relative standard uncertainty of measurement; CV_{INST}, within- and between day imprecision of single instrument (intermediate reproducibility); $CV_{PAR\text{-}CORR}$, coefficient of variation between parallel instruments, corrected for double inclusion of within-day imprecision with equation (7); *D*, difference of the new against the mean of the new and the replaced measurement procedure; DT, diagnostic testing; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine, mmol/mol unit; Mon, monitoring; *MU* = measurement uncertainty; NGSP, National Glycohemoglobin Standardization Program,

haemoglobin % unit; P-AmylP, pancreatic amylase in plasma; P-Crea, creatinine in plasma; P-LDL-C, low-density lipoprotein cholesterol in plasma; P-Na, sodium in plasma; RMS_D, root mean square of differences D; U-Alb, albumin in urine; z, Gaussian statistic; α, type I error of statistical testing (false positives); β, type II error of testing (false negatives); $1\text{-}\beta$, statistical power, sensitivity to detect a change.

Figure legends

Figure 1. Variation of measurements on parallel Siemens Atellica® instruments against the index instrument (CV_{PAR}), using pooled patient samples. The results from measurements on 6-12 parallel Atellica® instruments were compared pairwise to those on the Atellica® index instrument as planned during the verification. CV_{PAR} was calculated both for samples within the clinically important interval (vertical solid lines) and all samples. The mean difference against the index instrument is marked with a dashed horizontal line, and the trendline with a more solid, but thinner line. (A) Haemoglobin A_{1c} in blood, B-HbA_{1c}; (B) Albumin in urine, U-Alb; (C) Sodium in plasma, P-Na; (D) Pancreatic amylase in plasma, P-AmylP; (E) Low-density lipoprotein cholesterol in plasma, P-LDL-C; and (F) Creatinine in plasma, P-Crea.

Figure 2. Bland-Altman comparisons of measurements on Siemens Atellica® instrument. The individual relative differences (%) of measurements on Siemens Atellica® index instrument are shown against the means of individual measurements on the Siemens Atellica® and Abbott™ Architect™ index instruments. Clinically important intervals are marked with vertical solid lines. The observations below the lower limit of clinically important interval were excluded as less optimised concentration ranges (the number of specimens included in the calculations is shown in the grey boxes). The boxes also show the mean of individual Atellica® differences (D) against the means between the two procedures ($mean_D$); its variation is calculated as root mean square of the differences (RMS_D). The dashed horizontal lines are similar to those in Figure 1. (A) Haemoglobin A_{1c} in blood, B-HbA_{1c}; (B) Albumin in urine, U-Alb; (C) Sodium in plasma, P-Na; SRM = certified reference material; u_{ASSAY} = uncertainty of the adopted assay; (D) Pancreatic amylase in plasma, P-AmylP; (E) Low-density lipoprotein cholesterol in plasma, P-LDL-C; and (F) Creatinine in plasma, P-Crea.

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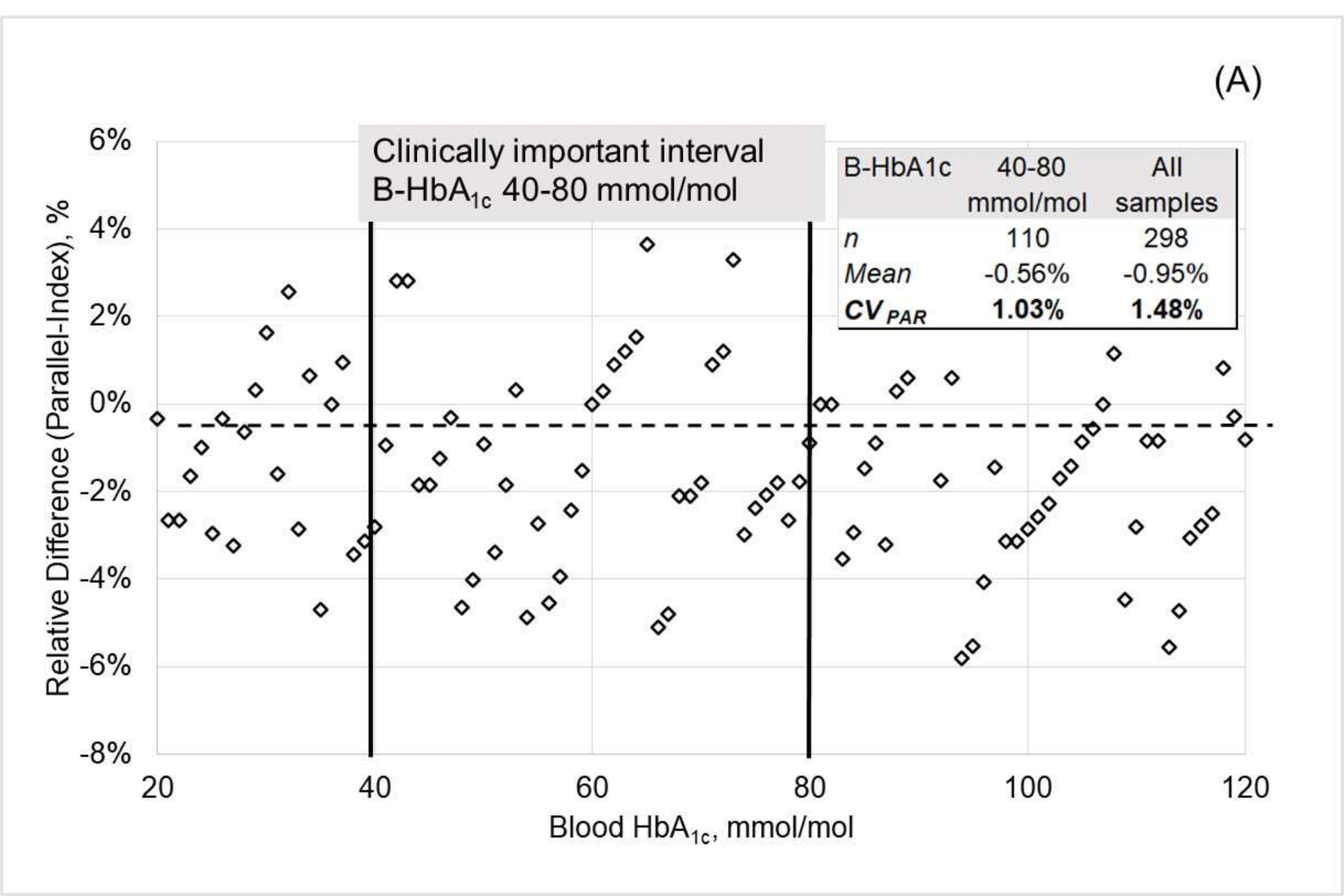
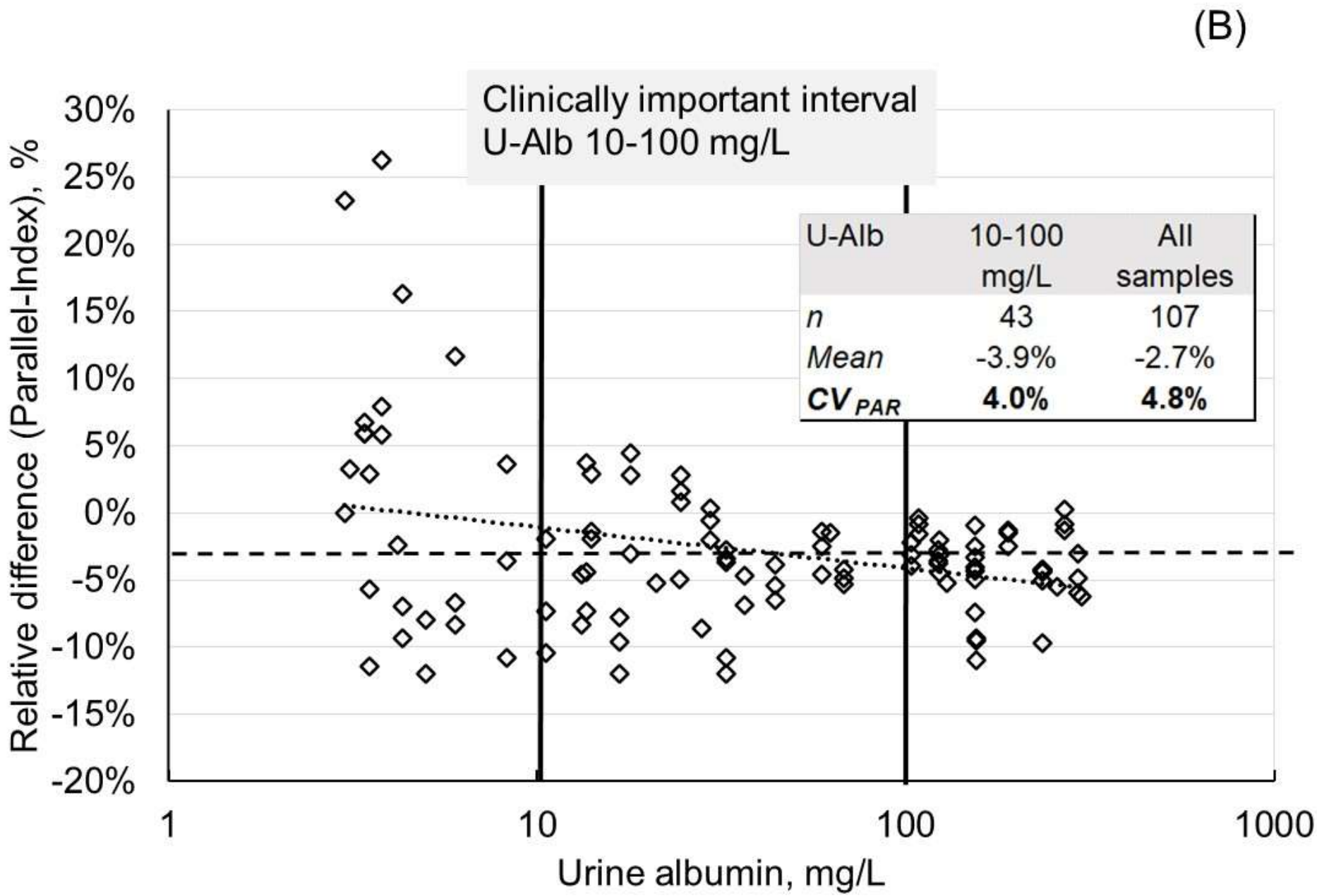
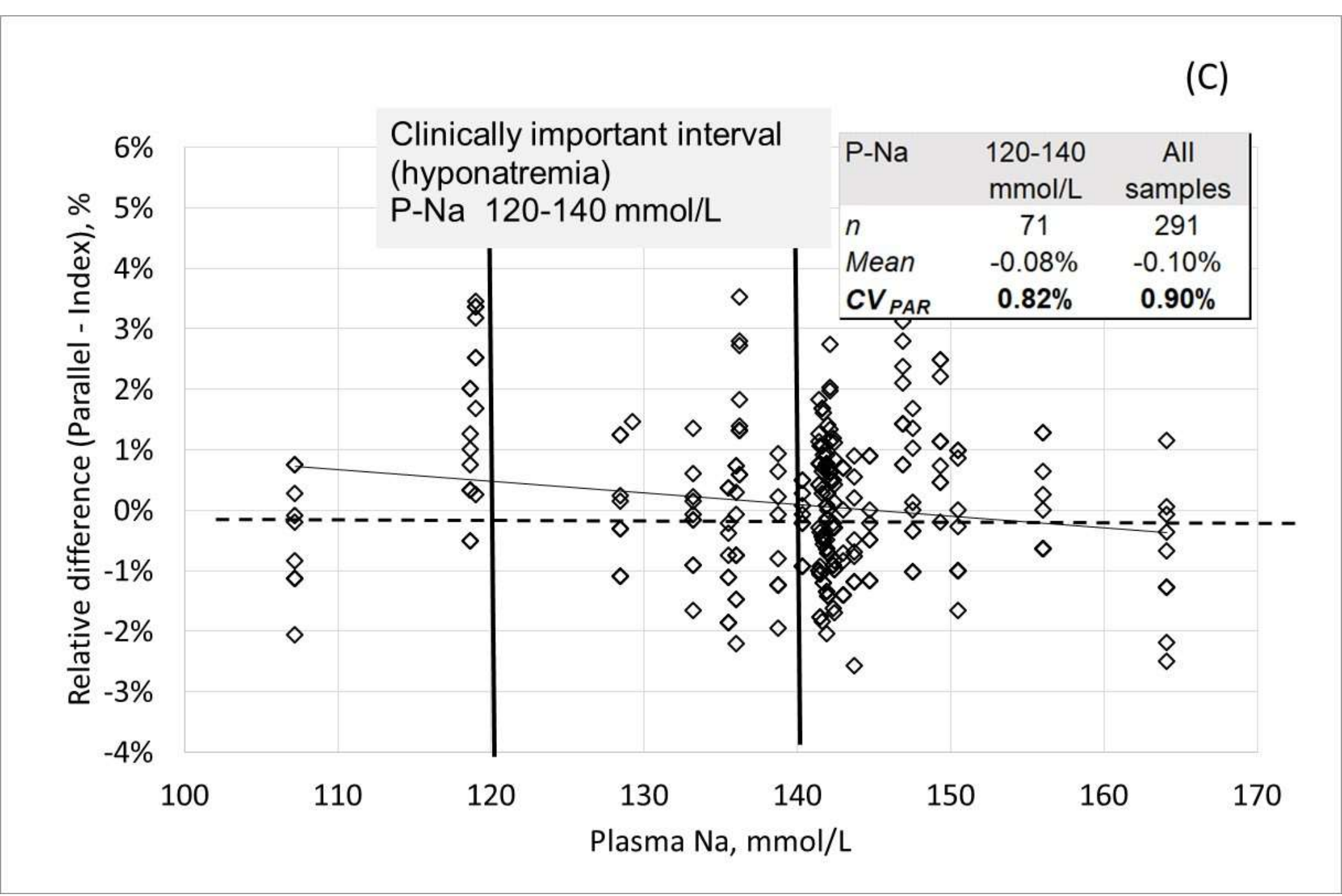
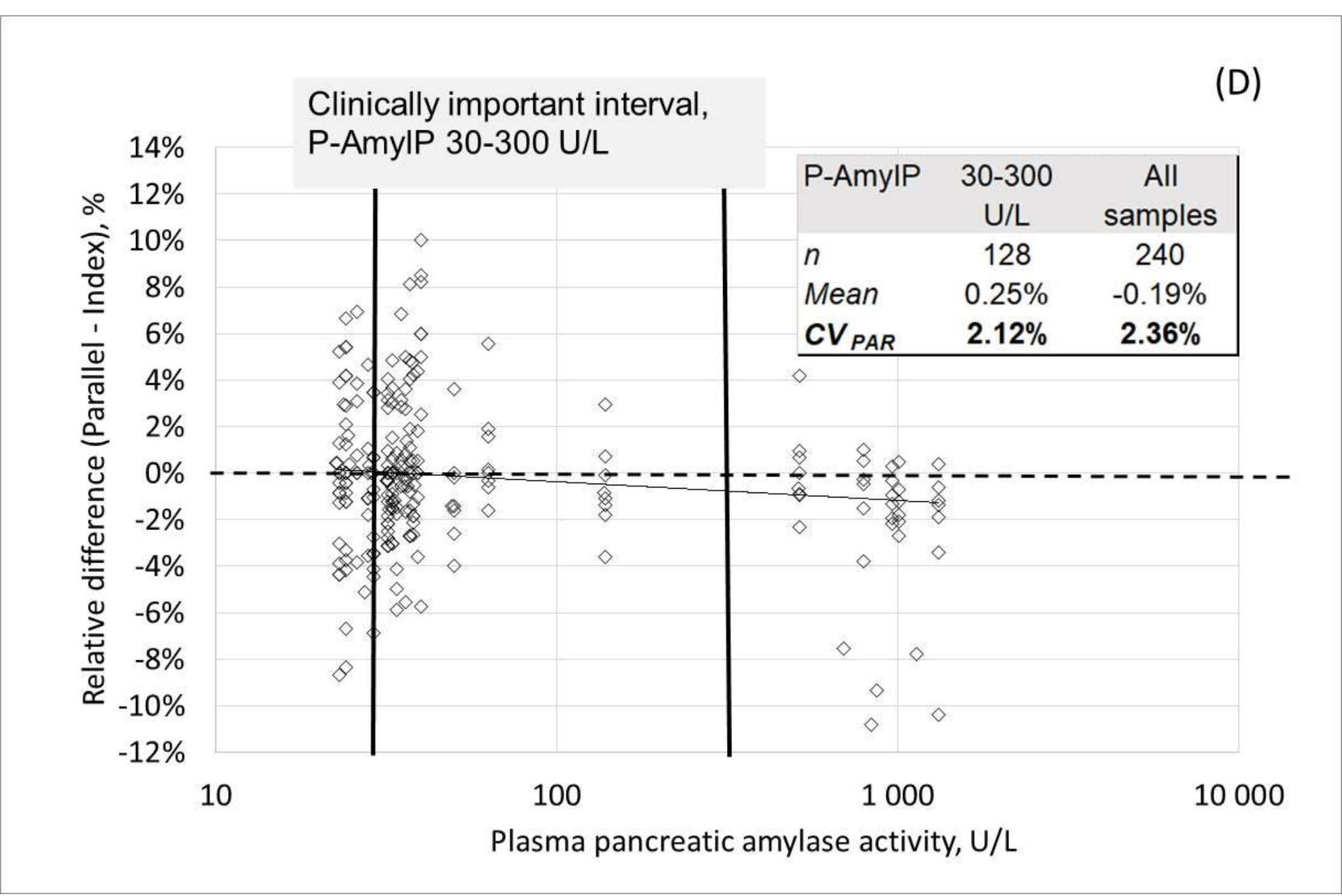
Verifying measurements on Siemens Atellica® instruments using clinically acceptable analytical performance specifications

Figure 1

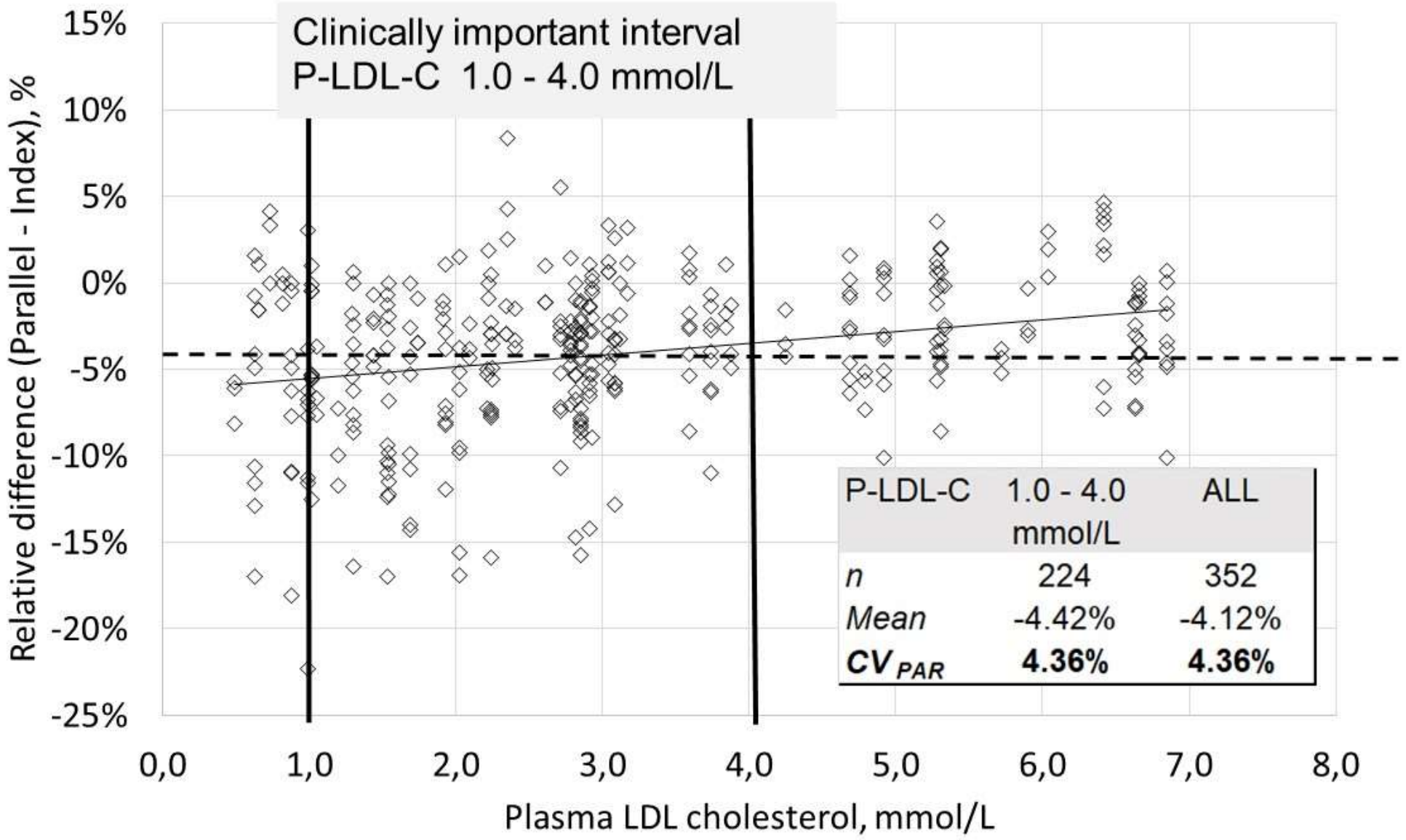

(A)
Clinically important interval
B-HbA1c 40-80 mmol/mol
B-HbA1c | 40-80 mmol/mol | All samples
n | 110 | 298
Mean | -0.56% | -0.95%
CV PAR | 1.03% | 1.48%
Relative Difference (Parallel-Index), %
6%
4%
2%
0%
-2%
-4%
-6%
-8%
20
40
60
80
100
120
Blood HbA1c, mmol/mol

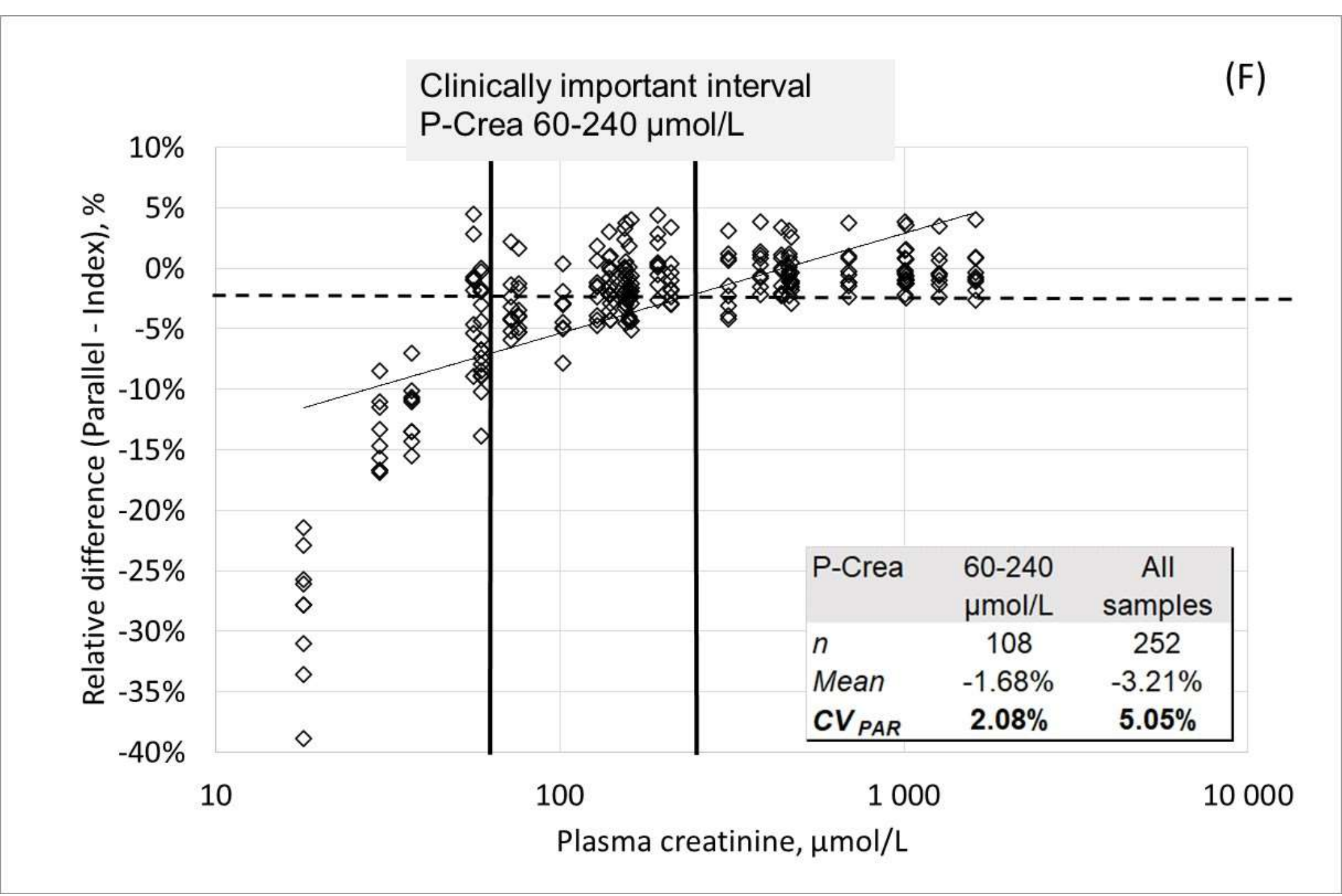

(B)
Clinically important interval
U-Alb 10-100 mg/L
U-Alb | 10-100 mg/L | All samples
n | 43 | 107
Mean | -3.9% | -2.7%
CV PAR | 4.0% | 4.8%
Relative difference (Parallel-Index), %
30%
25%
20%
15%
10%
5%
0%
-5%
-10%
-15%
-20%
1
10
100
1000
Urine albumin, mg/L


(C)
Clinically important interval
(hyponatremia)
P-Na 120-140 mmol/L
P-Na | 120-140 mmol/L | All samples
n | 71 | 291
Mean | -0.08% | -0.10%
CV PAR | 0.82% | 0.90%
Relative difference (Parallel - Index), %
6%
5%
4%
3%
2%
1%
0%
-1%
-2%
-3%
-4%
100
110
120
130
140
150
160
170
Plasma Na, mmol/L


(D)
Clinically important interval,
P-AmylP 30-300 U/L
P-AmylP | 30-300 U/L | All samples
n | 128 | 240
Mean | 0.25% | -0.19%
CV PAR | 2.12% | 2.36%
14%
12%
10%
8%
6%
4%
2%
0%
-2%
-4%
-6%
-8%
-10%
-12%
Relative difference (Parallel - Index), %
10
100
1 000
10 000
Plasma pancreatic amylase activity, U/L

(E)


Clinically important interval
P-LDL-C 1.0 - 4.0 mmol/L
15%
10%
5%
0%
-5%
-10%
-15%
-20%
-25%
Relative difference (Parallel - Index), %
0,0
1,0
2,0
3,0
4,0
5,0
6,0
7,0
8,0
Plasma LDL cholesterol, mmol/L
P-LDL-C 1.0 - 4.0 mmol/L ALL
n 224 352
Mean -4.42% -4.12%
CV PAR 4.36% 4.36%


(F)
Clinically important interval
P-Crea 60-240 µmol/L
10%
5%
0%
-5%
-10%
-15%
-20%
-25%
-30%
-35%
-40%
Relative difference (Parallel - Index), %
10
100
1 000
10 000
Plasma creatinine, µmol/L
P-Crea | 60-240 µmol/L | All samples
n | 108 | 252
Mean | -1.68% | -3.21%
CV PAR | 2.08% | 5.05%

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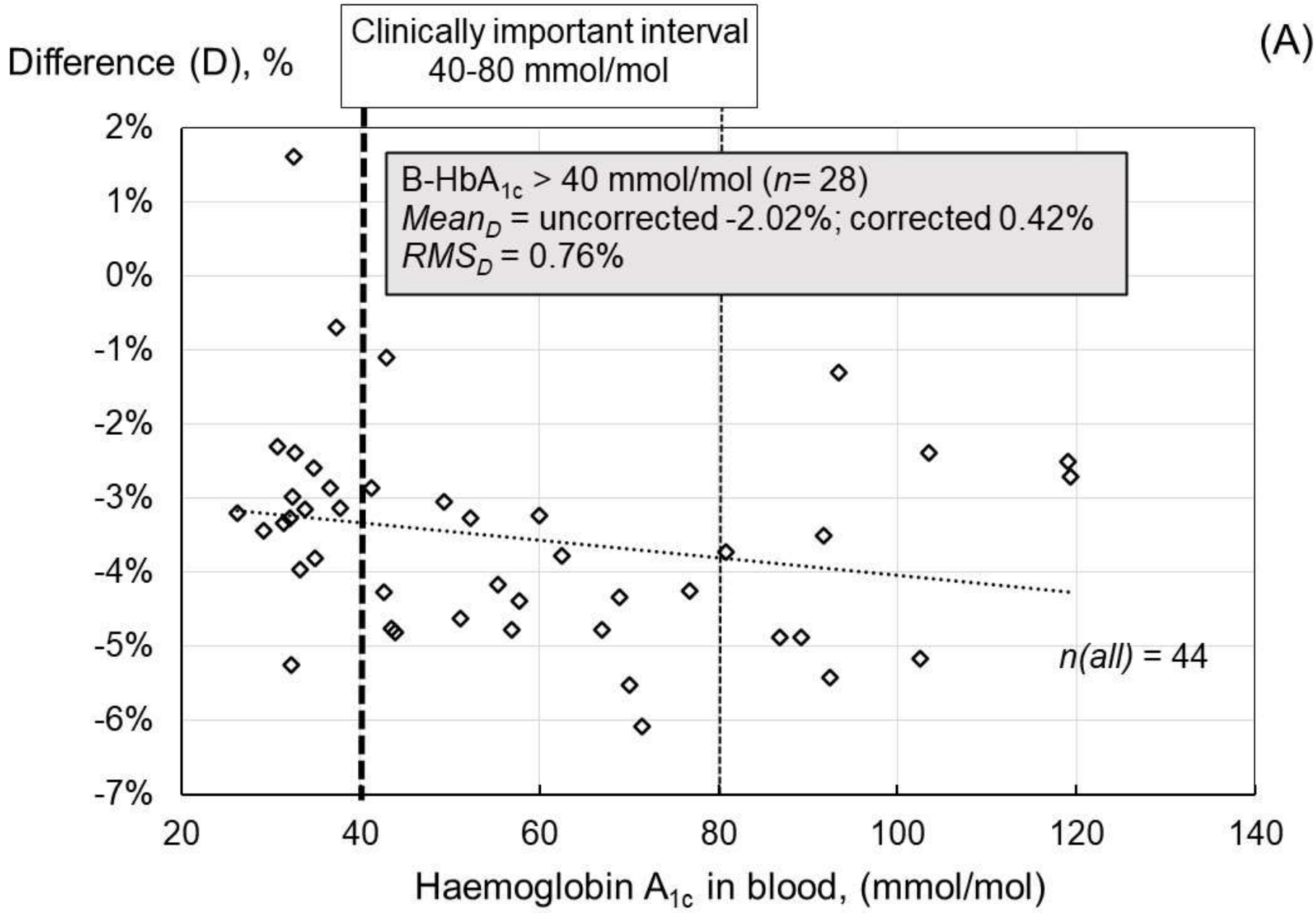
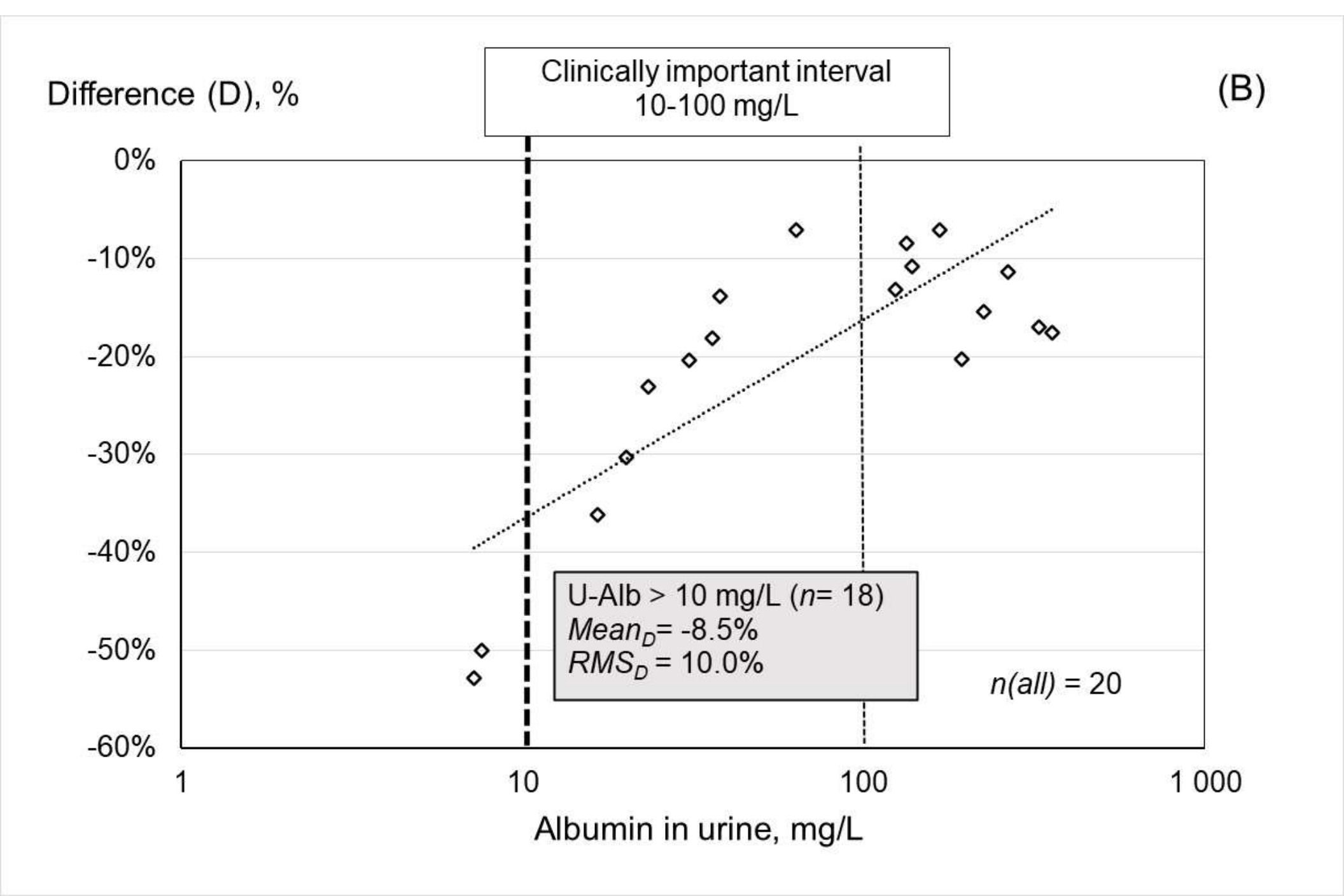
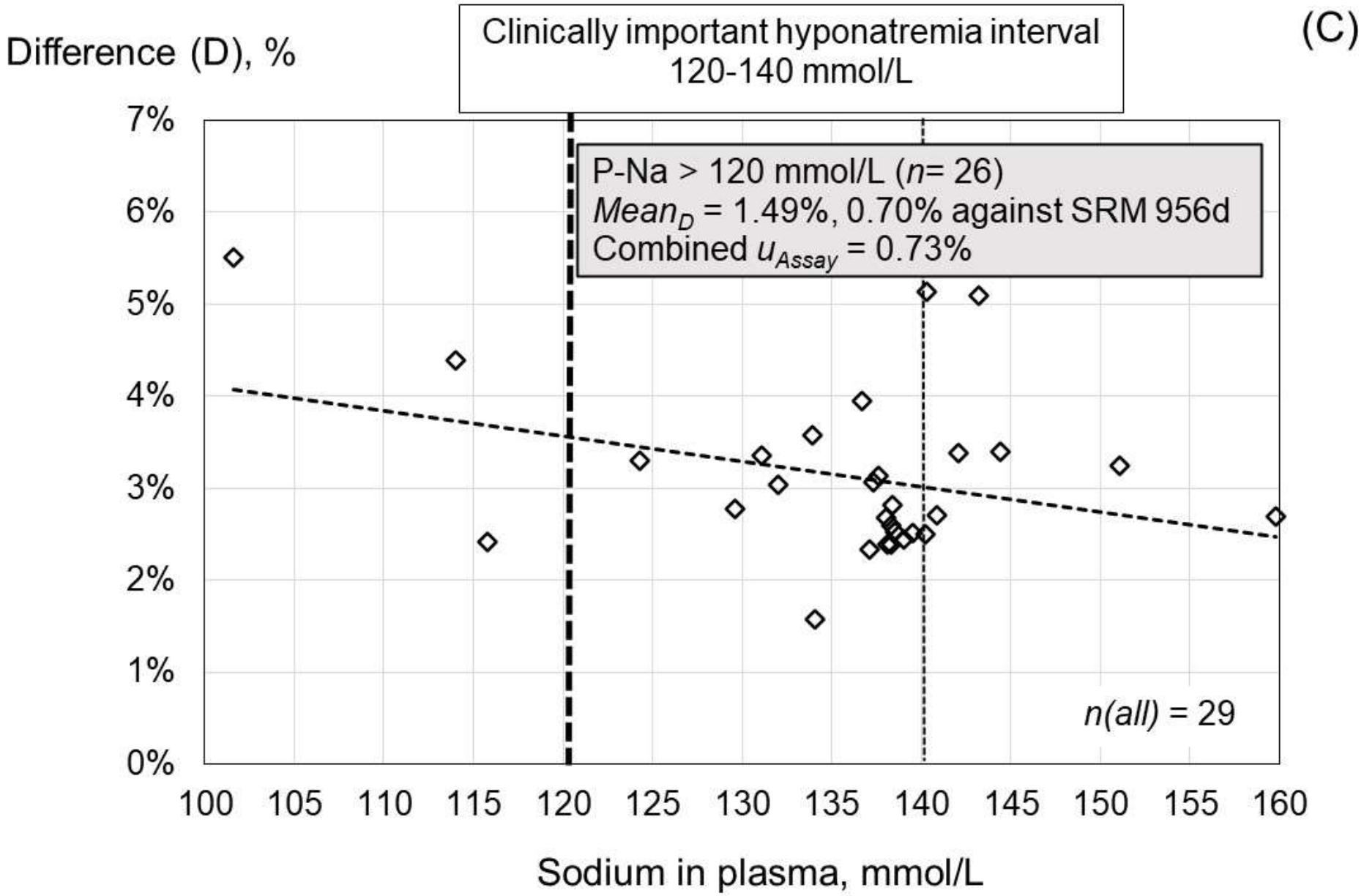
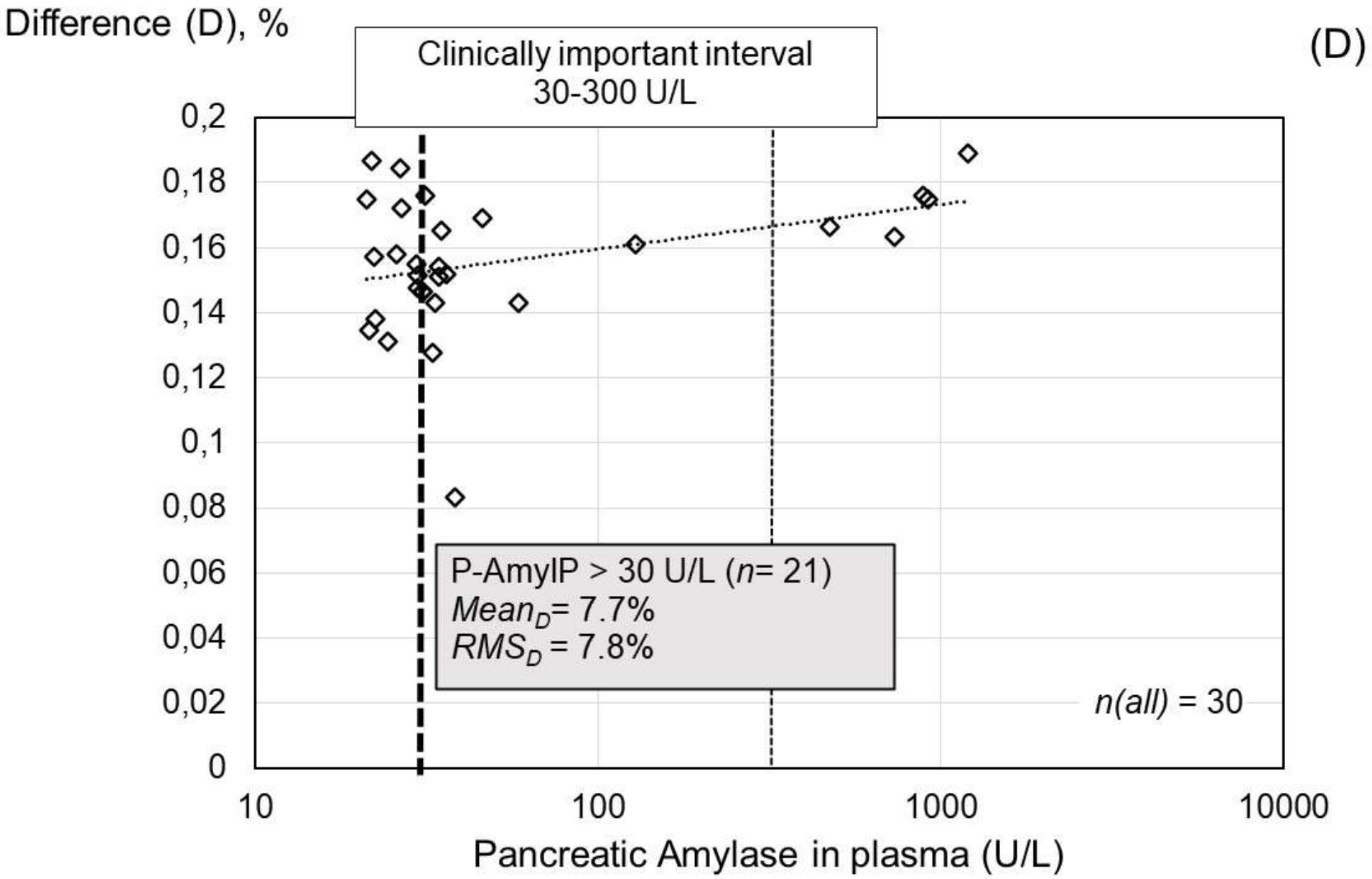
Verifying measurements on Siemens Atellica® instruments using clinically acceptable analytical performance specifications

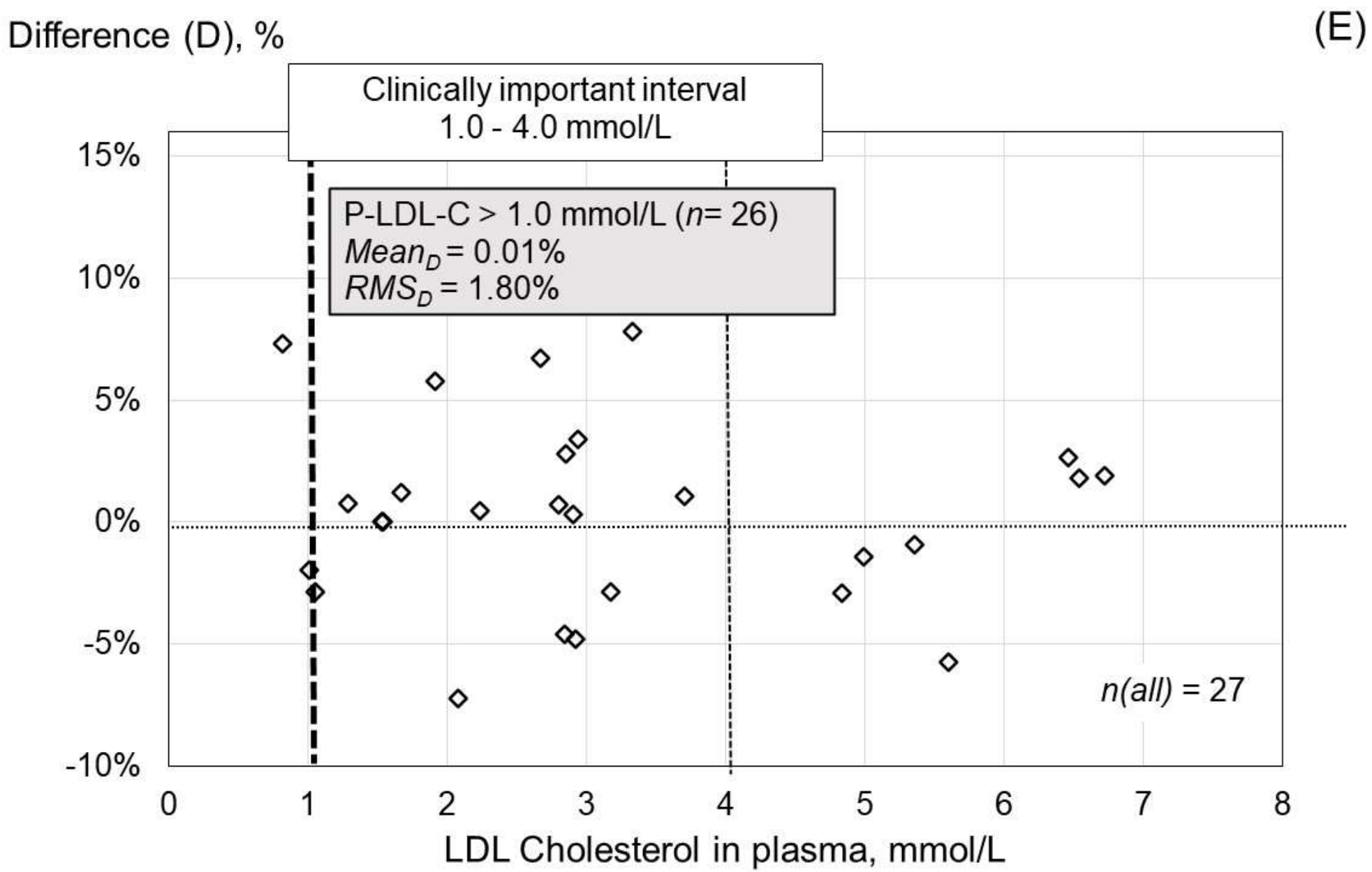
Figure 2

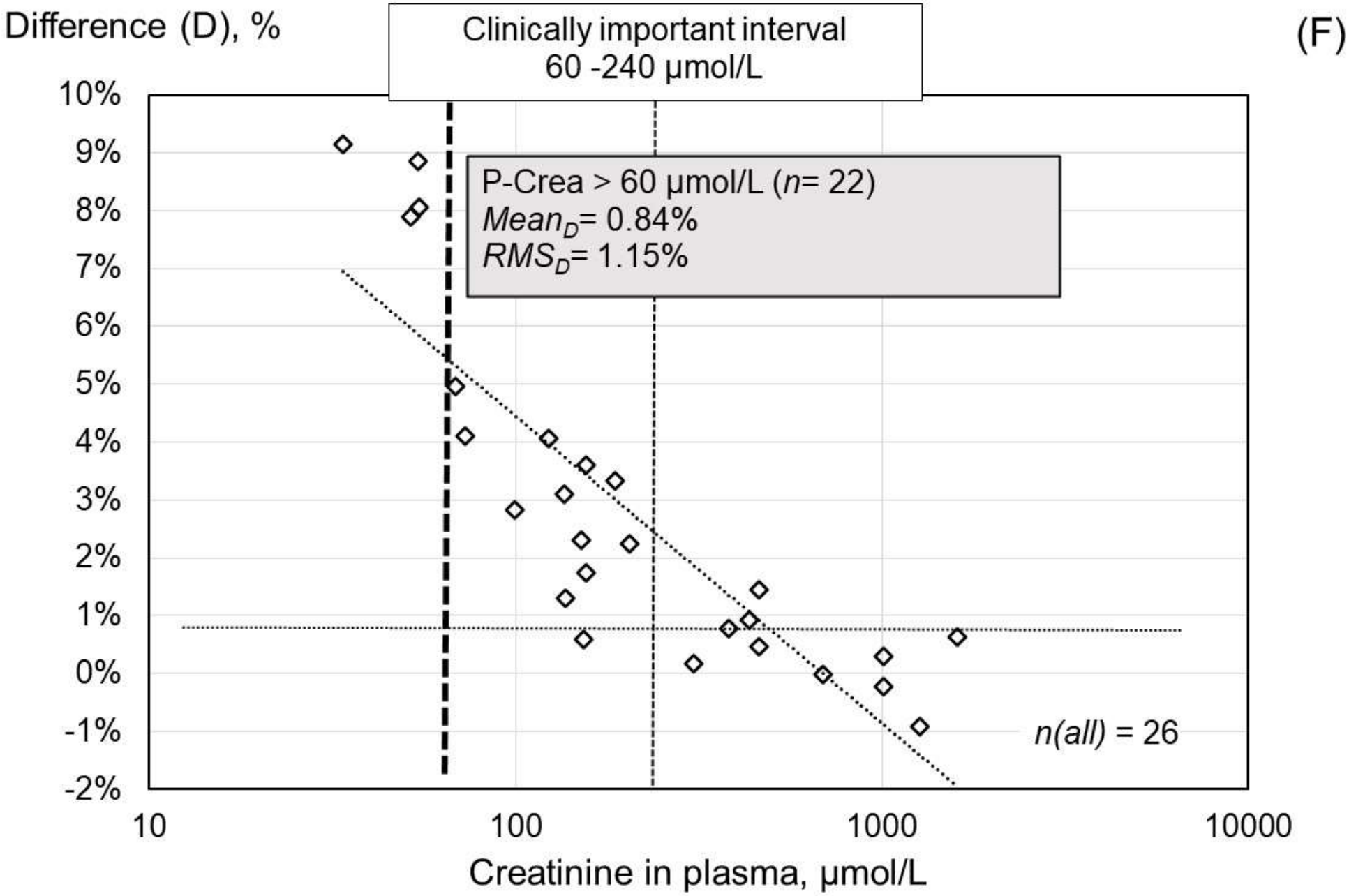

(A)
Difference (D), %
Clinically important interval
40-80 mmol/mol
B-HbA1c > 40 mmol/mol (n= 28)
MeanD = uncorrected -2.02%; corrected 0.42%
RMSD = 0.76%
n(all) = 44
2%
1%
0%
-1%
-2%
-3%
-4%
-5%
-6%
-7%
20
40
60
80
100
120
140
Haemoglobin A1c in blood, (mmol/mol)


Difference (D), %
Clinically important interval
10-100 mg/L
(B)
0%
-10%
-20%
-30%
-40%
-50%
-60%
U-Alb > 10 mg/L (n= 18)
Mean_D= -8.5%
RMS_D = 10.0%
n(all) = 20
1
10
100
1 000
Albumin in urine, mg/L


(C)
Difference (D), %
Clinically important hyponatremia interval
120-140 mmol/L
P-Na > 120 mmol/L (n= 26)
Mean_D = 1.49%, 0.70% against SRM 956d
Combined u_Assay = 0.73%
n(all) = 29
7%
6%
5%
4%
3%
2%
1%
0%
100
105
110
115
120
125
130
135
140
145
150
155
160
Sodium in plasma, mmol/L


Difference (D), %
(D)
Clinically important interval
30-300 U/L
0,2
0,18
0,16
0,14
0,12
0,1
0,08
0,06
0,04
0,02
0
P-AmylP > 30 U/L (n= 21)
Mean_D= 7.7%
RMS_D = 7.8%
n(all) = 30
10
100
1000
10000
Pancreatic Amylase in plasma (U/L)


Difference (D), %
(E)
Clinically important interval
1.0 - 4.0 mmol/L
P-LDL-C > 1.0 mmol/L (n= 26)
Mean_D = 0.01%
RMS_D = 1.80%
n(all) = 27
15%
10%
5%
0%
-5%
-10%
0
1
2
3
4
5
6
7
8
LDL Cholesterol in plasma, mmol/L


Difference (D), %
(F)
Clinically important interval
60 -240 µmol/L
P-Crea > 60 µmol/L (n= 22)
Mean_D= 0.84%
RMS_D= 1.15%
n(all) = 26
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
-1%
-2%
10
100
1000
10000
Creatinine in plasma, µmol/L