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Systematic review and meta-analysis of within-subject and between-subject biological variation data of coagulation and fibrinolytic measurands

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Abstract

Objectives: The diagnosis and monitoring of bleeding and thrombotic disorders depend on correct haemostatic measurements. The availability of high-quality biological variation (BV) data is important in this context. Many studies have reported BV data for these measurands, but results are varied. The present study aims to deliver global within-subject (CV_I) and between-subject (CV_G) BV estimates for haemostasis measurands by meta-analyses of eligible studies, by assessment with the Biological Variation Data Critical Appraisal Checklist (BIVAC).

Methods: Relevant BV studies were graded by the BIVAC. Weighted estimates for CV_I and CV_G were obtained via meta-analysis of the BV data derived from BIVAC-compliant studies (graded A–C; whereby A represents optimal study design) performed in healthy adults.

Results: In 26 studies BV data were reported for 35 haemostasis measurands. For 9 measurands, only one eligible publication was identified and meta-analysis could not be performed. 74% of the publications were graded as BIVAC C. The CV_I and CV_G varied extensively between the haemostasis measurands. The highest estimates were observed for PAI-1 antigen (CV_I 48.6%; CV_G 59.8%) and activity (CV_I 34.9%; CV_G 90.2%), while the lowest were observed for activated protein C resistance ratio (CV_I 1.5%; CV_G 4.5%).

Conclusions: This study provides updated BV estimates of CV_I and CV_G with 95% confidence intervals for a wide range of haemostasis measurands. These estimates can be used to form the basis for analytical performance specifications for haemostasis tests used in the diagnostic work-up required in bleeding- and thrombosis events and for risk assessment.

Keywords: analytical performance specifications; biological variation; haemostasis measurands; meta-analysis.

Introduction

Reliable measurements of haemostasis measurands are essential for the diagnostic work-up required for determining the risk of bleeding and thrombosis and for monitoring anticoagulant and bleeding disorder treatment. It is essential to apply relevant analytical performance specifications (APS) in order to ensure correct results that accurately represent the clinical status of the patient. During the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) a revision was made of previously defined models for APS, resulting in three models; (1) clinical outcome, (2) biological variation (BV) of the measurand or (3) state-of-the-art, which relates to the highest level of technically available performance of an assay [1].

APS based on clinical outcome are rare, because of the lack of relevant studies [2]. On the other hand, multiple studies on BV are available, and the BV model is the one most widely used in laboratory medicine to define APS. BV is defined as within-subject (CV_I) and between-subject (CV_G) variation. However, applying BV data for APS and other applications as reference change values, index of individuality and

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personalised reference intervals is hampered by variations in the BV data available for many measurands. These variations are likely related to differences in analytical methods applied, statistical approaches, and heterogeneity in study design [3–6]. For some haemostasis measurands, medians of BV estimates derived from different publications are already available in the historical online BV database, last updated in 2014 [7, 8]. However, a previous study demonstrated large variations in the BV data published, thus limiting the application of these data to set APS [9]. More reliable estimates are therefore needed, and we propose to achieve this by appraising publications by the Biological Variation Data Critical Appraisal Checklist (BIVAC) [3], which assesses the presence of essential elements that may affect the veracity and utility of the BV data.

The aims of the present study were to perform a literature review to identify BV studies in healthy persons for coagulation and fibrinolytic analytes, to generate up-to-date CV_I and CV_G data for these measurands by systematically appraising published BV studies by the BIVAC and subsequently combine the data in meta-analyses.

Materials and methods

Bibliographical search

A literature search was performed in PubMed (cut-date August 2022), using the following search words: biological variation, within-subject variation, between-subject variation, in combination with coagulation or haemostasis or together with a specific haemostasis measurand included in this study, as listed in Table 1. In addition, papers cited in a historical online 2014 BV database [7] and other publications derived from the private collection of the authors were included and reviewed. The total number of papers evaluated was 38.

Eligibility criteria and review

Publications fulfilling the following criteria were included in the review: study duration >1 week, study population consisting of healthy individuals, and three or more samples collected per study subject. Four papers were excluded because the study period was too short [10–13], two papers because they had collected only two samples per subject [14, 15] and six studies because they did not include data from healthy individuals [16–21]. No studies on children or the elderly were identified, and only studies performed on adults were therefore possible to include in our review. For all the remaining studies (n=26), details on the study subjects, sampling, pre-analytical handling and analytical methods were recorded, and the studies were appraised by the BIVAC [3]. The BIVAC includes 14 quality items (QI) focusing on the description of the study design and study subjects, preanalytical sample handling, measurement procedure, statistical analysis and reporting of results. QI are scored from A to D, in which A represents optimal study design and D indicates that the data are not considered fit for use. The QI with the lowest scoring determines the overall grading of the study.

Four independent assessors reviewed all the papers. When one study reported BV data for several measurands, appraisal was performed for each data set independently. Differences in how the assessors scored were discussed in detail and in the wider group until consensus was achieved.

Statistical analysis

The 95% confidence interval (CI) for each BV estimate was calculated for all the studies included as described previously [22, 23], if the required data were provided (mean number of subjects, mean number of samples and estimates of analytical variation [CV_A]). Meta-analyses were performed by a weighted mean approach separately for CV_I and CV_G, with BIVAC grades given arbitrary weights with A papers as 4, B papers as 2 and C papers as 1, as previously reported [4]. In the meta-analysis, healthy, non-pregnant subjects between 18 and 75 years were included. For studies reporting results both from the entire study population as well as subgroups for e.g. sex, only the results from the overall group were included. For studies only reporting subgroup estimates, these were combined into a common estimate, prior to inclusion in the meta-analysis. BV data sets with the following characteristics were excluded from the meta-analysis;

(a) BIVAC grade D; for QI4 analytical method: one data set for Von Willebrand factor (VWF) related antigen due to lack of information on reagent/method (not clear whether factor VIII or VWF was measured) [24] and three data sets for fibrinogen [25], tPA fibrinolytic activity [26] and APTT [27] because of the obsolete methods used,
(b) CV_I reported as "0" (protein S-free CV_I [28] thrombin time CV_I [29], von Willebrand factor: antigen (VWF:Ag) CV_I [30]),
(c) no CV_A estimate reported [31, 32],
(d) more than one CV_I and/or CV_G estimates for the same measurand reported in one publication due to the use of multiple reagents (e.g. factor VIII, both clotting and chromogenic methods), or the same results expressed in different units (e.g. both for PT in seconds and as a percentage). The following data sets were excluded: PT as a percentage [33], PT and INR using the Owren method [27], protein C clotting [34], factor VIII two-stage (male and female) [25] and factor VIII chromogenic method (male and female) [25].

When BV data were reported in the form of variances [24, 28, 30, 35], CVs were calculated as: $CV=[\sqrt{(variance)/mean}] \times 100\%$ and thereafter included. Differences between methods or expression of the same measurand were calculated by two-sided Student's t-tests and p-values less than 0.05 were considered to be statistically significant.

The mean level or concentration reported for each measurand was calculated on the basis of the mean result reported by all the eligible studies.

Results

In the 26 papers included in this review, BV data were reported for 35 measurands. The number of publications varied for the different measurands, with fibrinogen, antithrombin, factor VIII and APTT being assessed in the highest number of studies; 16, 9, 8 and 8 publications, respectively

(Table 1). For 9 measurands, only one study was identified reporting BV data (Table 1) and thus meta-analysis could not be performed. The majority of publications (74%) received a BIVAC grade C, one paper (4%) B and 20% as A. BIVAC C grade was mostly awarded to indicate the lack of outlier analysis (QI8) or variance homogeneity testing (QI10), and/or not reporting the number of results excluded following analysis of outliers and variance homogeneity (QI13). For most studies, all the data sets received the same BIVAC grade; the few exceptions were caused by an obsolete analytical method being used for specific measurands. Most publications reported results for female and male subjects combined, except for five publications, of which one reported results from two differently performed studies with only men in the one study and only women in the other [25], three publication reported results only for women [27, 36, 37] and one

Table 1: Number of reviewed biological variation papers for coagulation and fibrinolytic measurands and their Biological Variation Data Critical Appraisal Checklist (BIVAC) grade.

Measurands	N	n	Type of subgroups (gender or method)	BIVAC grade[a]				References
				A	B	C	D	
APTT	8	9	2 APTT reagents [27][b]	2	1	5	(1)	[27, 29, 30, 33, 34, 38–40]
APCR ratio	3	3		0	2	1	0	[37, 47, 48]
ADAMTS-13-Act	1	1		0	0	1	0	[49]
ADAMTS-13-Ag	1	1		0	0	1	0	[49]
Antithrombin-Ag	1	1		0	0	1	0	[24]
Antithrombin-Act	9	10	Male & female [25]	2	0	7 (8)	0	[24, 25, 29, 30, 33, 34, 37, 38, 46]
D-dimer	6	6		3	0	3	0	[28, 31, 36, 38, 44, 45]
Factor II	2	2		0	0	2	0	[24, 48]
Factor V	2	2		1	0	1	0	[29, 47]
Factor VII	5	6	Male & female [25]	0	0	5 (6)	0	[24–26, 30, 48]
Factor VIII	8	13	Male & female [25], 1-stage & 2-stage clot & chromogenic [25]	3	0	5 (10)	0	[24, 25, 27, 30, 34, 38, 47, 48]
Factor IX	2	2		1	0	1	0	[34, 47]
Factor X	3	4	Male & female [25]	0	0	3 (4)	0	[24, 25, 29]
Factor XI	1	1		1	0	0	0	[47]
Factor XII	1	1		1	0	0	0	[47]
Fibrinogen-clauss	15	16	Male & female [25]	2	1	11	1 (2)	[24–27, 29, 30, 32–35, 38, 40, 41, 43, 44]
Fibrinogen-Ag	1	1		0	0	1	0	[42]
Plasmin inhibitor	3	4	Male & female [25]	0	0	3 (4)	0	[25, 29, 33]
Plasminogen	3	4	Male & female [25]	0	0	3 (4)	0	[25, 29, 33]
Protein C-Act	6	7	Clot & chromogenic [34]	3	0	3 (4)	0	[33, 34, 37, 38, 46, 47]
Protein C-Ag	1	1		0	0	1	0	[30]
Protein S-Act	3	3		1	0	2	0	[33, 34, 37]
Protein S-total	3	3		0	0	3	0	[28, 34, 46]
Protein S-free	5	5		2	1	2	0	[28, 34, 37, 38, 47]
Prothrombin time, second	7	9	2 PT reagents [27], PT expressed in ratio and % [33]	2 (3)	1	4 (5)	0	[27, 29, 33, 34, 38, 40, 41]
Prothrombin time, INR	4	5	2 PT reagents [27]	2 (3)	0	2	0	[27, 33, 38, 39]
TAT	3	3		0	0	3	0	[33, 44, 48]
Thrombomodulin	1	1		0	0	1	0	[33]
t-PA Act	2	2		0	0	1	1	[26, 48]
t-PA Ag	5	5		0	0	5	0	[26, 28, 35, 44, 48]
PAI-1 Act	4	4		0	0	4	0	[26, 35, 44, 48]
PAI-1 Ag	5	5		0	0	5	0	[26, 28, 31, 44, 48]
VWF:RCo	3	4	Male & female [25]	0	0	3 (4)	0	[25, 34, 49]
VWF:Ag	4	5	Male & female [25]	1	0	3 (4)	0	[25, 27, 34, 49]
VWF:CB	1	1		0	0	1	0	[34]

N, number of papers included; n, number of datasets including all subgroups. [a]The number in parenthesis indicates the number of different datasets, i.e. derived on the basis of population subgroups or by use of several reagents, reported in some of the studies. [b]Only one APTT method was included in the meta-analysis as the other method was obsolete and graded as a "D". APTT, activated partial thromboplastin time; APCR, activated protein C resistance; Act, activity; Ag, antigen; TAT, thrombin-antithrombin complex; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; VWF, von Willebrand factor; RCo, ristocetin cofactor activity; CB, collagen binding.

only for men [26]. The European Biological Variation Study (EuBIVAS) reported results both for all study subjects, as well as for men and women, and women above and below 50 years, separately [38].

Activated partial thromboplastin time (APTT)

Eight papers fulfilled the inclusion criteria and reported data on CV_I and CV_G for APTT in seconds or as ratios [27, 29, 30, 33, 34, 38–40] (Table 1, Figure 1A), from which meta-analysis results were derived (Table 2). Six out of eight publications reported CV_I results at 3.3% or lower. Two publications reported values of above 6% (Figure 1A: C-1985 [29] and C-2016 [34]) (Figure 1A).

Prothrombin time (PT)/international normalized ratio (INR)

Seven papers fulfilled the inclusion criteria [27, 29, 33, 34, 38, 40, 41] (Table 1, Figure 1B), all reporting PT results in seconds. CV_I and CV_G which were included, ranged from 2.4 to 5.8% and from 2.8 to 5.7%, respectively, with the oldest publication reporting a considerable higher CV_I than the

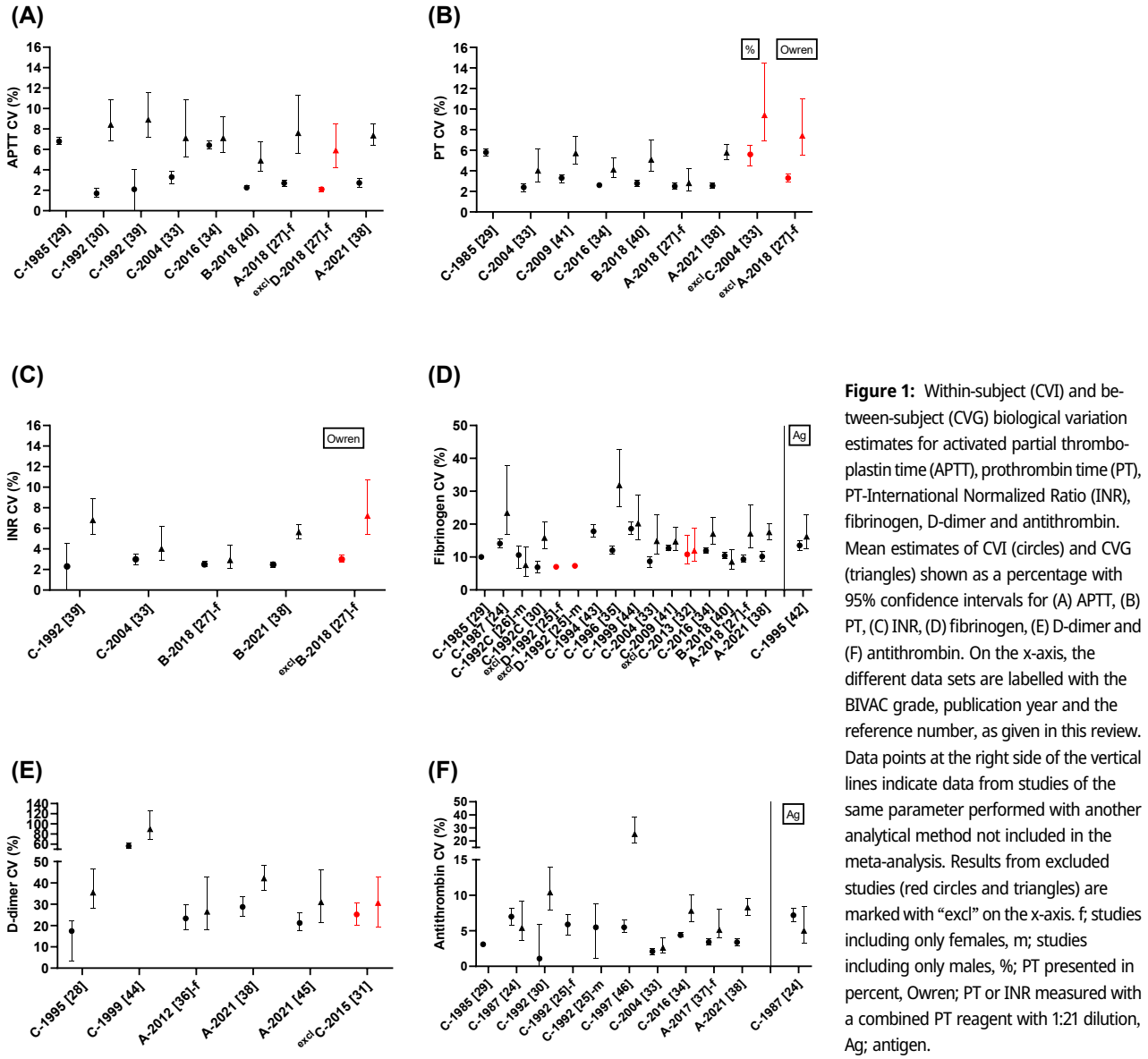

Figure 1: Within-subject (CVI) and between-subject (CVG) biological variation estimates for activated partial thromboplastin time (APTT), prothrombin time (PT), PT-International Normalized Ratio (INR), fibrinogen, D-dimer and antithrombin. Mean estimates of CVI (circles) and CVG (triangles) shown as a percentage with 95% confidence intervals for (A) APTT, (B) PT, (C) INR, (D) fibrinogen, (E) D-dimer and (F) antithrombin. On the x-axis, the different data sets are labelled with the BIVAC grade, publication year and the reference number, as given in this review. Data points at the right side of the vertical lines indicate data from studies of the same parameter performed with another analytical method not included in the meta-analysis. Results from excluded studies (red circles and triangles) are marked with "excl" on the x-axis. f; studies including only females, m; studies including only males, %; PT presented in percent, Owren; PT or INR measured with a combined PT reagent with 1:21 dilution, Ag; antigen.

Table 2: Meta-analysis derived within-subject (CV_I) and between-subject (CV_G) estimates with 95% CIs of coagulation and fibrinolytic measurands.

Measurands	n_{mean}	Mean (SD)	n_{CV}	CV_I (CI) %	CV_G (CI) %	Historical online 2014 BV database	
						CV_I %	CV_G %
APTT, second	6	ND	8	2.8 (1.7–6.8)	7.2 (4.9–8.9)	2.7	8.6
APCR ratio	3	2.6 (0.3)	3	1.5 (1.3–6.7)	4.5 (3.8–5.4)	NA	NA
ADAMTS-13-Act, U/dL[a]	1	120 (NA)	1	12.7 (9.7–15.8)	9.6 (5.6–16.5)	NA	NA
ADAMTS-13-Ag, µg/L[a]	1	682.0 (NA)	1	9.8 (0.0–13.4)	6.3 (1.9–11.6)	NA	NA
Antithrombin-Ag, U/dL[a]	1	103.0 (NA)	1	7.2 (6.3–8.2)	5.0 (3.4–8.3)	NA	NA
Antithrombin-Act, U/dL	7	108.7 (5.8)	10	3.4 (1.1–7.0)	7.8 (2.6–25.2)	5.2	15.3
D-dimer, ng/mL FEU	3	204.0 (73.2)	5	25.2 (17.4–56.4)	35.4 (26.5–89.5)	23.3	26.5
Factor II, U/dL	2	105.0 (4.2)	2	5.8 (5.7–5.9)	9.7 (7.0–15.4)	NA	NA
Factor V, U/dL	1	95.5 (NA)	2	5.3 (3.6–6.6)	18.7 (14.1–27.5)[a]	3.6	NA
Factor VII, U/dL	4	110.4 (19.0)	6	8.2 (6.9–14.2)	17.8 (16.7–19.4)	6.8	19.4
Factor VIII, U/dL	7	115.7 (18.2)	9	8.7 (4.9–16.0)	22.5 (15.5–31.4)	4.8	19.1
Factor IX, U/dL	2	101.8 (4.0)	2	6.9 (5.8–9.1)	16.3 (15.7–18.2)	NA	NA
Factor X, U/dL	1	90.0 (NA)	4	5.9 (4.6–8.5)	11.4 (8.2–18.2)	5.9	NA
Factor XI, U/dL[a]	1	107.3 (NA)	1	5.1 (4.2–6.3)	11.5 (8.5–17.5)	NA	NA
Factor XII, U/dL[a]	1	142.7 (NA)	1	4.0 (3.0–5.1)	23.3 (17.6–34.5)	NA	NA
Fibrinogen-clauss, g/L	11	2.7 (0.2)	13	10.2 (9.3–11.9)	17.1 (8.5–17.3)	10.7	15.8
Fibrinogen-Ag, g/L[a]	0	NA	1	13.5 (12.1–14.9)	16.2 (12.4–22.7)	NA	NA
Plasmin inhibitor, U/dL	1	115.7 (NA)	4	5.8 (4.8–5.8)	7.1 (5.2–10.8)	6.2	NA
Plasminogen, U/dL	1	111.1 (NA)	4	5.7 (4.2–7.7)	10.5 (7.8–15.8)	7.7	NA
PC-Act, U/dL	6	107.8 (6.3)	6	5.5 (5.3–7.9)	16.9 (9.1–55.2)	5.6	55.2
PC-Ag, µg/mL[a]	1	3.2 (NA)	1	2.2 (0.0–6.2)	13.3 (10.5–17.5)	NA	NA
PS-act, U/dL	3	96.2 (6.5)	3	7.3 (7.1–8.1)	20.3 (18.8–23.8)	NA	NA
PS-total, U/dL	3	103.9 (14.9)	3	6.7 (2.9–7.3)	13.3 (8.9–63.4)	5.8	63.4
PS-free, U/dL	4	96.0 (2.6)	4	4.2 (4.0–8.7)	16.9 (16.2–25.0)	NA	NA
Prothrombin time, second	6	ND	7	2.6 (2.4–5.8)	5.1 (2.8–5.7)	4.0	6.8
Prothrombin time, INR	3	1.06 (0.05)	4	2.5 (2.3–3.0)	4.6 (2.9–6.8)	NA	NA
TAT, ng/mL	3	2.3 (1.1)	3	19.0 (11.0–26.0)	33.3 (20.0–60.5)	NA	NA
Thrombomodulin, TU/mL	1	8.8 (NA)	1	11.4 (9.1–13.2)	16.5 (12.1–25.1)	NA	NA
t-PA Ag, ng/mL	5	6.0 (2.1)	5	13.3 (11.0–30.9)	38.1 (23.9–191.1)	NA	NA
t-PA Act, U/dL[a]	1	56.0 (NA)	1[b]	32.0 (27.6–37.4)	NA	NA	NA
PAI-1 Ag, ng/mL	4	16.3 (8.6)	4	48.6 (35.6–55.0)	59.8 (26.0–90.0)	NA	NA
PAI-1 Act, U/mL	3	12.6 (10.9)	3	34.9 (30.3–49.0)	90.2 (62.0–181.8)	NA	NA
VWF:RCo, U/dL	2	125.5 (2.1)	4	17.0 (8.1–21.3)	24.6 (18.5–31.2)	NA	NA
VWF:Ag, U/dL	3	99.0 (12.0)	4	12.7 (11.1–19.4)	29.9 (22.6–31.6)	2.5	27.3
VWF:CB, U/dL[a]	1	112.0 (NA)	1	25.6 (23.9–27.5)	28.0 (22.6–36.3)	NA	NA

For measurands where only one study was identified [a], the estimate represents that reported by the study with 95% CI. APTT, activated partial thromboplastin time; APCR, activated protein C resistance; Act, activity; Ag, antigen; PC, protein C; PS, protein S; TAT, thrombin-antithrombin complex; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; VWF, von Willebrand factor; RCo, ristocetin cofactor activity; CB, collagen binding; ND, not determined because methods are not calibrated; NA, not available; ND, not determined; n_{mean}, number of papers used to calculate the mean concentration; n_{CV}, number of papers included in the meta-analysis of CV_I and CV_G. [b]No result for CV_G in the study. CI, confidence interval; SD, standard deviation.

others (no CV_G given in that study) (Figure 1B). Meta-analysis delivered a CV_I of 2.6% and CV_G of 5.1% for PT (Table 2).

Four studies reported CV_I and CV_G for INR and fulfilled the inclusion criteria [27, 33, 38, 39]. CV_I and CV_G were similar when expressing the PT in seconds or as INR (Table 2, Figure 1B and C, $p>0.05$).

Two results derived from two different studies were excluded from the meta-analysis (PT as a percentage [33], PT Owren reagents [27]). For both measurands it was noticed that the mean CV_Gs were higher compared to the other PT CV_Gs data (Figure 1B and C).

Fibrinogen

Sixteen publications described BV results for fibrinogen [24–27, 29, 30, 32–35, 38, 40–44], of which 14 were included in the meta-analysis and where fibrinogen was measured using the Clauss method (Table 1, Figure 1D) [24, 26, 27, 29, 30, 33–35, 38, 40, 41, 43, 44]. Three studies were excluded; one used an immunological (ELISA) method [42], one used an obsolete method [25] and one study did not report CV_A [32]. The data sets included reported CV_I estimates ranging from 9.3 to 11.9% and CV_G estimates ranging from 8.5 to 17.3%,

with meta-analysis results of 10.2 and 17.1%, respectively (Table 2). The study utilising an immunological method reported similar results (CV_I 13.5% and CV_G 16.2%) [42].

D-dimer

Six publications were available for D-dimer [28, 31, 36, 38, 44, 45], of which one study was excluded because CV_A was not reported [31] (Table 1, Figure 1E). Varying results were reported, with CV_I and CV_G estimates ranging from 17.4 to 56.4% and from 26.5 to 89.5%, respectively. Sakkinen et al. reported about 2 times higher CV_I and CV_G values than the other studies [44] (1999C [44] in Figure 1E). No obvious reason for this discrepancy could be identified. Excluding the Sakkinen et al. study from the meta-analysis, did not change the results (data not shown) [44].

Antithrombin

Nine publications fulfilled the inclusion criteria [24, 25, 29, 30, 33, 34, 37, 38, 46] (Table 1). The majority of the studies measured antithrombin using a chromogenic method (antithrombin activity), and only one used an immunological (ELISA) method (antithrombin antigen) [24]. An average CV_I of 3.4% and CV_G of 7.8% were calculated in the meta-analysis (Table 2). For antithrombin antigen the CV_I and CV_G results were similar to those observed for antithrombin activity (Figure 1F).

Protein C and S

Eight publications reported BV estimates for protein C and/or protein S [28, 30, 33, 34, 37, 38, 46, 47] (Table 1). Protein C data were available for chromogenic and clot-based (both activity) and/or immunological (antigen) methods, all reporting similar BV results (Figure 2A). When including both protein C activity methods, the meta-analysis delivered estimates of CV_I of 5.5% and CV_G of 16.9%. Only one study reported BV data for protein C antigen, with results similar to those of the activity methods (Table 2 and Figure 2A).

BV data were reported for free protein S (immunological method), total protein S (immunological method) and/or protein S activity (clotting method) in the different studies (Figure 2B). Separate meta-analysis were performed for the different methods; there were no evident differences between the results of the three protein S methods (Table 2 and Figure 2B).

Factor VIII (FVIII)

Eight publications reported BV data for FVIII, with all studies including results based on the one-stage clotting method [24, 25, 27, 30, 34, 38, 47, 48]. One study in addition reported results for two-stage clotting and chromogenic methods [25] (Table 1). CV_I and CV_G for the one-stage factor VIII clotting method ranged from 4.9 to 16.0% and from 15.5 to 31.4%, respectively, with meta-analysis CV_I and CV_G results of 8.7 and 22.5%, respectively (Table 2, Figure 2C).

VWF

Five publications reported BV data for VWF, all including results for the VWF antigen (VWF:Ag) [25, 27, 30, 34, 49]. Three studies also reported for VWF ristocetin cofactor activity (VWF:RCo) [25, 34, 49] and one study for VWF collagen binding (VWF:CB) [34] (Table 1). No significant differences were observed between the BV estimates of VWF:Ag vs. VWF:RCo ($p>0.05$, Figure 2D).

Other haemostasis measurands

Fifteen publications reported BV data for one or more of the following haemostasis measureands: PAI-1 antigen and activity, t-PA antigen and activity, activated protein C resistance ratio (APCR), ADAMTS13 antigen and activity, thrombin-antithrombin complexes (TAT), plasmin inhibitor, plasminogen, thrombomodulin and coagulation factors II, V, VII, IX, X, XI and XII (FII, FV, FVII, FIX, FX, FXI, FXII) (Tables 1 and 2). The BV data reported differed widely. APCR ratio was associated with the lowest variability (CV_I 1.5%) and PAI-1 antigen and PAI-1 activity with high variability (CV_I 59.8 and 90.2%, respectively) (Table 2).

For measurands included in many different studies, such as fibrinogen and antithrombin, there was no clear difference or trend in BV estimates observed, when visually comparing studies with different grading or different year of publication (Figures 1 and 2). Furthermore, no significant differences were observed for measurands measured by different methods, such as PAI-1 antigen vs. activity or protein S free vs. clot activity ($p>0.05$, Figure 2B and Table 2). The meta-analyses also gave similar results, before and after exclusion of the most extreme CV_I's (e.g. CV_I's for APTT [29, 34] and CV_I for D-dimer [44], data not shown).

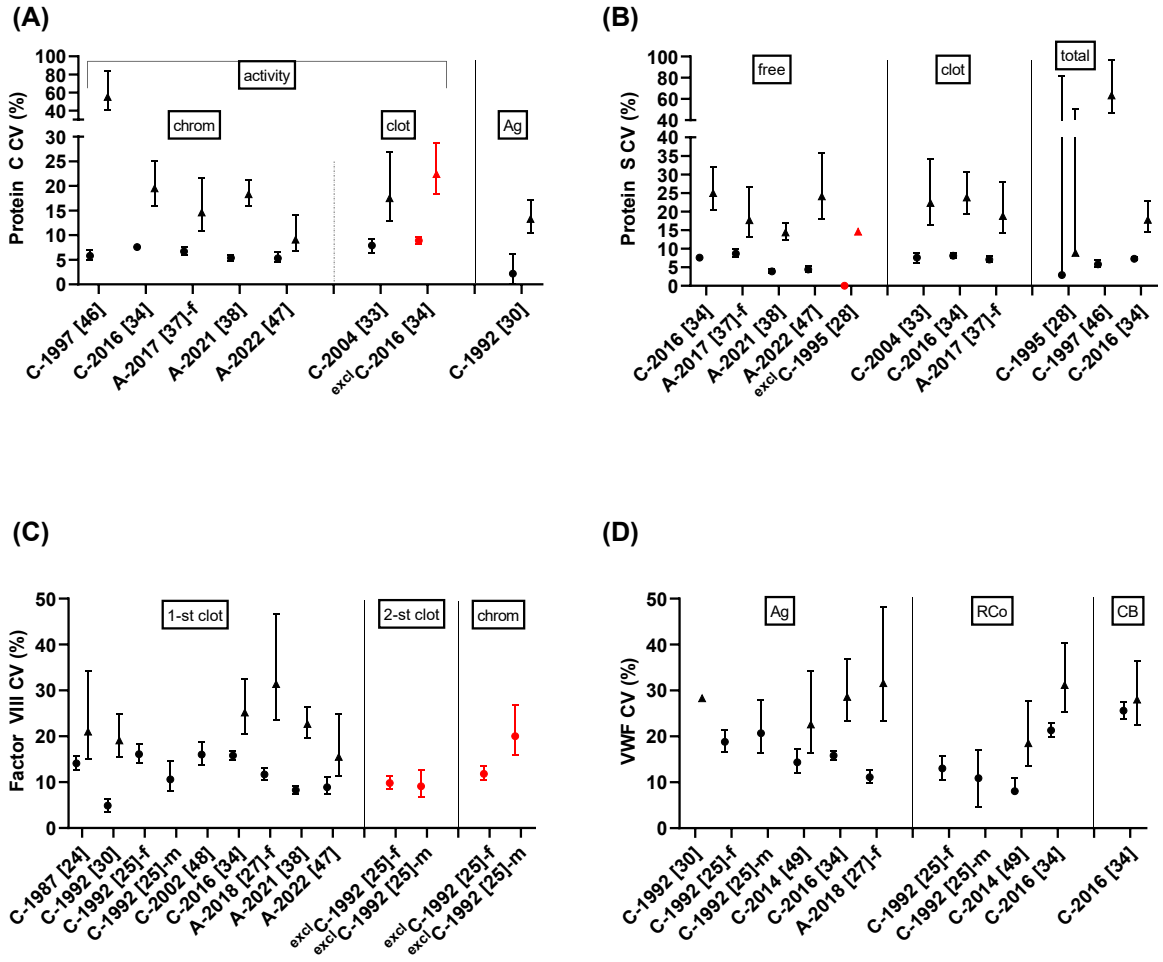

Figure 2: Within-subject (CVI) and between-subject (CVG) biological variation estimates for protein C, protein S, factor VIII and von Willebrand factor (VWF). Mean estimates of CVI (circles) and CVG (triangles) shown as a percentage with 95% confidence intervals for (A) protein C, (B) protein S, (C) factor VIII and (D) VWF. On the x-axis, the different data sets are labelled with the BIVAC grade, publication year and the reference number, as given in this review. The vertical lines divide data points where separate meta-analyses were performed, if more than one study was included, due to different analytical methodology. Results excluded in the meta-analysis (red circles and triangles) are marked with "excl" on the x-axis. Protein C activity, both clotting (clot) and chromogenic (chrom) methods, were separated by a half dotted vertical line, but were merged together in the meta-analysis. f; studies including only females, m; studies including only males, chrom; chromogenic methods, clot; clotting methods, Ag; antigen, free; free protein S, total; total protein S, 1-st clot; one-stage clotting method, 2-st clot; two-stage clotting method, RCo; ristocetin cofactor methods, CB; collagen binding methods.

Discussion

Different studies reported varying results for BV components for many measurands, including haemostasis measurands. In this study, we have performed a systematic review of BV studies of more than 1 week duration for haemostasis measurands, assessed their quality using the BIVAC and performed meta-analyses of eligible studies. For some measurands, only one study reporting BV data was identified (Table 1). Thus, it was not possible to perform meta-analysis, and the BV estimates we report for these measurands represent the results of single studies, with the associated 95% CI of that specific data set (Table 2). This emphasises the need for further high-quality studies, in particular for these 9 markers and also for other haemostasis measurands for which no data as of are yet available, such as thrombin time and factor XIII. The majority of the publications reviewed in our study were given a BIVAC grade C (Table 1), mostly on account of statistical issues related to the lack of outlier and variance homogeneity analysis, as has also been observed in other BV systematic reviews [4–6]. A BIVAC D-grade was given to a few subgroup data sets, mainly on account of obsolete methods being applied. The BIVAC criteria assess the information provided by the authors in their paper and thus depend on a clear description by the authors of how the study was performed. In the present study, the most difficult QIs to score were preanalytical procedures, steady state/trend analysis,

statistical method and number of the samples/results included, as the information on these aspects were not always fully provided or clearly described. The true methodological quality of the study may therefore have been higher than we were able to discern. For haemostasis measurands, adequate pre-analytical handling is particularly important to ensure correct results. We systematically assessed all publications for information related to blood sampling, citrate concentration of the tubes, centrifugation and freezing procedures and storage conditions. Many studies, however, provided little detail on the pre-analytical handling, as reflected by 37% of studies receiving a B or C score for this quality item.

For haemostasis measurands, summarised BV data are only available, to date, in the historical online BV database [8]. Here, median values for the 10 most common haemostasis measurands, based on 9 publications, have been published. Except for VWF:Ag, the CV_I and CV_G point estimates in this database were within the 95% CI of the meta-analysis-derived estimates found in our study. For VWF:Ag, the CV_I was significantly lower than the CV_I derived from the meta-analysis. This is likely the effect of the inclusion of additional publications and the exclusion of two studies from our meta-analysis [10, 30], one because of a too short study duration and the other because the CV_I was reported to be 0%. Furthermore, the CV_G of protein C and total protein S published in the historical BV database were higher than the estimates derived from the meta-analysis. This is likely caused by the fact that only one study with data on protein C and protein S, which reported very high CV_G estimates, was included in the historical database [46], while the present meta-analysis includes more studies that all reported lower CV_G values.

Large differences in BV data between the various haemostasis measurands were observed, which may have been influenced, for example, by: study design/statistical handling, the type of study population (gender and age-related) and external factors related to acute phase reactions, blood group and hormones. Since most studies identified in our review reported results for populations consisting of individuals of mixed gender and age, it was not possible to perform meta-analyses of the different population age or sex subgroups. However, the EuBIVAS, which is a large-scale multi-centre study assessed different age/sex related subgroups and reported significant differences in CV_I estimates between males and females ≤50 years for APTT, protein C, and protein S free [38]. Indeed, differences in concentration levels related to sex are observed in haemostasis and fibrinolysis in healthy individuals [50] and further studies on BV for haemostasis measurands other than those included in the EuBIVAS are warranted. Furthermore, the EuBIVAS data indicate that sex-specific BV estimates should be considered for e.g. reference change value application, if sex-specific data are available. No studies in children or the elderly were identified in our literature search and thus our review only includes data from healthy adults (18–75 years). No assessment could therefore be made to account for the impact of age. This demonstrates the need for additional high-quality studies in different population groups. Three studies in pregnant women demonstrated comparable BV results to our results in healthy individuals [27, 36, 37]. Studies reporting within-day estimates were not included in our review. Short-term or within-day BV estimates may be of value in the assessment of rapidly changing clinical situations such as COVID-10 and DIC and should be appraised in future studies.

Many coagulation and fibrinolytic proteins are acute-phase proteins [51], and acute-phase reactions may influence BV estimates, if not adequately controlled in the study. The highest CV_I and/or CV_G were observed for PAI-1, with meta-analysis derived CV_I of 48.6% for PAI-1 antigen and CV_G of 90.2% for PAI-1 activity. PAI-1 is an acute phase reactant, as previously discussed by Nguyen et al. [28]. When performing a BV study, any influence of the acute phase should be minimised by including only healthy persons, assessing for trends and excluding samples or subjects where acute phase influence is likely. We did not observe such high variation for other well-known acute phase reactants as fibrinogen and factor VIII, although the BV estimates for these measurands were slightly higher than other coagulation factors. However, PAI-1 levels are also subject to strong diurnal variation, which may also have an effect on the BV estimates [52]. However, all the studies included described standardized samplings in the morning and this is thus unlikely to be the explanation for the high PAI-1 BV estimates.

High BV estimates were also observed for VWF antigen, which increases during acute phase and also shows diurnal variation [53, 54]. However, most eligible studies reported that samples were collected in the morning and only from healthy individuals. Only one study reported having assessed for individual trends during the study period [27]. It is known that VWF levels are related to blood group [55] and increase with higher age [56], which could potentially explain the higher BV estimate observed for VWF compared to most of the other haemostasis measurands, particularly the between-subject variation. Furthermore, for other measurands an age-related effect has been reported, such as for D-dimer, protein C and protein S, which might have an effect on the BV [57, 58]. As expected no significant differences were observed between VWF:RCo and VWF:Ag. Data for more recent VWF activity methods were not identified (such as: Ristocetin-triggered GPIb-binding assay, gain of function mutant GPIb-binding assay and assays based on

monoclonal antibodies directed against the GPIb binding epitope of VWF to mimic platelets).

The high BV estimates found for D-dimer could be related to the low concentration of D-dimer in healthy individuals (mean concentration: 204.0 ng/mL FEU, Table 2). Furthermore, it has been shown that D-dimer results were heterogeneously distributed in the EuBIVAS, which applied a Bayesian model to deliver BV data [38]. Thus, an average CV_I estimate as delivered by classical statistical models applied in most BV studies will not adequately represent the mean CV_I of the study population for D-dimer. From this it follows that applying a BV model for setting APS for D-dimer must be done with caution [38]. Since high D-dimer levels are used as a tool for e.g. COVID-19 [59], disseminated intravascular coagulation (DIC) [60] and venous thromboembolism (VTE) [61], a clinical outcome model for APS would be preferable, as has also been recommended [62]. However, no outcome studies have yet been published.

In our review, we focused on BV data derived from healthy adults. However, for specific situations, BV data for patients in stable disease settings are of interest. A few studies on BV for INR in patients at steady-state vitamin K antagonist treatment have been published. These studies demonstrated that the CV_I was considerable higher in such patients (ranges of the studies: CV_I=8.0–13.3%) [18–21] compared to data derived from healthy individuals (Table 2). Thus, if APS are set on the basis of the BV estimates for INR derived from healthy adults, these will also be more than adequate for anticoagulated patients.

Two studies with BV data for fibrinogen from patients with cardiovascular disease have been published. One study assessing both healthy volunteers (CV_I: 12.0%, CV_G: 31.8%) and patients with stable angina pectoris (CV_I: 12.5%, CV_G: 39.7%) found comparable BV estimates in both groups [35]. The second study demonstrated similar estimates to those derived from the present meta-analysis in healthy adults (Table 2) (CV_I: 11.0%, CV_G: 17.5%) [16], thus, demonstrating that for this clinical situation BV estimates from both groups will result in similar APS.

In an earlier published study, it was shown that APS based on BV data derived from healthy adults and applied to the six-sigma concept on QC data for routine haemostasis factors frequently result in sigma values below the minimum acceptable value of 3.0 [9]. Therefore, the application of BV estimates as strict criteria for haemostasis measurands will be difficult. However, the new criteria could be used as a target on the horizon for further improvement in time.

In conclusion, this study provides a systematic review and updated estimates of CV_I and CV_G with 95% CIs for 35 clinically important haemostasis measurands. These data are of value when setting APS criteria for haemostasis tests used in the diagnostic work-up in bleeding- and thrombosis events and for risk estimation, as well as for other BV applications. More high-quality BV studies are necessary to increase our expertise in BV estimates for different population groups and states of health.

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