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# The European Biological Variation Study (EuBIVAS): Biological Variation Data for Coagulation Markers Estimated by a Bayesian Model

**Article:**
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*The European Biological Variation Study (EuBIVAS): Biological Variation Data for Coagulation Markers Estimated by a Bayesian Model*
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**Guest:** Dr. Aasne Aarsand is director of the Norwegian Porphyria Center and a consultant at the Department of Medical Biochemistry and Pharmacology at Hawk Lynn University Hospital and the Norwegian Organization for Quality Improvement of Laboratory Examinations in Bergen, Norway.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Coagulation markers are important in a variety of clinical settings, such as suspected Flambeau embolism or increased bleeding tendency, monitoring anticoagulant therapies, evaluation of liver function and as risk assessment markers to ensure correct interpretation of coagulation markers data on biological variation are necessary.

Biological variation data are used to set analytical quality specifications to assess changes in a measurand series within an individual by the reference value change to examine the utility of population-based reference intervals and to derive personalized reference intervals. However, estimates of biological variation must be reliable and representative of the populations to which they are applied.

A paper appearing in the September 2021 issue of *Clinical Chemistry* examined samples from the European biological variation study to determine biological variation of coagulation markers by a robust model to assess the applicability of these estimates in clinical practice. The lead author of that study, Dr. Aasne Aarsand, joins us for this podcast.

She is director of the Norwegian Porphyria Center and a consultant at the Department of Medical Biochemistry and Pharmacology at Hawk Lynn University Hospital and the Norwegian Organization for Quality Improvement of Laboratory Examinations in Bergen, Norway. She is also chair of the European Federation of Clinical Chemistry and Laboratory Medicine Working Group on biological variation.

So first of all, Dr. Aarsand, biological variation data have several applications and laboratory medicine, including setting analytical performance specifications for many measurands. What challenges do you generally see in publish biological variation data and are they fit for purpose?

Aasne Aarsand: Well, many studies have the over the years estimated reported biological variation data for commonly analyzed measurands. However, it's clear that estimates for the same measurand obtained from independent studies may vary substantially. And important factors for this variation are like the lack of harmonization in study design, applied methodology and the data handling between different studies. And clearly, some of these data, especially more historical data, are not really fit for purpose.

Biological variation data are reference data but they are often applied without this understanding, meaning that the biological variation data may be applied to populations with characteristics that are different from the reference population from which they were derived.

In the present study, we reported biological variation estimates for coagulation markets derived from the European biological variation study and this study is a large-scale highly power study including more than 90 participants from five different European populations and it follows best practice for estimating and reporting biological variation data.

The European biological variation study is one of several initiatives of the European Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biological Variation that aims to provide sufficiently characterized and high-quality biological variation estimates for use in laboratory medicine applications.

And another major initiative for us is the Flambeau biological variation database which reports detailed quality assessed information on biological variation studies for, as of today, more than 230 frequently requested measurands. And which real-time or automatically provides global estimate within and between subject biological variation derived from meta-analysis of studies of acceptable quality.

Bob Barrett: In your study, doctor, you applied a Bayesian model to derive biological variation estimates for coagulation markers. Can you please share with us why you chose this approach?

Aasne Aarsand: I would be happy to. The Bayesian approach, ELFIS has several advantages compared to classical methods such as ANOVA, analysis of variance. And firstly, the Bayesian model takes into account prior knowledge when estimating the data. In our case, we applied prior as based on previously published studies on biological variation or coagulation markers.

Secondly, the Bayesian approach or Bayesian model does not require fulfillment of formal statistical requirements related to outlying data and various homogeneity, which with some

 

data sets may require that you exclude a higher number of data than is desirable and then which again makes the data less representative. With our Bayesian model, however, we only had to exclude three clearly pathological single results out of the whole data set, which consisted of more than 50,000 results.

In addition, the Bayesian model provides estimates of biological variation for each individual, which we termed within-person, within participant estimate. When we talk about within-subject estimate, we typically refer to, as to be the mean estimate of the study population. Whereas the within-person within-participant estimate is the biological variation for that specific individual.

And having the estimate for each individual allows us to assess the distribution of the data that we use as basis for calculating the average estimates. And this is important because when using the mean estimate for calculating either reference change values or setting analytical performance specification, it's essential that its mean estimate is representative for the population or for the study from which it was derived. And that is one of the advantages we get with the Bayesian model.

Bob Barrett: So, what did application of your Bayesian model to these coagulation markers reveal?

Aasne Aarsand: Well, we did find that for all the markers except for D-dimer, the within-participant within person estimates were homogeneously distributed either in the overall study population or in the sub-groups i.e. there is partition by sex and age which made us deliver sub-group estimate for men and for women about below 50 years.

So, for all these measurand except D-dimer, a common mean within-subject biological variation estimate is adequate and we also found that the within-person estimate was not related to the participants from a static set points. And this is very important as that indicates that the variation does not depend on the concentration of the measurand, at least not in this group of healthy individuals that we assessed in this study. For unhealthy diseased individuals, it may be different. We don't have data for that yet.

For D-dimer on the other hand, data were not homogeneously distributed in either the overall study population or in the sub-groups. So, this means that using an average within-subject estimate for the D-dimer is not recommended, as this will not be really representative for the study population. And it's likely that the high amount of noise that we observed in the D-dimer data may be related to the low concentrations, so D-

dimer are typically having a healthy individual which is close to the limit of detection and associated with a high analytical variation.

Bob Barrett: Doctor, how well did your results compared to previously published studies? And if there were some differences what could be the reason?

Aasne Aarsand: Well, significantly, they were not necessarily the large differences. For example, for protein C, protein S3 and factor 8, we obtained estimates that were lower than those reported in previous studies, but for some of these studies direct comparisons are not necessarily applicable because they have employed different sampling intervals: some have employed once every week, some once every month. However, most significant finding was that we found lower within-subject estimates in men than we found in women below 50 years for APTT, protein C, and protein S3. And this test has not previously been reported, possibly due to previous studies not being sufficiently powered to sex differences. And sex differences of particular relevance for coagulation markers where we know that hormonal factors play essential role and where we think the higher within-subject estimates infertile women may be related to the radiation or hormones that are seen during the menstrual cycle.

Bob Barrett: Well, finally doctor, what are the clinical implications of your findings?

Aasne Aarsand: Well, the biological variation estimate reported by the European biological variation study in this and all the papers, they are well-characterized and documented and it's hopefully providing a level of understanding and confidence around the data to potential uses. And when using the Bayesian model, we have shown that for most coagulation markers, you can use an average or a mean within subject biological variation estimate. For example, setting analytical performance specification. However, if you use the data for reference change values or personalized reference intervals then sex as specific estimate should be applied for APTT, protein C, and protein S3. For D-dimer on the other hand, the data was heterogeneous that using a mean estimate is not appropriate. For example, for reference change value calculations. So, instead if this is of interest, you could use different percentiles so the predicted distribution depending on the clinical purpose or the clinical question that you would like to ask.

Bob Barrett: That was Dr. Aasne Aarsand from Norwegian Porphyria Center and the Department of Medical Biochemistry and Pharmacology at Hawk Lynn University Hospital in Bergen, Norway. She has been our guest in this podcast on biological variation of coagulation markers. She is lead author of a

 

paper on that topic that appears in the September 2021 issue of *Clinical Chemistry.* I'm Bob Barrett. Thanks for listening.