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Biological Variation of Adrenal-Related Endocrine Biomarkers Used for Investigation of Secondary Hypertension

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Guest: Dr. Kristin Aakre is a medical doctor and professor in medical biochemistry at the University of Bergen in Norway.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Secondary hypertension, or consistently elevated blood pressure caused by an identifiable medical condition, accounts for roughly 10% of all cases.

Endocrine disorders constitute one of the most important subgroups of secondary hypertension and are typically caused by dysregulated adrenal or pituitary hormone production. As hypertension is a significant risk factor for cardiovascular disease, prompt diagnosis and intervention is essential, and this process often starts with measurement of endocrine hormones like aldosterone, renin, and catecholamine metabolites. If normal, an endocrine cause is unlikely. Abnormal results, however, increase suspicion of an endocrine disorder and lead to imaging studies or provocative testing to establish a definitive diagnosis. To reliably identify abnormal values, we need to know how the concentrations of these hormones change in healthy individuals without hypertension. We also need to know what magnitude of change differentiates an underlying disease process from normal expected day-to-day variation.

A research article in the November 2026 issue of *Clinical Chemistry* tackles this issue by calculating the biological variation and reference change values for seven analytes critical to the evaluation of secondary hypertension. Today, we welcome the article's senior author. Dr. Kristin Aakre is a medical doctor and professor in medical biochemistry at the University of Bergen in Norway. Her main research interests are diagnostic and prognostic properties of cardiac biomarkers with a particular focus on acute coronary syndrome. And Dr. Aakre, let's start with the basics about biological variation. What is it? Why is it important? What is it used for in the laboratory? And how is it used clinically?

Kristin Aakre: Well, biological variation refers to the natural fluctuations in biomarker concentrations. And these occur both within an individual over time and between different individuals. So, in

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laboratory medicine, we usually call this within-subject biological variation, CV_I, and between-subject biological variation, CV_G. And I think understanding biological variation is important because laboratory results are not static. Even in healthy people, concentrations of biomarkers will vary due to just natural fluctuations from day-to-day and time point-to-point.

So, when we know the biological variation, we actually have a measure on how large these fluctuations are and what we can expect when we measure biomarkers over time. Also, when we know these fluctuations, we can use that to determine the analytical quality specifications for different biomarkers. Because, you know, if there is a large variation within the person itself or between the patients, we don't need to have an analytical variation that is very, very much lower compared to that. So, usually, we say analytical variation should be half of the within-subject biological variation, because if it's that good, it will not actually have any influence on the biomarker result itself. So that is another very useful application of this. And for clinical use, what I said earlier, we use it to determine what is the expected fluctuation in consecutive results.

Bob Barrett: How are endocrine markers used in the evaluation of hypertension? And why do we need to take their biological variation into account?

Kristin Aakre: Well, endocrine biomarkers play a very central role in the evaluation of hypertension, because usually or most cases of hypertension are just idiopathic. We don't know the reason, but there are some cases, maybe 10% around that, which are actually caused by underlying diseases, which could be hyperaldosteronism or pheochromocytoma, paraganglioma and cortisol excess syndromes. These are quite rare, but very important diseases and to diagnose them, we measure these specific endocrine biomarkers, which are related to the condition. So, that's a clinical use of the different markers like aldosterone, renin, metanephrine and normetanephrine, ACTH and so on, cortisol.

The challenge with all these hormones and the reason why we need biological variation data is that they are very responsive to physiological influences, like even body posture, if you are sitting or lying down, the intake of sodium, how stressed you are. Some of them have really large circadian rhythms, varying from morning to afternoon, evening, and also by physical activity.

So, as a result of this, we need to have a measure of how large variations can be expected within a subject itself and between subjects.

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Bob Barrett: Okay. So what are the main findings of your study and what are their clinical implications?

Kristin Aakre: The main findings -- or in this study, we did investigate the biological variation of the markers I mentioned earlier, like aldosterone, renin, aldosterone-renin ratio [ARR], ACTH, cortisol, cortisol-ACTH ratio, metanephrine, and normetanephrine. And we used very standardized study design, which has been recommended by the EFLM Biological Variation Group, where we took weekly samples for 10 weeks in a very standardized setting and all participants were healthy volunteers. Well, the main finding was that aldosterone, renin, and ARR showed substantial biological variation, larger than we had expected, actually. And, for instance, for aldosterone, the CV_I was nearly 50%.

In contrast to this, metanephrine and normetanephrine showed surprisingly low biological variation and lower than we had expected, actually. And the lowest variation was for metanephrine, which was around 14%. And also, the between-subject variation was quite low for these biomarkers.

And another important finding in this study was that all biomarkers we included had an index of individuality of less than one. And this means that for these biomarkers, you get more information if you measure them serially and you compare the result you get to the patient's own baseline, instead of comparing to population-based reference interval, which have been determined for a large group. Because if you start -- for a patient starting at a low concentration, they will need to increase substantially to cross the population-based reference interval, while for a patient who has a naturally high concentration, they only need to change a little bit to cross that line. While if you compare to their own baseline, you can actually discover significant changes much easier and much more accurate. So that was another important finding.

So just to sum up for clinical perspective, the low variation of metanephrine means that you can probably take one measurement and you can trust quite well the finding you do. For aldosterone-renin, in contrast, you might need to measure them more than once to be sure that the finding you get is not due to biological variation. And also, finally, for these markers, using personalized reference interval might be more useful than population-based reference interval. So that's clinical implications.

Bob Barrett: Well, finally, Dr. Aakre, where is this field going? Looking ahead, what is the future direction of biological variation studies?

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Kristin Aakre: Yeah, this is a very good question. So, you know, biological variation studies have been going on since the 1960s, more or less. They have mostly been used for defining analytical performance specifications and the study designs and everything. There hasn't been very much move in that field, maybe except for the last 10 years. And the EFLM Biological Variation Group has done a quite lot of progress in this and have improved the way these studies are doing.

However, what is new now and what I think will be the future for this scientific field is that we will take this into clinical practice and we will move from using this in a very rigid fashion to define analytical performance specifications into a much more dynamic usability where we will actually use this data to estimate personalized reference interval, which can be used in clinical practice. So there are some quite recent publications, also from our group, which suggest how this can be done.

However, one of the greatest challenges for implementing personalized reference interval are maybe the regulatory bodies, because you might need approvals for doing this. And the other thing is that the laboratory information system is not at all set up to report the data in such a way.

So there are things that need to be solved before we can use this in practice. But I think that is like in 10 years, maybe a little bit more, we will be there more or less for all biomarkers, hopefully.

Bob Barrett: That was Dr. Kristin Aakre from the University of Bergen in Norway. She wrote a research article in the November 2026 issue of *Clinical Chemistry* about determining biological variation of endocrine hormones for the evaluation of hypertension and she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.

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