Are Heart Failure Management Recommendations and Guidelines Followed in Laboratory Medicine in Europe and North America? The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) Study

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Guest:
Dr. Angelika Hammerer-Lercher is Deputy Director of Institute for Laboratory Medicine at the Kantonsspital Aarau, Switzerland.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Heart failure is a significant cause of decreased quality of life, morbidity, and mortality. Now currently, the most utilized biomarkers of heart failure are the natriuretic peptides, BNP and NT-proBNP. In 2012, the European Society of Cardiology, or ESC, released new guidelines regarding the appropriate cut-off concentrations of these biomarkers in ruling out acute and chronic heart failure. An article called, "Are Heart Failure Management Recommendations and Guidelines Followed in Laboratory Medicine in Europe and North America? The CARdiac MArker Guideline Uptake in Europe (CARMAGUE)" published in the March 2017 issue of JALM, commissioned a survey of laboratories in Europe and North America in order to investigate if labs were using the new ESC cut-off recommendations for BNP and NT-proBNP. Further, this survey sought to elucidate the reasons why labs measure one versus the other biomarker and whether the labs were accredited.

The first author of this article is Dr. Angelika Hammerer, Deputy Director of Institute for Laboratory Medicine at the Kantonsspital Aarau, Switzerland. She was a member of the recently concluded working group "Cardiac Markers" of the European Federation of Clinical Chemistry and Laboratory Medicine and she's our guest for today's podcast. Welcome, Dr. Hammerer.

First question, why is the natriuretic peptide testing so important?

Dr. Hammerer: Patients with acute heart failure show up with acute breathlessness and non-specific symptoms, so that the differential diagnosis is not always easy. Biomarkers like natriuretic peptides help to triage these patients.

Heart failure is a disease with a poor medium-term prognosis and decreased quality of life. In patients with acute heart failure the cumulative all-cause 1-year mortality is as high as 17%. The American Heart Association forecasted a 3-fold increase in costs within the next decade, attributed to an aging population. On the other hand, good therapies are available and medications have been developed to improve the outcome. One of these is the promising angiotensin receptor-neprilysin inhibitior, Entresto.

Randye Kaye: How well-established is the measurement of natriuretic peptides for the differential diagnosis of breathlessness like in heart failure?

Dr. Hammerer: Our survey showed that laboratories offering natriuretic peptide testing did not increase between 2009 and 2013 and stayed merely the same at around 6% to 7%. In North American Laboratories only around 58% offer these assays. We did not expect these rather low numbers particularly after the incorporation of natriuretic peptide testing into the guidelines over several years. However, most of the laboratories provided the 24-hour laboratory service.

Randye Kaye: What do the guidelines say concerning cut-off values for natriuretic peptides and are they used in the laboratories?

Dr. Hammerer: At the time of our survey, which was closed in August 2013, the 2012 European Society of Cardiology guidelines as well as the ESC recommendations had just been published and the American College of Cardiology Foundation/American Heart Association came out in 2013. The guidelines placed a high value on echocardiography besides natriuretic peptide testing. However, in the ACCF/AHA guidelines no explicit natriuretic peptide cut-off values were stated in 2013.

The ESC guidelines of 2012 showed a different algorithm than the ESC recommendations of the same year. Thus, in the ESC guidelines, single cut-off values for ruling out acute or chronic heart failure were recommended, which were confirmed in the most recent ESC guidelines of last year with a class I-A recommendation. What we have seen from our survey is, that only around 5% of participant laboratories measuring NT-proBNP followed the guidelines, whereas for BNP this was better, with around half of labororatories using the recommended 100 ng/L cut-off for acute heart failure.

There were several (around 20%) laboratories using the age-dependent rule-in cut-off values for NT-proBNP which were part of the recommendations. It seems that the publication of two different algorithm by the ESC in 2012 caused some confusion around which cut-off limits should be

applied, particularly for NT-proBNP. We found a substantial variability in decision limits used. Interestingly, there were a few laboratories who did not know the cut-off values. We hope that this situation improves within the near future.

Randye Kaye: I hope so too. How could this situation be improved?

Dr. Hammerer: Yeah, for a successful dissemination of guidelines, practitioners should have the four A's: awareness, agreement, adoption, and adherence. To address awareness and agreement, our working group for cardiac markers sought cooperation with cardiology societies and held joint sessions during symposia with clinical societies to educate professionals, for example at EUROMEDLAB in Milano in 2013 or last year at the EFLM Congress in Warsaw.

Adaptation and adherence can be addressed in many ways, including monitoring metrics established at individual medical institutions. This will be part of these scientific sessions and is also aided by our publications documenting that evidence is not widely implemented, such as presented here. And at best, written guidelines for heart failure work-up should be established jointly by laboratorians and clinicians.

Randye Kaye: Okay, very interesting. Are there any confounding variables to be considered when measuring natriuretic peptides?

Dr. Hammerer: Many heart failure patients show comorbidities, such as impaired renal function, that cause high natriuretic peptide values, because natriuretic peptides also regulate the salt-water balance in the body. Therefore, cut-off values should be higher in these patients. In contrast to the patients with impaired renal function, in obese patients natriuretic peptide values decline according to the increasing body mass index, which means that cut-off values should be lower in these cases.

However, the shifts in natriuretic peptides cut-off values for renal failure and obesity have not yet been defined in the new ESC guidelines. In addition, in patients treated with the new neprilysin inhibiting drug Entresto, higher BNP and lower NT-proBNP levels were reported several weeks after treatment initiation. However, the proBNP system, with its many circulating forms, is very complex and requires further investigation to find the optimal type of natriuretic peptide measurement for patient monitoring and maybe should include ratios.

As around half of the survey participants offered natriuretic peptide assays for serial in- or out-patient monitoring, medication with neprilysin inhibitors will certainly be a challenge for laboratorians and clinicians in measuring and

understanding natriuretic peptide values post-therapy with neprilysin inhibitors.

Randye Kaye: Very interesting. Thank you so much for joining us today.

Dr. Hammerer: You're welcome.

Randye Kaye: That was Dr. Angelika Hammerer from the Institute for Laboratory Medicine in Aarau, Switzerland talking about the JALM article, "Are Heart Failure Management Recommendations and Guidelines Followed in Laboratory Medicine in Europe and North America? The CARdiac MArker Guideline Uptake in Europe (CARMAGUE)" for this podcast.

Thanks for tuning in for JALM Talk. See you next time, and don't forget to submit something for us to talk about.