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Cardiac Biomarkers in Pediatrics: An Undervalued Resource

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Mary Kathryn Bohn, Shannon Steele, Alexandra Hall, Jasmin Poonia, Benjamin Jung, and Khosrow Adeli.
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Guest: Mary Kathryn Bohn is a Ph.D. candidate in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. Dr. Khosrow Adeli is the head of Clinical Biochemistry and the Department of Pediatric Laboratory Medicine at The Hospital for Sick Children as well as professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. He is also president of the International Federation of Clinical Chemistry and Laboratory Medicine, the IFCC.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine and Boston children's Hospital. I'm Bob Barrett.

The clinical use of cardiac biomarkers such as the troponins and natriuretic peptides is usually limited to adult populations in the assessment of heart failure or acute coronary syndrome. While the value of these markers in pediatric populations is not often considered, emerging evidence suggests that they may be useful in the diagnosis and prediction of cardiac and non-cardiac pathologies in neonates, children and adolescence, and an increasing number of pediatric hospitals are now routinely measuring cardiac markers in their clinical practice.

A review article titled "Cardiac Biomarkers in Pediatrics: An Undervalued Resource" appears in the July 2021 issue of *Clinical Chemistry*. This review summarizes and critically evaluates the current literature regarding the application of cardiac biomarkers for clinical decision making in the pediatric population. We are pleased to have two authors of that review article with us in this podcast. They are Mary Kathryn Bohn and Khosrow Adeli.

Mary Kathryn Bohn is a Ph.D. candidate in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. She has been actively involved in the recent work of the Canadian Laboratory Initiative on Pediatric Reference Intervals, or the CALIPER project at The Hospital for Sick Children.

Dr. Khosrow Adeli is the head of Clinical Biochemistry and the Department of Pediatric Laboratory Medicine at The Hospital for Sick Children as well, and professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. He is also president of the International Federation of Clinical Chemistry and Laboratory Medicine, the IFCC. We'll start with you, Dr. Adeli.

Over the past 10 years, there has been a strong focus on the value of cardiac biomarkers in adults. However, little attention has been paid to their use in children and adolescents. What do you think is the most common misconception about their use in pediatrics?

Khosrow Adeli: Traditionally, most physicians and lab professionals are not aware of the pediatric applications of cardiac markers such as troponin. Most believe that they are only appropriate for adult applications. However, in the last decade or more, there have been many indications in children, clinical indications where cardiac markers have been used for. Our hospital has been using cardiac markers for almost two decades and this application continues to increase so much so that we have started performing the tests here on site, and we perform both cardiac troponins, as well as NT-proBNP testing because of the increased demand for Pediatric use. So, certainly, there needs to be increased awareness of the potential application and benefits of using cardiac markers in children.

Bob Barrett: Okay, turning to you Ms. Bohn, despite this lack of clinical awareness, What pediatric conditions do you think would benefit for more routine cardiac marker testing, and should they be offered in all major hospitals or limited to certain departments?

Mary Kathryn Bohn: As Dr. Adeli mentioned, while the use of these biomarkers is often discounted in pediatric practice, current literature suggests a multitude of possible applications in both cardiac and non-cardiac settings. As an example, there is significant data on the value of troponin, a marker of myocardial injury in adults in pediatric myocarditis. Myocarditis is an inflammatory disease of the heart muscle, and it remains in the diagnostic challenge in kids due to its non-specific nature.

Measuring troponin in children suspected of myocarditis and other heart conditions such as heart failure, congenital heart disease, and even chest pain has shown to improve the time to diagnosis, as well as the clinical outcome. In addition, other immune conditions such as sepsis, shock and autoimmune disorders, as well as COVID-19 may benefit from additional cardiac testing to better identify multi-system organ failure and potential need for cardiac follow-up in kids.

It certainly is an undervalued resource that I think all tertiary pediatric hospitals should definitely consider implementing both troponin and natriuretic peptide testing into their clinical routines. But I think it's important to mention as well that test utilization should be carefully considered with consulting clinicians. Particularly, in settings where minimal data is available such as renal disease. Also, whether serial measurement of these measures is beneficial is unknown at

this time and it definitely requires more research to better define not only when clinicians should order these tests, but also how often.

Bob Barrett: It's often been stated that children are not just small adults. Do you think pediatric specific reference standards or clinical decision limits are needed for cardiac biomarker interpretation?

Mary Kathryn Bohn: Yes. Children are definitely not small adults and clinicians and patients alike may be surprised to know that for a long time, the reference standards or help associated benchmarks provided on pediatric patient charts for blood test interpretation were largely based on adult studies. This significantly increased the risk of misdiagnosis and inappropriate clinical follow-up in pediatric care.

Our team here at Sick Kids in Toronto, Canada has been actively involved trying to address this gap for the past 10 years by recruiting healthy children and adolescence through community-based initiatives, collecting small blood donations from these healthy children, and establishing reference intervals for important biomarkers of health and disease on various analytical assays.

This initiative is known as CALIPER, the Canadian Laboratory Initiative on Pediatric Reference Intervals, and it has really pushed pediatric lab medicine forward by demonstrating that many biomarkers vary significantly by age and sex during periods of growth and puberty, requiring appropriate stratification and blood tests interpretations. Cardiac biomarkers are no exception to this. Recently, our team published normative data in healthy kids for cardiac markers such as troponin and BNP, demonstrating age and sometimes sex specific concentration differences as well.

In particular, neonates appear to have physiologically higher values of BNP and troponin in comparison to older kids and adults, likely due to fetal expression in the skeletal muscle, transient hypoxia at birth, or cardiac leakage. These physiological variations should be considered by ordering clinicians when interpreting values in kids, and therefore the lab must prioritize providing pediatric interpretive recommendations for these tests when available for proper utilization and to minimize inappropriate flagging.

Bob Barrett: Well, finally, back to you Dr. Adeli. What do you think is the future of cardiac biomarker utilization in pediatrics?

Khosrow Adeli: Clearly, there has been increasing utilization of cardiac troponins in children, most recently because of the COVID-19 pandemic. Many children have developed this multi-inflammatory syndrome and are being monitored during

hospitalization with cardiac markers. There are additional indications in critical care medicine and other areas. Therefore, I see growing interest in cardiac markers (certainly in pediatrics) and our review hopefully will increase awareness of the importance of applying these important markers in many areas of pediatric care. But as indicated, of course, lab utilization of these tests should be carefully considered, and only appropriate clinical indications should be used to order and utilize these assays.

But certainly, there are significant number of areas of clinical use for both cardiac troponin, as well as BNP and NT-proBNP and there are a couple of other more novel cardiac biomarkers are being studied currently. So, I see increasing utilization, I should say that one area, for example, within our hospital that's been increasingly using the tests is the area of cardiac failure or heart failure. We have a heart failure clinic here that is increasingly using cardiac NT-proBNP and BNP, both, as well as troponin to monitor children. So, I think as awareness increases in hospitals around the world, there is going to be increase in trust in utilization of these tests. So, I see increasing interest and additional biomarkers coming on the scene and used to monitor children with cardiac damage.

Bob Barrett: That was Dr. Khosrow Adeli from The Hospital for Sick Children at the University of Toronto. He is currently serving as president of the IFCC. He was joined by Mary Kathryn Bohn from the same institutions in this podcast on Cardiac Biomarkers in Pediatrics. Their review article on this topic appears on the July 2021 issue of *Clinical Chemistry.* I'm Bob Barrett. Thanks for listening.