C-reactive protein, or CRP, is an acute phase reactant protein that has been measured in blood by clinical laboratories for decades as a biomarker of infection and inflammation.

In more recent years, CRP assays that are more analytically sensitive, termed high-sensitivity CRP, were developed to determine a patient’s cardiovascular risk in the absence of acute phase inflammation. The existence of different types of CRP assays, which may report results in different units and with different interpretive cut-offs, can be confusing for laboratorians, healthcare providers, and patients alike. Further, high-sensitivity CRP assays are more expensive than their conventional counterparts and the designation of the CRP assay used has implications for billing and reimbursement in the United States.

This complexity has led some researchers to ask whether a modern-day standard CRP test can be sufficient for all clinical purposes. In the November 2022 issue of JALM, Han et al. report the results from their retrospective observational cohort study that compare the performance of a standard CRP assay to a high-sensitivity CRP assay for cardiovascular risk prediction.

Also in the November 2022 issue of JALM is an accompanying editorial article that reflects on the differences between CRP and high-sensitivity CRP assays.

Today, we’re joined by the two authors of the editorial article. Dr. Anna Wolska is a Staff Scientist at the Lipoprotein Metabolism Laboratory of the National Heart, Lung, and Blood Institute in Bethesda, Maryland. Dr. Alan Remaley is a Senior Investigator at the National Heart, Lung, and Blood Institute and a senior staff member of the Department of Laboratory Medicine at the National Institutes of Health.
Medicine at the National Institutes of Health. Drs. Wolska and Remaley, welcome.

Let’s begin here. Why are there two different CRP tests, and how do they differ?

Anna Wolska: Yes, we have two different tests that measure CRP because each one measures a different range of CRP level in the blood and is used for different purposes.

So the first one is standard CRP test measures markedly high levels of the protein to detect diseases that cause significant inflammation. It measures the protein in the range from 0.3 to up to 500 mg/L. So it is used to detect major inflammation following an infection, heart attack, surgery, or any kind of trauma.

And since the early 1990s, numerous studies have shown that persistent and low level of inflammation plays a major role in atherosclerosis, which is narrowing of blood vessels due to the buildup of cholesterol and the other lipids often associated with cardiovascular disease. And for this, the second CRP test, the so-called high-sensitivity CRP test, was developed because it detects much lower levels of the protein than the standard CRP test. The range here is from 0.15 to 20 mg/L, and because of its high sensitivity it can be easily elevated in patients even with relatively minor inflammation or illnesses, and is recommended to be used only to evaluate stable patients for cardiovascular disease risk.

Randye Kaye: All right, thank you. Can you just say a little bit more about the role of CRP in cardiovascular disease [CVD] risk prediction?

Anna Wolska: Yes, of course. The primary prevention of CVD is dependent upon the ability to identify high-risk individuals long before the development of other events and this highlights the need for acute risk stratification in order to decide how to best manage these patients, particularly the use of lipid-lowering drugs.

The consensus by a joint committee between the American Heart Association and the Centers for Disease Control and Prevention is that universal hsCRP screening in general population is not recommended because of what just mentioned before--that this hsCRP can be very acutely elevated in patients with many types of acute illnesses.

Currently in the U.S., it is recommended that high-sensitivity CRP test is to be tested in stable patients with no other ongoing illness, whose ten-year risk score of CVD is between 7.5 and 20%, meaning that in individuals who have 7.5 to
20% chance of having a cardiac event within the next 10 years.

So if intermediate risk patients have their high-sensitivity CRP test results of 2mg/L or above, puts them at an increased risk for cardiovascular disease and these individuals could benefit from a lipid-lowering therapy.

In general, hsCRP, along with some other CVD risk markers like apoB, are considered as risk enhancer tests to help decide how to treat patients with intermediate risk based upon more conventional lipid testing. In addition, because of its high biological variability, it is recommended that this test be repeated to confirm that you have a persistent elevation. So ideally it should be used optimally between two weeks apart, repeated twice on fasting on fasting or non-fasting plasma, and in patients free of active infection or acute illness.

Randye Kaye: All right. Thank you. So, you’ve given us a lot of information. Dr. Remaley, are there any other inflammatory markers that can be used for cardiovascular disease risk prediction?

Alan Remaley: Yeah, I think for historic purposes, it’s probably worth mentioning that a very old test, older that CRP, it’s called the sedimentation rate, which is marker of inflammation. It’s not widely used because it’s a manual dependent test, but it highly relates to the level of fibrinogen, and fibrinogen levels also lead to cardiovascular risk. But neither one of those tests are recommended at this time, and there are tests that are being used that are more specific for different phases of inflammation for other clinical indications such as immunoassays or IL-6 or IL-1 beta, which measured different aspects of inflammation that people are starting to look at but they are again not widely recommended at this time.

I think two other things that are probably worth mentioning is GlycA. So GlycA is a NMR-derived test and is becoming increasingly popular where people are assessing cardiovascular risk using NMR to look at particle number and GlycA measures the glycosylation of abundant plasma proteins and seems to get different information than CRP and they work better for some populations, such as in psoriasis. So that test is available through reference labs.

And I think the future will probably depend on what the outcome of some ongoing clinical trials where people are actually actively looking at various anti-inflammatory agents and their impact in cardiovascular risk.

There is one test that is available, not widely used. It’s called lipoprotein-associated phospholipase for example that’s secreted by inflamed macrophages, and you can measure that and it shows increased risk.
But the reasons worth mentioning it is that there’s a drug that inhibits it that failed in clinical trials, probably because it wasn’t specific for that particular lipase. But I think the future will be monitoring inflammatory markers that are based on therapy but we’re not quite there yet.

Randye Kaye: All right. Thank you. So now it’s recognized that there’s a role that inflammation plays in the development of atherosclerosis. Dr. Wolska, you were talking about atherosclerosis earlier. How has this concept changed the approach to managing patients?

Anna Wolska: I think it’s a very good question because the cascade of inflammation is the body’s unique mechanism to maintain its integrity in response to macroscopic as well microscopic interest. And we now know that atherosclerosis is a chronic inflammatory disease of blood vessels and based on this understanding, patients with variety of illnesses that cause systemic chronic inflammation are considered to be also at increased risk for cardiovascular disease. For example, conditions such as chronic renal disease, lupus, rheumatoid arthritis, and even metabolic syndrome are all considered risk enhancers conditions.

So the patient, who is otherwise at intermediate risk based on more conventional lipid testing, has one of these chronic inflammatory conditions, regardless of their current hsCRP test value, should also be considered a potential candidate for lipid-lowering therapy.

Randye Kaye: Thank you. So, one final question, how do you envision standard CRP and high-sensitivity CRP assays being used in the future, Dr. Remaley?

Alan Remaley: Yes. So this gets us back actually to the paper that we wrote the editorial on, which I liked very much, but I think it maybe confused things a little bit but there’s actually a third CRP that’s important at least for regulatory reimbursement issues. So the FDA uses a term called cCRP, that means cardiac CRP. The paper that we wrote the editorial about demonstrated that a standard CRP had sufficient sensitivity in terms of its low-end range to identify patients that are at cardiovascular disease risk.

However, from a reimbursement issue, it’s necessary for the manufacturer of such assays to actually apply for a cCRP designation. Otherwise there becomes problems in terms of how the test is reimbursed, because the reimbursement rate for standard CRP is far less than hsCRP.

So, from the regulatory standpoint a standard CRP test that, like described in this paper, has sufficient sensitivity used to
be considered an hsCRP test, they actually have to compare their test to a pre-approved hsCRP test through like a 510(k) application or they have to do a clinical trial where they demonstrate that the CRP test can be used clinically in identifying patients at risk for cardiovascular disease, or the laboratory could potentially do this as a laboratory developed test.

So, I think the major advance in the paper that we commented on was that standard CRP tests may have sufficient sensitivity to be used like an hsCRP test, but there’s still lots of regulatory issues before that could be applied in practice.

Randye Kaye: All right. Thank you so much for joining us today.

Alan Remaley: Thank you, Randye.

Anna Wolska: Thank you.

Randye Kaye: That was Drs. Anna Wolska and Alan Remaley describing their JALM editorial article entitled, "CRP and High-Sensitivity CRP: “What’s in a Name?”" Thanks for tuning into this episode of JALM Talk. See you next time, and don’t forget to submit something for us to talk about.