In predicting CKD risk, eGFR better when based on cystatin C

Anne Paxton

Like turning around an ocean-going tanker, changing widely accepted testing practices in kidney disease, one of the nation's most common disorders, may have to be done gradually. But the latest study comparing the biomarkers cystatin C and creatinine, published in the Sept. 5 New England Journal of Medicine (2013;369:932–943), is the most sweeping study to date and should provide new impetus to wider use of cystatin C.

Filling in one of the last missing pieces, the study, "Cystatin C versus creatinine in determining risk based on kidney function" demonstrates that an estimated glomerular filtration rate (eGFR) using cystatin C offers the best means of predicting not only end-stage renal disease but also death from all causes across diverse populations. The findings, together with the adoption in 2012 of standard cystatin C-based eGFR equations and the increased use of cystatin C in certain patients, "will probably push clinical laboratories to incorporate this kidney biomarker," says an editorial in the same is- sue of the journal (974–975).

"By having 90,000 subjects from 16 cohorts across a worldwide distribution, this is the most definitive and well-powered study to really capture the nuance of what cystatin C offers in relation to creatinine," says Michael Shlipak, MD, MPH, lead author of the article and chief of general internal medicine at the San Francisco VA Medical Center.

Written by the Chronic Kidney Disease Prognosis Consortium, which includes about 200 collaborators and data from 40 countries, the study is a meta-analysis of 11 general-population studies (with 90,750 participants from the United States, Europe, and Australia) and five studies of participants with chronic kidney disease (2,960 participants) for whom standardized measurements of serum creatinine and cystatin C were available.

The authors compared the association of kidney function, as calculated by the measurement of creatinine, cystatin C, or the combination of creatinine and cystatin C, with the rates of death, death from cardiovascular causes, and ESRD. They also compared kidney disease stages that were classified alternatively by creatinine or cystatin C. The kidney function stages categorized by cystatin C were much better at reflecting future risk than were the stages based on creatinine-based estimates of kidney function.

Using a cystatin C-based calculation of eGFR, 42 percent of the study participants were reclassified from a creatinine-based eGFR of 45 to 59 mL per minute per 1.73 m2 to a higher eGFR lower risk stage, while 14 percent of participants with a creatininebased eGFR of 60 to 89 mL per minute per 1.73 m2 were reclassified to a higher risk stage.

The study found that with an eGFR of 85 mL per minute per 1.73 m2 of body-surface area, when using cystatin C, "that is where your mortality risk begins to elevate, whereas if you use creatinine you don't see the threshold for detection of CKD until an eGFR of 60," says Dr. Shlipak. "So you're completely blind to accumulated risk from 85 to 60. And for a normal person it can be 10 to 15 or even 20 years before you'll go from 85 to 60."

"We don't know yet whether we can slow that decline, to slow the rate of getting to 60. But at least now we can see it, so we can begin testing strategies. That becomes possible when you can actually track kidney function in the normal range." And those strategies will be the subject of the next set of studies, Dr. Shlipak says.

“Through early detection, we believe we can prevent or delay the onset of chronic kidney disease,” he says. “This has never been done. There is no trial that has ever tested whether CKD screening, even with conventional methods, improves outcomes for non-diabetic persons. In my research group that is our goal. We think with the new testing, it will be that much better because we’ll capture kidney disease more specifically and that much earlier.”

The new study does more than just aggregate existing research because it employs individual level meta-analysis, says study coauthor Josef Coresh, MD, PhD, the consortium’s principal investigator and professor in the Johns Hopkins Bloomberg School’s Department of Epidemiology. “That means we reanalyzed the data in every single one of the participating cohorts to answer the research question, using the same methods in every cohort. So the study is not just looking at papers published. We actually go to the original data and say this is our question of interest. We really produced a brand-new thing rather than just a summary of what was there before.”

The evidence now is fairly unequivocal, Dr. Coresh says. “We applied the new equations for eGFR with cystatin C and eGFR with cystatin C and creatinine combined, and those were only published in the NEJM last year by Dr. Inker, et al.” (Estimating glomerular filtration rate from serum creatinine and cystatin C. (N Engl J Med. 2012;367:20–29). “So this new study takes a big step toward making cystatin C part of the clinical care paradigm rather than the research paradigm.”

The study appears only eight months after clinical guidelines for the treatment of chronic kidney disease, by the working group of the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) foundation , which recommended the use of cystatin C-based eGFR as a supplemental test biomarker in patients with kidney-function ranges in which the creatinine-based eGFR has reduced accuracy. So while the application to each country will depend on resources and the local setting, “The consensus is now broad and global,” says Dr. Coresh.

“We can call this a definitive answer. Now we really need to work this test into clinical practice and help laboratories make the test available,” says Dr. Shlipak, who is also a professor of medicine, epidemiology, and biostatistics at the University of California at San Francisco. Study co-author Lesley A. Inker, MD, MS, associate professor of medicine, Tufts University School of Medicine, stresses that the new study shows once again that a combination of cystatin C and creatinine together is a more accurate estimate of GFR. “For prognosis, cystatin C alone and the combination are similar and perhaps cystatin C better, but for GFR estimation, it is clear, both from our work and now others , that the combination is better.”One of the new study’s strengths, Dr. Inker adds, is that it includes a broad cross-section of patients. “The study certainly has a lot of data on people from different populations, and it used all the available data on cystatin C for prognosis. It could only include people who were in the cohorts, so it can’t include people too sick to be included in observational studies. So there are always some limitations to the different patient results.” But for showing the value of cystatin C for prognosis, she says, further studies are not likely to be needed.

John H. Eckfeldt, MD, PhD, a professor in the Department of Laboratory Medicine and Pathology, University of Minnesota Medical Center, says the new study, with which he was not involved, corroborates what most of the other studies have found. “But it combines data from a very large number of other studies, with both normal patients and people with kidney disease, in a meta-analysis that tends to confirm prior observations that cystatin C is not only useful for predicting kidney function GFR, but seems to be substantially more useful than creatinine in predicting all-cause mortality,” he says.
In the 2012 NEJM study, of which Drs. Eckfeldt, Inker, and Coresh were co-authors, the conclusion was that cystatin C and creatinine together are better at predicting than either alone. “I think there are some advantages to actually looking at eGFR from cystatin C alone, as well as from creatinine alone,” Dr. Eckfeldt says. “Because if you compare the two eGFRs and they are widely disparate, it suggests there’s something going on with one or both of them. Whereas if you combine the two biomarkers into one equation, you won’t know that.”

While Dr. Eckfeldt believes additional work remains to be done on improving the accuracy of cystatin C measurements, the National Institute of Diabetes and Digestive and Kidney Diseases is funding research

aimed at discovery of other biomarkers for predicting not only current renal function status but also, more importantly, how to better stratify long-term risks of developing ESRD, other disorders, and premature death. Ways to reduce those risks can then be developed, either through lifestyle changes or treatment of primary causes such as diabetes or hypertension, plus potentially even drugs that might reduce the risk of progression of kidney disease and other adverse outcomes. “Early kidney disease is just like hypertension,” Dr. Eckfeldt says. “It’s a silent disease. You can have major damage being done and the patient knows nothing about it. It’s only late in the disease that the manifestations become apparent to the patient. So the goal is to diagnose it early.”

The main obstacle to getting universal use of cystatin C is primarily cost, he says. “Costs and charges don’t always line up in laboratory medicine. But the reagents for cystatin C are probably at least 10 times more expensive, and clinical charges are often 10 to 30 times more than for creatinine measurement.” However, Dr. Eckfeldt believes the cost will trend downward. “In the past, most cystatin C measurements were made on special immunoassay analyzers, but more recently, there have been several reagent manufacturers with reagents usable on general liquid chemistry analyzers.” Gentian, a company for which Dr. Eckfeldt is a consultant, is one such manufacturer.

Dr. Shlipak finds the Gentian cystatin C test to be a solid assay. “Through my work, I’m convinced it’s the most stable over time. It has not had the drift issues that have kind of plagued cystatin C. And when you’re measuring something biological like kidney function, you really need to get stable test results when patients come back.”

At the San Francisco VA Medical Center, Gentian’s test has been available since January and Dr. Shlipak uses the test, which is on an automated platform, in his own clinical practice. “Cystatin C doesn’t have to be a boutique or expensive test. It’s automated. It’s ready. And we really need to focus on having labs make it available.” However, Dr. Coresh says, estimating GFR through creatinine is still useful and should be the dominant tool for looking at CKD. “I think it’s a non-starter that creatinine would get completely replaced by cystatin C in the U.S., where there are 300 million creatinine tests done yearly. But there are situations in which there’s a reason to measure cystatin C, especially in the subset of patients where you want to know specific things about the risk of death and ESRD for your clinical action. There, using cystatin C is an additional task, an additional expense. But what this shows is if you do the additional test, you will get something back.”

How much testing might fall into that category is hard to know, Dr. Coresh adds, but one group likely to be affected includes patients who have earlier stages of kidney disease with a GFR in the 3A category, the range of 45 to 59 in the absence of albuminuria. “This group is particularly important because they have no protein biomarkers in their urine and just moderately reduced kidney function, and they are four percent of all persons in the U.S. That’s a large number of people. For them, the cystatin C could make a difference if it turns out they just have a lot of muscle and may not have kidney disease.”

“As with most diseases,” Dr. Coresh continues, “the least severe group has the most people, so it could be 50 percent of the people with kidney disease where you would get more information with cystatin C. So we say confirmatory testing with the use of cystatin C could allow substantial reclassification in this group with more appropriate resource utilization for patients at increased risk of complications.” Cystatin C is also useful for better assessment of kidney function in those whose body composition is abnormal. For example, in a patient with malnutrition or in a patient with amputation, the creatinine could be way off, Dr. Coresh says. Adoption of cystatin C testing is a process that has to occur one laboratory at a time, Dr. Shlipak says. “There is work being done by the clinical chemistry leadership to try to provide authoritative recommendations to all labs on which cystatin C measurements they should use,” but individual labs need not wait for official guidance.

Where should cystatin C first be used?

“The strongest recommendation is if a patient has a clinical situation where knowing kidney function is very important, and that could be because they are getting a treatment or procedure that might threaten their kidneys. Then the clinician needs either a direct GFR measurement, which is almost never available, or a cystatin C result,” Dr. Shlipak says. “In these situations, creatinine is not good enough. Cystatin C is still too expensive to replace creatinine across the board.” But there is a long way to go, Dr. Shlipak says, characterizing the level of clinician awareness on the value of cystatin C as “dismal.” “In the nephrology world there is awareness, but there’s been so much controversy it has distracted the community from moving forward. The whole field has been waiting for consensus and we’re finally at that point, so it’s an important time to clarify our message. In the generalist community, which I represent, there’s very minimal awareness except for the early adopters or people who have bumped into one of my colleagues.”

Some leaders in the CKD field suggest that clinicians are overwhelmed trying to figure out creatinine and shouldn’t be asked to change horses in midstream, Dr. Eckfeldt says. There is still some feeling that the “emerging consensus” is being driven by nephrologists while general practitioners or internists do not give a new kidney disease biomarker a high priority. But the National Kidney Foundation, Dr. Shlipak says, has been active in disseminating the new clinical guidelines. “That work is just hitting full swing. And it has multiple components, including expanded albuminuria testing and cystatin C education worldwide, in multiple languages.”

The biggest obstacle to getting clinicians to order cystatin C more regularly, in Dr. Inker’s view, is the lack of an assay that’s traceable to higher-order reference materials. “This is a huge issue, because if the assay is off by a certain factor, the estimated GFR will be off, and the whole test result will not be consistent with published data. We spent a lot of time figuring this out for our research studies, but it is as critical in clinical practice too.” “I’m a big proponent of implementation of research, but I can’t recommend something if I know the clinicians can’t use the test accurately,” Dr. Inker says. Once labs are using properly calibrated cystatin C assays, “we will be working with them as much as we can to help develop a reporting tool that allows eGFR from cystatin C and the combination to be reported alongside eGFR from creatinine. “It’s definitely time to use cystatin C. We just have to do it in the right manner,” she says. While there is an international reference material now, that doesn’t mean companies are using it appropriately yet, Dr. Shlipak says. “So the best practices that clinical chemists use, let’s say for creatinine because it’s been here for a long time, have not been applied yet to cystatin C.”

Dr. Coresh agrees with Dr. Inker that proper clinical cystatin C measurement procedure standardization is still a work in progress. “But with these major papers in hand and the clinical practice guidelines, now the manufacturers should have a greater incentive to finish calibration and implementation, and work with organizations like the National Kidney Disease Education Program and professional societies in clinical chemistry to get standardization issues improved and monitored across the country and across the globe.”

As the CKD Prognosis Consortium continues to be active and growing, “The topics we’re tackling now relate to assessment of kidney disease progression. We hope if we’re able to measure progression better, we would be able to conduct clinical trials with somewhat shorter duration and slightly smaller sample size and costs. And that might make companies have higher incentives to test more therapies and have more successes,” Dr. Coresh says. Until now, “we’ve had too few trials and too few successes.”

To improve laboratory testing, the CAP is in the midst of trying to develop a better Survey material to have accuracy-based cystatin C proficiency testing, says Dr. Eckfeldt, a member of the CAP Standards Committee and of the Accuracy-Based Surveys Workgroup. “I suspect within the next year we will be changing the current cystatin C Survey, because a question of matrix effects or what is called noncommutability of some of the current Survey materials makes ambiguous the interpretation of performance of laboratories measuring cystatin C in that Survey.”

“CAP Survey data suggest that the accuracy of many clinical cystatin C measurements is lacking, but potential noncommutability of the Survey material clouds the issue considerably,” Dr. Eckfeldt continues.

“So I think we’re going to try to develop fresh frozen serum pools from patients to get a better sense of how labs are actually performing, because right now the values can vary more than 50 percent among measurement procedures, which translates into roughly a 50 percent error in GFR estimates.”

These efforts to improve the accuracy of clinical cystatin C measurements are an important context for new evidence of cystatin C’s usefulness. “This study is a very elegant meta-analysis of a huge number of patients and studies, and it found consistently that cystatin C is a useful marker, and that will very likely lead to its broader acceptance in the clinical community,” says Dr. Eckfeldt. “But the laboratory community has to improve the accuracy of its measurements if cystatin C is ever going to be very useful clinically.”

That there are also now international clinical guidelines from KDIGO for the use of cystatin C may or may not step up acceptance of the biomarker, says Dr. Shlipak. “But I can say it’s a tremendous tool to have an impartial multinational collaborative statement that is authorized and validated by all the relevant organizations. That has a clear message. So all the controversy, while it hasn’t gone away, becomes a little more like white noise.”

In the meantime, Dr. Shlipak is using cystatin C daily at the San Francisco VA Medical Center. “We know in our practice that it does make a difference. We know for common conditions like diabetes that we can prescribe medications more safely by having a better test of kidney function. I think clinicians everywhere are ready to use it, and laboratories just have to put in the legwork of getting it ready on their platform.”

This new study of the benefits of cystatin C, he emphasizes, shows that “there is a bright future for improving kidney screening, treatment, and outcomes with an earlier and more accurate test.”

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Dr. Coresh

Dr. Eckfeldt

Dr. Inker

Dr. Shlipak