Heart failure high-wire act

Karen Titus

July 2013—After weeks of bewilderment, W. Frank Peacock, MD, finally solved the mystery of one of his so-called frequent fliers in the Emergency Department.

At the time, Dr. Peacock was vice chair, Emergency Medicine, at the Cleveland Clinic. Every Monday morning, week after week, a local pastor would show up with symptoms of possible heart failure. It turned out that every Sunday evening, the pastor attended his church's community dinner, where duty compelled him to try every last casserole. "He ended up with a salt load every Sunday night, and every Monday morning we'd see him," recalls Dr. Peacock, who's now professor, associate chair, and research director for Emergency Medicine at Baylor College of Medicine, Houston.

Would that all heart failure cases could be handled by telling patients to avoid Protestant potlucks. As it turns out, heart failure cases—never simple to begin with—now have a new, potentially costly wrinkle. Last fall, the CMS began cracking down on hospitals with higher than expected 30-day readmission rates for heart failure (as well as for acute myocardial infarction and pneumonia). That has launched among clinicians and administrators fresh scrutiny of how well HF is managed, from diagnosis to guiding therapy to risk stratification.

With heart failure readmission rates getting attention, biomarkers are too. Troponins and BNP/NT-proBNP are in wide use. "Now all we're saying is just get a couple more, at least maybe one more, before they leave the hospital," says Dr. Alan Maisel, above center, on rounds in the CCU at the San Diego VA. [Photo: Sandy Huffaker]

"It's a topic of intense discussion just about anywhere you go, because it is a major cost center," says Alan Wu, PhD. "I think in the very near future, with pay-for-performance in the new health care initiative, this is going to be even bigger. If you have really high readmission rates, your reimbursements might be

affected," says Dr. Wu, professor, laboratory medicine, University of California, San Francisco, and laboratory director, Clinical Chemistry Laboratory, San Francisco General Hospital.

While it may not be a lab issue right now, it will be in the very near future, says Dr. Peacock. "Every hospital administrator is scared to death of this," he says. Their concern has trickled down to emergency medicine and cardiology physicians, with the lab not far behind.

Readmissions historically haven't been closely tracked, explains Dr. Peacock, because no one felt personally responsible if a patient returned. Likewise, no one felt the sting financially.

That's now changing. Readmission rates are now serious business, emphasis on the business. Some hospitals are turning with new enthusiasm to old measures, while others are looking at new measures to reduce rates. In both scenarios, biomarkers might be important, with clinicians looking at new uses for standard markers as well as searching for novel ones.

All these efforts come with a catch, however. With so little emphasis placed on heart failure readmissions in the past, physicians have precious little data to guide them. "We've never really looked at what predicts 30-day outcome," Dr. Peacock says.

They're starting to find out.

Even the number 30 is a little shaky. In general, readmission is worse than nonreadmission. But if a patient does return for care, it's not always the fault of the hospital, says Adam Singer, MD, professor and vice chair for research, Department of Emergency Medicine, Stony Brook (NY) University. Heart patients can be notoriously hard to manage, and mortality rate for heart failure is high—almost 50 percent within two years. "These are sick patients," says Dr. Singer.

Heart failure therapies haven't advanced much in recent years, he continues. Yes, biomarkers have improved, as has physicians' understanding of the disease. But treatments themselves are treading water. There have been plenty of hopefuls, says Dr. Singer, including nesiritide and other endothelial receptor antagonists as well as other novel therapies, but when tested they've failed to show clinical benefit. "It's been disappointing. I'm not sure how we expect, all of a sudden, we're going to do much better in managing heart failure patients, when the armamentarium hasn't shifted much."

Dr. Peacock sees 30 days as a marker of who's sick. Patients who have more visits die at a higher rate than those who don't, he says. "After your fourth revisit, you're probably going to die really soon." And the sickest people come back soonest, he says.

But why not 29 days, or 31 days, or even 60 days, when 58 percent of readmissions occur (O'Connor CM, et al. Am Heart J. 2010;159[5]:841–849)? "You have to pick something," says Peter Pang, MD, associate chief and associate professor, emergency medicine, and associate professor, medicine, Northwestern University Feinberg School of Medicine, Chicago. "Do I think it's the best? Not necessarily. Do I think it's a place to start? I do." Noting the lack of success in improving heart failure outcomes in the last decade, he says, "You can clearly see why they had to start somewhere."

To Dr. Singer, the 30-day mark is arbitrary. "There's no evidence that that means the patient was mismanaged and that there was an error. You could have patients who were managed well, but that's the nature of the disease. Some people have severe disease and are very brittle." In some cases, he posits, it might even be better for patients to have several one- or two-day admissions over a month than one two-week stay.

That lines up with the longstanding approach of focusing on shorter length of stay. DRGs, says Dr. Peacock, encourage hospitals to move sick people out the door. And if they came back, hospitals "simply bill them another DRG." Little wonder, he says, that the CMS is now focusing on readmissions—it's the next logical step financially.

But improving heart failure outcomes—or, to be precise, lowering readmission rates—is a problem without a clear answer. In fact, it's hard to figure out where to start looking, the result of which is hospitals are looking almost everywhere.

Are readmissions the result of diagnostic failure? Treatment failure? Are patients being discharged at the right time? Are the right ones leaving the hospital? Is followup care adequate? Are the right ones staying hospitalized, for the right amount of time? Is this even a heart failure issue at all?

And where do biomarkers fit in?

If it were possible to improve care for heart failure patients by clinical means alone, says Dr. Peacock, "we'd already be doing it. For years we've been bad at this. The medical community cannot tell who is a low-risk patient. We send them all home, and a third of them come back."

Enter biomarkers, which tend to be a fairly inexpensive, easy-to-use way to risk stratify patients. For years they've been used as diagnostic markers, but now physicians are looking at using them prior to discharge.

The reigning heart failure marker remains natriuretic peptide (NP), either B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP).

Alan Maisel, MD, professor of medicine and cardiology, University of California, San Diego School of Medicine, and director, coronary care unit and heart failure program, Veterans Affairs San Diego Healthcare System, is a big fan of using NPs in risk prediction algorithms. The usual tools for preventing 30-day readmissions (including medicine reconciliation with pharmacists, home nursing, telehealth monitoring) have not proved helpful. Not because they're bad tools, Dr. Maisel says, but because not everyone is using the information they provide to make changes, which in turn might reduce readmission rates.

At the San Diego VA, policy recommends using NT-proBNP prior to discharge for two reasons: 1) it lets physicians know whether the patient's NP level is as low as it should be, and 2) if it's high, it might encourage physicians to continue monitoring the patient, because higher levels increase chances the patient will be readmitted.

Troponin also looks like a good marker of risk stratification in heart failure patients, Dr. Maisel says. If it's high in a patient who's sent home, it indicates lurking subendocardial ischemia. When high-sensitivity troponins become approved for clinical use in the United States, reliance on troponin for risk stratification will increase, he says.

Two other markers have already been approved. Dr. Maisel says he's most familiar with galectin-3, having been involved in multiple research studies involving the marker. Galectin-3, a marker for fibrosis, runs high in 40 to 50 percent of heart failure patients, he says. When a heart failure exacerbation occurs, more collagen is secreted, related to the inflammatory insult. This will lead to slower recovery and prolong demise and likely is important in 30-day readmissions, he says.

Dr. Maisel says at least three published studies (plus data from other studies) suggest that levels above the 17.8 ng/mL cutpoint predict a two to three times higher readmission rate than levels below the cutpoint. It's helpful, too, he says, that galectin-3 levels remain steady. Unlike BNP, which needs to be measured at discharge, rather than at admission, galectin-3 levels at admission can help physicians plan accordingly if the level is high.

If it's high in the ED, he continues, it may indicate a patient should be admitted, rather than treated in an observation unit and then sent home. For inpatients, high galectin-3—along with a high NP or troponin, as well as other indicators of early readmission, such as older age and renal dysfunction—might suggest to physicians that a patient should receive home monitoring as well as quicker uptitration of cardiac medications, says Dr. Maisel. In fact, he adds, the REGAL study, scheduled to begin this summer, will measure galectin-3 in acute heart failure patients; if it's high, they will be randomized either to a control or to spironolactone (an aldosterone blocking agent; aldosterone makes fibrosis through the galectin-3 pathway). "This furthers the notion that you can use a biomarker not just to risk stratify a patient, but to start them on a treatment," says Dr. Maisel, who's involved in the REGAL study.

Dr. Peacock

At Baylor, Dr. Peacock and his colleagues looked at galectin-3 for predicting 30-day outcome. Declining to provide details (they've submitted their work for publication), he says, "There's a cutpoint on that molecule that says you will be alive, guaranteed, in 30 days, with five percent heart failure revisits. That's what I need, because now I know who I can throw out of the hospital early and get my financial benefit from the DRG."

The greatest need for new biomarkers, as Dr. Peacock sees it, is to identify low-risk patients, that is, those who can be sent home safely. Troponin takes care of the high-risk end of the spectrum. "Your troponin is positive, you usually go to the cath lab or you're going to die," as Dr. Peacock puts it.

High-risk markers aren't useful in low-risk patients, Dr. Peacock continues. "When your creatinine is low, when your troponin is low, when your BNP is low, does that mean you're not sick? No! You can drop dead with a normal troponin."

ST2 is the other hopeful. It, too, is FDA approved. It interacts with IL-33, a vasodilator of the heart. High ST-2 levels are bad—it's both a stretch marker as well as an inflammation marker, Dr. Maisel explains. Unlike IL-33, ST2 levels change with treatment. "So it's quite possible—we've actually done this before—that you'd try to titrate down your treatment, both ST2 and BNP, during hospitalization, to make sure you have the best therapy to try to cut down the number of readmissions," he says.

Not yet approved in the United States (though it is approved in Europe) is NGAL, a marker of kidney injury, which occurs about 30 percent of the time in heart failure patients. The GALLANT trial showed that if NGAL and BNP are high when a patient is released, the readmission rate is high, Dr. Maisel says.

"So this is a group of biomarkers that I think will potentially be important for telling us which patients a) should be admitted in the first place, and b) are at high risk, so should get earlier followup and maybe biomarker-guided therapy," says Dr. Maisel.

While it's easy for clinicians to say "Add a marker," Dr. Maisel concedes that doing so places a burden on the lab. To make room for new assays like galectin-3 and ST2 at the San Diego VA, myoglobin and CK were removed from the acute coronary syndrome rule-out menu.

Since troponins and BNP/NT-proBNP are already in wide use, Dr. Maisel says, “Now all we’re saying is just get a couple more, at least maybe one more, before they leave the hospital, so you can identify high-risk patients.” But how many, and when, are unknowns. Dr. Pang, who was part of a roundtable discussion on NPs in 2012 in Chicago, which focused on acute HF and readmissions (Pang PS, et al. Congest Heart Fail. 2012;18[5 Suppl. 1]:S5–S8), agrees that both BNP and NT-proBNP are valuable diagnostically and prognostically. “However, there are data going in both directions in terms of how much serial changes help you, at least in acute heart failure.”

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Labs need to help keep an eye on test utilization, says Allan Jaffe, MD, a clinical cardiologist and professor of medicine and laboratory medicine and pathology, Mayo Clinic, and chair of the Division of Clinical Core Laboratory Services in Mayo’s Department of Laboratory Medicine and Pathology. “It would be easy to run up a big bill running a variety of poorly validated tests. You don’t want this effort to run amuck and be self-defeating, by generating so much lab testing that it is difficult for clinicians to interpret.”

While conceding that individual markers are making strong showings, Dr. Jaffe is pulled inexorably in other directions. If this were a horse race, while smart bettors were laying their money on ST2 and galectin-3, Dr. Jaffe would have wandered away from the track and be asking questions about the racing industry as a whole.

Dr. Jaffe’s fear is that the focus on 30-day readmissions will obscure other, possibly more important issues. In some ways, there’s no point in arguing the issue: CMS has spoken, and hospitals are jumping. But neither is his concern easily dispelled.

Of the heart failure patients who are readmitted 30 days after discharge, says Dr. Jaffe, one- third come back for recurring heart failure. The rest return due to other comorbidities that may not be related to heart failure. Many of these patients are older, he notes, and thus may have abnormalities in kidney function and be prone to falling or to getting infections. While renal function tracks with HF, other factors do not. Many of the HF readmissions might be due to lack of care integration or handling problems coincident with HF when patients are in the hospital, Dr. Jaffe suggests. Nonetheless, the penalties will still be levied. “If you have heart failure stamped on your forehead as your original diagnosis, it doesn’t matter what brings you back,” Dr. Jaffe says. It could be cancer; it could be a bump on the head after a fall. “That’s a readmission.”

“Part of that is unfair, but part of that is fair, too,” Dr. Jaffe says. “Clinicians should care for the patients, not just the disease. Why should we ignore other comorbidities?” Reimbursement for heart failure admission is modest, however, and there is pressure to move patients out of the hospital rapidly. The tension here is clear. In the past, heart failure has been treated as an acute, intermittent disease, he says, but the emphasis may be shifting to treating it as a more chronic disease.

Cardiovascular reasons don’t always drive the readmissions for heart failure patients, Dr. Pang agrees. “Managing the noncardiovascular comorbidities is equally important,” he says. Then, too, there are psychosocial and socioeconomic factors to consider, as well as self-care and health literacy. Dr. Pang calls it the patient’s “total journey,” and labs need to ride along, if for no other reason than financial necessity demands it.

The laboratory link is not tenuous, says Dr. Peacock. “The lab and clinicians are in the same boat on this,” he says, with all sharing the same financial risk. That, indeed, is the strategy behind reimbursement changes—to get everyone not only to recognize they’re in the same boat, but to get them all pulling the same way, he says.

Dr. Jaffe

But what can labs do? Ostensibly, says Dr. Jaffe, they'll help identify patients at high risk for a readmission, and both galectin-3 and ST2 appear to work well for that, he says. But if two-thirds of heart failure patients are being readmitted due to non-HF reasons, focusing on HF biomarkers will be of limited value. And even if they prove to be useful in that narrow setting, says Dr. Jaffe, "I would argue that some of this could be shortsighted." Financial pressures have made 30 days the magic number, he says, "But what you'd really like to know is whether the patient has a marker that will help the patient not only at 30 days but longer term as well. We've got it turned around—we're asking for a marker that will help save the system money."

With the move-'em-out approach still dominating HF treatment, there's no telling how patients might fare if they're kept longer and treated more effectively. "Maybe that solves the problem, and you wouldn't need these markers. Because maybe the markers are simply telling you who's substantially sick," Dr. Jaffe says.

Not that there's ample data to suggest that keeping patients longer will lead to better outcomes. "So we're trying to play this both ways," Dr. Jaffe says.

Even if galectin-3 and ST2 identify patients at risk, then what? What do you do with these at-risk patients?

Most patients seem to respond nicely to aldosterone antagonists. Dr. Jaffe says these agents have been advocated for use in high-risk patients for years, but have been substantially underused, for two reasons. One, they cause a rise in potassium. Two, the traditional agent, Aldactone (the aforementioned spironolactone), causes gynecomastia in some male patients. Dr. Jaffe offers no opinion about the legitimacy of these reasons, simply saying, "Maybe these tests [for galectin-3 and ST2] will get people to overcome that."

He's more focused on another question: Are the agents good for everyone? If so, he says, testing will be unimportant. And even if they work perfectly in the one-third of heart failure patients whose readmissions are HF-related, that still leaves two-thirds of returnees who will need care that's more integrative. At his institution, such care includes bringing HF patients back for a followup visit one week after discharge.

Dr. Singer sees hospitals trying to develop standardized approaches to treating heart failure patients. This might include set criteria as to who gets discharged, who gets admitted, and who gets moved to the next level of care, as well as titrating medications based on weight, renal output, etc. While not focusing on new markers, such approaches could help ensure that current markers are used more efficiently.

Dr. Pang

Dr. Pang says his colleagues are looking at measures that are known to be effective but often overlooked. "In the past, people might check the box saying they'd given discharge instructions," says Dr. Pang. But, he notes, handing out instructions and making sure patients understand them are two different things.

Labs are also joining in, says Fred Apple, PhD, medical director, clinical laboratories, Hennepin County Medical Center, Minneapolis, and professor, laboratory medicine and pathology, University of Minnesota School of Medicine.

In attending clinical directors' meetings at Hennepin, he says, it quickly became apparent to him that physician test ordering, including for heart failure, was often more quirky than uniform.

Such insights have led the lab to make changes in troponin ordering, for starters. Later this summer, he says, the lab plans to limit order sets (0, 3, 6, 9 hours) for troponin to one. Should an attending physician want to order a second set, they'll have to justify it via computer validation. If house staff want a second set, they'll need to confirm that their attending or a cardiology fellow approved it. "We do about 30,000 troponins annually," Dr. Apple says. "I think we'll be able to save 10,000 orders a year."

Heart failure testing will be next. In early summer the lab did an EPIC survey to identify NT-proBNP ordering patterns and look for places to cut back on unnecessary testing. "We have to be more rigorous in understanding why they're ordered and maybe challenge some of the orders indirectly. This is being driven by the office of the medical director with—in this case—my help," Dr. Apple says. "Why do you have a three-day standing order set when you only need a two-day standing order set? You have to ruffle some feathers among clinicians."

"It's surprising," Dr. Apple continues, "when you start doing it, how much waste you see."

The waste might stem, in part, from clinicians who neglect biomarkers' limitations. That's the case even with BNP and NT-proBNP, which have a long history of clinical use. Both, over the years, have followed the familiar trajectory. "When they first came out," says Dr. Singer, "this was the perfect test: If it's positive, you have heart failure; if it's negative, you don't have heart failure. And just like with any other thing in medicine, as time goes by, people find out that, yes, it's helpful—but." The "but" with NPs is that while they're good at the low and high ends of, respectively, ruling out and ruling in HF, they're less useful in the middle zone, where many patients fall.

Unfortunately, says Dr. Singer, not all clinicians appreciate those limitations. "I think there are still people who are relying solely on biomarkers to make a diagnosis," he says, "and of course that's a mistake." Or, as Dr. Peacock likes to say, "A fool with a tool is still a fool."

Dr. Apple says that he and Dr. Wu did a survey on who ordered BNP when the test first became available: 40 percent of orders came from the ED, 40 percent from cardiology, with the remainder from other locations. Dr. Apple recently repeated the survey with a Hennepin resident. The ED still accounted for 40 to 45 percent of orders, "which makes sense," Dr. Apple says. Cardiology had dropped to 10 to 20 percent, a decline Dr. Apple attributes to cardiologists "learning how to order the test." Now, he found, family practitioners are ordering the remainder of tests—and likely inappropriately, he says. He explains: "We're trying to cut back on how many orders we get. Instead of following the NP number (concentration)—which is what family practitioners may be doing—we want to follow the patient's clinical course."

In short, new biomarkers, though they might prove helpful, won't solve even older problems.

And if a new biomarker does prove its worth, gaining traction takes time, given the usual marathon of educating clinicians about its use. Apart from the clinical evidence—no small matter—much depends, says Dr. Pang, on how compelling the problem is, and how striking the resultant benefit would be.

Thanks to the new CMS penalties, however, the problem of heart failure readmissions looks freshly compelling, as do the potential benefits of reducing them. As Dr. Apple puts it, "If there's a financial incentive, there will be a focus."

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