A New Analysis of the COURAGE Trial

Experts weigh in with their opinions of a new analysis looking at crossover patients.

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What are the main take-home points from the recent analysis of the COURAGE trial?

Dr. Spertus: A criticism raised by many is that, in the COURAGE trial, a significant number of patients who were randomized to receive medical therapy alone were crossed over to angioplasty, and that is part of the reason that the results did not more strongly favor angioplasty. We wanted to understand which patients crossed over early (within 1 year) and if there were any adverse consequences by delaying angioplasty. This is important because, until the COURAGE trial, it had been common practice to offer angioplasty once significant coronary disease was discovered.

We found that 16% crossed over in the first year. This is different from the widely quoted 33% rate of crossovers, which included patients in the medical group who underwent revascularization throughout the entire period of follow-up. However, if a patient crosses over at 4 or 5 years, it may be due to progression of the disease in other vessels, rather than the vessel that you were concerned about when you first enrolled the patient into COURAGE. The critical period that seems to indicate that you made the wrong decision by offering medicine alone is during that first year of therapy. We found that only one in eight patients crossed over in that first year, and the strongest predictors of crossing over were persistence of symptoms or dissatisfaction with the treatment during randomization for angina.

Finding that patients dissatisfied with their angina treatment were more likely to cross over early makes a lot of sense. If you were already unhappy with your medical treatment and were randomized to continue on medications, it makes sense that you would be unhappy. Such a patient would surely be more likely to cross over than someone who was satisfied with their treatment prior to randomization.

Another critical variable that was associated with early crossovers was the health system in which the patient was treated. The Veteran's Administration (VA) tended to have the fewest crossover patients, Canada

ANALYSIS OF COURAGE CROSSOVER PATIENTS SUPPORTS AN INITIAL TRIAL OF OPTIMAL MEDICAL THERAPY FOR STABLE ISCHEMIC HEART DISEASE

July 9, 2013—An analysis of the frequency, predictors, and consequences of crossing over to revascularization within 12 months of randomization to optimal medical therapy (OMT) in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial was published by John A. Spertus, MD, et al on behalf of the COURAGE trial investigators and coordinators in *Circulation: Cardiovascular Quality and Outcomes* (2013;6:409–418).

In the COURAGE trial, some patients with stable ischemic heart disease randomized to OMT crossed over to early revascularization; however, the predictors and outcomes of these crossover patients are unknown, noted the investigators.

As summarized in *Circulation: Cardiovascular Quality and Outcomes*, the COURAGE investigators compared characteristics of OMT patients who did and did not undergo revascularization within 12 months and created a Cox regression model to identify predictors of early revascularization. Patients' health status was measured with the Seattle Angina Questionnaire (SAQ). To quantify the potential consequences of initiating OMT without percutaneous coronary intervention (PCI), the investigators compared the outcomes of crossover patients with a matched cohort randomized to PCI.

The investigators reported that among 1,148 patients randomized to OMT, 185 (16.1%) underwent early revascularization. Patient characteristics independently associated with early revascularization were worse baseline SAQ scores and health care system. Among 156 OMT patients undergoing early revascularization matched to 156 patients randomized to PCI, rates of mortality (hazard ratio, 0.51 [0.13–2.1]) and nonfatal myocardial infarction (hazard ratio, 1.9 [0.75–4.6]) were similar, as were 1-year SAQ scores. OMT patients, however, experienced worse health status over the initial year of treatment and more unstable angina admissions (hazard ratio, 2.8 [1.1–7.5]).

The investigators found that among COURAGE patients assigned to OMT alone, patients' angina, dissatisfaction with their current treatment, and, to a lesser extent, their health system were associated with early revascularization. Because early crossover was not associated with an increase in irreversible ischemic events or impaired 12-month health status, these findings support an initial trial of OMT in stable ischemic heart disease with close follow-up of the most symptomatic patients, concluded the investigators in *Circulation: Cardiovascular Quality and Outcomes*.

was in the middle, and the non-VA sites in the United States had the most crossovers, which is congruent with practice patterns because the non-VA United States sites tended to be the most aggressive.

Another critical finding in this study was our effort to explore possible adverse consequences of delaying angioplasty (ie, trying medicines for a while and only crossing patients over if they fail medical therapy). In fact, we found no differences in survival nor in heart attacks. There were more episodes for unstable angina, but that's part and parcel of not being able to control your angina well enough with medicines alone.

We did find, however, that during the first year of therapy, patients who crossed over had worse angina, more physical limitations, and worse quality of life within that year of therapy, until they crossed over. However, by the time 1 year came around, they were no different than the patients who were offered angioplasty up front.

My interpretation is that if patients have significant coronary disease, optimal medical therapy should be tried first. If the disease is not adequately controlled with the medicines alone, I would then offer angioplasty, knowing that even though the medicines alone didn't work well enough, I haven't put them at an increased risk of dying or having a heart attack by taking a more conservative strategy.

Dr. Fearon: My main take-home point is that patients with coronary disease and stable angina shouldn't all be lumped together as one group. There is a spectrum, and some patients who have less severe disease, smaller amounts of ischemia, and milder symptoms will likely do just as well, if not better, with medical therapy alone. However, on the other end of the spectrum, there are patients who have more severe disease, a larger burden of ischemia, and more severe symptoms. This analysis suggests to me that this latter group of patients may benefit from percutaneous coronary intervention (PCI) earlier on in their treatment instead of trying medical therapy alone.

Dr. Brindis: I think that the main take-home point from this analysis of COURAGE is twofold. The first point is that we probably can do better at identifying patients up front who would fail medical therapy and

may want to utilize an earlier strategy of revascularization. I think what's fascinating here is that assessing functional status (in this case, using the Seattle Angina Questionnaire) has proven to be a valuable tool for such cases. We surely have to acknowledge Dr. Spertus' leadership in the creation of the Seattle Angina Questionnaire tool.

One of the challenges that we face as clinicians as we try to implement appropriate use criteria (AUC) for coronary revascularization is the poor quantification and documentation of symptoms such as anginal burden in patients with coronary artery disease. For example, AUC for coronary revascularization have turned out to be a major challenge to properly apply, because frequently, the actual angina status of the patient is not being adequately documented in the medical record.

The second key point is that we're in an era of trying to truly implement shared decision making as a key component of patient-centered care. In fact, I serve on an RO1 grant that is working on creating an evaluation tool so we can assess the actual success of patient decision-making strategies from the patient's perspective. Shared decision making is kind of a warm fuzzy term that we all may endorse, but the actual assessment of what is good shared decision making is more than fuzzy, and we don't really have a good tool to do so yet.

However, it is clear, particularly to interventional cardiologists, that shared decision making is a very important part of how we approach patients with stable angina and coronary artery disease. This gets back to adequate documentation of patients' quality of life and symptom burden as it is related to their angina with coronary disease.

Do you think this analysis will affect current practice patterns?

Dr. Spertus: I think that it could give physicians the confidence to try medical therapy without worrying that their patients are at increased risk by not offering them angioplasty right away. My hope is that if you are seeing a patient who becomes very symptomatic and you then diagnose significant coronary disease, that you will follow them a little bit more closely because they may need angioplasty during the first year of treatment. If medical therapy is failing to control their symptoms, then you want to be sure to offer angioplasty promptly.

Dr. Fearon: I think these findings should highlight and remind us of the importance of risk stratifying patients with stable coronary disease. Perhaps we should be more aggressive with early PCI with some patients (ie, those who have more severe symptoms and a poorer quality of life), and be more conservative in those with less severe symptoms by starting them on medical therapy alone.

Dr. Brindis: I hope that as clinicians and patients work together to try and figure out the best treatment strategies, better quantification of symptom burden will be pursued by clinicians in their subjective assessments. That may, indeed, lead to more patient-focused, effective delivery of care. One of the challenges is that although the preface to the AUC document discusses shared decision making and patient preference, one could argue that our actual AUC clinical scenarios do not adequately incorporate patient decision making. The AUC do of course incorporate anginal burden, but there is not an embedded patient-shared decision-making aspect in implementing a treatment strategy. I'm hopeful that the understanding of symptom burden and its adequate documentation in the patient's medical records will not only lead to better care, but may even lead to novel changes of some of our AUC in clinical scenarios.

Do the AUC need to be updated based on these results?

Dr. Spertus: I think the results are fairly supportive of the AUC. I don't see it as being incongruent with what the AUC recommend, so I don't think they'll change much.

Dr. Fearon: I'm not sure because they already incorporate symptom status, but there may be some patients who have significant symptoms who are on no or minimal therapy who were previously graded as uncertain or less appropriate. This may shift them to a more appropriate grade. Based on the fact that patients with severe symptoms seem to cross over rather quickly, it may be more appropriate to treat them up front with PCI.

Dr. Brindis: AUC is still a science in its awkward adolescence. We are seeing continued improvement in the process of creating AUC for coronary revascularization that reflects updates or changes related to randomized clinical trials and studies. We are also growing in our own understanding of how AUC are implemented and its effect on practice patterns.

To this point, we've already had one revision of our AUC from the initial publication in 2009, we had a follow-up publication in 2012 that updated clinical scenarios, and we are presently undertaking a third update. We have received more than 1,100 comments and

critiques from both the interventional community and the surgical community that are now being evaluated for potential direction for the writing group overseeing this AUC update to be published next year.

I would say that this particular COURAGE analysis would factor into that update, but I certainly have no prediction in terms of how/if it may directly affect any of the specific clinical scenarios.

Do you think that people will be surprised by the results of this analysis?

Dr. Spertus: It depends on whom you talk to. For a lot of the interventionists who had railed against the crossover rate, I think they'll be surprised and hopefully feel that the care being given is not inferior with a medication-first approach. I hope it will bolster those who have maintained a more conservative approach to managing coronary disease.

Dr. Fearon: I doubt anyone is going to be surprised. The analysis suggests that it's reasonable to incorporate additional factors, such as the severity of symptoms and quality of life, into our decision making about treatment strategy. However, I think most of us would have anticipated that patients with more severe symptoms would be more likely to cross over and require revascularization sooner than those who were less symptomatic.

Dr. Brindis: I don't think so. What I would like to say, and the interventional community talks about this a lot, is that although the COURAGE trial is an extremely important trial and has offered great value to the clinical community in managing these patients, there are a lot of unanswered questions related to patients with stable angina. This reflects upon the entire methodology of the COURAGE trial, in which the patients were randomized after an initial diagnostic catheterization, that a huge number of patients were excluded from randomization, and that patients and clinicians having that coronary catheterization data in front of them may have resulted in refusal to participate in the randomization process.

One of the challenges we have with this study of COURAGE is that it cannot be broadly applied to all patients with stable coronary disease. It is not fully applicable to compare our patients to those who never had a diagnostic catheterization and never underwent randomization. In fact, I would like to use this opportunity as a plea to our readers in the interventional cardiology community to strongly consider participating in the ISCHEMIA trial, which I think will answer many of the unknown questions here. I believe we still have substantial equipoise in the management of stable angina. The ISCHEMIA trial has a very ingenious methodology that studies patients who have undergone noninvasive testing and were shown to have findings of myocardial ischemia involving > 10% of their myocardium and who are then randomized to optimal medical therapy or early catheterization. These randomized patients will also undergo CT angiography at the actual study site, with the patient and physician blinded as to the patient's CT angiography findings.

The study's central core CT angiography reading center will be able to screen out patients who, for example, have no coronary disease, as well as those who have left main disease in which the data are quite good for revascularization. Those patients whose CT angiogram demonstrated normal coronary arteries and left main disease will have their results shared with the treating clinicians so that they can be managed accordingly. Therefore, the ISCHEMIA trial will truly randomize patients with stable angina and significant ischemia but who do not have critical disease or no significant coronary disease.

I think ISCHEMIA is a fascinating study because we still don't really understand how best to manage these patients. Again, it will add substantial value to the important lessons from the COURAGE trial that do not necessarily apply to all of our patients with stable coronary disease.

What role did patient dissatisfaction play in this analysis, and why?

Dr. Spertus: I think it is a reflection that many patients were being managed with chronic medical therapy when they were enrolled into COURAGE. If they were unhappy with their current treatment approach to coronary disease, then they're presumably going to remain somewhat unhappy if they were randomized to continue medical therapy alone. They will then be more likely to return to the doctor to complain, often leading the doctor to offer more aggressive treatment to help them (ie, angioplasty).

Dr. Fearon: I think this is a key point. To some patients, I think quality of life is just as important, if not more important, than quantity. Clearly, death and myocardial infarction are important endpoints, but I don't think we should forget about how the patient feels. We perform a number of noncardiac surgical procedures (eg, orthopedic procedures) to improve quality of life, but which have no effect on rates of death or myocardial infarction.

I think that if PCI only improves quality of life but does not change the rate of death or myocardial infarction, this should not necessarily diminish its value as a treatment strategy. In my opinion, sometimes we focus too much on these hard endpoints. This study reminds us that quality of life is important, and it is a big driver in decision making—and rightly so.

Dr. Brindis: This study truly assesses and validates the role of patient feedback and patient satisfaction for treatment strategies in the management of stable angina. It was clear in this study that patients who have high symptomatic burden or difficulty or challenges taking medications are unhappy. Those are the patients who were predicted to cross over to angioplasty.

Again, if we could try to predict this up front, we may be able to cherry pick patients who might be best to undergo an earlier revascularization strategy; that may be the best answer for them in terms of their own quality of life.

This analysis provides some guidance to predict which patients will cross over from optimal medical therapy. How likely are you and your colleagues to consider PCI as the initial treatment for these types of patients?

Dr. Spertus: My approach, even in symptomatic patients who have stable coronary disease, is to try medication first. If medical therapy alleviates their angina and improves their quality of life, then I'm very happy and will stop there. I take this approach because if I were to recommend an invasive revascularization approach without first trying medications, and then something goes wrong during the procedure, I would feel terrible. I would wonder, as I reflected on that patient's care, "What if the medicines had worked? Did I do the wrong thing by going straight to angioplasty?" In contrast, if I try medicines first, and they fail to control the patient's symptoms, then I would know that if something bad happens during PCI, I did try everything I could to avoid the procedure but the patient ultimately needed it.

Dr. Fearon: The authors argued that even though the more symptomatic patients cross over more quickly, there was still no harm because they didn't see a difference in death and myocardial infarction rates. However, these patients did feel worse, had higher rates of unstable angina, and tended to have higher rates of myocardial infarction. I do think that in these patients, who are more symptomatic, we should consider being more aggressive in our approach to treatment.

There are some data from the FAME II trial demonstrating that patients who present with stable coronary disease, which is associated with an abnormal fractional flow reserve, derive benefit from up front PCI in that these patients have significantly lower rates of unplanned hospitalization requiring urgent revascularization. Recently, an economic evaluation of the FAME II trial showed an attractive cost-effectiveness ratio to this approach of PCI first, when guided by fractional flow reserve. I think in my practice, this would tend to make me more aggressive in my approach to these types of patients.

Dr. Brindis: There is a strange phenomenon going on in the United States right now, and that is the increased scrutiny by external agencies and external stakeholders of the practice of interventional cardiology in terms of concerns of overstenting or inappropriate stenting, particularly in patients with stable angina. I'm not talking about issues of fraud, I'm talking about the issues of overuse.

The role for AUC for coronary revascularization was set forth by professional societies to help aid clinicians by using it as a population-based tool to view practice patterns in a benchmarked form to be able to assess one's treatment strategies in comparison with their fellow interventional cardiologists.

Payers are now feeling increasingly empowered in their efforts to bend the cost curve. The AUC is now being used in a manner to potentially deny payments on an individual case-by-case basis as opposed to utilizing AUC as a population tool assessing practice patterns as a method to improve care.

When payers do this, it concerns clinicians in the interventional community that they're ignoring the issue of patient preference, shared decision making, and issues of anginal burden, which this crossover analysis has shed substantial light on. Maybe this analysis can help us in our interactions with payers so that they think about the AUC more as a population-based tool as opposed to guidelines to allow denial of payment.

How important was the type of health care system in the use of early revascularization?

Dr. Spertus: I can't answer that perfectly, but my guess is that these different practice environments have different cultures of care. Across the three systems, the VA tends to be the most conservative. The doctors there are somewhat more prone to evidence-based practice. I don't mean that disparagingly of those who aren't at the VA; I think that in my anecdotal experience, there's a tremendous focus on providing guide-

line-based care as if those are the clear rules. In the non-VA United States sites, we tend to be a little bit more aggressive with treatment, and Canada is somewhere in between. I think it's just a cultural difference that is reflected in the way they operate.

Dr. Fearon: There are a few potential contributing factors. The patient populations may be different between the different health care systems, with some groups less tolerant of symptoms compared to other groups and therefore pushing more for alternative therapy. The physician's willingness and/or incentive to perform PCI may be different, and this may also affect the outcome. Finally, I think there could be differences between the health care systems in terms of the availability of resources, which may have had an impact on the outcome as well.

Dr. Brindis: This does not surprise me. Certainly, we know the differences related to practices in Canada versus the United States in terms of the presence of significant coronary disease found on diagnostic catheterization, as well as in the prevalence of revascularization. I have just retired from Kaiser Permanente, but within this system, our utilization of revascularization strategies is certainly less than outside the Kaiser community. Yet, if you're a Kaiser Permanente patient in Northern California, your chance of dying related to cardiovascular disease is 30% less than if you are a non-Kaiser patient (even when adjusted for patient age and sex). That reflects what we've learned from the article by Ford et al[1] that was published earlier this decade: the most important aspects that led to the decreasing mortality from coronary disease came from aggressive utilization of primary and secondary prevention measures for treating the disease and the relevant related risk factors with the appropriate medications. Coronary revascularization, although clearly important, represented a minority of the reasons for the decreased mortality in coronary artery disease over the recent decades.

No matter which system we're in, whether it is globally capitated, a fee-for-service environment, or a VA environment, all physicians are trying to do what is best for their patients. However, we each have a different perspective and, in all honesty, practice in different reimbursement systems that may influence the delivery of care. ■

1. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary eisease, 1980–2000. N Engl J Med. 2007;356:2388–2398.