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Perspective Roundtable: CABG vs. Stenting: Clinical Implications of the SYNTAX Trial.

DR. THOMAS LEE: Welcome to a Perspective Roundtable of the *New England Journal of Medicine*. I'm Tom Lee, an associate editor of the *Journal*. And today I'll be here with two of my colleagues, discussing a trial that's just being released at the *Journal's* Web site, the SYNTAX trial, which compares the impact of coronary-artery bypass graft surgery and percutaneous coronary intervention in patients with severe coronary disease.

On my right is Dr. David Hillis, chairman of medicine at the University of Texas Health Science Center at San Antonio. And on my left is Dr. Elizabeth Nabel, who's director of the National Heart, Lung and Blood Institute. Welcome to our Perspective Roundtable. And thank you for your insights today. Dave, why don't we start with you. And can you give our viewers a high level summary of the trial and the key results?

DR. DAVID HILLIS: This was an international, multicenter, randomized, controlled comparison of bypass surgery, CABG, versus PCI with drug-eluting stents in 1800 patients, all of them with left main or three-vessel coronary artery disease. They were randomized, as I mentioned, to one of those two therapies. They were then followed for one year, 12 months. And during that 12 months, the authors looked for an adverse event. Adverse events were defined as one of four: number one, all cause death; number two, myocardial infarction; number three, stroke; and number four, repeat revascularization. So, it was a combined end point of any one of those four events occurring within 12 months of randomization.

The main bottom-line results of the study was that, at one year, about 12% of the CABG patients had had one of these four adverse events. In contrast, 18% of the PCI patients had had one of those adverse events. So the bottom line conclusion of the authors was that CABG remains the standard of care for patients with left main and three-vessel coronary artery disease.

DR. LEE: Well, for people who just read the last couple lines of an abstract, that would be the message they walk away with, is that CABG seems to be the better approach. But it's more complicated than that. And Betsy, why don't you help us pick apart the outcomes that are used in this trial a little bit more.

DR. ELIZABETH NABEL: If we look at the primary end point, which Dr. Hillis articulated was a combination of death, MI, stroke and the need for revascularization, if we drill down further, there was no difference between the two groups in death, MI, and stroke at one year. The primary end point was really driven by an increased need for revascularization in the PCI group. So that is an important distinction that we must remember. Furthermore, if we look at the complication rate, there was a 1.6% higher incidence of stroke in the CABG group, compared to the PCI group.

DR. LEE: Dave, I'm going to ask you, make that argument that CABG is the standard of care, the first choice for patients with severe coronary disease.

DR. HILLIS: Tom, I think that for patients with left main and three-vessel disease, CABG is certainly still the treatment of choice. The more complex the coronary anatomy — that is, the higher the SYNTAX score — the better the patients did with CABG as opposed to PCI. If the SYNTAX score was low, the two therapies seemed similar to one another.

Now secondly, I think it is important that patients who undergo CABG be treated with intensive medical therapy. One of the reasons that the stroke rate may have been higher in the CABG patients than in those randomized for PCI, was that the CABG patients were not treated as intensively with platelet inhibitors, ace inhibitors, and statins. So, if the patients go to surgery, one should not neglect their medical therapy.

DR. LEE: And Betsy, the case for thinking first about coronary intervention?

DR. NABEL: I think that there are patients who have complex coronary anatomy who would prefer to undergo PCI. They would prefer to accept the possibility of requiring a repeat revascularization, but do not want to subject themselves to an increased risk for stroke or to an increased recovery time that might occur from a sternotomy. So in this case, cost and quality of life might be important issues that would sway them towards preferring PCI.

DR. LEE: So, in the real world currently, I guess one reason why a lot of patients are getting the strategy not recommended by the conclusion, that is, going right to angioplasty, is the decisions are being made while the patient is lying on the table. But, in this case, there was time to step back and weigh both.

DR. HILLIS: Absolutely. I think it's an important point of the study, and that is, that what they referred to as a — quote, unquote — heart team sat down and, in a very detailed fashion, did a complete and thorough evaluation of each patient, including the patient's angiogram, after — and this team was composed of a cardiac surgeon and an interventional cardiologist. And they came to a consensus agreement on which of the two therapies would be better for that individual patient. In other words, the intervention was not done at the same time, or linked closely in time to the angiogram.

DR. LEE: Now Betsy, this trial was not funded by the NHLBI. This trial was funded by a manufacturer of drug-eluting stents. So one of the first things that a lot of readers do is look — could that have influenced the design of the trial in any way? What's your comment on that?

DR. NABEL: I think two points are salient, Tom. First is the trial design actually stacked the cards against the PCI intervention by combining both the hard end points of death, MI, and stroke, and the soft end point, the need for revascularization, into a combined primary end point. If the trial design had separated those end points, the primary end

point would have been equivalent, and there would have been a difference in the secondary end point. So, in other words, the device manufacturer, in some ways, stacked the cards against themselves.

But the second important point is this study is an example of comparative effectiveness research, which is receiving a lot of attention in Washington, DC, these days. Comparative effectiveness research is a rigorous evaluation of two different types of treatments or two different approaches towards the same medical condition and evaluates the effectiveness of both of those approaches. We're going to see much more research in this area coming down the pike. But I think the industry is to be congratulated for conducting this type of heads-on comparison in the manner in which they did.

DR. LEE: The pro-angioplasty approach points out the 1.6% higher stroke rate in bypass surgery. But when you really started looking carefully at, you know, Table 3 of the paper, which has the outcomes in some detail, the cardiac mortality is 1.6% higher in the angioplasty group than the bypass group. The total mortalities are similar, but the cardiac mortality is higher. Your comments on that?

DR. NABEL: Well, I think it's an interesting debate, Tom. On the one hand, CABG led to more complete revascularization with a higher stroke rate and, I'd also point out, a higher noncardiac mortality rate. On the other hand, we know PCI leads to less complete revascularization, perhaps a numerical difference in cardiac mortality, but a smaller stroke rate, and certainly easier on the individual, in terms of procedure recovery time and other factors.

I think subsequent studies will be looking at greater detail the differences between these groups and these factors, looking at cost-effectiveness, as well as quality-of-life issues. It may be that we're really — what we're coming down to, Tom, is a discussion between the patient and the medical and surgical team, really focusing on patient preferences, complexity of coronary anatomy, and potential risks and benefits, depending upon their medical state and their comorbidities.

DR. LEE: Well Betsy, there are a lot of unanswered questions, clearly. And you probably have as good or better insight than anyone in the country about what's coming, in the way of new trials to address those questions. So your summary of the big questions that need to be answered, and the trials that might answer them for us?

DR. NABEL: The NHLBI is now sponsoring the Freedom trial, which is a head-on comparison in diabetic patients between CABG and PCI. In this study, the primary end point will be the hard clinical end points of death, MI, and stroke. And need for revascularization will be a secondary end point. There will be intricate neurological assessments at various times along the study, so that we can get not only the stroke rate, but more subtle cognitive effects that might occur as the result of CABG or PCI.

In addition, we'll be looking at cost-effectiveness and quality-of-life measures in patients receiving both therapies. And finally, we'll have a 4-year follow-up period, so that we'll be able to see the outcomes over a longer period of time. So again, we need to understand, particularly in diabetic patients, whether CABG versus PCI achieves improved clinical outcomes.

DR. LEE: Well, you know, the issues are complicated. Medicine's complicated. And I think that patients should have a chance to articulate their preferences and weigh the risk of stroke versus risk of other kinds of outcomes. The SYNTAX trial will surely make those discussions much more informed and probably make them happen much more reliably. And I want to thank you two for your comments, because I think that they will help guide many of our audience members in those discussions. Thanks very much.