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Key Words: percutaneous, CABG, PCI, low EF

Discussion
Presenter: Dr Ibrahim Sultan

Dr John D. Puskas *(New York, NY)*. Good morning, and congratulations to Dr Sultan and his colleagues from the University of Pittsburgh Medical Center on their study that addresses an important question, namely whether coronary artery bypass grafting (CABG) imparts superior survival and freedom from major adverse cardiac and cerebrovascular events (MACCE) compared to multivessel percutaneous coronary intervention (PCI) in patients with left ventricular ejection fraction (LVEF) <50%. They've analyzed an institutional database over 7 years, including patients who had either multivessel PCI by a single-stage approach or isolated CABG. They identified 324 propensity-matched pairs, and demonstrated that the baseline characteristics are well balanced, with a median LVEF of 38%.

While 30-day mortality was similar between groups, overall mortality during a median 3.2 years follow-up was

significantly higher for PCI at 37%, versus CABG at 21% with a significant *P* value. Total and cardiac-related repeat hospitalizations during follow-up were approximately twice as frequent in the PCI group as in the CABG group. Myocardial infarction occurred in 7.7% of PCI patients during follow-up, and in 1.8% of CABG patients—a more than 3-fold difference in favor of CABG, with a highly significant *P* value. Similarly, MACCE and repeat revascularization were approximately twice as frequent after PCI as after CABG. Multivariate analysis confirmed these results generating hazard ratios of 0.52 for mortality, 0.5 for MACCE, and 0.35 for repeat revascularization in CABG versus PCI.

Of course, these results are music to the ears of coronary surgeons, and are consistent with a very recent report from Ontario by Sun and colleagues published in *JAMA Cardiology* online just a couple weeks ago. Those Canadian investigators retrospectively reviewed the Ontario provincial database, selected data from patients with multivessel coronary disease and LVEF <35% who underwent PCI or CABG over an 8-year period ending in 2016. They found a total of approximately 12,000 patients, used propensity matching on 30 baseline characteristics, and generated almost 2400 propensity-matched pairs, demonstrating a CABG hazard ratio of 0.62 for mortality, 0.71 for cardiac mortality, 0.5 for MACCE, 0.27 for repeat revascularization, and 0.31 for repeat hospitalization for myocardial infarction, CABG compared with PCI. Of course, all of these were statistically significant and consistent with the findings from the University of Pittsburgh Medical Center study presented today.

So, Dr Sultan, I have 4 questions and will ask them 1 at a time.

Why were patients who had multivessel PCI by a staged approach, which is very commonly used in multivessel disease, excluded from your study? Including patients who had multivessel PCI by a staged approach would have certainly changed the ratio of PCI to CABG in your initial sample population of all revascularization procedures. Could that exclusion criteria have introduced selection bias or other confounding into your retrospective trial?

Dr Ibrahim Sultan *(Pittsburgh, Pa)*. Thank you, Dr Puskas. I really appreciate your summary and your questions. The reason we excluded those patients is because a lot of times those patients are not necessarily intended to be treated as staged PCI, and it is challenging to tell that retrospectively. Perhaps the plan could have been to stent the left anterior descending artery in a certain patient and follow the circumflex disease or right coronary disease medically, and not necessarily treat that. However, at a later time if the patient were to experience myocardial infarction or a persistent angina, then that patient may end up getting PCI again. That was a big confounding factor that we wanted to avoid.

We wanted to try to keep the groups as similar as possible. That was the primary reason we wanted to go with a single-stage approach.

Dr Puskas. Second question. What definition of myocardial infraction was used for PCI and for CABG? Was it the same definition for early periprocedural infarcts as for later follow-up infarctions during prolonged follow-up? Did the definition that was chosen favor CABG? Of course, you report a threefold higher rate of myocardial infarction in PCI than in CABG, which is frankly unusual. Especially early on when we see a periprocedural cardiac enzyme release that's higher in PCI than in CABG, we wonder about the definition used or some kind of selection bias, because that is an unusual finding.

Dr Sultan. Yeah, I think there's definitely selection bias. In fact, I think particularly in the periprocedural setting because biochemical markers are not consistently measured for post-CABG patients. I think a lot of those patients were left out. I don't think that that's a good representative of what the difference is in periprocedural myocardial infarction, and we didn't really focus on that in the manuscript either.

However, myocardial infarctions in follow-up were determined based on universal definition—biochemical and electrocardiogram evidence—that is what was used. We corresponded that with the diagnosis codes when the patients were admitted.

Dr Puskas. Very good. Third, are there any other biases that you think might have been influencing the result of your study? In particular, could the heart team at University of Pittsburgh Medical Center have systematically assigned more sturdy or hardy patients to CABG, and less hardy or more frail patients to PCI? Your propensity score matching was on 16 characteristics that did not include specific metrics of frailty. Is this another potential source of selection bias? Again, I note that your 30-day mortality was numerically higher in the PCI group than in the CABG group, not significant from a statistical point of view, but it is unusual that 30-day mortality would be higher in the PCI group than in the CABG group in a PCI versus CABG comparison. We expect to see that over a longer-term follow-up, but rarely do we see that at 30 days. Is this evidence of unbalanced or unadjusted selection bias?

Dr Sultan. Yeah, I completely agree. I think there's definitely a selection bias. Frailty was not appropriately coded in our data sets and that's why we do not utilize it, and I think that's a huge confounding factor that would allow us to not necessarily pick the frail patients for CABG. I think that's number 1.

The other thing that's not accounted for are targets. For instance, if the surgeons believed that the targets were poor and the patient may not get complete revascularization, that's another group of patients which may have been diverted toward PCI. I think what we've done over

the past year is, any patient who is considered high-risk, which may be because of severely reduced ejection fraction or a variety of other baseline factors is then discussed within the team of surgeons themselves who are not part of the patient's care who then take a look at the patient's angiogram and clinical characteristics, and then make an independent adjudication of whether or not that patient should really have CABG or PCI to really minimize these kind of confounding errors.

Dr Puskas. Don't get me wrong. I personally am very much in favor of assigning more frail patients to PCI and more sturdy patients to coronary bypass. I think that that parses out the relative risk and benefit appropriate among our patients and that 30-day outcome from your study may indicate that your heart team is doing its job.

Last question: in conclusion, Dr Sultan, I think your data are compelling. Are they compelling enough to change referral patterns in clinical practice at University of Pittsburgh Medical Center? If so, then by what mechanism would that change occur? And if not, why not, and what should then be done? Congratulations and thank you.

Dr Sultan. Thank you, Dr Puskas. This started off as a sort of a quality improvement internal audit for us for the heart team. This has now launched into multiple research questions and manuscripts. We've looked at majority of subsets with patients who had multivessel disease, not just the reduced ejection fraction, but patients who had diabetes, patients from a gender perspective, from an ethnicity perspective, socioeconomic perspective, and of course multi-arterial versus third-generation stent. From every single subset, CABG appears to have a survival benefit for overall survival and for MACCE. I do think referral patterns may change from primary cardiologists. I think there's a much more vigorous discussion because I think it's 1 thing for us to read a manuscript from another institution and make judgments on that or give that information to patients, but when it's our own patients that we have taken care of and we know what those results look like, I think we're much more honest with ourselves and I think that goes a long way.

Dr Marc Ruel *(Ottawa, Ontario, Canada)*. Ibrahim and John, I thought this was an excellent discussion. It adds to the weight of evidence that we increasingly have gained regarding the role of CABG versus PCI in revascularization of coronary artery disease patients with depressed ejection fraction.

In this regard, there's definitely a selection of patients that may occur, and as such it is possible that surgery patients might be more cherry-picked than patients who are relegated to PCI. One way that we can methodologically address this was utilized in our *JAMA Cardiology* piece—and I think, Ibrahim, that this might be something feasible within your University of Pittsburgh Medical Center database: it was to examine falsification end points. Essentially, this method helps you decipher whether patients are frailer in 1 group versus another. For instance, are events that are not mechanistically related to revascularization occurring more frequent in 1 group versus another?

Louise Sun, Mario Gaudino, Rob Chen, and I compared readmissions for pneumonia or for hip fractures between the 2 groups over the long-term. Adding support to our conclusions, we found that readmissions for those occurrences over a median of 5.2 years were similar in incidence between the PCI and CABG groups, adding credibility to the significant differences seen with regard to major adverse cardiac events. Do you think that you could examine falsification end points within your own dataset?

Dr Sultan. Yes, we've looked at overall hospital readmissions, not just cardiac, and not just heart failure. So, interestingly the PCI readmissions are higher. We haven't really parsed out the exact reasons why, but the most common reason does end up being pneumonia or some sort of respiratory complication; that's how it's coded in our data set. So yes, we have definitely looked at that and we've noticed that the hospital readmissions over 5 years are significantly higher in the PCI group.

Dr Ruel. That would suggest that your PCI patients were sicker patients at baseline, unfortunately.

Dr. Sultan. Absolutely.