Roxana Mehran, MD: Hello. My name is Roxana Mehran from Mount Sinai School of Medicine in New York. It's my pleasure to welcome you to this editorial program in which we will look into how FFR usage differs in Europe vs the United States.

I'm joined by my colleagues Justin Davies from Imperial College London and, of course, Ron Waksman, an old friend, from the Washington Hospital Center in DC. Welcome.

Ron Waksman, MD: Thank you.

Dr Mehran: We thought today we'd have a conversation about fractional flow reserve and the use of functional studies in guiding our interventional procedures. This has become a very interesting and important modality that has been incorporated, now, more and more into the cath lab.

Let's begin, Justin. Maybe you could tell us: what is FFR? How do we use it? What do you think about it? How important is it to have? Does every cath lab need to have FFR?

Justin E Davies, MD: I think that it provides cath labs with an objective measure of stenosis assessment that is quick and relatively easy to use. Often you find people don't come to cath labs with preprocedural ischemic assessment, so it enables a physician in the lab to see if there is ischemia and to effectively document that. It has clearly got a good, strong evidence base, which has been developed over a number of years with the founding studies of **DEFER** and **FAME**—and **FAME-2**, now, which has led to the technique getting into guidelines and which has propelled its use to widespread practice.

Dr Mehran: There's no question that functional assessment is quite important, but what do you think about patients coming into the cath lab, especially in the United States, without an ischemic assessment? How often are you seeing that and would you even use [FFR] in a patient who has got a 90% stenosis or 80% stenosis, Ron?

Dr Waksman: I think we are in a period of transformational culture, now, in terms of appropriate-use criteria and justifying every lesion that we are doing. I think that interventional cardiologists are on the defensive—because we have to justify almost any angioplasty that we are doing, especially with an intermediate lesion. I think physicians are more flexible in using FFR and looking it as guidance to support their decision-making.

I would say, still, if it is a 90% lesion even without a functional test I don't think it is required, but the 90% is on the eyes of the beholder, so you know that if you take it to the core lab it is not going to be probably 90%, it is usually going to be less than that.

And as you know, we have been scrutinized by looking at films and, again, [we need to] justify. It is true that in the past the algorithm was having a functional test and going to the cath lab. But this [step] has delayed things, and now people presenting with some chest discomfort, [who] have risk factors, they sometimes would be sent to the cath lab as the first method of assessment. I think we have to take this more carefully and incorporate a functional ischemic assessment in the cath lab—especially when those lesions are not necessarily unambiguous, we don't clearly know that they would derive ischemia.

Dr Mehran: It seems like that is really the way to go. You talked to us about FAME, FAME-2, [that FFR is] the only modality in the cath lab that actually improves hard end points like death and MI. I think that was how it got into the guidelines, obviously. Very important studies. But at what cost? Can we afford to do this in every single patient who presents with, let's say, multivessel disease, as they did in FAME?

Dr Davies: I think, actually, that this is a tremendous opportunity because I think for us as cardiologists, as Ron said, it is very easy to get yourself into a little bit of a hole stenting lesions that are not as significant as you may think, and I think this obviously provides a justification and a safety net for people to deploy stents. But also I think increasingly going forward when you are taking on potentially more challenging techniques and you have got three-vessel disease, [FFR] enables us to assess multivessel disease and perhaps convert a three-vessel PCI into a two- or [even] a single-vessel PCI, which may move them from getting a CABG to angioplasty.

Dr Mehran: So actually decreasing the number of stents. Reducing your devices—hopefully even radiation exposure and contrast media. If you actually just do an FFR and say, okay, I am done. But you know that we have all [discussed]: if you want to treat the lesion you use an IVUS; if you don't want to treat the lesion you use an FFR. What do you think about that, Ron? Is that something that is going on in your lab?

Dr Waksman: No. We try to stay away [from that]. I know that is said. But I would still think that FFR is oversold. For the controversy, I would [argue] that those studies were investigator-sponsored studies and I don't think the data are so relevant today. In DEFER there was a balloon angioplasty. Even in FAME-1, it was with first-generation stents, and it was not really practice to go after every lesion.

I think we have to take these [data] with a grain of salt. To my view, not everything is definitive. Nevertheless, we do see uptake of the FFR usage in the lab and for something that used to be under 3% in the US—only a couple of years ago—it is now reaching up to 20%. More and more people are using [FFR].

There are other modalities that you can use. I think that we try to do a conversion between the anatomical [minimum lumen area] (MLA) to the IVUS / FFR. It is controversial, but it is another option. I think we need to learn to use the tool when we really need it, not to be obsessed with it.

Often, we would have a scenario [where] a patient presents with chest pain. It is classical angina. It is relieved by nitroglycerin. You have what you think is about 70% lesion in the proximal LAD and then you stick [in] the FFR wire and you get 0.81. Then you have a problem. You can repeat the study. You shoot another adenosine and now it is 0.79. Then you shoot another one and it is 0.80. It is very hard for me when you have a binary number to make a decision [based] on that number. I don't think we should lose our clinical judgment. It is a nice tool, but don't abuse it. Use it when it is really helpful.

Dr Davies: I will share my view. I have to say I agree wholeheartedly with Ron. To me, if you ask them what are the most important numbers in FFR, people will say: 0.80 or 0.75. Actually, I think the two most important numbers are 0 when it is completely occluded and 1. As you get nearer to 0.80 you know that you are approaching a place where it is going to be likely ischemia and a high probability of events. Ron is absolutely right. If you have a type A, 90% lesion and you have an FFR of 0.81—I know [that] in the US you are in difficulties, at the moment, with these kinds of lesions. I think with the commonsense kind of medical entirety/holistic approach that would say you should probably stent these people.

Dr Mehran: But isn't that just so important? Those are really important points because it is not about the dichotomous number of 0.80 or 0.75. It is about the clinician and what they feel the scenario is and how it all fits together.

Dr Waksman: I would say even though it is getting very hard to support by studies but I may not have an 80% or 70% lesion. I would rather have an FFR of 0.92 or 0.96 than 0.81.

Dr Davies: Absolutely.

Dr Mehran: Of course.

Dr Waksman: If I have the choice. You also have to realize that the stents of today are not the stents of yesterday. I think we see [many fewer] events. I think that the price of stenting and the likelihood that we would have events is much lower than in the past. So even if we deviate a little bit, it I don't think we do an injustice to the patients [or] put them at high risk. I would challenge that if you would [do] the same study today as DEFER, with the new second-generation stents, I am not sure that the results would be the same—as robust—as they were in the past. As a matter of fact, if you are looking even [at] FAME-2, at the two groups—[those who] were medically treated and those who were [interventionally] treated, the curves were actually very similar. I would challenge

that you [would not be replicating these results] with second-generation [stents]. You have to be taking [FFR] when you really need. I don't think [that] systematically you go [to] every lesion and if it meets the criteria of 0.80, you don't treat. If it is less, you treat.

Dr Davies: And there are some people who see this as a weakness, but we don't do that in any other form of medicine we practice, and I see it as a strength that you get a continuous range of values. I think the one thing, which we have also done, is using these techniques purely as an outcome base. But really if you look back they were designed to describe ischemia and chest pain, so really it is a very good tool for seeing if chest pain is genuine and if it is likely to benefit from a stent.

Dr Mehran: That's right.

Dr. Davies: And that hasn't been thoroughly explored since the original studies.

Dr Mehran: Those are really excellent points. Now, we have alternatives to FFR. We talked a little bit about IVUS, but we also know now that, Justin, you have done a lot of the work on [instantaneous wave-free ratio] iFR. Maybe you can just tell us: what is iFR? How is it different from FFR and where are we in that? Do you believe it will replace FFR?

Dr Davies: iFR is a technique which is very similar to perform as FFR. You use the same pressure wire. It is a software change in the console that essentially allows us to make a measurement of stenosis severity over a particular phase of the cardiac cycle without the need for a drug. It typically takes a few seconds to measure and is very quick.

There have been, to date, about 3000 patients studied, in five clinical trials, which—with the exception of one study—have all shown, essentially, the same findings.

And we know at the EuroPCR meeting this was, again, replicated this week. At the moment, we are in a situation where we are advocating the use of a hybrid approach, similar to the big **RESOLVE** study, which essentially says that if you are above an iFR threshold of 0.93 you are safe to defer and below 0.86, to treat. That gives you about a 90% to 95% agreement with FFR and overall classification, and the **ADVISE-II** study shows it saves about 70% of adenosine. There are potentially quite marked savings in the cath lab.

I think this is out there in clinical practice—in a limited release, in terms of certain labs around the world on three continents. The general experience has been very, very good from people in terms of just facilitating the use of physiology. What I mean by that: I take centers that were relatively small users of FFR and they found they have done the same number of cases in three months as they

would have done over the whole year. If you ask them why, it's because it lowers the burden of doing [the cases]. I think if we then move on to doing triple-vessel-disease assessment I think it takes five seconds of each.

Dr Mehran: I think there is no question that taking away the adenosine is music to a lot of people's ears. We all know that adenosine is not being given perfectly right in certain laboratories. It really should be an intravenous injection. There is time needed for nurses to put it together, to put in the IV, the intra-arterial [injection] has been refuted, etc.

But when I look at iFR I start to think that we are pushing ourselves toward what Ron was just talking about. I think the validations need to take place. It would be great to have technology that is well validated, studied, that actually correlates with events without adenosine. I think that part of it is brilliant. But are we there today?

Dr Davies: We have had a very good response taking the stuff from the research lab into the cath lab, so this is what we are using this as a tool, certainly, within the framework of studies. I think now we are in a position to do large studies. I will give you an example: we asked all of the investigators who have got these machines if they are willing to contribute to analysis at the time of PCI. [In the space of] for four weeks—most of them only had the device that length of time, they managed to get together 400 cases. [This shows that] doing very large studies of 1500 or 2000 patients is extremely feasible and very easy to do.

Dr Mehran: I hope you are designing them and actually performing them.

Ron, what do you think about iFR? I love to hear your scrutiny.

Dr Waksman: I think it hasn't been validated, obviously. I [would] like to get rid of the adenosine. But I like to see reproducibility of any test. Again, I would say, we don't have to lose our brains just because we have numbers. We have a patient in front of us. He has symptoms and we have lesions that we have to treat. Obviously if you have a proximal lesion, it's going to behave differently than a mid or distal vessel. We know that, for example, if you look at most of the studies, at just a circumflex of FFR. Most of them will be above 8.0. But you take most proximal LADs, they probably would fit more into the predictability of ischemia vs nonischemia. We have to, again, use our brains when we use the numbers and understand what they mean.

I think that there will be other technologies that [will] try to be alternatives to FFR—not that FFR is necessarily bad, but there are other ways that you can do it. There is the heart flow option with a CT. I still think that IVUS is an option. Not all of them are ideal, but it gives you a variety of options. The message is: we are trying to treat only the vessels that need to be treated. I think that can also change the paradigm of treatment. For example, we may turn "three vessel" to

"one vessel" and change the whole syntax score and move patients from CABG to PCI—which is very attractive for interventional cardiologists.

One other thing that is interesting: recently I heard that SJ Park was presenting a systematic use on all patients with FFR—which is amazing! It is over 70%. It was not a randomized study but what he did show by systematically using FFR in his practice [is that] he reduced, by a lot, the number of PCIs, the number of stents, and the outcome of those patients was good. You have to compare it in a randomized fashion. What would be the alternative? And that is the challenge. You really have to show [efficacy] in a randomized clinical trial. I recognize there were studies in the past, but they have limitations. I think we [are] moving to another phase that this has to be tested.

Dr Mehran: Quickly touching on what you just said about noninvasive functional assessments. More and more we are getting patients who come in with a multislice CT. Can we use that technology to actually do some of the functional assessment right then and there? The **DEFACTO** trial, in my mind, is a negative study. Where are we with that technology?

Dr Davies: You are absolutely right to say a lot of these patients have CTs and it is a question of whether we can use information from that CT. As Ron said, there is HeartFlow technology, which enables you to effectively get a noninvasive preprocedural virtual FFR measurement. Certainly from a theoretical perspective, it should be possible to do these calculations. I think the problem that the HeartFlow team has is translating the computational flow dynamic theory in a perfect research environment into the clinical practice of getting good-quality CTs. I think there is probably more work in progress to see that really translate.

Dr Mehran: That's right.

Dr Waksman: But what we are seeing in the US right now is [that] there is a decline in the nuclear test and there is increased uptake in FFR. There is a change in paradigm because of many reasons. Some of them have nothing to do with medicine. It is more the reimbursement. Because reimbursement went down on nuclear tests, we see less nuclear tests being performed. Now we are getting the patients actually to be assessed in the lab and we get [to have] more confidence with FFR or other technologies. I think we are shifting the traditional assessment of ischemia, which was in the old days was nuclear or dobutamine echo, more into those [tests performed] in the lab. And I do believe that the fact that studies were negative is not the end of the story. We still have to fine-tune. This is all about software validation and finding the sweet spot. What is the window that allows you to get good matching? That you can feel comfortable [with]?

Dr Mehran: So great technology to look forward to in the future. We are looking for that kind of noninvasive assessment of functional studies. Let's now turn to

why we are really here, which is about the regional differences of FFR. In the UK, in Europe, in the United States, are there regional differences? Let's better understand that. And, if so, why? Justin, maybe you could tell us about the UK and Europe?

Dr Davies: I think [FFR penetration] is somewhere between 15% and 20% of cases in the UK, which is very high on a worldwide basis. I think some of that has to do with reimbursement and some of it is to do with the way that doctors are reimbursed, as well. In terms of the UK, if we put a stent in or not, it has no net effect on the income to ourselves. So it is very easy for us to follow guidelines and, in fact, if we don't, [we] get rapped around the knuckles and told off for not doing so. I think that is a strong incentive to do it.

I think there are obviously differences from us in other parts of the world with regard to the reimbursement—the cost of the bits of kit and the availability of the kit. In some labs around the world, and some territories, getting adenosine is simply not possible or it is [so] outrageously expensive that people would just say I am not going to make this measurement and they defer to angiography or, as Ron said, to IVUS.

Dr Mehran: It seems like the penetration is a little bit the same between the UK and US? What do you think about the United States?

Dr Waksman: Not yet**.** I would actually take from what Justin just said. I think that the main motivation in Europe for the penetration of FFR was monetary. It was actually to save money to the operator, to the cath lab. This never was the case in the US. I think the [explanation] in the US of the uptick is more related to the appropriateness[-criteria guidelines] and to be on the defensive. The interventionalist now has to defend himself for every procedure [he is] doing and to have a backup [as to] why they did this procedure. That was not the case in the European continent, [where] the main drive was to reduce overall costs on the capitation system. I always had a problem with that because this is the way that it was presented and I think that we should give the best to our patients.

We also have to realize that the reason for the uptick could be because of appropriateness. We actually learned to turn this into a helpful tool for us [and] to use it not just for those ancillary decisions—that probably should not be related to the patient (whether it is a cost or whether it is appropriateness), but [also for] what [it is] really good [for]: to see how we can utilize [it] to do the right procedure to the right vessel. So it's another tool.

But as I mentioned before, I think we are seeing an uptick. I don't think we are crossing the 20% and we are not as broad as in Europe. When are we going to get there? It is a question of how much push we are going to see, but one thing you see [now is] more companies providing FFR systems. That means that there will be more reps in the labs and more opportunities, and that is usually what will

populate the usage of the device. I have no doubt that we are going to continue to see an increase.

Dr Davies: It is interesting. I know from the US, and some of the data there, there is a big difference between diagnostic use of FFR and actually the PCI use. It is almost used in the US to justify PCI, and I think the angiography use is somewhere around 3%. If you take that study that SJ Park has just done and you compare that 70% percent that he was doing with the 3%, there is obviously a huge potential.

Dr Mehran: Isn't it interesting that maybe the driving force of doing a functional assessment in the lab is different in the UK vs the US or Europe vs the United States? I believe that at the end of the day they both will come to the same conclusion of doing the right procedure to the right patient, making the correct diagnosis, treating the right lesion for the right patient, but at the end of the day actually decreasing costs. While maybe we are seeing in the United States that appropriate-use criteria is why we are doing this, it has, perhaps, to do with capitation, as well, for us in the United States, and enhancing the cost in the system, hopefully, with this kind of functional assessment?

Dr Waksman: I think there is one more important collateral benefit from using the FFR. That I would say is that we are changing the paradigm. In the old days we thought we have to treat all the three vessels; we have to have complete revascularization. I think FFR taught us that actually we may not need to treat all the three vessels. That is a big advantage of technology. As we are using it we are starting to see maybe we just have to treat the culprit lesion and move on and then leave the others either on medical therapy or not treat them at all. That is a huge change in paradigm.

Dr Mehran: This has been a fantastic conversation among the three of us, and I just want to close and I want you each to close for me. What do you think is the future of FFR? What should we be looking forward to as alternatives and what incorporation of functional assessment in the cath lab as we move to the next decade of interventional cardiology. Ron?

Dr Waksman: I think that the FFR will continue to grow. I think that there is a good future for iFR without the adenosine, the wireless, and better wires that you can use. I think you [could] incorporate an IVUS probe in them—FFR on an IVUS probe, so you can do both. I think that the combination of anatomical and physiological [testing] is important. We learned that with IVUS you can optimize the outcome of the PCI, not only just determine whether you treat or not. So the future is there. We are coming to do more sophisticated PCIs, and these data will help us to get better outcomes and also to triage the patients to what should be the treatment of choice. In the long run—even though the short run shows reduction of the PCIs—if we use [FFR] carefully it will open us or enable us to do more complex patients and meet the outcome that is expected.

Dr Mehran: That's great. Justin?

Dr Davies: I would agree with Ron's thoughts and also extend them to say I think we will be doing more of these measurements, but I also think we should be doing more smartly. As we discussed earlier, if you get these very borderline lesions in patients who clearly have angina, then this is an indication for treating your patient and looking at the patient as a whole.

I think we are really going to embrace technology. Medicine is always a little bit behind the kind of technological leaps compared with smartphones, for instance. I think techniques such as the HeartFlow technique, techniques such as the ones we have been working on with iFR, I think will continue to move forward. I think whereas we only today have discussed things from the purely diagnostic single ischemic perspective, I think within one or two years you are going to have techniques freely available in the cath lab that enable us to coregister the FFR/iFR images onto angiogram in real time, enable you to plan PCI by selecting which lesions may or may not benefit from therapy, even before you deploy a stent. I think this, in the **SYNTAX** era, where we know the potential benefits of minimizing angioplasty, like Ron said, will really facilitate our practice, and I suppose the most important thing is lead to the better results for our patients.

Dr Mehran: I think that you both did a beautiful job telling us about the current and the future technology and even if there are regional differences, at the end of the day what we are trying to do is use the functional assessment to enhance outcomes for our patients with cardiovascular disease, to make the right diagnostic and therapeutic choices in these patients. And the combination of these technologies that currently exists and hopefully will exist in the future will absolutely get us there.

Thank you so much for your time this morning and I hope our audience enjoys this conversation as I did. Thank you.