SAFE-PCI Trial

Sunil V. Rao, MD, shares his experience with the SAFE-PCI trial and the impact it may have on PCI treatment for women.

What factors led to the formation of SAFE-PCI?

We published an article a few years ago that looked at the almost nationally representative ACC/NCDR database, looking at the proportion of procedures that were performed transradially in the United States. We found that only about 1.3% of procedures were being performed by the radial approach. Despite this low prevalence, the association between the radial approach and fewer complications compared with the femoral approach was still present.

We were a little curious about why the United States seemed to have a much lower radial approach rate relative to other countries. We subsequently published some articles looking at other countries as well. In the background of all of this, we had been working with the FDA through an organization called the Cardiac Safety Research Consortium, which is a group of industry partners, FDA representatives, and academic physicians who are trying to look at overall cardiovascular safety with respect to devices and drugs. We had an idea that, because the radial approach was associated with such a low risk of bleeding, we could potentially make antithrombotic drugs safer if we used the radial approach. For example, patients who receive IIb/IIIa inhibitors are at an incredibly high risk for bleeding, and if you use the radial approach in those patients, you can lower the risk.

We had a think tank at the FDA a few years ago and discovered that there was a tremendous appetite for a randomized trial in the United States. We also discovered that there were two gaps. The first was an education gap in the United States—operators simply were not trained in the radial approach. The second was a research gap, in that interventionists in the United States wanted to see a large, adequately powered, multicenter randomized trial comparing radial versus femoral that took place predominantly in the United States because our practice patterns are so unique.

We thought it would be great to perform a randomized trial of radial versus femoral, but it is very challenging because a femoral operator who doesn't know radial procedures simply can't randomize to radial. They don't know how to do those procedures. Radial operators, especially in the United States, probably switched to radial for a reason (maybe they had a bad bleeding complication in the past, and so a radial operator may be unwilling to randomize in this trial). In essence, femoralists can't randomize; radialists won't randomize.

We had to come up with a patient population in whom even the radial operator would feel comfortable randomizing and going into that patient's room and saying, "I honestly don't know what's better, radial or femoral."

After more examination of the American College of Cardiology database, we discovered there were significant gaps in who underwent radial versus femoral access: older patients and women tended to undergo femoral access more often. This is an interesting risk/treatment paradigm. We know that older patients and women are both at risk for bleeding, yet radial is used less often.

We decided to try and figure out which of these groups a radial operator would be comfortable randomizing. It turns out that elderly patients, among high-volume radialists, were routinely undergoing a radial approach; radialists did not feel comfortable randomizing those patients. On the other hand, women represented a unique group because even the radial operators felt comfortable randomizing female patients to the femoral approach. It appears that women are even at risk for local bleeding complications after a radial procedure.

This is where we hit upon a group that is at high risk for bad outcomes, particularly bleeding, and the radial operators would feel comfortable randomizing. This group is what formed the background for the SAFE-PCI trial.

The design of the SAFE-PCI trial is to examine both an efficacy endpoint, which is bleeding, as well as a feasibility endpoint, which is if the procedure can be completed from the assigned access site.

In that context, most radial operators that we talked to said that SAFE-PCI is a trial in which radial could actually lose because, although you may have less bleeding, you may actually have higher procedural failure, which is exactly what we wanted to hear. We wanted to make sure that we had a certain level of equipoise for these patients so that operators could comfortably randomize their patients.

SAFE-PCI is a unique trial for several reasons. First, it is the only interventional trial being performed exclusively in women. Second, it is the first large, multicenter, randomized trial of radial versus femoral being performed in the United States. Third, the structure of the trial is unique.

We're using the ongoing ACC registry as the backbone for the trial. Patients in the registry who are undergoing PCI will have all their data entered into the registry. Why would we have the site duplicate the work?

Therefore, we built a software interface between the registry data and our case report form for the trial, so that at

the site level, 70% of the case report form is automatically populated with the data that are going to be entered. This has made it incredibly efficient in terms of actually enrolling patients and getting the data entered. I think the sites have found that to be an extremely valuable way of doing things.

What is the structure of the SAFE-PCI trial?

The trial comprises 3,000 women undergoing elective or urgent PCI, to be randomized to radial versus femoral. We know that the majority of procedures in the United States are performed by an ad hoc approach, so we are going to have to randomize 3,000 patients to get 1,800 patients undergoing PCI. Our power calculation is based on 1,800 patients.

How many sites are participating in SAFE-PCI?

Right now, we have 28 sites, but we're still looking for others. Our goal is to reach 45 to 60 sites.

What does this mean for the female population, specifically?

Our hypothesis is that the radial approach will, in fact, be associated with a 40% to 50% reduction in bleeding complications. If the trial turns out to prove this hypothesis, I think we have found a very safe approach to performing PCI in a patient population that is at an incredibly high risk of bleeding complications. We think it is an important study because it is the first interventional trial being done solely in women, and we know that they are an understudied population overall.

What are the risk factors of postprocedural bleeding from the femoral approach?

The risk factors have been very clearly delineated, and they can be separated into patient level, vascular access level, and pharmacological level. At the patient level, we know that patients who have low weights and incredibly heavy patients (the extremes of body weight) are at high risk. We know that older patients, women, and patients with chronic kidney disease are at high risk.

At the procedural level, we know that the use of very aggressive antithrombotic therapy, particularly failure to adjust antithrombotic therapy for renal function, is a risk factor for bleeding. And we know that femoral arteriotomy outside of the femoral artery (either too high [above the hypogastric artery] or too low [below the bifurcation]) are also risk factors for bleeding complications.

The pharmacological issues deal with dosing and failure to adjust for renal function.

What are the mortality and morbidity differences between radial and femoral and between bleeding and no bleeding?

It has been difficult to show a mortality benefit with the radial approach, primarily because the outcomes from PCI are so good. We have started to see an association between radial and improved survival in the highest-risk patients. There are a series of studies, both randomized and cohort studies, which have shown an association between the radial approach and reduced mortality among STEMI patients. We know that STEMI patients are at incredibly high risk for bleeding. It could be that because of their high baseline risk, an intervention that reduces bleeding may, in fact, translate into improved survival.

As far as bleeding versus no bleeding, multiple published papers show a very clear relationship between in-hospital bleeding complications and both short- and long-term morbidity and mortality, including death, stroke, recurrent myocardial infarction, and even stent thrombosis.

What questions should a woman ask her physician when she is told that she needs catheterization?

This is a great question. I think there are a variety of different questions that need to be asked that deal with both the indication and the procedure itself.

In terms of the indication, I think it is important for patients to understand why they are undergoing a heart catheterization and exactly what information the physician hopes to gain from the procedure itself. I think they need to have an understanding of what the flow of the day will be (ie, the patients will have to stop eating after midnight, they may have to come in early, how long they can expect to be in the hospital, etc.).

One of the most important topics to discuss is the type of risks involved—not just bleeding, but also the risk of dying, stroke, or heart attack during the procedure. One of the most important things for patients to be prepared for is the fact that they may go on, from a diagnostic procedure, directly into an interventional procedure if there is a lesion that is amenable to that and it is clinically indicated.

I think patients also have to understand that there are potential issues related to stent choice (ie, bare-metal vs drug-eluting) and what that means in terms of medication adherence. There are some really good programs out there that actually list all the risks.

Like many centers, we prefer to see all of our outpatients in a separate clinic so they have time to reflect on these risks

and are not going into the procedure right after hearing about it without time to process it.

I would encourage any woman who is approached for the SAFE-PCI trial to seriously consider it because we are hoping that the study will actually advance women's health care.

What do you think needs to happen to get a national database or a national registry of radial operators on the books, since currently one does not exist?

Fundamentally, we need the professional will. ACC/NCDR is getting pretty close; in many states, it is a mandatory registry that places have to belong to. In other countries (ie, Sweden), it is required that every cath lab in the country belong to a registry. In the United States, it is required that every VA cath lab belong to a registry. We haven't gotten there yet for private, non-VA hospitals.

A lot of this also comes down to the costs associated with belonging to these registries. I think that cost is coming down over time. My guess is that it is going to become increasingly common for sites to belong to a registry like NCDR.

Do you think SAFE-PCI will facilitate this shift?

I think it will in an indirect way. All of our sites right now belong to the NCDR, so they are already part of the registry.

But, I think there are a lot of sites that do not belong that also participate in clinical research. I think when they see how efficient the workflow is by belonging to a registry and doing a trial at the same time, there is going to be a lot of interest in doing that kind of thing.

Why do you think this issue is not more visible? Do women realize that they are at greater risk?

In general, I think female patients are very savvy about their risks. The issue of women's health in general doesn't get a lot of play, and I think that the lack of recognition of the bleeding risk is just part and parcel of that. ■

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