

Is It Time to Change the Guidelines for STEMI?

Sripal Bangalore, MD, discusses the results of his recent STEMI meta-analysis and makes the case for a possible change to the guidelines.



Recently, in *Circulation: Cardiovascular Interventions*, you published a network meta-analysis that compared first-generation drug-eluting stents (DES), second-generation DES, and bare-metal stents (BMS) in patients with ST-elevation myocardial infarction (STEMI). Why were you interested in the STEMI setting?

In patients with STEMI, the choice of stent has always been controversial. In the initial trials evaluating BMS versus DES in patients with STEMI, such as the PASSION and the DEDICATION trials, there was a strong trend toward reduction of restenosis. However, this did not reach statistical significance.

More important was the risk of very late stent thrombosis. An article published last year,¹ which mainly looked at first-generation DES (sirolimus-eluting or paclitaxel-eluting stents), showed an increase in stent thrombosis after 1 year with DES when compared to BMS. As such, when you look at practice patterns both in the United States and elsewhere, if there is one indication for BMS, it has been STEMI. This is also echoed in the guidelines; they don't make a strong case for DES in STEMI.

What did you learn from this meta-analysis?

In an analysis of 28 randomized trials with 34,068 patient-years of follow-up, we found that the newer-generation DES were not only much more efficacious at reducing the risk of restenosis, but surprisingly were also safer with reduced risk of stent thrombosis when compared to BMS. However, cobalt chromium everolimus-eluting stent was safer, having the lowest rate of stent thrombosis when compared with first-generation stents or BMS.

We conducted this analysis due to the concerns of very late stent thrombosis with DES after 1 year, mainly stemming from first-generation DES. In our analysis, we

looked at the data to see if there is any signal to suggest an increased risk of stent thrombosis beyond 1 year. Interestingly, we did not find that with the newer-generation stents. There was a trend toward worse outcomes with the first-generation stents, but not with the newer-generation stents.

Based on your findings that DES reduce the risk of target vessel revascularization and stent thrombosis, you make a strong recommendation that guidelines should be changed for treating STEMI patients. What is the main reason the guidelines still recommend BMS for STEMI patients?

There are three reasons. First, early data, especially for first-generation DES, showed an increase in very late stent thrombosis. The reason for this increase in very late stent thrombosis is because, frequently, these stents are placed in arteries that are full of thrombus, which later gets reabsorbed, resulting in acquired late stent malapposition. In addition, the first-generation DES have thicker stent struts and thicker polymer with nonuniform coating of the polymer surface, all of which increase inflammation, cause hypersensitivity reaction, and thereby increase thrombogenicity. So, the guideline recommendations are based on concerns about worse long-term safety outcomes.

Second, in patients presenting with a STEMI, very often than not, the culprit lesion is in a proximal artery, which are usually of larger diameters. It has been questioned whether DES provide the same magnitude of benefit at preventing restenosis in large arteries when compared with smaller arteries.

Third, it is difficult to ascertain whether a patient is going to be compliant with dual-antiplatelet therapy in an emergent situation, such as that during a STEMI. I think these are the major reasons for the guidelines not to have a strong enough indication for DES.

How likely is a change to the guidelines, and how long will it take such a change to happen?

First, we need to step back and evaluate what our guidelines are routinely based on. For the STEMI guidelines, only 18% of the class I recommendations are based on robust randomized clinical trial data. In other words, most of the guideline recommendations are based on weaker levels of evidence or on expert consensus. With this in mind, let's look at the data we have to support second-generation DES use in STEMI. In our analysis, we had access to approximately 28 randomized trials and more than 34,000 patient-years of follow-up, and the data clearly attested to the efficacy of DES. With the newer-generation DES and especially with the cobalt chromium everolimus-eluting stent, there is a suggestion that they might even be safer than a BMS, with a reduced risk of stent thrombosis. This has also been shown in a recently randomized trial (EXAMINATION trial) and in observational studies (such as that from the Bern-Rotterdam registry and the SCAAR registry).

I would say that we have a strong case to make for the use of newer-generation DES as a class I recommendation. Of course, physicians and patients will have to weigh the risks and benefits and assess the best path of treatment for each patient. But I think we have a strong case to change the guidelines.

Some next-generation DES have been shown to significantly reduce the risk of stent thrombosis versus BMS and first-generation DES. What is driving these improvements in target vessel revascularization and stent thrombosis rates?

I would say that the newer-generation stents have thinner strut thickness and thinner polymers. Both of these factors have been shown to reduce the risk of restenosis, the amount of inflammation, and also thrombogenicity around the stent. These two modifications have dramatically reduced the risk of restenosis, as well as thrombosis.

In addition, the polymer on the newer-generation DES may have something to do with the superior safety. For example, the Xience stent (Abbott Vascular, Santa Clara, CA) has a fluoropolymer. There are data published by Elezar Edelman's group in Boston, in both ex vivo and animal models suggesting that fluoropolymer is thromboresistant even when compared to a BMS, which is pretty fascinating. It's kind of a paradigm shift in our understanding of the way these stents work. We always considered BMS to be the safety benchmark, but findings from the fluoropolymer seem to suggest otherwise, showing thromboresistance and causing less inflammation with the everolimus-eluting stents.

In addition, there have been improvements in the polymer coating technology; there is less surface irregularity

with these polymers, which results in less inflammation. I think all of these factors put together have created a stent that is much better than what we have seen before, with low inflammation, low thrombogenicity, and better deliverability—all of which lead to improvements in clinical outcomes.

How do you think your findings from this meta-analysis will change practice patterns, if at all?

I think the meta-analysis definitely has this potential, as the findings are supported by similar data from large-scale registries. Such registries include the Bern-Rotterdam registry and also from the SCAAR registry, both of which showed reductions in stent thrombosis rates, even when compared to BMS, and the EXAMINATION randomized control trial comparing the Xience stent versus a BMS. In this head-to-head trial, there was a significant reduction in stent thrombosis rates at 1 year and 2 years with Xience when compared with a BMS.

We now have compelling data with endpoints that are clinically relevant, so I would say this definitely has the potential to change practice patterns.

What is the value of meta-analyses? What are their limitations, and does this particular meta-analysis have any limitations?

This meta-analysis, just like any other meta-analysis, has limitations. The strength of any meta-analysis, especially a network design like the one we performed provides more power to evaluate rare events. Stent thrombosis is one of these rare events, and frequently, individual randomized trials are not powered to detect a difference. When you pool together 24,000 patient-years of follow-up, we do have sufficient power to study these rare events.

The flip side is that a meta-analysis is only as good as the trials that go into it and is still considered hypothesis generating. If you include a lot of trials that are extremely small and have problems in the design, a meta-analysis cannot correct for any of those flaws.

There are currently several meta-analyses evaluating the use of stents in STEMI patients. Presuming that these are all evaluating the same underlying datasets, is it possible for them to reach different conclusions?

The only way you can reach a different conclusion is by doing something differently. Our meta-analysis looked at 28 trials, while the other meta-analyses published recently on this topic included much fewer. It is easy to miss trials if you do not search the literature hard enough. Another way to reach different conclusions using the same set

of trials would be to lump multiple different stent types together. Some of the previous meta-analyses lumped paclitaxel-eluting stents and sirolimus-eluting stents as one common platform. We know that the Cypher stent (Cordis Corporation, Bridgewater, NJ) is not the same as the Taxus stent (Boston Scientific Corporation, Natick, MA); lumping both of them together is wrong!

These are the two major ways where you can get results that are different, but if you analyze the same trials in two similar analyses, you should get similar results.

In this meta-analysis, there is a dataset for the zotarolimus and Resolute zotarolimus (Medtronic, Inc., Minneapolis, MN). Is this referring to two different stents with the same drug?

The zotarolimus-eluting Endeavor stent (Medtronic, Inc.) is the previous version of the Resolute stent. With the Resolute stent, the polymer and the drug-elution kinetics were changed. In the newer zotarolimus-eluting Resolute stent, the drug elutes for longer periods, and because of that, it has shown superior results. Previously, the zotarolimus-eluting stent was considered to be a “DES-lite stent” because it was a DES, but it used to behave like a BMS in that there was rapid endothelialization. The Resolute stent has much longer drug-elution kinetics, and so it is now much different, and the efficacy and safety data have dramatically improved.

Why wasn't a more definitive conclusion reached about the Resolute stent, which showed favorable data when included in the analysis?

The Resolute data are based off of a small subgroup of patients with STEMI from the RESOLUTE All-Comers trial, and this subgroup included 281 patients only. If you look at the confidence intervals for the Resolute stent and not just the point estimate, which is how one should more appropriately assess all of these data, they are pretty wide and imprecise, and hence we cannot be fully confident with the results for this stent. We simply need more data to show efficacy and safety of the Resolute stent in the STEMI setting.

To what extent do you believe that the improvements in target lesion revascularization are due to stent platforms, improved physician training (including patient selection and techniques), and/or dual-antiplatelet therapy?

I think each of these components has a role. Clearly, a big part is due to changes in stent platform—improvements in the strut thickness, the polymer coating technology, and the type of polymer used, as discussed previously. Part of it is also due to physician training. Our early experi-

For the STEMI guidelines, only 18% of the class I recommendations are based on robust randomized clinical trial data.

ence with DES has taught us to have a good PCI hygiene to ensure that the stents are well deployed and properly expanded. We also realized the importance of dual-antiplatelet therapy, which now drilled down to the patients and referring physicians.

That being said, in a contemporary trial such as the EXAMINATION trial, where hopefully physicians and patients did the same process (stent deployment and dual-antiplatelet adherence) in both the DES and BMS groups, we saw a significant difference in target lesion revascularization and target vessel revascularization, which is not surprising. We also saw a significant difference favoring DES with regard to stent thrombosis. To me, this suggests that, yes, patient selection, techniques, and dual-antiplatelet therapy are important, but maybe there is also something to say about the stent itself.

Do you have any parting commentary that you wish to convey to our readers?

I think that we seriously need to step back and rethink whether a BMS is the way to go in patients with STEMI. The reason I say that, in addition to our meta-analysis, is based on the COMFORTABLE AMI trial, which looked at BMS versus a biodegradable polymer DES. At 2 years, there was a reduction in death and myocardial infarction with the biodegradable polymer DES.

We have a consistent message from multiple sources: the EXAMINATION trial, which showed an increase in stent thrombosis, and the COMFORTABLE AMI, which showed an increase in cardiac death and myocardial infarction with BMS. I would say that these are clinically relevant events; they are hard outcomes that all of us look for when treating our patients. I think it is high time to challenge whether BMS should be the way to go for patients with STEMI. ■

Sripal Bangalore, MD, is Associate Professor, Department of Medicine, Cardiology Division at NYU Langone Medical Center in New York, New York. He has disclosed that he is on the advisory board and receives honoraria from Abbott Vascular and Medtronic, and that he receives research grants from Abbot Vascular and NHLBI. Dr. Bangalore may be reached at (212) 263-3540; sripalbangalore@gmail.com.

1. De Luca G, Dirksen MT, Spaulding C, et al. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med.* 2012;172:611-621; discussion 621-622.