DISRUPT PAD III Trial Summary

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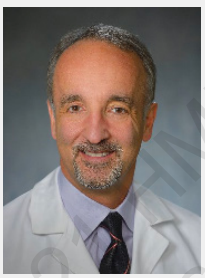
The trial included 306 patients with moderate or severe calcification in the femoropopliteal artery who were randomly assigned to vessel preparation with intravascular lithotripsy (IVL) or percutaneous transluminal angioplasty (PTA) prior to treatment with drug-coated balloon (DCB) or provisional stenting.

Results: Primary endpoint: procedural success, defined as residual stenosis ≤30% without flow-limiting dissection, prior to DCB or stenting: 65.8% for IVL vs 50.4% for PTA (P=.01).

Other findings (IVL vs PTA):
Percentage lesions with residual stenosis ≤30%: 66.4% vs 51.9% (P=.02)
Flow-limiting dissection: 1.4% vs 6.8% (P=.03)
Any dissection: 18.5% vs 32.3% (P =.009)
Stent placement: 4.6% vs 18.3% (P <.001)
Final residual stenosis following DCB or stenting: 21.5% vs 20.7% (P=.39)

An interview with William A. Gray, MD

Main Line Health, Lankenau Heart Group, Wynnewood, Pennsylvania.



Why did you do the study and what were your findings?

The study was done to demonstrate what was felt to be the specific advantage of intravascular lithotripsy (IVL), an energy-augmented balloon angioplasty, in heavily calcified—and not necessarily undilatable—lesions. The early data from DISRUPT PAD I and II suggested that heavily calcified SFA/popliteal lesions could be successfully dilated using IVL at low pressure, 4 to 6 atmospheres, without significant need for stenting or significant dissection. The DISRUPT PAD III trial was intended to test the hypothesis that IVL was superior to standard PTA in this commonly encountered lesion set. When IVL was directly compared to standard of care PTA alone in heavily calcified lesions it was demonstrated that, indeed, IVL at relatively low pressures compared to PTA (at any pressure) was associated with lower residual stenosis, less dissection and less stent use.

Importantly, the trial was done in a population that has actually never before been tested in a randomized fashion, that being patients with heavily calcified lesions. Prior trials which have led to approval for a whole host of other devices have not included these lesions, so while we may employ them, there are little data to guide performance expectations or clinical outcomes. So, it's a valuable trial, not only because it

An interview with Christopher J. White, MD

Ochsner Medical Center, New Orleans, Louisiana.

Your editorial that accompanied the publication of the DISRUPT PAD III trial was fairly critical. Can you summarize your issues with the trial?

There has been a real dearth of head-to-head clinical trials with these devices that work adjunctively to percutaneous transluminal angioplasty (PTA) and drug-coated balloons (DCB) or stenting, so this trial is welcome. But I think the trial design stacked the deck unfairly in that they used a post-IVL (intravascular lithotripsy) and pre-definitive therapy endpoint—that being residual stenosis ≤30% without flow limiting dissection. This is where I said they made lemonade out of lemons because there was superiority in the IVL arm for this interim endpoint, but then there was no difference in the final outcome of the procedure after definitive therapy, which is what is really important. Final residual stenosis following DCB or stent placement did not differ between IVL and PTA, so why spend the time and money on the lesion prep?

To be fair, the authors acknowledge in their paper that this outcome is "novel" and have focused on their findings showing that IVL is superior to PTA for vessel preparation, but I still think that this endpoint was designed to guarantee a win for IVL.

demonstrates the value of the technology, but it also addresses a population which is fairly common in our practice, but has been very understudied.

In an editorial, Christopher White suggested that the more meaningful endpoint would be residual stenosis at the end of the procedure, and for this, no difference was seen between IVL and PTA. What was the thinking behind the choice of primary endpoint?

At the end of the procedure, I would say we saw success in both arms in terms of final residual stenosis. The question is how much effort, time and expense does it take to get that success? And, remember, the premise most of us are working under is that we're living in a DCB world now and we try to do things without stents in the femoropopliteal region to the extent that we can in many cases. So, given this, the implantation of a stent is not exactly a failure, but it's an additional cost, additional time in the lab, additional radiation, additional contrast—all the usual things that are in play in a more complex procedure. If you can make a complex lesion simple by using IVL, that is an important benefit.

More importantly, from a scientific standpoint, we needed to see whether IVL mechanistically had a better effect on calcium than angioplasty alone. In early studies, it was absolutely clear that it did, but we needed to do a randomized trial and not just speculate whether IVL would be better than PTA for dilating lesions.

Stents, mostly bare metal stents, were used more often in the PTA arm. Dr. White also pointed out that we know from studies that bare-metal stents are inferior to DCB, thereby perhaps stacking the deck against the PTA arm in longer-term follow-up. Can you comment on this?

Because of either incomplete dilation or a flow-limiting dissection, both of which are consequences of calcified lesion dilation, the operators felt they needed to use stents more often in the PTA arm. So, I would answer that criticism by suggesting that the differences seen in final treatment were a function of the mechanistic benefits gained from IVL in the study arm. A better preliminary result after IVL allowed for lower inflation pressure and resulted in fewer dissections, and therefore, less stent placement in the PTA arm—and by extension, more consideration of DCB in the IVL arm. Now, as Chris rightly pointed out, DCB use was higher in the IVL arm, but we couldn't protocolize how the operators completed the case since there is no ethical basis to do so, so we let them finish the case in whatever way they felt was needed, and that's where all the variability in final treatment arises.

Can you explain what you think the role of intravascular lithotripsy is?

There are two strategies that work hand-in-hand and from which you can view all these ancillary devices like lithotripsy or atherectomy. One of them is called lesion preparation, which means that you're doing something to the lesion to allow a definitive outcome to be obtained. The other is definitive therapy—can the device stand alone? Nobody is suggesting that IVL be used as definitive therapy. The point of IVL is to fracture the calcium so that you can dilate the lesion and inflate a balloon, but then the lesion still needs definitive therapy, a DCB or a stent, in most cases. We have IVL in our cath lab and we use it for undilatable lesions to permit full balloon or stent expansion. I have no argument with using this technology for that small subset of lesions.

You felt there was also some bias in the use of definitive therapy in this trial?

The choice of definitive therapy was up to the operator and the trial was unblinded. Patients in the plain old balloon angioplasty group didn't get drug-coated balloons. They were more likely to get bare-metal stents, which we know loses to DCB technology. So, I would say the definitive therapy was also weighted towards the IVL group and if we see better patency at one year, what we're really seeing is that DCB is better than BMS, which we already knew.

Now, I always tell my fellows that what we're after is long-term patency and it's all determined by acute gain—you want to make the artery as big as you possibly can without tearing it or rupturing it. And that's the theory behind fracturing calcium. When you can't inflate a balloon, that's when you need to do something to dilate the lesion, and fracturing calcium is an option. But, again, I see that as being relevant in only a few percent of patients coming with these heavily calcified lesions where the balloon is indeed restricted—not in the 70%-80% of calcified lesions where you can inflate the balloon.

I'd like to see a lot more trials of these other new technologies so that we can really assess what we're getting because they're expensive and it's hard to not lose money on these procedures, so we really need to see effectiveness.

The possibility of a synergistic interaction between DCB and IVL promoting the long-term effectiveness of revascularization is actually something we're interested in looking at more closely, because there has been some concern that DCBs are less effective in heavily calcified lesions. Accordingly, there is a pre-specified analysis of patency outcomes IVL versus PTA at one year, and we will need to assess outcomes not just using the varied strategies in each arm, but also in the populations who only received DCB to remove any confounding effects.

Where do you see IVL in 5 years?

Well, I think in the cycle of technologies, people are seeing value and benefit from IVL, and we're in the rapid adoption phase. Hopefully, we'll see reimbursement follow the datasets we're developing and that should help increase uptake over time. I think in 5 years, it will certainly be used more than it is now and will be considered one of our standard tools in these lesions.

REFERENCES

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