NEW YORK -- Renal denervation will have to go "back to square one," proving that the blood pressure effect is real, a think-tank report from industry, academics, and government suggested.

"We felt that prior to exposing several hundred, even a thousand people to a pivotal phase III trial, there should be some evidence that the device is efficacious," said William White, MD , chief of hypertension and clinical pharmacology at the University of Connecticut's Calhoun Cardiology Center in Farmington.

His group's report released in the May issue of the *Journal of the American Society of Hypertension* and discussed at a symposium at the society's annual meeting here came from discussions held before the announcement that the pivotal U.S. trial SYMPLICITY HTN-3 for Medtronic's catheter was stopping for futility and then St. Jude also halted its device's pivotal trial.

Despite the roughly 30/10 mmHg blood pressure drops seen in earlier phase trials , catheter-based renal artery nerve ablation yielded less than half that reduction, and the sham control group unexpectedly did almost as well in SYMPLICITY HTN-3.

Other recent randomized, controlled trials have supported a blood pressure lowering effect but only amounting to the effect of one antihypertensive drug -- far less than initially hoped, Sverre E. Kjeldsen, MD, PhD , of Ullevaal Hospital in Oslo, and colleagues noted in an editorial accompanying the think-tank scientific statement.

There are plenty of explanations for the failure of the SYMPLICITY HTN-3 trial, all raising issues that must be addressed in further trials, experts at the meeting pointed out.

"It remains unclear if the lack of superior efficacy in the only sham-procedure controlled trial is secondary to an ineffective radiofrequency catheter, operator variability, the patient population

and their complex antihypertensive treatment regimens, specifics of study design, off-protocol medication use by patients, issues related to study conduct, or 'all of the above,'" the editorialists wrote.

Medtronic has announced that trials are moving forward , and Sidney Cohen, MD, PhD, of the University of Pennsylvania in Philadelphia and a senior adviser for the company, explained what the first will be.

The first phase has two parallel trials:

- SPYRAL HTN-OFF MED with about 100 patients with 150-180/90+ mmHg hypertension taken off any antihypertensive medications and randomized to ablation with the company's newer generation renal denervation catheter or a sham procedure.
- SPYRAL HTN-ON MED with about 100 similar patients in the same randomization while on a thiazide diuretic, calcium channel blocker, and ACE inhibitor or angiotensin receptor blocker (ARB). While there is no requirement for being at a maximum tolerated dose, urine and plasma drug adherence testing and witnessed pill-taking before blood pressure checks are mandated.

After those trials, the pivotal SPYRAL HTN trial would commence based on lessons from the initial phase and include cost-effectiveness and quality of life data collection.

The OFF MED trial should "minimize the confounding effect of behavioral issues that likely impacted the SYMPLICITY HTN-3 trial outcomes," Cohen suggested.

All three would use ambulatory blood pressure monitoring in the primary endpoint, rather than office blood pressure as in prior trials, which should reduce variability, White said at the session. The trial ought to at least show 8 mmHg difference against the sham to be declared effective, he said.

"They've put a lot of thought into it," commented William Elliott, MD, PhD , chief of pharmacology at Pacific Northwest University in Yakima, Wash. "In 2018, I would be shocked if we end up with a bunch more negative trials."

Demonstrating safety isn't going to be enough, all agreed.

There's "general agreement we need to approach this in the same manner they do in bringing a new pharmaceutical agent to treating hypertension and first obtain data in the absence of antihypertensive drugs so there's no confusion about the blood pressures and the interactions," Cohen said.

Beyond just efficacy in reducing blood pressure, there ought to be an outcomes study as has been required in diabetes, William Cushman, MD , of the VA and University of Tennessee Medical Centers in Memphis, argued from the audience at the session.

"I don't know that the FDA will make it a requirement," he later told *MedPage Today*. "They don't have yet the marker, if you will, of potential harm that was seen with some of the diabetes drugs that led to their requiring long-term outcomes studies with the diabetes drugs.

"My personal opinion -- and I think I'm not alone in this -- is that any intervention approved to be given to patients long-term, year-in and year-out, should be submitted to randomized trials," he said. "The postmarketing observation, there are some things they will be able to pick up, but there are other things they won't be able to pick up in a registry because its not randomized.

"You really won't know if mortality is increased. You really don't know unless it's a strong marker that you're increasing the incidence of end-stage renal disease because you have no comparison group."

"I've sat on many guideline committees," he noted. "I was on JNC7 and JNC8. We could not recommend something unless there's data showing that outcomes are benefited. The FDA has more of a perspective that if it lowers blood pressure and it's relatively safe, we can approve it. They're not interested in whether this should be recommended by guideline committees or not. It's a different standard in my opinion."

There's no question that a registry was always going to be required as part of FDA and CMS approval, White noted. But, he said, "it's too soon to talk about that. It's back to square one."

But "right now, we're just happy with showing it works," Cohen said.

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