

# TRIUMPH: Triple Low-Dose Combo Pill a Success in Hypertension

Sue Hughes

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ORLANDO — A pill combining low doses of three antihypertensive medications decreased blood pressure faster and more effectively and increased the number of patients reaching goal compared with usual care, without increasing adverse effects, in a new study.

The TRIUMPH trial was presented here at the American College of Cardiology (ACC) 2018 Annual Scientific Session by Ruth Webster, MBBS, from The George Institute for Global Health at the University of New South Wales in Sydney, Australia.

"This approach of triple low-dose therapy from the start of antihypertensive treatment is appropriate for all parts of world as many patients are not reaching target blood pressure everywhere," she said. "But the most urgent need is for effective implementation and scale up in low- and middle-income countries, which have the greatest hypertension burden."

Discussing the trial at an ACC press conference, Karol Watson, MD, professor of medicine/cardiology at the David Geffen School of Medicine at the University of California Los Angeles, described the results as "a home run."

"This is something we've known about for a long time but we don't do it," she said. "We've been told in older guidelines to up-titrate drugs as far as we can and then add in a second drug, but with this approach you get increased adverse effects and not much better efficacy."

"Now we have new guidelines saying we can start with two drugs if the patient has really high pressure," she added. "But with this approach of using low-dose triple therapy we can go in straight away with three drugs and the patient doesn't even have to be that high."

In her presentation, Webster explained that despite the availability of a wide variety of cheap effective antihypertensive drugs, most people receive only one or maybe two drugs, and only one third manage to reach their target blood pressure.

"We are leaving efficacy on the table and as a consequence many more heart attacks and strokes are occurring than necessary," she said. "We don't necessarily need a new blockbuster drug, we need a novel way of using what we already have."

She noted that the advantages of low-dose combinations include additive benefits of multiple different mechanisms from different drug classes but minimal side effects. "Eighty percent of the effectiveness of blood pressure medication is achieved at half the standard dose — you only get an extra 20% efficacy by titrating up to the full dose. But most of the side effects happen in that higher part of the dose."

The TRIUMPH trial, which was conducted in Sri Lanka, enrolled 700 patients (average age, 56 years; 58% female) with an average blood pressure of 154/90 mm Hg. Over half (59%) were not receiving any blood pressure treatment, and 32% had diabetes or chronic kidney disease.

Patients were randomly assigned to receive usual care or the triple combination pill, which included telmisartan (20 mg), amlodipine (2.5 mg), and chlorthalidone (12.5 mg).

Webster said, "The actual drugs included are probably are not as important as the idea of using low doses of three different antihypertensive drug classes."

The primary endpoint was the proportion of patients reaching target pressure of 140/90 mm Hg or less (130/80 mm Hg or less in those with diabetes or chronic kidney disease) at 6 months.

The target was achieved in 69.5% of the triple therapy group vs 55.3% of the usual care group (RR, 1.23; 95% CI, 1.09 - 1.39).

Webster said the 55% figure for the usual care group was better than would be expected in the real world "probably because the patients and the physicians knew they were in the trial."

The mean overall difference in blood pressures were  $-9/8$  mm Hg for systolic and  $-5$  mmHg for diastolic in the triple therapy group. The difference was achieved by 6 weeks and was maintained out to 6 months.

In terms of safety, the triple combination was well tolerated, with no difference in adverse effects or withdrawal due to adverse effects compared with usual care.

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## Will It Be Embraced in the United States?

Commenting for *theheart.org* | *Medscape Cardiology*, George Bakris, MD, director of the ASH Comprehensive Hypertension Center at the University of Chicago, Illinois, said the approach made perfect sense and while it could be a great strategy for lower- and middle-income countries, he thought cultural and commercial barriers may prevent it from taking off in the West, at least in the near future.

"It's an obvious strategy — if you use three drugs with complementary mechanisms you will get better blood pressure lowering," Bakris said. "The problem is getting family doctors — who are the ones who will be treating these patients — to do this.

"They have not been trained to prescribe like this. It is difficult enough getting them to prescribe a two-pill combination, but to ask them to prescribe a three-pill combination would really need a shift in attitude," he said. "They believe more drugs equals more side effects. This is clearly not case if they are used in low dose, but it is not in their culture to do this."

While the availability of a single pill containing the three medications would make the situation much easier, Bakris does not see this happening in the United States.

"These drugs are all generic and there is no money to be made from them. I doubt that a generic manufacturer would make a triple combination product as the culture is not there to prescribe it."

Bakris does, however, believe this triple therapy approach could be successful in lower- and middle-income countries. "This would be especially true if some health organization manufactured a triple therapy pill. An awful lot of good could be done with widespread use of such a pill."

Also commenting for *theheart.org* | *Medscape Cardiology*, Franz Messerli, MD, professor of medicine, University of Bern, Switzerland, said the trial was "well done" and the better results with triple therapy were of "little surprise." But he raised a few points for consideration.

"We are left somewhat in the dark what exactly was done in this usual care arm," he said. "But most patients remained on monotherapy, which presumably was up-titrated. Time and again it has been documented that combination therapy is several times more efficacious in lowering blood pressure than is up-titration."

He added that the triple combination contained chlorthalidone, "which is an exceedingly efficacious antihypertensive drug. Presumably hydrochlorothiazide would have been used in the usual care arm, which is short-acting and one of the weakest antihypertensives."

Finally, he added, "there is little question that some patients in the triple arm could have been controlled with one or two drugs so thus received more drugs than they needed, although potential adverse effects were still acceptable." Messerli suggested that more care would be needed if an angiotensin-converting enzyme inhibitor had been used instead of an angiotensin blocker.

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