Evidence-Based Triple Antihypertensive Therapy Yields Lower Mortality in Older Patients With Diabetes Mellitus

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The use of initial single-pill combination antihypertensive therapy has been present since 1966 with the single-pill combination of reserpine, hydrochlorothiazide, and hydralazine widely available and used. Since the 1980s, there have been several antihypertensive combinations using drug classes with complementary pharmacological mechanisms joined in a single pill or given independently to help achieve blood pressure (BP) goals. The post hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial in the current issue of the journal extends our data on the use of antihypertensive combinations to help achieve BP goals.

Initial single-pill combination therapy for treatment of hypertension has been strongly supported by guidelines in both the United States and Europe since 2003. The data are now overwhelming that the use of single-pill combination antihypertensive agents is associated with improved adherence, fewer adverse effects, and a higher attainment of BP goals. A randomized multicenter clinical trial to assess achievement of BP goals using an angiotensin-converting enzyme inhibitor plus a thiazide diuretic versus a conventional approach demonstrated superiority of the single-pill combination. The only cardiovascular outcome trial to randomize single-pill combinations, however, was the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH). This trial randomized a single pill of benazepril plus amlodipine versus benazepril/hydrochlorothiazide. The trial was stopped early because of a 20% greater cardiovascular risk reduction in the benazepril plus amlodipine group.

One hypothesis for this benefit is the potential additive benefit of amlodipine plus benazepril on NO increases and improvement in endothelial function observed in animal models, an effect not seen with thiazide diuretics. Such effects are reported for perindopril and amlodipine in animals and in humans. The current post hoc analysis of the ADVANCE trial further expands our knowledge about combination therapy by demonstrating that the group of patients with type 2 diabetes mellitus receiving the triple combination of perindopril plus indapamide plus a calcium channel blocker (CCB) had lower total mortality and fewer cardiovascular deaths than those not receiving a CCB. It is unclear what the major drug used to represent CCBs was as the different CCBs used in the trial are not listed. It is also of note that the sicker patients based on risk factors in the trial received the CCB, whereas others did not. Therefore, one could say that sicker patients requiring better BP control may benefit from a CCB as an additional therapy to an angiotensin-converting enzyme inhibitor and thiazide-type diuretic.

The benefit on total and cardiovascular death was seen independent of BP reduction because the group on CCBs had a 4.7 mmHg systolic BP reduction, whereas the non–CCB group had a 6.2 mmHg reduction. Yet there was a 28% reduction in risk of death in the CCB group versus a 5% in the non–CCB group (P homogeneity, 0.02).

What are the possible explanations for this outcome? It is clear that patients that require a third medication to achieve BP control tend to have worse kidney function. Unfortunately, these data were not presented in the article because single-pill combinations of CCBs with angiotensin-converting enzyme inhibitors have better outcome on kidney disease progression. Another explanation is that the triple combination used in this trial had 2 of the 3 components (ie, perindopril and indapamide have proven to reduce cardiovascular outcomes in 2 other trials besides ADVANCE). Thus, adding a CCB, especially one that may affect the vascular endothelium, such as amlodipine, may have provided that additional benefit seen in ACCOMPLISH and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trials. Another point of this trial taken together with the other trials that randomized perindopril and indapamide is that all the patients were older with a mean age at baseline ranging from 66 to 83 years. Hence, the data from the current study have demonstrated proven safety and efficacy in older patients with diabetes mellitus.

There are 2 approved single-pill triple therapy combinations in the United States, olmesartan plus amlodipine plus hydrochlorothiazide and valsartan plus amlodipine plus hydrochlorothiazide. These have not been tested in outcome trials and neither has a diuretic that has proven efficacy in a clinical outcome trial; however, it is safe and does lower BP but with a shorter half-life when compared with indapamide that is also 10-fold more potent. There are no direct clinical trial comparisons of triple combination BP-lowering agents, but the benefit in ADVANCE was independent of BP differences. Hence, although controlling BP is key to reducing cardiovascular risk, the use of a triple combination with agents that have been shown to be of benefit in outcome trials by themselves and act synergistically at the vascular level.
portend a better cardiovascular outcome than using conventional agents without such data.

Disclosures
Dr Bakris is a consultant for AbbVie, Daiichi-Sankyo, Takeda Pharmaceutical Company Limited, Novartis, Medtronic, Reglypsa, Boeringher-Ingelheim, Janssen Pharmaceuticals, Inc, Eli Lilly and Company, and Bristol-Myers Squibb. Dr Yamout reports no conflicts.

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