Initial combination therapy for hypertension in patients of African ancestry: a systematic review and meta-analysis

L.M. Brewster[1], A. Boermeester[2], Y.K. Seedat[3], G.A. Montfrans[4]

[1]CK Science Foundation, Amsterdam, Netherlands (The); [2]School of Pharmacy - Faculty of Science - Universiteit Utrecht, Utrecht, Netherlands (The); [3]University of KwaZulu Natal, Internal Medicine, Durban, South Africa; [4]Academic Medical Center, Internal Medicine, Amsterdam, Netherlands (The)

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Background: Initial antihypertensive combination therapy is considered the standard of care in most patients with hypertension. However, while monotherapy with calcium channel blockers (CAB) or Diuretics is known to have greater blood pressure lowering efficacy than other drugs in African ancestry (AA) patients, it is unclear which initial combination therapy is most effective. Therefore, we systematically reviewed the existing evidence on different initial dual combination therapies in these patients.

Methods: We searched for published and unpublished randomized controlled trials (RCTs) in AA adults with uncomplicated, primary hypertension, which compared two or more initial dual combination drug therapies, and reported blood pressure, morbidity, or mortality outcomes. Searches were conducted without language restriction in electronic databases including PubMed, Embase, CENTRAL, preprint servers, and clinical trial registers, from their inception through March 31, 2021. In addition, we conducted hand search, and contacted authors and pharmaceutical companies for missing information. Trial quality was assessed using the Jadad score.

Results: We retrieved 1728 reports yielding 10 RCTs (Jadad score 1 to 4, median 3) conducted on 4 continents. Trials' treatment duration was 4 to 156 (median 10) weeks, using combinations of 6 classes of drugs in 23 treatment arms, and providing data on blood pressure (n=10 trials) and morbidity/mortality (n=1 trial) in 3715 patients (34.2% men) aged 18 to 79 years.

Initial combination therapy with Diuretics+CAB (vs Diuretics+ACE-inhibitors (ACEI) or Angiotensin II type 1 receptor antagonists (ARB); 4 comparisons) resulted in comparable systolic (SBP) (n=467; –0.10 [–0.23 to –0.03] mm Hg), and diastolic blood pressure (DBP) (n=408; –0.03 [–0.19 to 0.12]). Adverse effects included more hypokalaemia and hyperglycaemia with Diuretics+CAB than Diuretic+ACEI/ARB. No morbidity or mortality outcomes were available.

Initial combination therapy with CAB+ACEI/ARB (vs Diuretics+ACEI/ARB; 7 comparisons) also resulted in comparable blood pressures (n=2266; SBP: –0.49 [95% CI, –0.87 to –0.12] and DBP –0.55 [–0.97 to –0.14]); but CAB+ACEI/ARB showed less adverse effects (hypokalaemia, hyperglycaemia), and a trend toward reduced cardiovascular disease and mortality (n=1414; mean follow up 3 y; Amlodipine/Benazepril vs HCT/Benazepril, combined cardiovascular disease and mortality (6.6 vs 8.9%, P=0.10), without significant differences in Stroke (2.2 vs 2.1%, P=0.97), or heart failure (1.7 vs 2.2%, P=0.50).

Conclusion: In relatively young AA patients with uncomplicated hypertension, initial dual combination therapy including CAB, Diuretics, or Diuretics+CAB results in comparable blood pressures, but adverse metabolic effects are lower without a diuretic. Knowledge gaps include data on biomarkers to replace race/ancestry, data by sex and in the elderly, and end point data, including on Diuretic/CAB and CAB/ARB combinations.