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Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial

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Summary

Background

Treatment inertia is a recognised barrier to blood pressure control, and simpler, more effective treatment strategies are needed. We hypothesised that a hypertension management strategy starting with a single pill containing ultra-low-dose quadruple combination therapy would be more effective than a strategy of starting with monotherapy.

Methods

QUARTET was a multicentre, double-blind, parallel-group, randomised, phase 3 trial among Australian adults (≥18 years) with hypertension, who were untreated or receiving monotherapy. Participants were randomly assigned to either treatment, that started with

the quadpill (containing irbesartan at 37·5 mg, amlodipine at 1·25 mg, indapamide at 0·625 mg, and bisoprolol at 2·5 mg) or an indistinguishable monotherapy control (irbesartan 150 mg). If blood pressure was not at target, additional medications could be added in both groups, starting with amlodipine at 5 mg. Participants were randomly assigned using an online central randomisation service. There was a 1:1 allocation, stratified by site. Allocation was masked to all participants and study team members (including investigators and those assessing outcomes) except the manufacturer of the investigational product and one unmasked statistician. The primary outcome was difference in unattended office systolic blood pressure at 12 weeks. Secondary outcomes included blood pressure control (standard office blood pressure <140/90 mm Hg), safety, and tolerability. A subgroup continued randomly assigned allocation to 12 months to assess long-term effects. Analyses were per intention to treat. This trial was prospectively registered with the Australian New Zealand Clinical Trials Registry, ACTRN12616001144404, and is now complete.

Findings

From June 8, 2017, to Aug 31, 2020, 591 participants were recruited, with 743 assessed for eligibility, 152 ineligible or declined, 300 participants randomly assigned to intervention of initial quadpill treatment, and 291 to control of initial standard dose monotherapy treatment. The mean age of the 591 participants was 59 years (SD 12); 356 (60%) were male and 235 (40%) were female; 483 (82%) were White, 70 (12%) were Asian, and 38 (6%) reported as other ethnicity; and baseline mean unattended office blood pressure was 141 mm Hg (SD 13)/85 mm Hg (SD 10). By 12 weeks, 44 (15%) of 300 participants had additional blood pressure medications in the intervention group compared with 115 (40%) of 291 participants in the control group. Systolic blood pressure was lower by 6·9 mm Hg (95% CI 4·9–8·9; p<0·0001) and blood pressure control rates were higher in the intervention group (76%) versus control group (58%; relative risk [RR] 1·30, 95% CI 1·15–1·47; p<0·0001). There was no difference in adverse event-related treatment withdrawals at 12 weeks (intervention 4·0% *vs* control 2·4%; p=0·27). Among the 417 patients who continued, uptitration occurred more frequently among control participants than intervention participants (p<0·0001). However, at 52 weeks mean unattended systolic blood pressure remained lower by 7·7 mm Hg (95% CI 5·2–10·3) and blood pressure control rates higher in the intervention group (81%) versus control group (62%; RR 1·32, 95% CI 1·16–1·50). In all randomly assigned participants up to 12 weeks, there were seven (3%) serious adverse events in the intervention group and three (1%) serious adverse events in the control group.

Interpretation

A strategy with early treatment of a fixed-dose quadruple quarter-dose combination achieved and maintained greater blood pressure lowering compared with the common strategy of starting monotherapy. This trial demonstrated the efficacy, tolerability, and simplicity of a quadpill-based strategy.

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