

Treating hypertension with a pill containing very low doses of four antihypertensive agents compared with standard dose irbesartan



Abubaker Eltayeb,¹ Teck K Khong²

¹St George's University Hospital NHS Trust, London, UK

²Clinical Pharmacology, St George's University of London, London, UK

Correspondence to Dr Teck K Khong; tkhong@sgul.ac.uk

Commentary on: Chow CK, Atkins ER, Hillis GS, *et al.* 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. *Lancet.* 2021;398:1043–52.

Series co-ordinator: Dr Teck Khong, DTB Associate Editor Clinical Pharmacology, St George's, University of London, UK

Key learning points

- ▶ Evidence indicates that management of hypertension is suboptimal with many people not achieving good blood pressure control.
- ▶ Clinical inertia, concerns over the risk of adverse effects from multiple antihypertensive medication and low rates of adherence, may explain why treatment is often suboptimal.
- ▶ A double-blind randomised controlled trial compared the effect of initial treatment with a pill containing low doses of four antihypertensive medications compared with monotherapy with a standard dose of irbesartan.
- ▶ The combination pill resulted in greater blood pressure reduction with higher rates of blood pressure control compared with monotherapy over a 12-week and 52-week period.
- ▶ The combination pill was associated with increased reports of bradycardia as well as episodes of systolic blood pressure <100 mm Hg and dizziness.

Summary

This multicentre double-blind randomised trial showed that initial treatment with daily dosing of a single combination pill containing four medicines at a quarter of their standard dose (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg and bisoprolol 2.5 mg) resulted in faster and greater blood pressure (BP) reduction with higher rates of BP control compared with monotherapy with irbesartan 150 mg/day in 591 hypertensive individuals over a 12-week and 52-week period. At 52 weeks, the number of serious adverse events was similar in both groups.¹

Study details

This Australian multicentre, double-blind, active control, randomised trial compared a once-daily single pill containing low doses of four antihypertensive medicines with monotherapy using irbesartan

150 mg/day for 12 weeks for people with hypertension.¹ The quadpill contained irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg and bisoprolol 2.5 mg and was formulated to appear identical to irbesartan monotherapy. The study recruited adults (≥18 years) with untreated hypertension or those receiving antihypertensive monotherapy based on BP readings taken within the preceding 12 weeks. Untreated patients had a clinic systolic BP (SBP) of 140–179 mm Hg and/or diastolic BP (DBP) of 90–109 mm Hg; or, an average daytime SBP ≥135 and/or DBP ≥85 mm Hg on 24-hour ambulatory BP (ABP) monitoring (ABPM). Patients on monotherapy had a clinic SBP of 130–179 mm Hg and/or DBP of 85–109 mm Hg; or an average day-time SBP ≥125 mm Hg and/or DBP ≥80 mm Hg based on 24-hour ABPM. Patients on monotherapy were asked to stop their treatment at randomisation. The

primary outcome was the difference in the mean of unattended SBP at 12 weeks based on three automated unattended office measures. Secondary outcomes included unattended office DBP at 12 weeks and 52 weeks, and unattended office SBP at 52 weeks; attainment of BP control (<140/90 mm Hg standard office measurement) at weeks 6, 12, 26 and 52; attainment of tight BP control (<120/80 mm Hg); 24-hour ABPM; requirement for step-up treatment and safety and tolerability. Patients were assessed at baseline, 6 weeks and 12 weeks. At 12 weeks, participants were invited to continue in a follow-up phase up to 52. At week 6, amlodipine 5 mg/day could be added if BP >140/90 mm Hg. Where needed, additional open-label BP-lowering medication was initiated at the discretion of the treating doctor with advice provided regarding maximum recommended doses for such therapy.

A total of 591 patients (60% men, mean age 59 years) were randomised and the study's authors reported that 82% were white and 12% were Asian.¹ At baseline, 54% were not being treated for hypertension, 8% had diabetes, 8% were current smokers and 0.2% had chronic kidney disease. Patients had unattended and observed office BP of 141 (\pm 13)/85 (\pm 13) mm Hg and 153 (\pm 15)/89 (\pm 11) mm Hg, respectively, total cholesterol 5.3 (\pm 1.1) mmol/L, and body mass index of approximately 31 kg/m².

At 12 weeks, in those randomised to the quadpill, 15% had received additional antihypertensive medication (with 11% being on the quadpill plus one additional antihypertensive and 0.4% being on the quadpill and two additional antihypertensives).¹ In those randomised to irbesartan monotherapy, 40% had received additional antihypertensive medication (with 32% being on irbesartan plus one additional antihypertensive and 7% being on irbesartan plus two additional antihypertensives). Adherence to the study medication was 87% and 84% in the intervention and control groups, respectively.

The primary outcome of unattended office BP was 120 (\pm 14)/71 (\pm 10) mm Hg and 127 (\pm 13)/79 (\pm 10) mm Hg in the intervention and control groups, respectively, with a mean SBP difference between the groups of -6.9 mm Hg (95% CI -4.9 to -8.9 ; $p < 0.001$).¹ The mean 24-hour systolic ABP was 7.5 mm Hg lower (95% CI -9.0 to -5.9) in the intervention compared with the control group. Office BP control $< 140/90$ mm Hg was achieved in 76% versus 58% in the intervention and control groups, respectively (relative risk (RR) 1.30, 95% CI 1.2 to 1.5; $p < 0.0001$).

At 12 weeks, SBP < 100 mm Hg occurred in 6.0% of the intervention group and 2.5% ($p < 0.01$) of the control group, and a heart rate < 50 bpm was found in 12.4% of the intervention group and 0.4% of the control group ($p < 0.01$).¹ Dizziness was recorded in 31% and 25% (RR 1.27, 95% CI 0.98 to 1.64; $p = 0.07$) in the intervention and control groups, respectively. Serious adverse events occurred in 3% of the intervention group and 1% in the control group. The difference between the groups in withdrawals due to adverse events was not statistically significant.

In all, 417 of the study participants took part in the extended follow-up period.¹ At 12 months, the mean unattended office BP was 121 (\pm 13)/71 (\pm 9) mm Hg in the intervention group and 128 (\pm 13)/76 (\pm 9) mm Hg in the control group, with a mean difference in SBP between the groups

of -7.7 mm Hg (95% CI -5.2 to -10.3 ; $p < 0.0001$). The mean 24-hour systolic ABP was -6.0 mm Hg (-8.8 to -3.2) lower in the intervention compared with the control group. Office BP control $< 140/90$ mm Hg was attained by 81% compared with 62% in the intervention and control groups, respectively (RR 1.3, 95% CI 1.2 to 1.5; $p < 0.0001$).

At 12 months, serious adverse events were reported in 7.3% in the intervention group and 6.6% in the control group, with treatment discontinuation due to any adverse event occurring in 7.3% and 3.8% (RR 1.92, 95% CI 0.83 to 4.35; $p = 0.12$) in the intervention and control groups respectively.¹

Authors' conclusion

The authors concluded that early treatment with a fixed-dose combination pill containing four antihypertensive medicines at a quarter of their standard dose achieved and maintained greater blood pressure lowering compared with the common strategy of starting monotherapy.

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Trial registration

The trial was registered with the Australian New Zealand Clinical Trial Registry (<https://www.anzctr.org.au/>): ACTRN12616001144404.

Commentary

High blood pressure remains a major risk factor for preventable morbidity and mortality across the globe.² Despite multiple treatments available, in the UK, over 40% of individuals with diagnosed hypertension have poor and inadequate BP control, with suboptimal adherence a key factor.^{3,4} The latter is positively correlated with the number of pills prescribed such that non-adherence rates rise from $< 10\%$ when one pill is prescribed to $\geq 40\%$ when three or more are prescribed.⁵ It is also recognised that combining lower doses of antihypertensive agents acting on different pathways can reduce adverse effects and be more effective than maximal-dose monotherapy. Thus, findings from this study add to the literature on the additive effects of a rational combination of lower doses of different antihypertensives^{6,7} and the potential benefits of a fixed-dose

combination therapy in improving adherence.^{6,7} These are highly relevant to strategies—both at an individual patient level and at a system-wide level—aimed at tackling the adverse outcomes of hypertension.

The QUARTET trial compared the use of ultralow doses of four antihypertensive agents in a single formulation (described by the authors as a quadpill rather than a polypill) with standard dose irbesartan in the initial management of hypertension.¹ It showed that BP reduction with the quadpill over a 12-week and 52-week period was sustained, faster and greater (by approximately 7 mm Hg for SBP) than initial monotherapy with irbesartan 150 mg/day; and, was associated with a higher likelihood of achieving BP control. While its findings are clearly positive, further consideration of several aspects of the trial may be helpful.

The study was designed to compare the quadpill with routine practice. However, it is unclear how representative the use of irbesartan 150 mg/day is of clinical practice or of recommended and best standard of care in patients, who, in this study, were predominantly white with a mean age of 59 years and SBP of 153 mm Hg. Guidance from the National Institute for Health and Care Excellence recommends initial treatment of hypertension with calcium channel blockers for those aged ≥ 55 years who do not have diabetes, and an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist for those who have diabetes or are aged < 55 years—reflecting the effect of age on BP-lowering responses to the respective antihypertensive agents.⁸ In fact, other major guidelines^{7,9} suggest combination therapy be considered as initial management of hypertension in the majority, reserving monotherapy for those with BP $< 150/90$ mm Hg and low cardiovascular risk, very high-risk patients with high-normal BP and frail older patients.^{7,9} Such a strategy is advocated because monotherapy is insufficient to achieve BP control in the majority of hypertensive individuals; and, as evidence suggests, fixed dose regimens, which reduce pill burden can improve adherence, overcome prescriber inertia, lead to faster and greater rates of BP control.

Although containing quarter-maximal doses of its constituent antihypertensives, the quadpill included bisoprolol at a low but therapeutic dose of 2.5 mg. Beta-blockers appear to be less effective in preventing stroke as well as some other markers of target organ damage in hypertension, increase the risk of new-onset diabetes, have a less favourable adverse effect profile and are associated with higher rates of

treatment discontinuation. Consequently, major guidelines do not recommend beta blockers for the initial management of uncomplicated hypertension but for specific indications such as resistant hypertension, individuals with concomitant coronary heart disease or heart failure and those in or planning pregnancy.⁷⁻⁹ With the quadpill, greater number of people were recorded as having bradycardia, SBP <100 mm Hg and to report dizziness; and so, caution will be required with its use.

Furthermore, in contrast to the extensive evidence base for the safe and effective long-term use of existing combinations of antihypertensive agents at therapeutic doses—including fixed-dose combination formulations—longer term safety (including on incidence of diabetes) and outcome data with the quadpill are presently limited. In addition, in contemplating use of the quadpill, direct comparisons with established antihypertensive combinations will also be desirable. Thus, overall, a potential role for the quadpill in clinical practice and within current management algorithms for the initial management of uncomplicated hypertension remains uncertain and to be determined.

Notwithstanding, the QUARTET trial has importantly highlighted the need and challenges of treating hypertension adequately, and the potential role of combination antihypertensive therapy—including those containing low doses of multiple anti-hypertensive, in helping achieve BP control.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

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