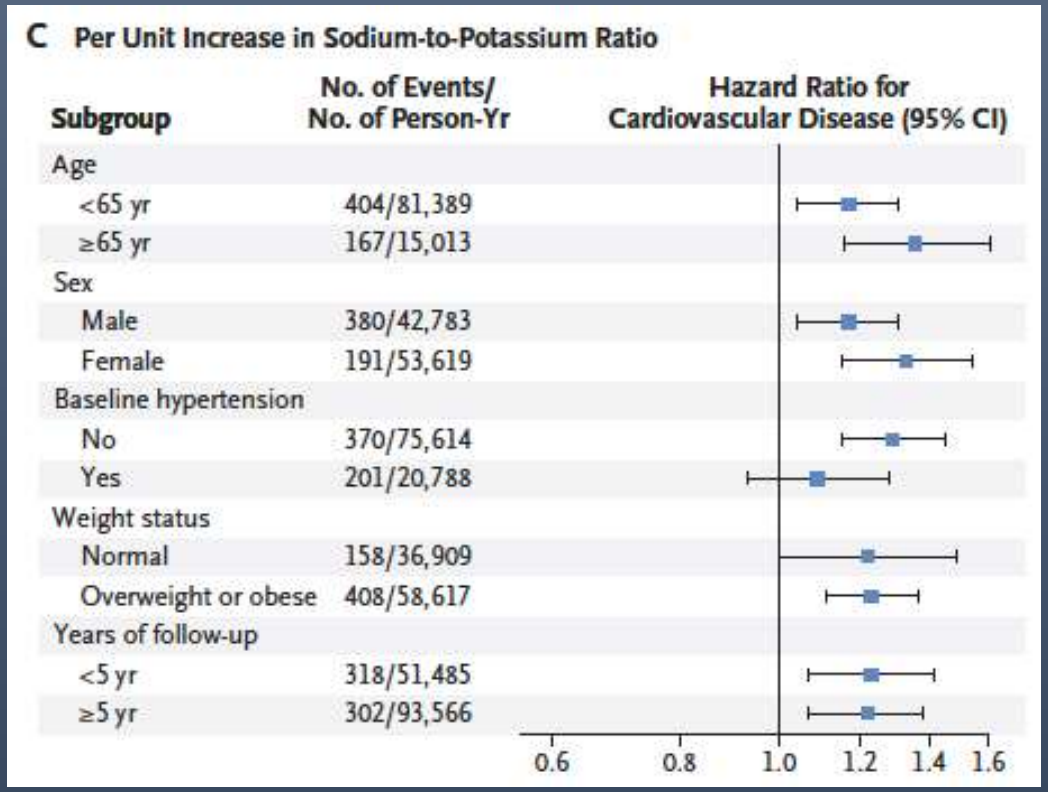
- Potassium supplementation of ≥60 mmol per day (>2.5 g/day) lowered SBP by ~4.4 mm Hg, and DBP by ~2.5 mm Hg in hypertensive subjects

- Potassium supplementation lowered SBP by ~1.8 mm Hg and DBP by ~ 1.0 mm Hg in normotensive subjects

- Antihypertensive effect was independent of a baseline potassium deficiency, and was greater at higher levels of sodium excretion

N Engl J Med 2007;356:1966-78.

Urinary Na: K ratio and CV risk



24% increase in risk for CV events for each unit of increase in Na: K ratio in a healthy population

N Engl J Med 2022;386:252-63.

Summary

- Homeostasis of sodium and potassium plays an important role in endothelium-dependent vasodilatation which is defective in primary hypertension.
- Urinary K: Na ratio bore a stronger relationship to BP than did either sodium or potassium excretion alone
- Recommended daily sodium intake 50 – 55 mmol (2.9 – 3.8g NaCl/day) and potassium 120 mmol (4.7 g/day) in the general population, modifications for special groups

N Engl J Med 2007;356:1966-78.

Which statement is true?

A. People with >100 mmol of sodium intake per day are hypertensive
B. Patients with chronic kidney disease have reduced salt sensitivity
C. Urinary K to Na ratio has an inverse relationship with BP
D. Increase in urinary Na to K ratio is associated with increased CV risk

K to Na ratio appears to be **more strongly** associated with BP outcomes than urinary sodium or potassium alone in hypertensive patients

Antihypertensive treatment initiation

- The most common approach to HTN management is still on starting patients on monotherapy
- Treatment inertia and concerns regarding adverse events are common barriers to effective management of hypertension
- Low dose, single pill combinations help to overcome these barriers
- Combination of 2 drugs at low doses may mutually interfere with compensatory responses, and hence improve SBP control with a significantly higher proportion of patients attaining target BP without adverse events

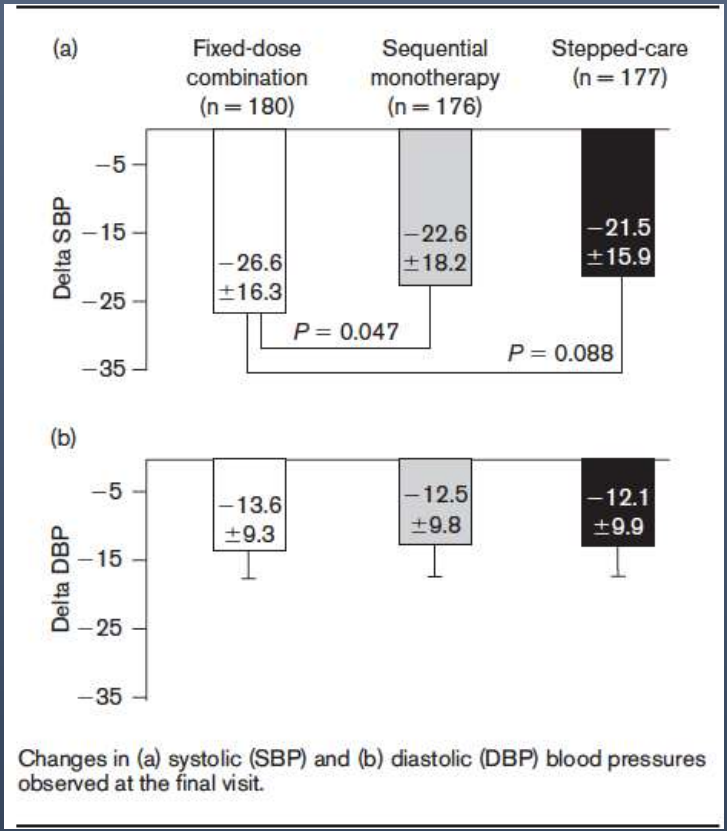
First line low-dose combination therapy compared with stepped-care approach and sequential monotherapy

- Combination: Perinodpril + Indapamide (2/0.625 mg) → 3/0.937 mg → 4/1.25mg
- Sequential: Atenolol 50mg/d → Losartan 50mg/d → Amlodipine 5mg/d
- Stepped care: Valsartan 40mg/d → Valsartan 80mg/day → addition of HCTZ 12.5mg

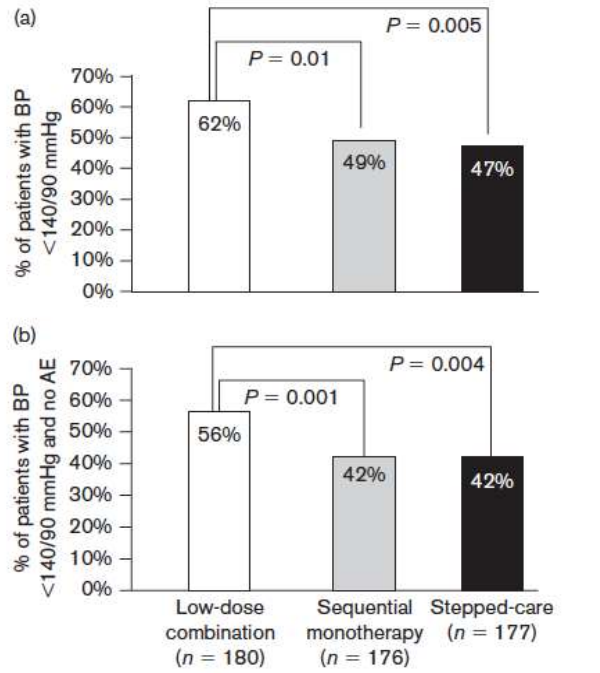
Titrated at 3 & 6 months

Investigators of the STRATHE trial. J Hypertens 2004; 22: 2379 – 2386.

Low dose combination therapy: greater SBP reduction without excess adverse events at 6 months



Changes in (a) systolic (SBP) and (b) diastolic (DBP) blood pressures observed at the final visit.



(a) Percentage of patients having their blood pressure (BP) normalized (< 140/90 mmHg) at the last visit of the trial. (b) Shows the percentage of patients who normalized their BP without developing any adverse event (AE).

Adverse events similar in 3 groups

19% (combination)
22% (sequential)
20% (stepped care)

Investigators of the STRATHE trial. J Hypertens 2004; 22: 2379 – 2386.

Combination antihypertensive therapies

- Limited BP reduction with monotherapy agents
  - 26 – 40% achieve goal BP targets
- Inter-patient variability of different antihypertensive agents
  - Interfere with counter-regulatory responses
- Combination therapies improve tolerability
- Adherence may be improved by single pill combinations
  - Caveat: ACEi or ARB combination with sub optimally-dosed hydrochlorothiazide

Table
Drug Combinations in Hypertension: Recommendations

Preferred
ACE inhibitor/diuretic*
ARB/diuretic*
ACE inhibitor/CCB*
ARB/CCB*
Acceptable
β-blocker/diuretic*
CCB (dihydropyridine)/β-blocker
CCB/diuretic
Renin inhibitor/diuretic*
Renin inhibitor/ARB*
Thiazide diuretics/K+ sparing diuretics*
Less effective
ACE inhibitor/ARB
ACE inhibitor/β-blocker
ARB/β-blocker
CCB (nondihydropyridine)/β-blocker
Centrally acting agent/β-blocker

ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker.
* Single pill combinations available in the United States.

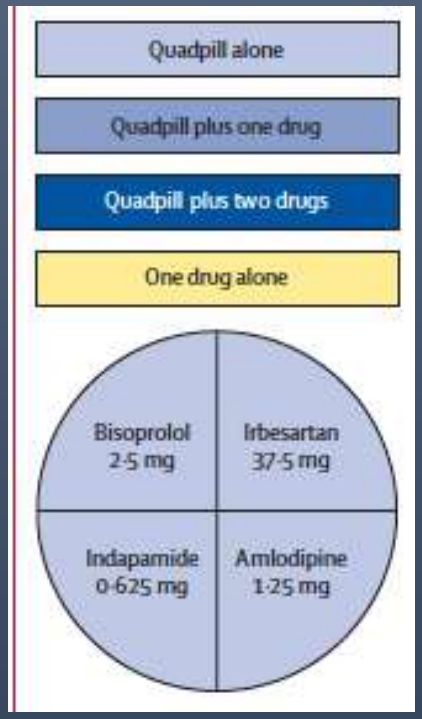
American Society of Hypertension Writing Group. J Am Soc Hypertens 2010;4:90 – 98.

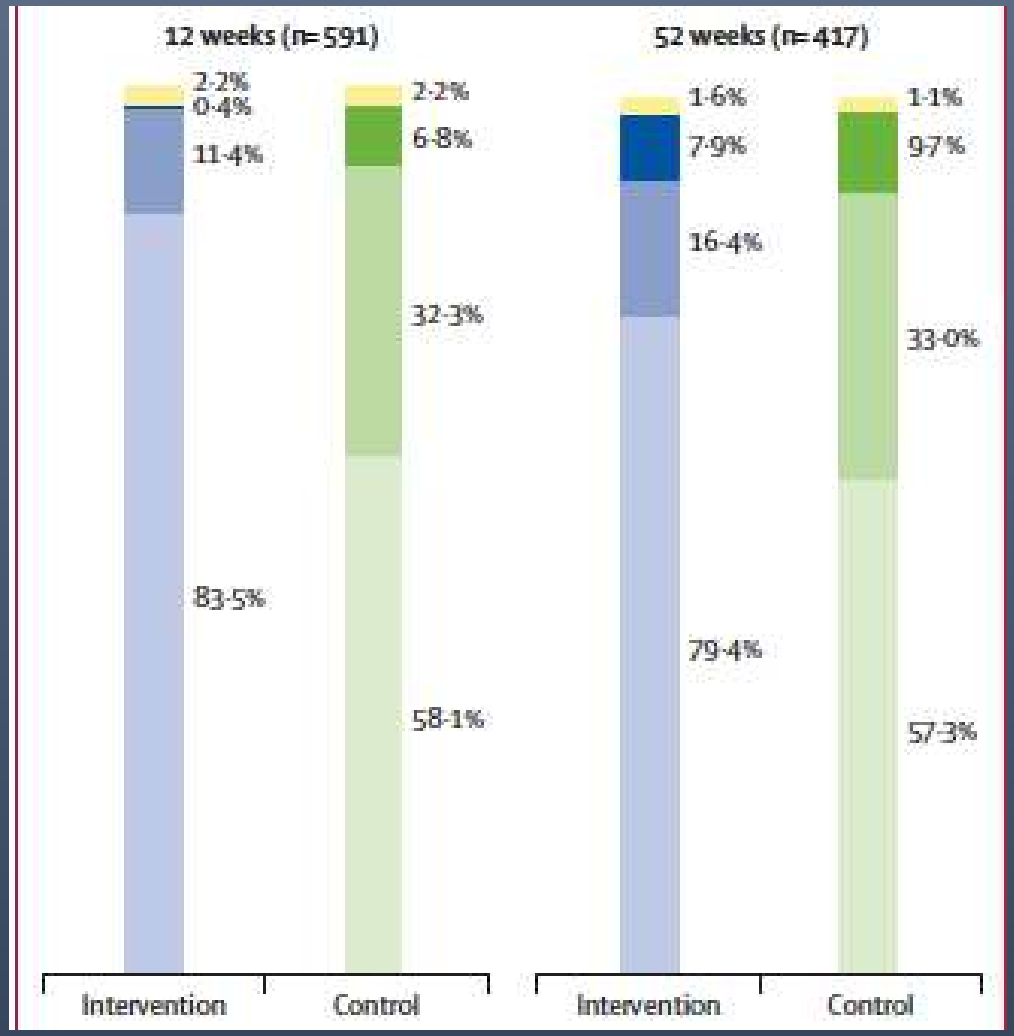
Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial

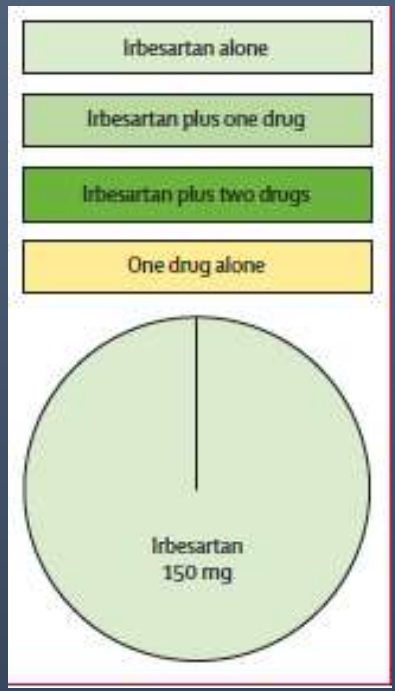
Clara K Chow, Emily R Atkins, Graham S Hillis, Mark R Nelson, Christopher M Reid, Markus P Schlaich, Peter Hay, Kris Rogers, Laurent Billot, Michael Burke, John Chalmers, Bruce Neal, Anushka Patel, Tim Usherwood, Ruth Webster, Anthony Rodgers, on behalf of the QUARTET Investigators

- Australian multicentre, double-blind Phase 3RCT
- 12 week trial
- Untreated hypertension or receiving monotherapy (N=591)
- Quadpill (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg and bisoprolol 2.5 mg) vs sequential treatment
- Baseline office BP 141/85 mmHg

***Lancet* 2021; 398: 1043–52**

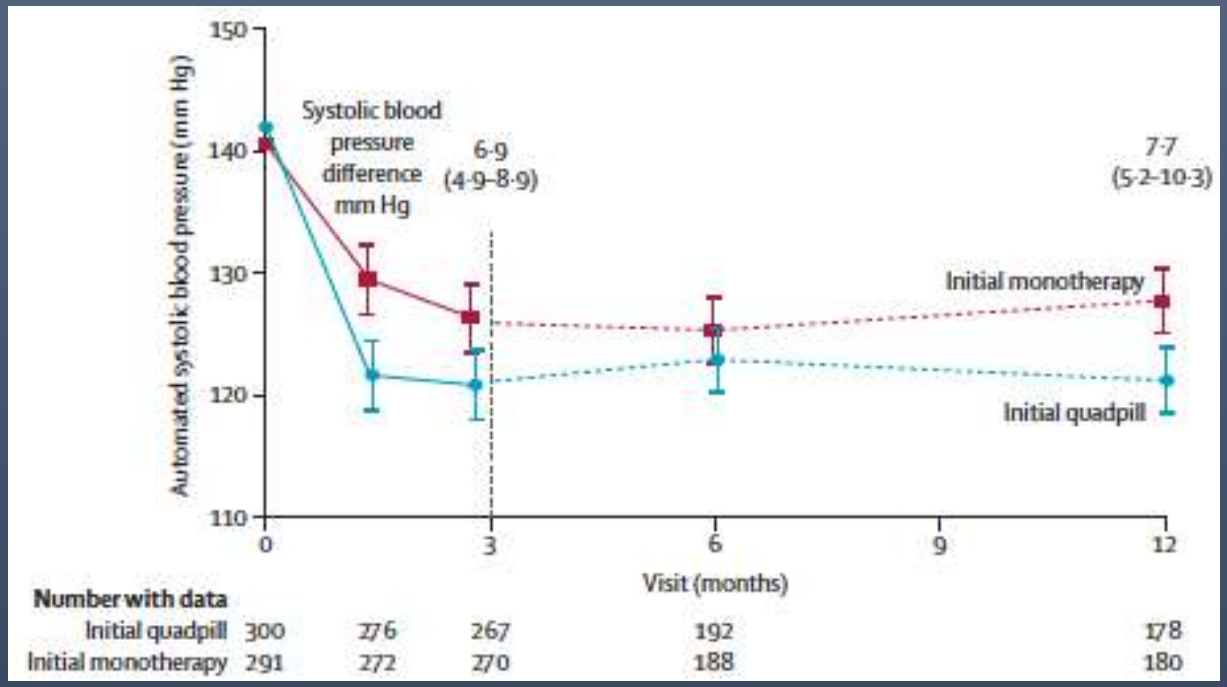






By 12 weeks, 15% had additional BP medications in intervention group vs 40% in control group to maintain BP <140/90 mmHg

Fixed dose quadruple ¼ dose combination and effect on BP



1. SBP was lower by 6·9 mm Hg (95% CI 4·9–8·9; p<0·0001)
2. BP control rates in the intervention (76%) versus control group (58%); relative risk [RR] 1·30, 95% CI 1·15–1·47
3. Sustained at 52 weeks
4. 3% vs 1% adverse events

Lancet 2021; 398: 1043–52

Summary

- Starting low dose (1/4 dose) combination therapy achieved and maintained BP control more effectively than sequential increase in monotherapy
- Tolerable with similar side effects
- Offers a strategy to overcome treatment inertia

Lancet 2021; 398: 1043–52

Thanks for your attention

- Questions?