



Quadruple Ultra-low-dose tReaTment for hypErTension

Efficacy and Safety of a Quadruple Ultra-low-dose Treatment for Hypertension (QUARTET USA): A Randomized Controlled Trial

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SYDNEY



The George Institute
for Global Health

Disclosures



Grants: R33HL139852, R01HL144708, UG3HL152381, D43TW011976

Intellectual: Pending patent for heart failure polypill.

Travel: World Heart Federation

Institutional: George Health Enterprises Pty Ltd (GH) and its subsidiary, George Medicines Pty Ltd, have received investment funds to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. GH is the social enterprise arm of The George Institute for Global Health where I have a secondary appointment.

Rationale

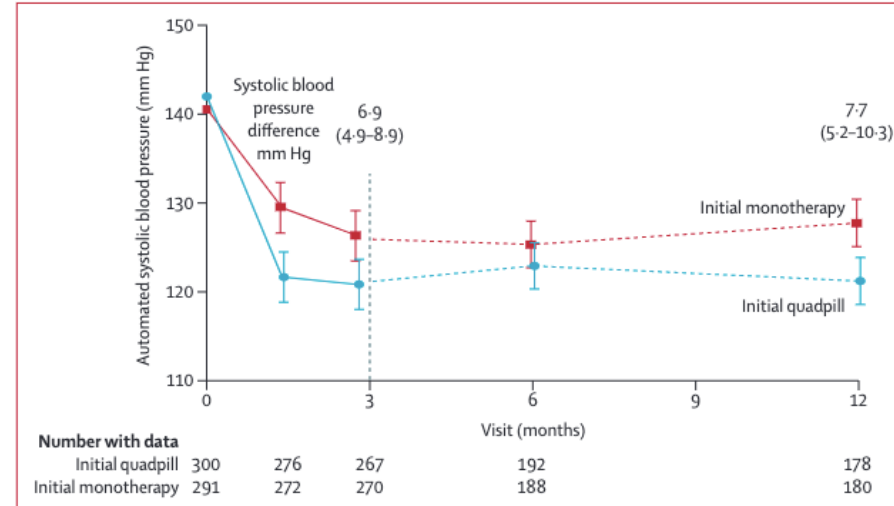
Persistently low hypertension control rates demonstrate the need for a new approach.

Ultra-low-dose combination therapy has a favorable balance between blood pressure lowering effect, tolerability, and adherence.

QUARTET (n=591 adults) demonstrated greater blood pressure lowering effect with a 4-drug combination at quarter doses* at 12 weeks compared with irbesartan 150 mg daily.

- SBP: -6.9 mmHg (95% CI: -4.9, -8.9)
- DBP: -5.8 mmHg (95% CI: -4.4, -7.2)

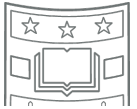
*Irbesartan 37.5 mg + amlodipine 1.25 mg + indapamide 0.625 mg + bisoprolol 2.5 mg



Treatment withdrawal due to side effects: 4.0% intervention v. 2.4% control

Chow CK, et al. Lancet. 2021; 398:1043-1052.

Methods: Design



Design: Randomized (1:1) controlled, parallel group, type I hybrid trial (Aug 2019 – May 2022)

Participants: Treatment naïve: 140-179/90-109 mmHg, Monotherapy: 130-159/85-99 mmHg

Intervention: Candesartan 2mg + amlodipine 1.25mg + indapamide 0.625mg + bisoprolol 2.5mg

Comparator: Candesartan 8 mg daily

Outcomes: 1°: mean change in automated SBP

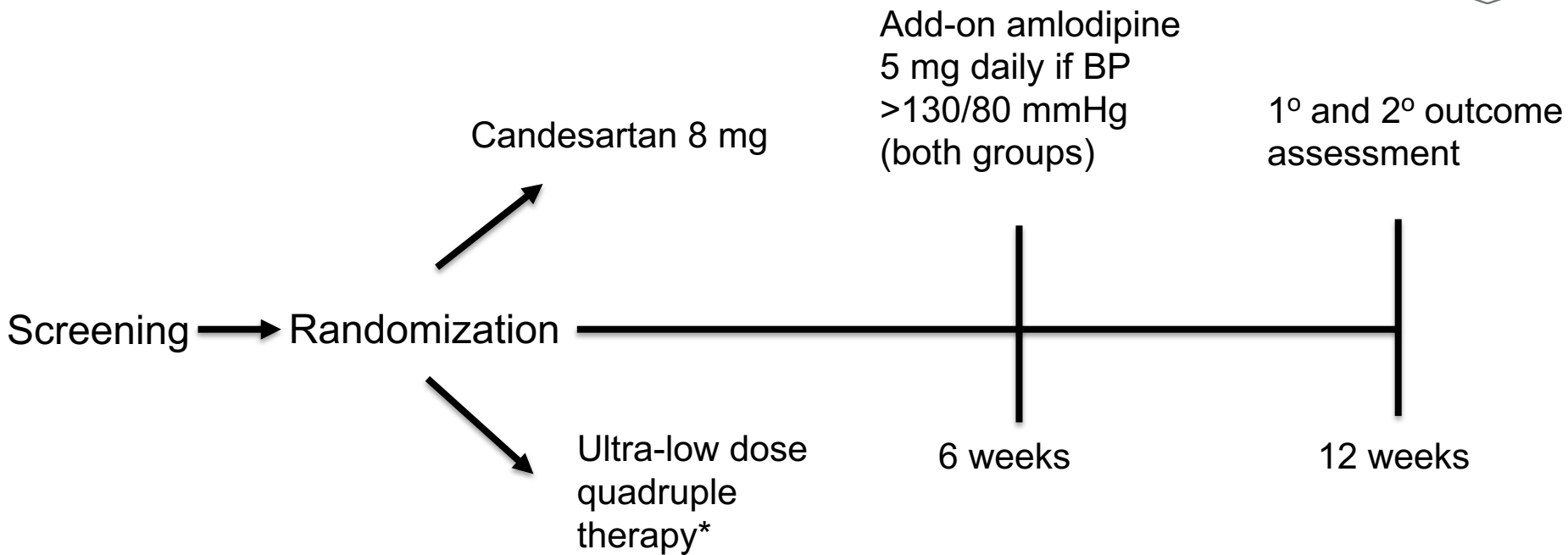
2° (selected): mean change in automated DBP, hrQOL, adherence

Safety: SAEs, AEs

Time course: 12 weeks

Setting: Access Community Health Network, Chicago

Methods: Schema



ULDQT: Candesartan 2 mg + amlodipine 1.25 mg + indapamide 0.625 mg + bisoprolol 2.5 mg

Baldrige AS, et al. Am Heart J. 2022; 254:183-93.

Methods: Statistical analysis

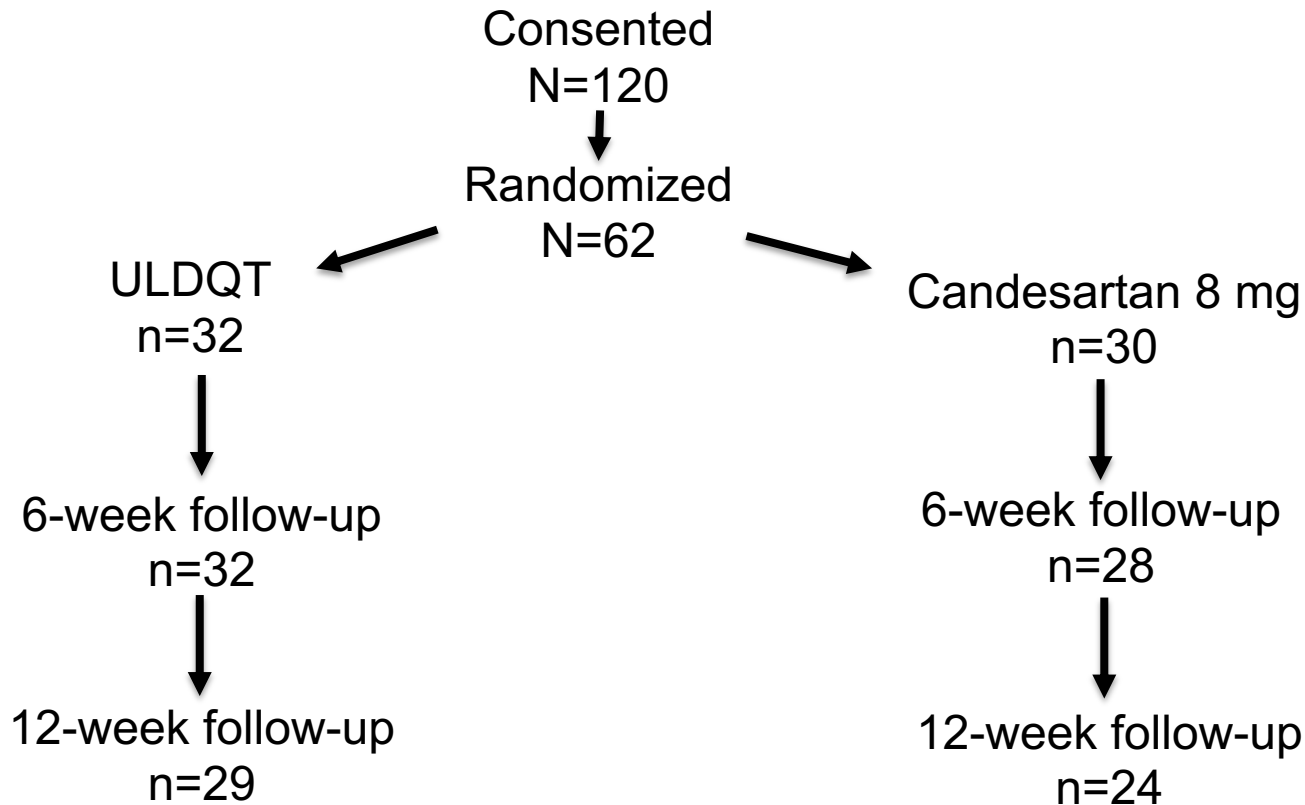


Interim power analysis was recommended by the DSMB based on low recruitment during the COVID-19 pandemic.

Primary study analysis was a linear mixed model with fixed study arm and baseline outcome value effects and a random participant effect to account for within-participant correlation.

Adverse event rates were tabulated, and exact methods evaluated the differences across arms in event rates at the participant level.

Results: CONSORT flow chart



ULDQT: Candesartan 2 mg + amlodipine 1.25 mg + indapamide 0.625 mg + bisoprolol 2.5 mg

Results: Baseline characteristics



	Comparator n=30	Intervention (ULDQT) n=32
Age, years, mean (SD)	52 (10.5)	52 (12.6)
Female, n (%)	13 (43.3)	15 (46.9)
Race/ethnicity, n (%)		
• Hispanic	21 (70.0)	24 (75.0)
• Black	7 (23.3)	4 (12.5)
Household annual income <\$25,000, n (%)	15 (50.0)	19 (59.4)
SBP, mmHg, mean (SD)	138.7 (10.8)	137.6 (11.8)
DBP, mmHg, mean (SD)	84.3 (11.5)	84.3 (9.6)
HR, bpm, mean (SD)	71.7 (11.7)	71.5 (10.0)
Monotherapy, n (%)	24 (80.0)	24 (75.0)

Results: Unadjusted



	Comparator	Intervention (ULDQT)
SBP, week 6, mmHg, mean (SD)	130.1 (18.8)	122.9 (13.1)
SBP, week 12, mmHg, mean (SD)	124.2 (12.6)	121.2 (11.9)
DBP, week 6, mmHg, mean (SD)	78.9 (14.2)	72.3 (9.8)
DBP, week 12, mmHg, mean (SD)	77.0 (7.7)	73.2 (8.9)
HR, week 6, bpm, mean (SD)	73.0 (13.2)	67.9 (11.0)
HR, week 12, bpm, mean (SD)	71.6 (13.4)	68.0 (11.6)
Add on amlodipine, n (%)	16 (53.3)	6 (18.8)

Results: 1° and 2° outcomes



1° outcome:

Adjusted mean change in SBP at 12 weeks:
-4.8 mmHg (95% CI: -10.7, 1.2)

2° outcome:

Adjusted mean change in DBP at 12 weeks:
-4.9 mmHg (95% CI: -8.6, -1.1)

Results: Safety and tolerability



	Comparator n=30	Intervention (ULDQT) n=32
Serious adverse event	0 (0)	2 (6.3)*
Any adverse event	14 (46.7)	20 (62.5)
Any adverse event, at least possibly related	3 (10.0)	8 (25.0)
Adverse event leading to discontinuation	8 (26.7)	2 (6.3)

*Neither SAE was deemed to be related to study drug by the safety monitor.

Interpretation



Initiating a four-drug, quarter-dose BP lowering combination led to a **-4.8/-4.9 mmHg greater reduction in change in BP** from baseline to 12 weeks compared with standard-dose ARB monotherapy in patients with mild to moderate hypertension*.

Differences in SBP were not statistically significant, which is likely due to limited power related to the sample size.

Adverse events were more common in the intervention group, but the rate of discontinuation was higher in the comparator group. No SAEs were related to the study drug.

*Even with 53% up-titration in control group.

Conclusions



New approaches are needed to achieve lower BP targets, especially for patients and communities with a high burden of hypertension and hypertension-related diseases.

QUARTET USA was the first trial of 4-drug, ultra-low dose BP lowering combination therapy in the US.

The direction and magnitude of blood pressure lowering effect were similar between QUARTET and QUARTET USA, despite different study populations with lower baseline BP in the current study, thus strengthening the case for this new approach.

Acknowledgements



QUARTET USA patients, study team members, and **DSMB** members (Paul Muntner [chair], Emily Anderson, Perla Herera, Ken Jamerson, Chris Lindsell)

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