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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NCT03640312

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THE UNIVERSITY OF SYDNEY

The George Institute for Global Health

Disclosures

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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.

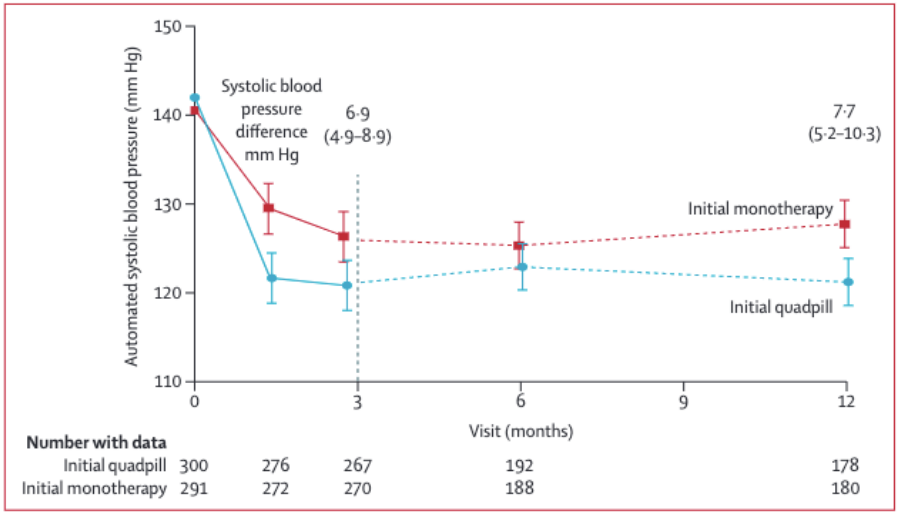
Rationale

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)



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

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

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

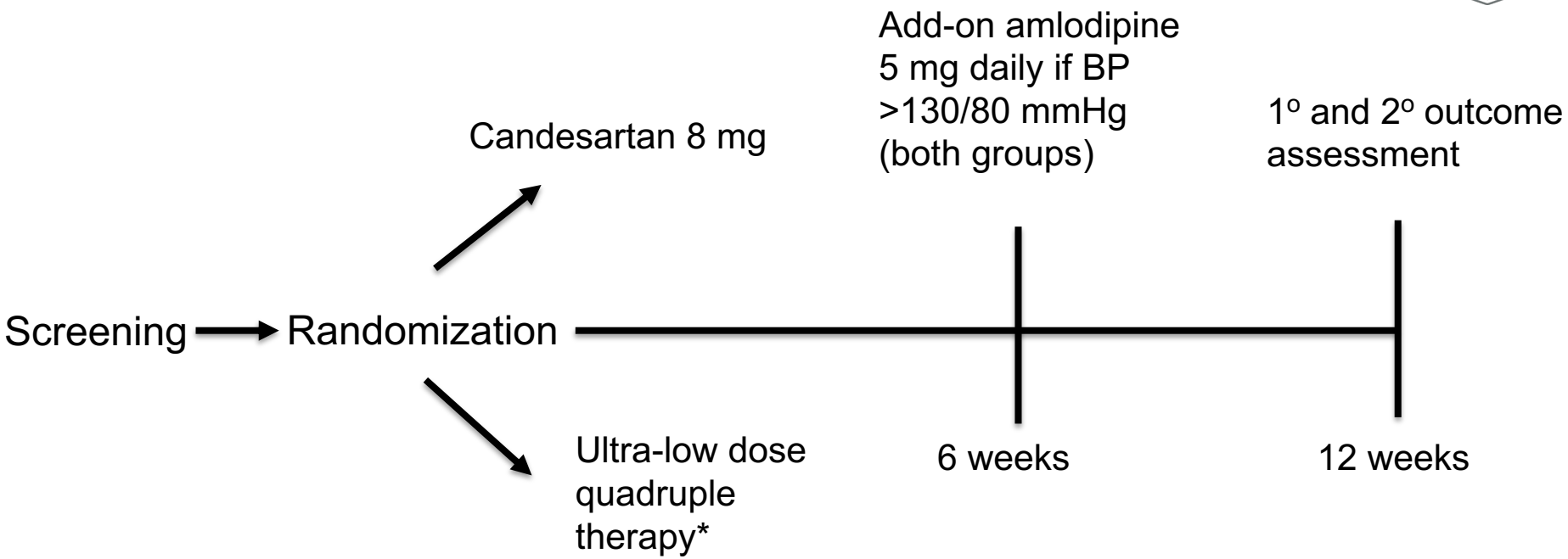
Outcomes: 1^{o}: mean change in automated SBP
2^{o} (selected): mean change in automated DBP, hrQOL, adherence
Safety: SAEs, AEs

Time course: 12 weeks

Setting: Access Community Health Network, Chicago

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

Methods: Schema



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

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

Methods: Statistical analysis

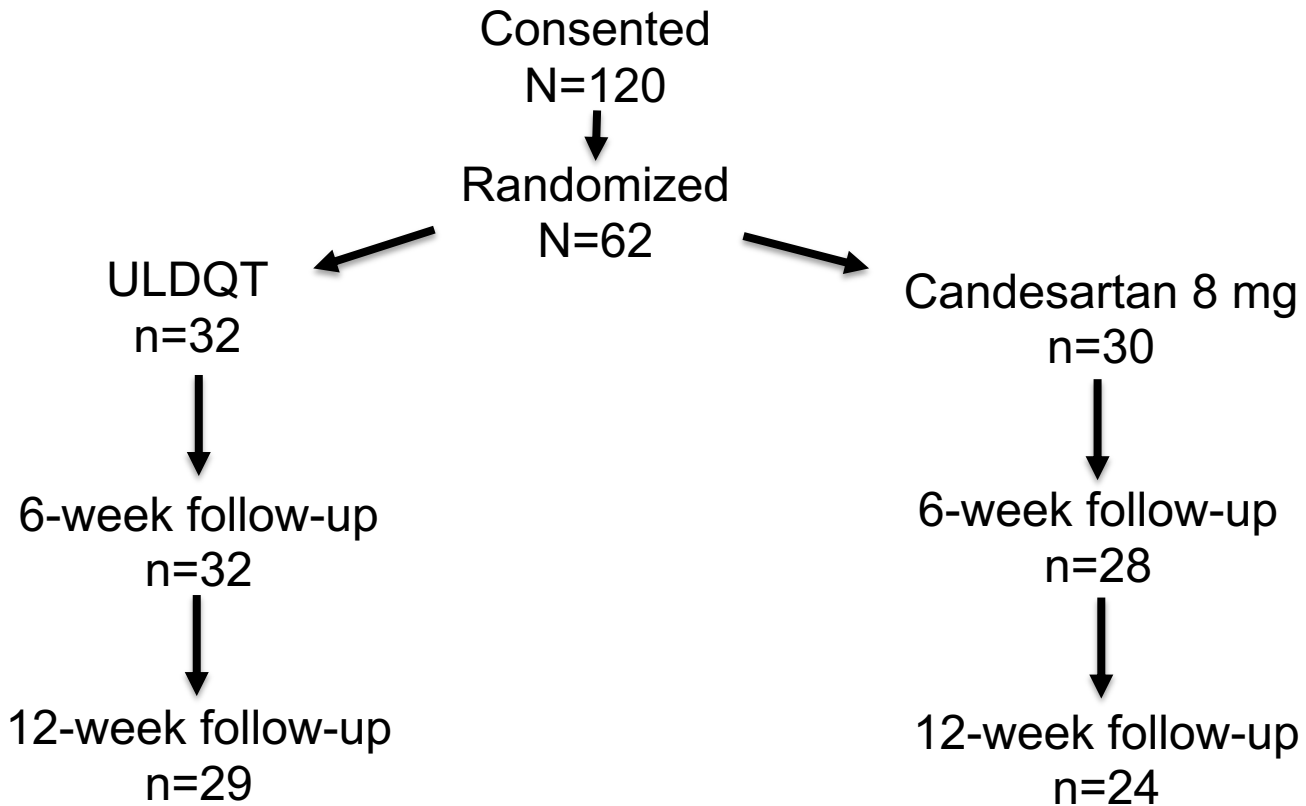
Interim power analysis was recommended by the DSMB based on low recruitment during the COVID-19 pandemic.

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.

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

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: 1º and 2º outcomes

1º outcome:

Adjusted mean change in SBP at 12 weeks:

-4.8 mmHg (95% CI: -10.7, 1.2)

2º 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

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