Short Report

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Sex differences in blood pressure lowering of initial treatment with ultra-low dose combination therapy versus monotherapy. A secondary analysis of QUARTET

Edel T. O'Hagan[a], Simone L. Marschner[a], Desi Quintans[a], Graham S. Hillis[b], Emily R. Atkins[c], Sarah Zaman[a,d], Markus P. Schlaich[e], Anthony Rodgers[c], and Clara K. Chow[a,d]

Women with hypertension are more likely than men to have ineffective treatment where blood pressure (BP) is treated but not controlled. The aim of this study was to investigate whether a quadpill based strategy differs between males and females.

A secondary analysis of The Quadruple UltrA-low-dose tReaTment for hypErTension (QUARTET); randomized controlled trial. In this analysis the primary outcome was sex differences in unattended office systolic BP at 12 weeks.

The QUARTET study recruited 591 participants (40% female) with mean age 59 (standard deviation 12) years [male 57 (12); female 62 (11)]. Males and females recorded a similar reduction in unattended systolic BP at 12 weeks with no interaction between group allocation and sex [male:mean difference (MD) in mmHg −6.95 (95% CI −9.53 to −4.38), female: MD −6.34 (95% CI −9.50 to −3.18), interaction $P = 0.77$].

The quadpill strategy was similarly effective in men and women. Initiating BP control with a quadpill in women presents a promising approach to achieving similar BP control levels to men.

Keywords: adherence, fixed-dose combination, high blood pressure, inertia, quadpill, safety, tolerability, women

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; mmHg, milligrams of mercury; QUARTET, Quadruple UltrA-low-dose tReaTment for hypErTension; RR, relative risk; SD, standard deviation

INTRODUCTION

Several initiatives have improved awareness of cardiovascular disease (CVD) in women during the past decade, yet health-care providers and patients still tend to underestimate cardiovascular risk in women [1]. Strategies to improve hypertension treatment in women seem necessary to stem the burden of CVD in women.

Fixed-dose combination therapy improves blood pressure (BP) control via simplifying treatment regimens, more efficient use of dose, and minimizing therapeutic inertia [2–4]. Increasingly three or four antihypertensive medicines are being combined [4–8], capitalizing on drugs in combination being additive [9].

In the Quadruple UltrA-low-dose tReaTment for hypErTension (QUARTET) trial systolic BP was lower by 6.9 mmHg (95% CI 4.·9–8.9; $P < 0·0001$) and BP control higher in the intervention (76%) vs. control group [58%; relative risk (RR) 1·30, 95% CI 1.15–1.47; $P < 0·0001$] [5]. However the trial did not extensively examine the disaggregated effects in women and men on key outcomes.

The aim of this study was to assess whether the effectiveness of the quadpill strategy differed between men and women in terms of effect on BP, adherence, treatment inertia, safety, and tolerability.

METHODS

The QUARTET study was a multicentre, parallel-group, active control, double-blind, randomized, controlled, phase 3 trial that compared initial treatment with the quadpill or active control [5]. The current analysis is a secondary analysis of QUARTET.

Blood pressure assessment included: office BP, unattended BP and 24-h ambulatory BP. Adherence to the blinded study medication was defined as the number of pills taken per number prescribed ×100%. Participants were considered adherent if this measure was more than

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[a]Westmead Applied Research Centre, Faculty of Medicine and Health, The University of Sydney, Australia, [b]Department of Cardiology, Royal Perth Hospital, [c]The George Institute for Global Health, UNSW Sydney, [d]Department of Cardiology, Westmead Hospital and [e]Dobney Hypertension Centre, Medical School Royal Perth Hospital Unit, The University of Western Australia, Australia

Correspondence to Edel T. O'Hagan, PhD Research Fellow, Westmead Applied Research Centre, Faculty of Medicine and Health, The University of Sydney, Level 5, Block K, Entrance 10, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Sydney, Australia. E-mail: edel.ohagan@sydney.edu.au

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80%. Treatment inertia was defined as failure to intensify treatment despite the participant's BP not reaching target. Treatment intensification included prescription of a new BP lowering drug or increasing the dosage of existing BP lowering drug(s). The target BP was defined as an unattended reading below 140/90 mmHg. Safety was measured as the number of serious adverse events and tolerability was measured as the number of adverse events that were related to the trial medicine.

The primary outcome was unattended systolic BP at 12 weeks. Secondary outcomes were unattended systolic BP at 6, 26 and 52 weeks, unattended diastolic BP at 6, 12, 26 and 52 weeks; 24-h ambulatory systolic and diastolic BP (12 and 52 weeks); BP control achieved (<140/90 mmHg office BP) and tight BP control achieved (<130/80 mm Hg office BP) (6, 12, 26 and 52 weeks); adherence (12 and 52 weeks); treatment inertia (6, 12, 26 and 52 weeks); safety (12 weeks); and tolerability (12 weeks).

For the primary analysis, a regression model was used to estimate the effect of treatment group allocation on unattended systolic BP at 12 weeks for males and females and an interaction term of sex and treatment assessed if the treatment has a different effect between the sexes. We applied this approach to the secondary outcomes but adjusted for the additional time effects for these outcomes by adding a random effect for each participant due to repeat measures. Comparisons of males and females between the two treatment groups for adherence, treatment inertia, safety and tolerability was presented descriptively.

RESULTS

The QUARTET study recruited 591 participants with a mean age (SD) 59 (12) years [male 57 (12); female 62 (11)] and 40%($n = 235$) were female. At baseline, participants recorded an average unattended BP of 141/85 mmHg [male 141/85 mmHg; female 141/84 mmHg]. Full details of the participant characteristics are available in Table 1.

The treatment effect on unattended systolic BP at 12 weeks was similar between males and females [male: mean

TABLE 1. Baseline characteristics

		Men $n = 356$		Women $n = 235$	
	Overall $n = 591$	Intervention $n = 178$	Control $n = 178$	Intervention $n = 122$	Control $n = 113$
Age, years; mean (SD)	59 (12)	56 (11)	57 (12)	60 (12)	63 (10)
Healthcare concession card holder	23% ($n = 137$)	17% ($n = 30$)	19% ($n = 34$)	29% ($n = 35$)	34% ($n = 38$)
Race or ethnicity					
White	82% ($n = 483$)	81% ($n = 145$)	80% ($n = 143$)	85% ($n = 104$)	81% ($n = 91$)
Asian	12% ($n = 70$)	11% ($n = 20$)	12% ($n = 21$)	10% ($n = 13$)	14% ($n = 16$)
Other[a]	6% ($n = 38$)	7% ($n = 13$)	8% ($n = 14$)	4% ($n = 5$)	5% ($n = 6$)
Baseline BP treatment					
Not treated[b]	54% ($n = 321$)	63% ($n = 113$)	53% ($n = 94$)	49% ($n = 60$)	48% ($n = 54$)
On monotherapy; % (n)	46% ($n = 270$)	37%($n = 65$)	47% ($n = 84$)	51% ($n = 62$)	52% ($n = 59$)
Baseline BP, mmHg					
Unattended systolic; mean (SD)	141 (13)	142 (12)	141 (12)	142 (14)	140 (15)
Unattended diastolic; mean (SD)	85 (10)	86 (10)	85 (10)	85 (10)	82 (11)
Office systolic; mean (SD)	153 (16)	152 (15)	152 (13)	153 (16)	154 (19)
Office diastolic; mean (SD)	89 (10)	90 (10)	89 (11)	88 (10)	87 (11)
24h ABPM, systolic; mean (SD)	137 (11)	138 (11)	137 (10)	136 (11)	137 (10)
24h ABPM, diastolic; mean (SD)	79 (9)	81 (9)	81 (8)	77 (8)	77 (9)
Daytime ABPM, systolic; mean (SD)	144 (11)	145 (10)	144 (11)	144 (11)	143 (11)
Daytime ABPM, diastolic; mean (SD)	84 (9)	86 (8)	86 (8)	82 (9)	81 (9)
Nighttime ABPM, systolic; mean (SD)	124 (13)	124 (13)	124 (13)	123 (13)	124 (13)
Nighttime ABPM, diastolic; mean (SD)	69 (10)	71 (10)	71 (10)	67 (9)	67 (9)
Baseline heart rate, beats per minute; mean (SD)	72 (12)	70 (11)	71 (12)	74 (11)	74 (11)
Body-mass index, kg/m^2; mean (SD)	30 (6)	31 (5)	30 (5)	30 (7)	29 (6)
Ever smoked; % (n)	38% ($n = 22$)	43% ($n = 76$)	42% ($n = 75$)	32% ($n = 39$)	31% ($n = 35$)
Current smoker	8% ($n = 48$)	9% ($n = 16$)	11% ($n = 20$)	6% ($n = 7$)	4% ($n = 5$)
Former smoker	30% ($n = 177$)	34% ($n = 60$)	31% ($n = 55$)	26% ($n = 32$)	27% ($n = 30$)
Alcohol once or more per week; % (n)	64%($n = 376$)	77% ($n = 137$)	72% ($n = 129$)	53% ($n = 65$)	40% ($n = 45$)
Diabetes; %(n)	7.6% ($n = 45$)	6.2% ($n = 11$)	7.9% ($n = 14$)	8.2% ($n = 10$)	8.8% ($n = 10$)
Chronic kidney disease; % (n)	0.2% ($n = 1$)	0	0.6% ($n = 1$)	0	0
Coronary artery disease; % (n)	4.4% ($n = 26$)	6.7% ($n = 12$)	3.4% ($n = 6$)	1.6% ($n = 2$)	5.3% ($n = 6$)
Creatinine, μmol/l; mean (SD)	75 (14.1)	83.0 (14.3)	80.5 (11.7)	66.0 (9.6)	65.4 (9.1)
eGFR, ml/min per 1.73 m^2; mean (SD)[c]	78.1 (9.7)	76.6 (10.6)	80.1 (9.3)	77.6 (9.8)	78.0 (8.5)
Sodium, mmol/l; mean (SD)	140.3 (2.3)	140.0 (2.1)	140.2 (2.2)	140.4 (2.2)	140.6 (2.7)
Potassium, mmol/l; mean (SD)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.3 (0.4)	4.3 (0.4)
Total cholesterol, mmol/l; mean (SD)	5.3 (1.1)	5.2 (1.1)	5.3 (1.1)	5.4 (1.0)	5.4 (1.0)
HDL cholesterol, mmol/l; mean (SD)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.6 (0.4)	1.6 (0.4)
Fasting glucose, mmol/l; mean (SD)	5.5 (1.3)	5.8 (1.7)	5.5 (1.0)	5.4 (1.4)	5.3 (0.8)

Data are mean (SD) or n (%).
ABPM, ambulatory blood pressure monitoring; eGFR, estimated glomerular filtration rate.
[a]Included Black, Hispanic, Middle Eastern, Australian Aboriginal or Torres Strait Islander, Pacific Islands, Maori, and other.
[b]Not taking blood pressure-lowering medications, or not currently taking treatment for at least 4 weeks.
[c]eGFR estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation.

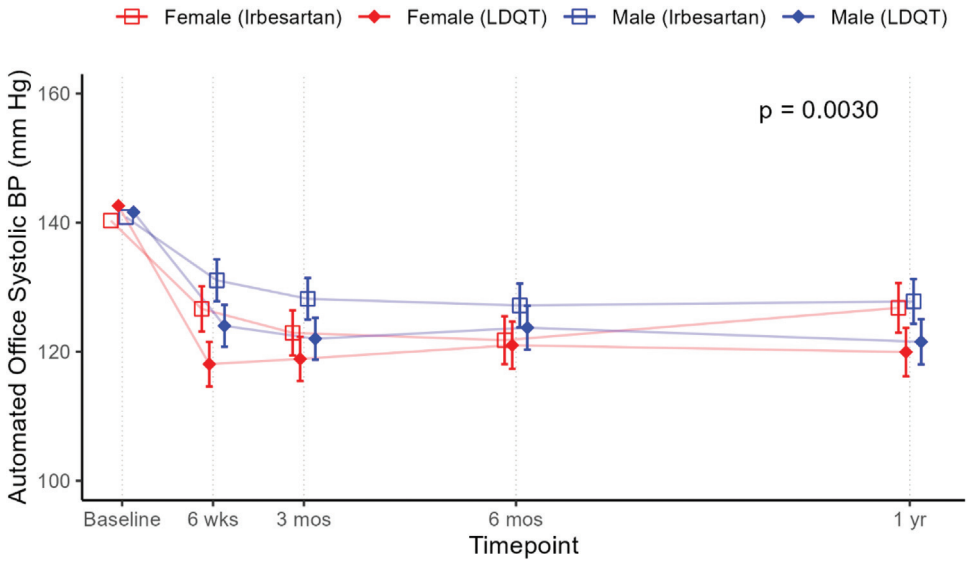

FIGURE 1 Mean automated systolic blood pressure to month 12, by group and sex.

difference (MD) in mmHg −6.95 (95% CI −9.53 to −4.38), female: MD −6.34 (95% CI −9.50 to −3.18), interaction $P = 0.77$] (Fig. 1). There was a difference in treatment effect of >3 mmHg on unattended systolic BP at 6 weeks [male: mean MD in mmHg −7.82 (95% CI −10.44 to −5.19), female: MD −10.86 (95% CI −14.04 to −7.67), interaction $P = 0.15$] in females, but no significant heterogeneity was found. Similarly no significant heterogeneity were found for other BP measures (Table 2, and Supplement 3, 4 and 5, Supplemental Digital Content, http://links.lww.com/HJH/C700).

Both male and female participants in the intervention group were more likely to achieve BP control of less than

TABLE 2. Mean differences in outcome between intervention and control groups by sex and the three-way interaction effect

	Men			Women			
	mmHg (95% CI)	Mean difference between intervention and control in males (95% CI)	*P*-value	mmHg [95% CI]	Mean difference between intervention and control in females (95% CI)	*P*-value	Interaction Group∗Sex∗Time
Unattended systolic BP							0.003***
6 weeks							
Quadpill	124 (121; 127)	−7.82 (−10.44; −5.19)	<.0001	119 (114; 123)	−10.86 (−14.04; −7.67)	<0.0001	0.1487#
Irbesartan	131 (128, 134)			127 (123; 131)			
Primary outcome							
12 weeks							
Quadpill	122 (119; 125)	−6.95 (−9.53; −4.38)	<.0001	119 (115; 124)	−6.34 (−9.50; −3.18)	<0.0001	0.7677#
Irbesartan	128 (125; 131)			123 (119; 128)			
26 weeks							
Quadpill	124 (121; 127)	−4.21 (−7.27; −1.14)	0.0073	121 (117; 126)	−3.08 (−6.78; 0.62)	0.1026	0.6451#
Irbesartan	127 (124; 130)			122 (118; 127)			
52 weeks							
Quadpill	122 (119; 125)	−7.03 (−10.31; −3.75)	<.0001	120 (115; 125)	−9.15 (−13.06; −5.24)	<0.0001	0.4147#
Irbesartan	128 (125; 131)			127 (123; 132)			
Unattended diastolic BP							0.0138***
6 weeks							
Quadpill	72 (71; 74)	−6.95 (−8.77; −5.13)	<.0001	70 (67; 73)	−9.06 (−11.27; −6.85)	<0.0001	0.1479#
Irbesartan	78 (77; 80)			76 (73; 79)			
12 weeks							
Quadpill	72 (71; 74)	−5.48 (−7.23; −3.73)	<.0001	71 (69; 74)	−6.16 (−8.31; −4.00)	<0.0001	0.6319#
Irbesartan	77 (75; 78)			74 (72; 77)			
26 weeks							
Quadpill	73 (71; 75)	−4.10 (−6.26; −1.94)	0.0002	72 (69; 75)	−4.43 (−7.04; −1.82)	0.0009	0.8459#
Irbesartan	76 (74; 78)			74 (71; 77)			
52 weeks							
Quadpill	72 (70; 73)	−5.55 (−7.65; −3.45)	<.0001	72 (69; 74)	−7.19 (−9.69; −4.68)	<0.0001	0.9573#
Irbesartan	76 (74; 78)			76 (73; 79)			

TABLE 2 (*Continued*)

	Men			Women			
	mmHg (95% CI)	Mean difference between intervention and control in males (95% CI)	*P*-value	mmHg [95% CI]	Mean difference between intervention and control in females (95% CI)	*P*-value	Interaction Group∗Sex∗Time
24hr systolic ABPM							0.3253***
Week 12							
Quadpill	123 (121; 125)	−7.06 (−9.04; −5.09)	<.0001	119 (116; 122)	−7.65 (−10.08; −5.22)	<0.0001	0.7133#
Irbesartan	129 (127; 131)			128 (124; 131)			
Week 52							
Quadpill	125 (123; 127)	−4.50 (−6.87; −2.13)	0.0002	122 (118; 125)	−6.57 (−9.45; −3.69)	0.0002	0.2776#
Irbesartan	128 (126; 130)			129 (126; 133)			
24 h diastolic ABPM							0.5056***
Week 12							
Quadpill	70 (69; 71)	−4.98 (−6.22; −3.75)	<.0001	66 (64; 68)	−5.07 (−6.59; −3.56)	<0.0001	0.9266#
Irbesartan	75 (74; 76)			71 (69; 73)			
Week 52							
Quadpill	75 (74; 76)	−3.91 (−5.38; −2.44)	<.0001	67 (65; 69)	−4.37 (−6.16; −2.58)	<0.0001	0.6945#
Irbesartan	75 (70; 72)			72 (70; 73)			

*ABPM at 12 weeks; males $n = 144$, females $n = 105$.
**ABPM at 52 weeks; males $n = 100$, females $n = 75$.
***P-value relates to the significance of the interaction term as part of the overall model.
#P-value relates to the significance of the interaction between sex, group and specific timepoint.

140/90 mmHg on standard office measures at 12 weeks in comparison with those in the control group [male: intervention 72% vs control 59%; relative risk (RR) 1.22, 95% CI 1.01 to 1.47; $P = 0{\cdot}04$, female: intervention 81% vs. control 65%; RR 1.25, 95% CI 1.04 to 1.52; $P = 0{\cdot}02$], as well as tight BP control at less than 130/80 mmHg on standard office measures at 12 weeks (male: intervention 39% vs. control 26%; RR 1.46, 95% CI 1.00 to 2.13; $P = 0.05$; female: intervention 53% vs. control 32%; RR 1.68, 95% CI 1.15 to 2.44; $P = 0.01$) (Supplement 1, Supplemental Digital Content, http://links.lww.com/HJH/C700).

There were no significant differences in adherence at 12 weeks. 80% of men and women respectively were adherent in the quadpill group, whereas 72% of men and 78% of women in the monotherapy group were adherent to study treatment. At 52 weeks, 72% of women and 70% of men in the quadpill group were adherent to study treatment, whereas 79% of women and 63% of men in the monotherapy group were adherent to study treatment.

Treatment inertia was significantly reduced for both women and men in the quadpill group at 6 weeks, and for men only at 52 weeks. At 6 weeks, 7.5% of men and 4.3% of women were not at target and did not have their treatment intensified in the quadpill group, whereas 25% of men and 8% of women were not at target and did not have their treatment intensified in the monotherapy group (Supplements 2 and 6, Supplemental Digital Content, http://links.lww.com/HJH/C700).

While there was a difference in the rate of serious adverse events (male 2 events; female 8 events) none were causally related to the trial medication. In relation to tolerability, women generally reported higher rates of low-risk adverse events compared to men. At 12 weeks. 26% men vs. 39% women in the quadpill group reported dizziness, whereas 26% of men and women respectively in the monotherapy group reported dizziness. 4% of men vs. 12% of women in the quadpill group pedal oedema, whereas 6% of men vs. 11% of women in the monotherapy reported pedal oedema. 11% of men vs. 26% of women the in quadpill group reported gastrointestinal complaints whereas 9% of men and 18% of women in the control group reported gastrointestinal complaints. There were no differences in the rates of hypotension (systolic BP < 100 mmHg) or bradycardia between the sexes (Table 3).

DISCUSSION

The QUARTET trial demonstrated the efficacy of a quadpill in comparison with single therapy in the treatment of high BP. The current study found there was no heterogeneity in treatment effects by sex, with women just as likely to achieve lowering of their mean BP and overall BP control in the quadpill arm compared to men. Adherence to study medications and rates of treatment inertia were also comparable between women and men. Compared with men, women reported low risk adverse effects more frequently. Given women in the community are less likely to achieve BP control with current strategies, the quadpill strategy may be usefully applied to women to achieve better BP control.

We had access to a wide range of BP measures allowing for a comprehensive understanding of the differences in BP at multiple time points. Yet, this study has some weaknesses to consider. Firstly this QUARTET trial was not powered to investigate sex differences between the intervention and control groups. There were differences in age and preexisting monotherapy between male and female participants, but sample size limitations precluded adjustment for these factors in the analysis. Adherence was assessed by pill count only without biochemical validation. The limitations of this method were noted in the primary trial. Future studies incorporating objective adherence measures could provide additional insight.

TABLE 3. Safety and tolerability for males and females at 12-weeks

		Male $n = 356$		Female $n = 235$	
	Overall $n = 591$	Intervention $n = 178$	Control $n = 178$	Intervention $n = 122$	Control $n = 113$
Safety at 12 weeks, *n* (%)					
Serious adverse event	10 (1.8%)	1 (0.6%)	1 (0.6%)	6 (5.3%)	2 (1.9%)
Not causally related	10 (1.8%)	1 (0.6%)	1 (0.6%)	6 (5.3%)	2 (1.9%)
Possibly causally related	0	0	0	0	0
Hospitalization	9 (1.6%)	1 (0.6%)	1 (0.6%)	5 (4.4%)	2 (1.9%)
Medically significant event	2 (0.4%)	0	1 (0.6%)	1 (0.9%)	0
Life threatening event	1 (0.2%)	0	1 (0.6%)	0	0
Tolerability at 12 weeks, *n* (%)					
Dizziness	167 (28.3%)	46 (25.8%)	45 (25.3%)	47 (38.5%)	29 (25.7%)
Pedal oedema	43 (7.3%)	7 (3.9%)	10 (5.6%)	14 (11.5%)	12 (10.6%)
Muscle cramps	127 (21.5%)	37 (20.8%)	32 (18.0%)	29 (23.8%)	29 (25.7%)
Hypersensitivity	58 (9.8%)	13 (7.3%)	18 (10.1%)	15 (12.3%)	12 (10.6%)
Gastrointestinal complaints	73 (12.4%)	11 (6.2%)	16 (9.0%)	26 (21.3%)	20 (17.7%)
Musculoskeletal complaints	83 (14.0%)	17 (9.6%)	20 (11.2%)	21 (17.2%)	25 (22.1%)
Headache	86 (14.6%)	21 (11.8%)	18 (10.1%)	22 (18.0%)	25 (22.1%)
Other	213 (36.0%)	63 (35.4%)	63 (35.4%)	46 (37.7%)	41 (36.3%)
Systolic BP <100 mmHg	50 (8.5%)	23 (12.9%)	7 (3.9%)	15 (12.3%)	5 (4.4%)
Heart rate <50	71 (12.0%)	37 (20.8%)	7 (3.9%)	23 (18.9%)	4 (3.5%)

CONCLUSION

A single pill containing quarter-standard doses of four types of BP-lowering medicines is an effective and safe option bring BP lowering in women on par with men.

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Conflicts of interest

The George Institute for Global Health (TGI) has submitted patent applications in respect of low fixed-dose combination products for the treatment of cardiovascular or cardiometabolic disease. A. Rodgers and C. Chow are listed as inventors. A. Rodgers is employed by TGI and seconded part-time to George Medicines Pty Ltd (GM). George Health Enterprises Pty Ltd (GHE) and its subsidiary, GM, have received investment funds to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. GHE is the social enterprise arm of TGI. A. Rodgers and C. Chow do not have direct financial interests in these patent applications or investments. The other authors report no conflicts.

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