

Supplementary material
Clinical Drug Investigation

The Safety and Efficacy of Quadruple Ultra-Low-Dose Combination (Quadpill) for Hypertension Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Running Title.

Quadpill for Hypertension.

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Keywords.

Hypertension; blood pressure; RCT; antihypertensive; systematic review; meta-analysis.

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Database	Search Terms	Search Field	Search Results
PubMed	(Hypertension OR “High Blood Pressure”) AND (quadpill OR” quadruple combination” OR “Low-Dose Quadruple Antihypertensive” OR “quarter-dose quadpill”)	All Field	15
Cochrane	#1 (Hypertension):ti,ab,kw OR (High Blood Pressure):ti,ab,kw 87940 #2 (quadpill):ti,ab,kw OR (quadruple combination):ti,ab,kw OR (Low-Dose Quadruple Antihypertensive):ti,ab,kw OR (quarter-dose quadpill):ti,ab,kw 545 #3 #1 AND #2 18	All Field	18
WOS	(Hypertension OR “High Blood Pressure”) AND (quadpill OR” quadruple combination” OR “Low-Dose Quadruple Antihypertensive” OR “quarter-dose quadpill”)	All Field	15
SCOPUS	TITLE-ABS-KEY ((hypertension OR "High Blood Pressure") AND (quadpill OR " quadruple combination" OR "Low-Dose Quadruple Antihypertensive" OR "quarter-dose quadpill"))	Title, Abstract, Keywords	16
EMBASE	#3. #1 AND #2 #2. quadpill:ti,ab,kw OR 'quadruple combination':ti,ab,kw OR 'low-dose quadruple antihypertensive':ti,ab,kw OR 'quarter-dose quadpill':ti,ab,kw #1. hypertension:ti,ab,kw OR 'high blood pressure':ti,ab,kw	All Field	14

Table S1: Search Strategy.

Outcome	No. of participants (Quadpill/control)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			MD/R R	95% CI	Z value	p-value	df	p-value	I2 (%)
Automated (unattended office) SBP (4-6 weeks)									
All studies	372/425	4	-13.00	[-17.22, -8.78]	6.04	< 0.00001	3	0.007	75
Omitting Chow et al. 2017 (1)	354/407	3	-11.39	[-14.28, -8.50]	7.72	< 0.00001	2	0.14	49
Omitting Chow et al. 2021 (QUARTETE) (2)	72/134	3	-14.34	[-21.18, -7.51]	4.11	< 0.0001	2	0.01	78
Omitting Mahmud et al. 2007 (3)	350/339	3	-13.21	[-21.62, -4.79]	3.08	0.002	2	0.003	83
Omitting Huffman et al. 2022 (QUARTETE-USA) (4)	340/395	3	-14.10	[-18.76, -9.44]	5.93	0.00001	2	0.006	80
Target BP (140/90 mm Hg) (4-6 weeks)									
All studies	241/313	3	1.77	[1.26, 2.51]	3.25	0.001	2	0.10	57
Omitting Chow et al. 2017 (1)	223/294	2	1.49	[1.29, 1.72]	5.49	< 0.00001	1	0.38	0
Omitting Chow et al. 2021 (QUARTETE) (2)	40/104	2	2.16	[1.40, 3.33]	3.48	0.0005	1	0.25	23
Omitting Mahmud et al. 2007 (3)	219/226	2	1.90	[1.00, 3.61]	1.96	0.05	1	0.04	76
Any adverse event leading to drug dissociation									
All studies	350/339	3	0.89	[0.19, 4.11]	0.15	0.88	2	0.07	63
Omitting Chow et al. 2017 (1)	332/321	2	0.68	[0.10, 4.64]	0.39	0.69	1	0.03	80
Omitting Chow et al. 2021 (QUARTETE) (2)	50/48	2	0.57	[0.05, 6.14]	0.47	0.64	1	0.15	52
Omitting Mahmud et al. 2007 (3)	318/309	2	1.74	[0.72, 4.20]	1.23	0.22	0.72	1	0

CI: confidence interval; df: degrees of freedom; RR: risk ratio.

References.

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2. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, 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(10305):1043–52.
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