

# **Terapia Combinada Versus Monoterapia na Redução da Pressão: Meta-análise com 11.000 participantes de 42 Estudos**

**Apresentado por Fernanda Oliveira Coelho  
na reunião da Unidade de Hipertensão  
do Hospital das Clínicas da Faculdade de Medicina  
da Universidade de São Paulo  
em 09 de Abril de 2009**

CLINICAL RESEARCH STUDY

THE AMERICAN  
JOURNAL *of*  
MEDICINE®

## Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

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*The American Journal of Medicine (2009) 122, 290-300*

# Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

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## ABSTRACT

**OBJECTIVE:** To quantify the incremental effect of combining blood pressure-lowering drugs from any 2 classes of thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers over 1 drug alone and to compare the effects of combining drugs with doubling dose.


**METHODS:** Meta-analysis of factorial trials in which participants were randomly allocated to 1 drug alone, another drug alone, both drugs together, or a placebo.

**RESULTS:** We identified 42 trials (10,968 participants). With a thiazide used alone, the mean placebo-subtracted reduction in systolic blood pressure was 7.3 mm Hg and 14.6 mm Hg combined with a drug from another class. The corresponding reductions were 9.3 mm Hg and 18.9 mm Hg with a beta-blocker, 6.8 mm Hg and 13.9 mm Hg with an angiotensin-converting enzyme, and 8.4 mm Hg and 14.3 mm Hg with a calcium channel blocker. The expected blood pressure reduction from 2 drugs together, assuming an additive effect, closely predicted the observed blood pressure reductions. The ratios of the observed to expected incremental blood pressure reductions from combining each class of drug with any other over that from 1 drug were, respectively, for thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers: 1.04 (95% confidence interval [CI], 0.88-1.20), 1.00 (95% CI, 0.76-1.24), 1.16 (95% CI, 0.93-1.39), and 0.89 (95% CI, 0.69-1.09); the overall average was 1.01 (95% CI, 0.90-1.12). Comparison of our results with those of a published meta-analysis of different doses of the same drug showed that doubling the dose of 1 drug had approximately one fifth of the equivalent incremental effect (0.22 [95% CI, 0.19-0.25]).

**CONCLUSION:** Blood pressure reduction from combining drugs from these 4 classes can be predicted on the basis of additive effects. The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug.

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**KEYWORDS:** Angiotensin-converting enzyme inhibitor; Beta-blocker; Blood pressure; Calcium channel blocker; Combination blood pressure therapy; Randomized trial; Thiazide



**Conflict of Interest:** Nicholas J. Wald and Malcolm Law hold patents (EU1272220 and GB2361186) for a combination pill for the prevention of cardiovascular disease (Polypill) and together with David Wald have interests in its development.

# Introdução

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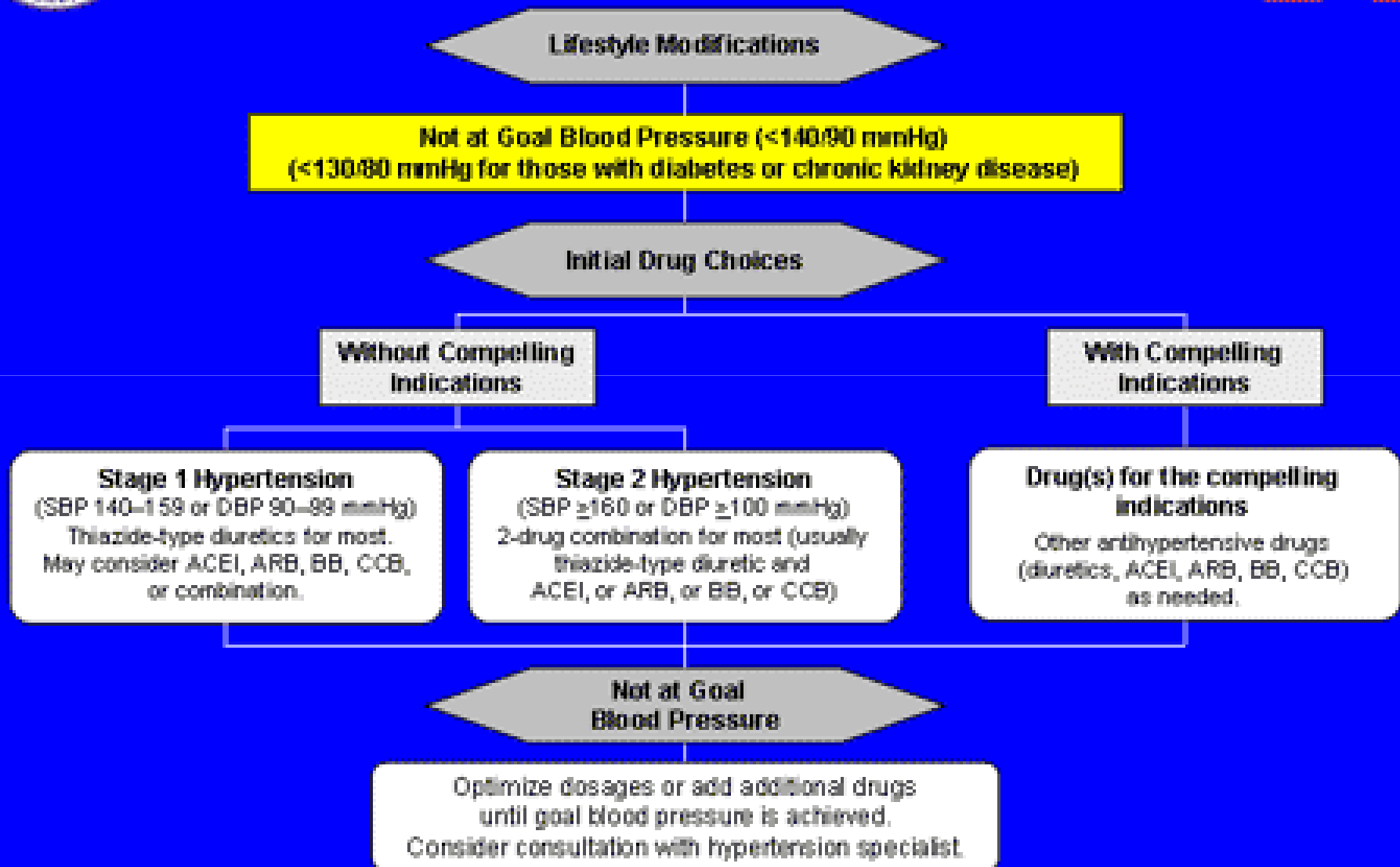
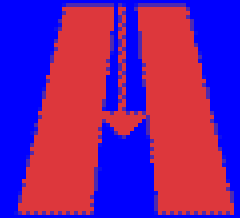
- Monotherapy is the standard initial treatment for reducing blood pressure, with stepwise increases in dose if the desired decrease in blood pressure is not achieved.

- Combining drugs from different classes is approximately 5 times more effective in lowering blood pressure than increasing the dose of 1 drug.

- Combination therapy is the preferred initial strategy in the treatment of high blood pressure.



# Algorithm for Treatment of Hypertension



# Métodos

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- Ensaios clínicos desenho factorial
- Medline, EMBASE, Cochrane
- Língua inglesa
- Período: 1966-Março 2008
- Nomes genéricos ou marcas
  - 4 classes: Tiazídicos, betabloqueadores, iECA, bloqueadores canais de cálcio
- Estudos com placebo como controle
- 42 artigos selecionados

# Ensaio clínico (RCT)

## ESTUDO FACTORIAL

POPULAÇÃO  
DO ESTUDO

GRUPO I  
EXPERIMENTAL

GRUPO II  
EXPERIMENTAL

GRUPO II  
EXPERIMENTAL

GRUPO IV  
CONTROLE

INTERVENÇÃO I

INTERVENÇÃO II

INTERVENÇÃO  
COMBINADA

NÃO INTERVENÇÃO

# Análise estatística

- Redução média da PA comparando cada grupo de intervenção com placebo
- Equivalência de doses
  - Doses `standart`: dose de manutenção usual
  - Doses utilizadas: Múltiplos da dose `standart`
- Efeito esperado da associação:  
$$0,95 (A+B)$$
- Efeito esperado da duplicação da dose:  
$$0,95 \times 2A$$

# Resultados

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- 42 estudos
- 101 comparações entre pares de drogas
- 10690 participantes
- Pacientes extrahospitalares sem história de DAC, AVC, DM ou doença renal
- Follow-up 4-12 semanas
- Idade 46-71 anos
- PA 136-173 / 84-110 mmHg

**Table 1** Details of the 42 Trials Included in the Meta-analysis

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)		
								Systolic	Diastolic	
Thiazide + beta-blocker Bateman <sup>10</sup>	1979	15	4	54	Cross-over	chlorthalidone	1	}	155	104
						atenolol	2			
Chalmers <sup>11</sup>	1976	16	8	45	Cross-over	HCTZ	2	}	163	106
						pindolol	2			
Chalmers <sup>12</sup>	1976	20	8	44	Cross-over	HCTZ	2	}	159	99
						timolol	3			
Chalmers <sup>13</sup>	1982	16	8	53	Cross-over	indapamide	1	}	164	94
						pindolol	0.67			
Chrysant <sup>14</sup>	1992	256	4	55	Parallel group	HCTZ	0.5	}	148	97
						atenolol	0.5			
Durel <sup>15</sup>	1992	5	4	47	Cross-over	atenolol	1	}	147	93
						chlorthalidone	2			
Erwtelman <sup>16</sup>	1984	50	4	46	Cross-over	chlorthalidone	1	}	143	94
						metoprolol	2			
Frishman <sup>17</sup>	1994	512	4	53	Parallel group	HCTZ	0.25	}	148	97
						HCTZ	1			
						bisoprolol	0.25			
						bisoprolol	1			
La Courciere <sup>18</sup>	1994	240	12	52	Parallel group	bisoprolol	4	}	147	96
						HCTZ	0.5			
						HCTZ	1			
						nebivolol	0.2			
Zachariah <sup>19</sup>	1993	1059	4	47	Parallel group	nebivolol	2	}	149	95
						HCTZ	0.25			
						bisoprolol	1			

**Table 1** Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Thiazide + ACE inhibitor Brown <sup>20</sup>	1990	40	4	58	Parallel group	HCTZ** perindopril	1 1	170	99
Canter <sup>21</sup>	1994	460	8	53	Parallel group	HCTZ HCTZ HCTZ quinapril quinapril quinapril	0.25 0.5 1 0.125 0.5 2	159	102
Chalmers <sup>22</sup>	1986	21	4	61	Cross-over	HCTZ enalapril	2 2	173	92
Chrysant <sup>23</sup>	1994	505	8	53	Parallel group	HCTZ HCTZ lisinopril	0.5 1 1	148	98
Chrysant <sup>24</sup>	1996	334	6	53	Parallel group	HCTZ benazepril	1 1	159	98
Fernandez <sup>25</sup>	1994	67	8	53	Parallel group	HCTZ fosinopril	0.5 2	144	93
Kayanikis <sup>26</sup>	1987	211	8	54	Parallel group	HCTZ captopril	1 1	161	93
Pool <sup>27</sup>	1997	550	8	52	Parallel group	HCTZ HCTZ HCTZ fosinopril fosinopril fosinopril	0.2 0.5 1.5 0.25 1 4	147	96
Pordy <sup>28</sup>	1994	1162	4	54	Parallel group	HCTZ HCTZ cilazapril cilazapril	0.5 1 0.2 2	144	95

**Table 1** Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)			
								Systolic	Diastolic		
Thiazide + calcium-channel blocker Burris <sup>30</sup>	1990	297	6	52	Parallel group	HCTZ HCTZ HCTZ diltiazem diltiazem diltiazem diltiazem	0.5 1 2 0.5 0.75 1 1.5	152	99		
Pool <sup>31</sup>	1993	298	6	53	Parallel group	HCTZ diltiazem	1 1				
Salveti <sup>32</sup>	1991	66	4	55	Cross-over	chlorthalidone nifedipine	1 1			158	97
Weir <sup>33</sup>	1992	298	4	54	Parallel group	HCTZ HCTZ diltiazem diltiazem diltiazem	0.5 1 0.5 0.75 1			149	95
Wing <sup>34</sup>	1997	19	4	71	Cross-over	HCTZ	1			163	85
			4	71		lacidipine	1				

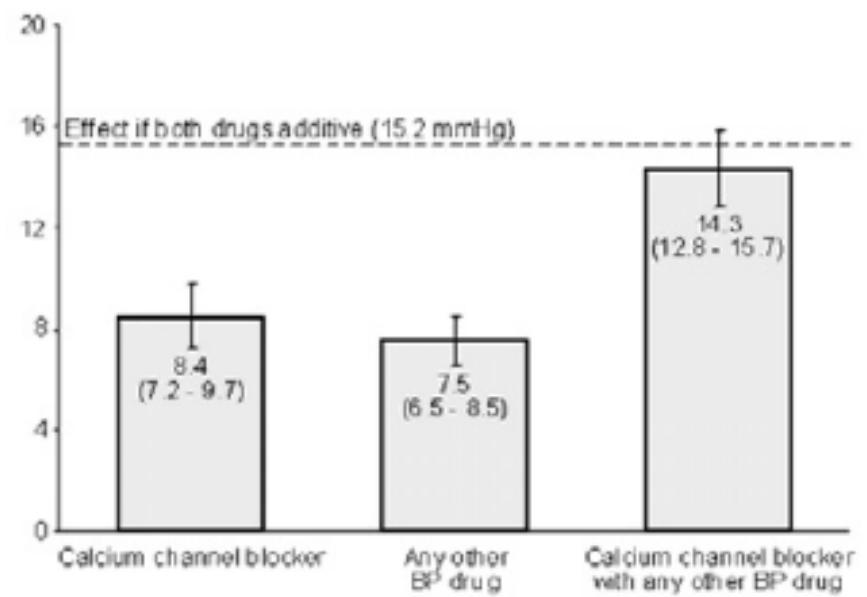
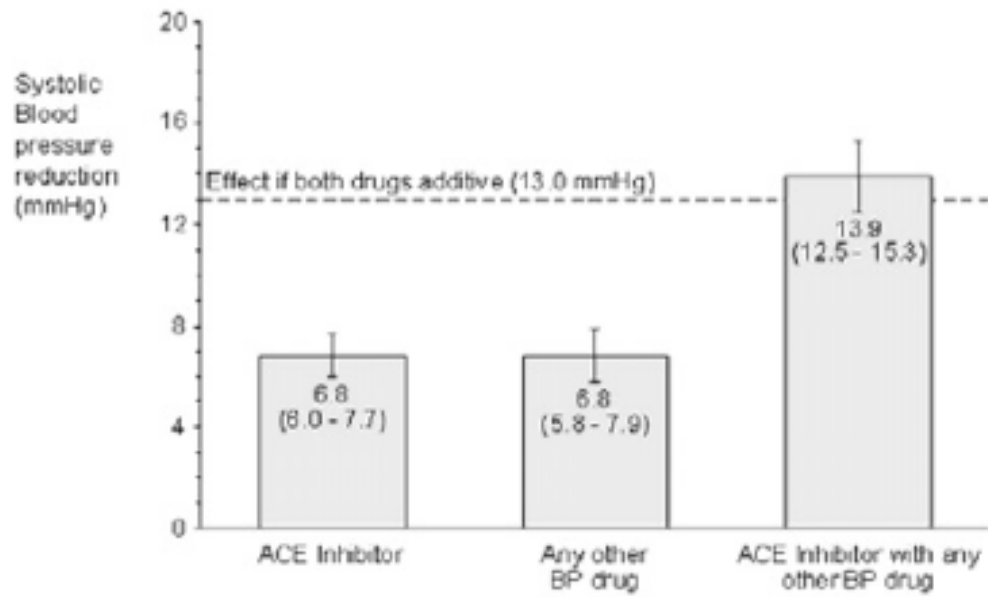
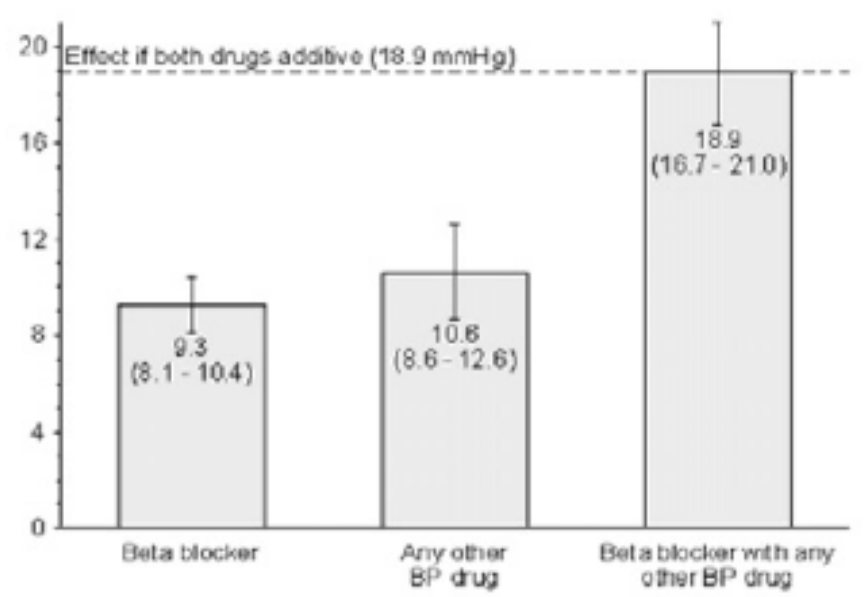
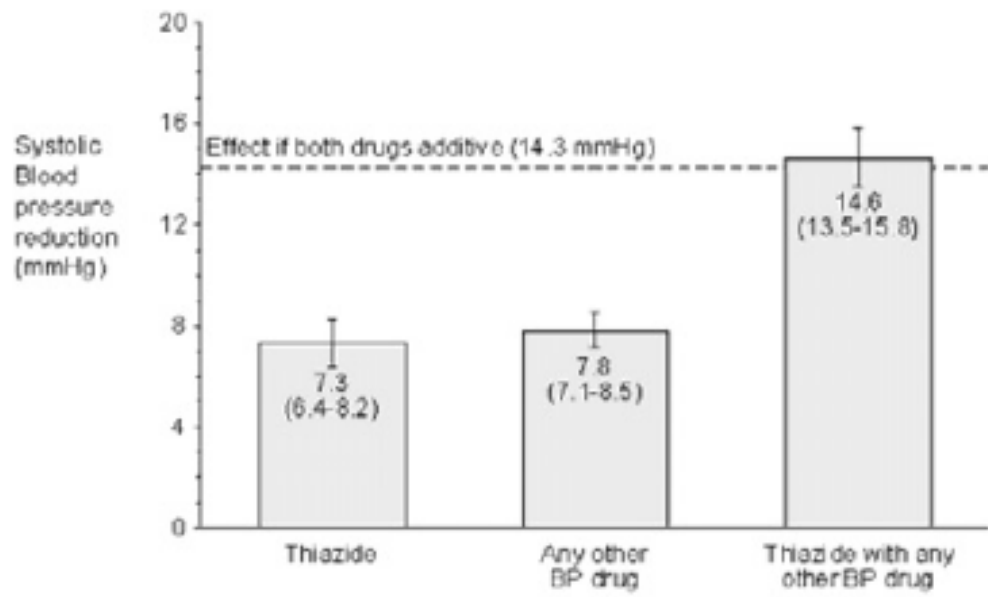
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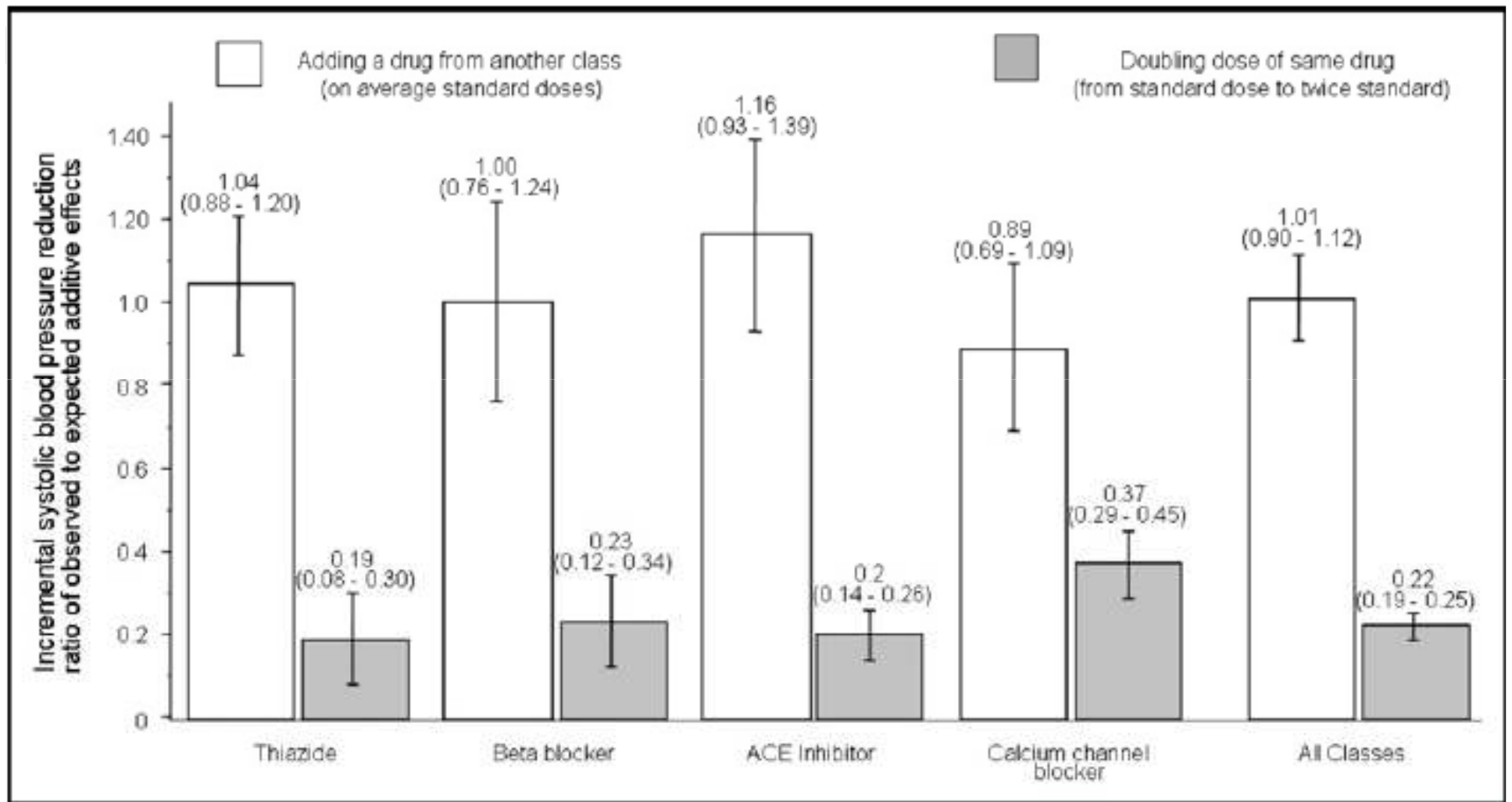
Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)		
								Systolic	Diastolic	
<b>Beta-blocker + ACE inhibitor</b>										
Wald <sup>35</sup>	2008	47	4	62	Cross-over	atenolol lisinopril	0.5	}	136	84
Wing <sup>36</sup>	1988	16	4	59	Cross-over	atenolol enalapril	1		}	171

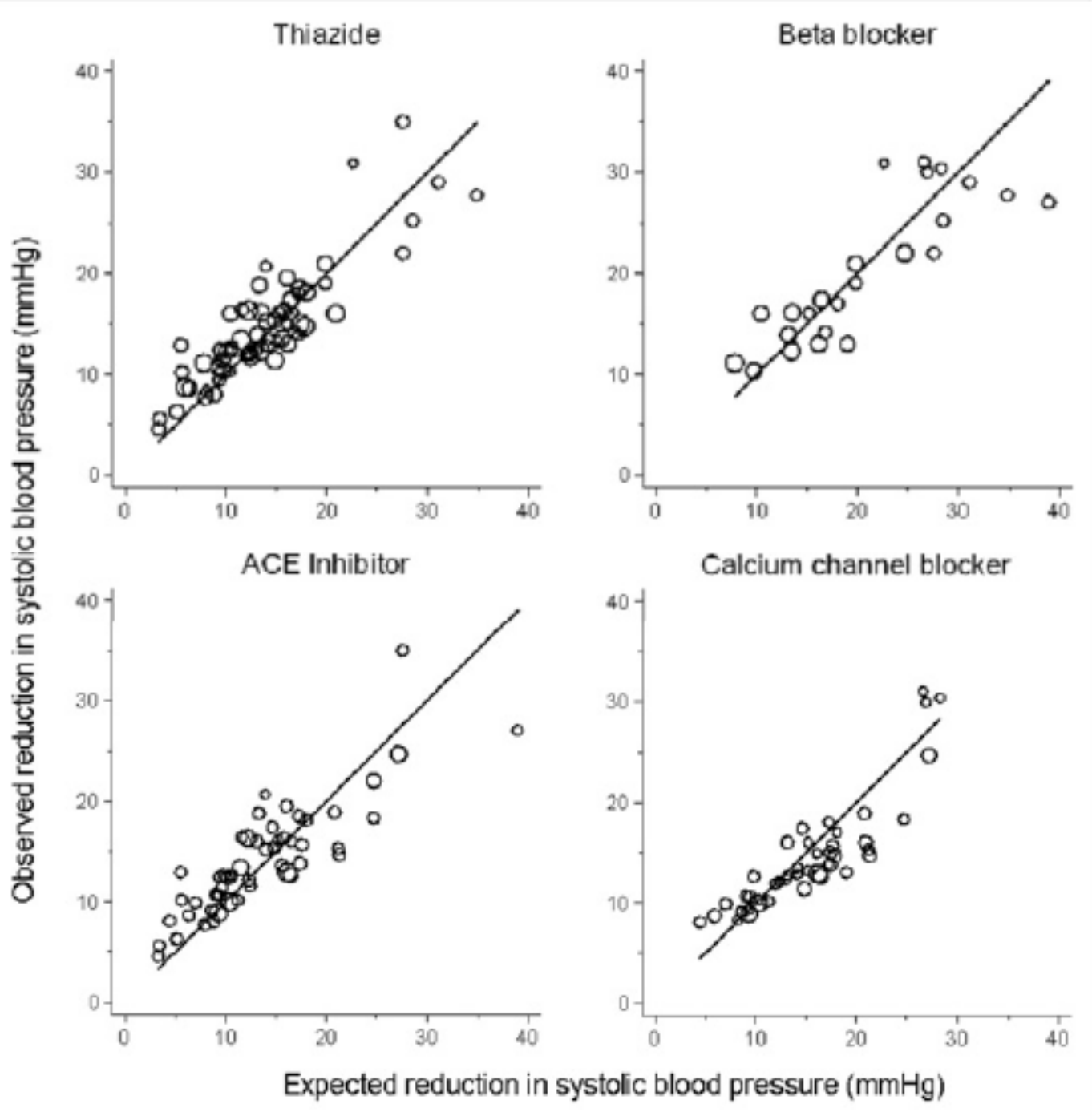


**Table 1** Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Calcium-channel blocker + ACE inhibitor	Chan <sup>43</sup>	1997	156	12	71	Parallel group	lisinopril 1 diltiazem 0.5 diltiazem 1	167	104
	Cushman <sup>44</sup>	1998	891	12	56	Parallel group	enalapril 0.5 diltiazem 0.75		
	Frishman <sup>45</sup>	1995	401	8	54	Parallel group	benazepril 0.5 amlodipine 0.5	157	101
	Kuschnir <sup>46</sup>	1996	30	8	56	Parallel group	benazepril 1 amlodipine 1		
	Levine <sup>47</sup>	1995	186	4	56	Parallel group	enalapril 1 verapamil 0.5 verapamil 1	153	100
	Messertl <sup>48</sup>	1998	631	6	54	Parallel group	trandolopril 4 verapamil 1		
	Scholze <sup>49</sup>	1998	456	6	55	Parallel group	trandolopril 0.5 trandolopril 1 trandolopril 2 verapamil 0.5 verapamil 0.75	163	104
	Scholze <sup>50</sup>	1999	507	6	50	Parallel group	ramipril 1 ramipril 2 ramipril 4 felodipine 1 felodipine 2		
	Veratran <sup>51</sup>	1997	272	8	51	Parallel group	trandolopril 1 verapamil 0.75	149	97







# Conclusões

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- A combinação de drogas de diferentes classes para redução da PA é aproximadamente 5x mais efetiva que dobrar a dose de 1 droga.
- Para maximizar a eficácia da terapia combinada é preferível usar doses baixas para minimizar os efeitos adversos.