Carotid Intima-Media Thickness and Antihypertensive Treatment

A Meta-Analysis of Randomized Controlled Trials

Ji-Guang Wang, MD, PhD; Jan A. Staessen, MD, PhD; Yan Li, MD, PhD; Luc M. Van Bortel, MD, PhD; Tim Nawrot, PhD; Robert Fagard, MD, PhD; Franz H. Messerli, MD; Michel Safar, MD

Background and Purpose—Hypertension promotes carotid intima-media thickening. We reviewed the randomized controlled trials that evaluated the effects of an antihypertensive drug versus placebo or another antihypertensive agent of a different class on carotid intima-media thickness.

Methods—We searched the PubMed and the Web of Science databases for randomized clinical trials, published in English before 2005, and included 22 trials.

Results—In 8 trials including 3329 patients with diabetes or coronary heart disease, antihypertensive treatment initiated with an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, or a calcium-channel blocker (CCB), compared with placebo or no-treatment, reduced the rate of intima-media thickening by 7 μm/year ($P=0.01$). In 9 trials including 4564 hypertensive patients, CCBs, ACE inhibitors, an angiotensin II receptor blocker or an α-blocker, compared with diuretics or β-blockers, in the presence of similar blood pressure reductions, decreased intima-media thickening by 3 μm/year ($P=0.03$). The overall beneficial effect of the newer over older drugs was largely attributable to the decrease of intima-media thickening by 5 μm/year ($P=0.007$) in 4 trials of CCBs involving 3619 patients. In 5 trials including 287 patients with hypertension or diabetes, CCBs compared with ACE inhibitors did not differentially affect blood pressure, but attenuated intima-media thickening by 23 μm/year ($P=0.02$). The treatment induced changes in carotid intima-media thickness correlated with the changes in lumen diameter ($P=0.02$), but not with the differences in achieved blood pressure ($P>0.53$).

Conclusions—CCBs reduce carotid intima-media thickening. This mechanism might contribute to their superior protection against stroke. **(*Stroke*. 2006;37:1933-1940.)**

Key Words: blood pressure ■ carotid arteries ■ meta-analysis ■ randomized controlled trials

Intima-media thickness (IMT) in the carotid arteries can be measured by using high-resolution ultrasonography. Hypertension is a major risk factor for carotid intima-media thickening. Antihypertensive treatment prevents stroke and coronary heart disease. Several recent trials tested the effects of antihypertensive drugs on carotid IMT.[1–18] In the present meta-analysis, we investigated whether antihypertensive treatment reduced carotid IMT, whether new antihypertensive drugs were more effective than old agents in the prevention of carotid intima-media thickening, and whether angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers (CCB) were equally effective in this regard. We also studied the relevance of using IMT as an intermediate outcome measure for the prevention of mortality and cardiovascular events.

Methods

Acquisition and Selection of Trials

We searched the PubMed and the Web of Science citation databases for randomized controlled trials, published in English before August 2005, using as key terms "IMT," "blood pressure (BP)," and "randomized clinical trial."

We identified 24 trials,[1–24] published between 1996 and 2005. We excluded 1 trial because the follow-up time duration was only 2 months[23] and 1 study because out of the 57 patients randomized to

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From the Studies Coordinating Centre, Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, University of Leuven, Belgium (J.G.W., J.A.S., R.F., T.N.); the Centre for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Shanghai Institute of Hypertension, Shanghai Jiaotong University, China (J.G.W., Y.L.); the Heymans Institute of Pharmacology, University of Ghent, Belgium (L.V.B.); the Hypertension Program, Division of Cardiology, St. Luke's-Roosevelt Hospital, New York, NY (F.H.M.); and the Diagnosis Center, Hopital Hotel-Dieu, Paris, France (M.S.).

Correspondence to Ji-Guang Wang, MD, PhD, Shanghai Institute of Hypertension, Ruijin 2nd Road 197, Shanghai 200025, China. E-mail jiguangwang@netscape.net

Reprint requests to Jan A. Staessen, MD, PhD, Laboratory of Hypertension, Campus Gasthuisberg, Herestraat 49, Leuven 3000, Belgium. E-mail jan.staessen@med.kuleuven.be

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TABLE 1. Characteristics of Trials

		Total No. of Patients		Main Selection Criteria				Antihypertensive Treatment	
Trial	Masking*	Randomized	Analyzed	Age, y	IMT, mm	SBP/DBP, mm Hg	Primary Outcome	Control	Experimental
Active treatment vs placebo or no-treatment									
Migdalis[1]	Open	40	40	Any	Any	≥160/95 or treated	Change in CBIMmax	No-treatment	Fosinopril
PART-2[2]	Double	617	586	≤75	Any	100–160/≤100	Change in CM	Placebo	Ramipril
SECURE[3]	Double	732	693	≥55	Any	≤160/90	PR in CBIMmax	Placebo	Ramipril
Hosomi[4]	Open	98	98	Any	Any	...	PR in CM	No-treatment	Enalapril
PREVEND[19]	Double	864	642	28–75	Any	<160/100 untreated	Change in CM	Placebo	Fosinopril†
BCAPS[5]	Double	793	783	49–70	>1.2	≤160/95	Change in CM and Bmax	Placebo	Metoprolol†
ELVA[6]	Double	103	92	20–70	>1.0	...	Change in CM and Bmax	Placebo	Metoprolol
PREVENT[7]	Double	377	...	30–80	Any	–/<95	PR in CBIMmax	Placebo	Amlodipine
New vs old drugs									
MIDAS[8]	Double	883	839	≥40	1.3–3.5	–/90–115	PR in CBIMmax	HCTZ	Isradipine SR
VHAS[9]	Open	498	377	40–65	Any	≥160/95	PR in CBIMmax	Chlorthalidone	Verapamil SR
INSIGHT[10]	Double	439	324	55–80	Any	≥150/95 or ≥160	PR in CM	HCTZ/A	Nifedipine (GITS)
ELSA[11]	Double	2334	2035	45–75	≤4.0	150–210/95–115	Change in CBMmax	Atenolol	Lacidipine
CELIMENE[12]	Double	98	82	Any	Any	–/90–120	Change in CM	Celiprolol	Enalapril
Roman[13]	Double	60	50	38–69	Any	–/95–114	Change in CM	HCTZ	Ramipril
PHYLLIS[20]	Double	508	508	45–70	1.3–4.0	150–210/95–115	PR in CBMmax	HCTZ	Fosinopril†
LAARS[14]	Double	280	225	35–65	0.8–1.5	–/90(95)–115	PR in CM	Atenolol	Losartan
DAPHNE[22]	Double	80	80	45–70	Any	≤ 200/95–115	Change in CBIM and CBIMmax	HCTZ	Doxazosin
CCBs vs ACEIs									
Koshiyama[15]	Open	22	22	Any	≤2.0	...	Change in CM	ACE inhibitors	Amlodipine
Topouchian[16]	Double	46	39	29–76	<2.0	–/95–114	Change in CM	Trandolapril	Verapamil SR
Pontremoli[17]	Open	31	31	29–62	Any	≥140/90 or treated	Change in CM	Lisinopril	Nifedipine (GITS)
Stanton[18]	Double	69	69	20–80	Any	140–220 or/90–120	Change in CM	Lisinopril	Amlodipine
ELVERA[21]	Double	166	126	60–75	Any	160–220 or/95–115	Change in CBIMmax	Lisinopril	Amlodipine

SBP/DBP indicates systolic/diastolic blood pressure; CBIMmax, mean maximum IMT of the common carotid arteries, bifurcations and internal carotid arteries; CM, mean IMT of the common carotid arteries; CBMmax, mean maximum IMT of the common carotid arteries and bifurcations; PR, progression rate; HCTZ, hydrochlorothiazide; HCTZ/A, hydrochlorothiazide/amiloride; CCB, calcium-channel blocker; SR, slow release; GITS, gastrointestinal therapeutic system. See figure legends and text for trial acronym expansions.

*In VHAS,[9] the study medication was administered in a double-blind fashion during the initial 6 months and thereafter in an open way; †possible association with pravastatin (40 mg daily)[19,20] or fluvastatin (40 mg daily)[5] in a 2×2 factorial design.

quinapril or losartan, 14 crossed over and were not analyzed.[24] According to the study design, we classified the remaining 22 trials into 3 groups: 8 trials compared antihypertensive drugs with placebo[2,3,5–7,19] or no-treatment,[1,4] 9 trials compared new with old drug classes,[8–14,20,22] and 5 trials compared ACE inhibitors and CCBs.[15–18,21]

Data Extraction

We based our analysis on the summary statistics reported in the literature. For carotid IMT, we extracted for the experimental and control groups separately means and standard deviations at baseline and during follow-up and if available in the published report also changes over time. Within each trial, the control group consisted of patients left untreated[1,4] or allocated placebo,[2,3,5–7,19] the patients randomized to old drug classes,[8–14,20,22] or the patients who received ACE inhibitors in trials comparing these agents with CCBs.[15–18,21] The number of patients by randomization group was not reported in the IMT substudy of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT).[7]

Statistical Analysis

For each comparison within each trial, we calculated the absolute difference in the mean changes over time in carotid IMT (μm per year) between the experimental and control groups, and computed the standard error (SE) of the difference as described previously.[25] The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). Heterogeneity of effect sizes was tested across trials using the χ^2 test. If trials were homogeneous ($P<0.10$), a fixed-effects model was used to calculate pooled effect sizes. Otherwise, a random-effects model was applied. The funnel plot technique was used to evaluate publication bias.[25] The effect sizes of carotid IMT were plotted against the sample size of the 22 studies.

We performed a meta-regression analysis to explore whether the effects of antihypertensive drugs on carotid IMT were mediated by effects on BP or lumen diameter. We correlated the differences in carotid IMT between experimental and control treatment with the corresponding differences in BP and lumen diameter. Net treatment

TABLE 2. Characteristics of Patients

Trial	No. of Patients*		Mean Age (SD), y	Mean LDL-C (SD), mmol/L	Mean SBP/DBP (mm Hg)		Percent of Patients					Follow-Up, y§
	Control	Experimental			At entry	Difference During Follow-Up†	Women	Smokers	Carotid Plaques (IMT, mm)‡	CV Complications	Diabetes Mellitus	
Migdalis[1]	20	20	58 (5)	...	168/94	+22/+12	50	23	...	...	100	1.0
PART-2[2]	309	308	61 (8)	4.2 (1.0)	133/79	+5/+4	18	17	...	100	9	4.7
SECURE[3]	244	488	65 (7)	3.5 (1.0)	132/76	+4/+3	24	10	...	≈90	34	4.5
Hosomi[4]	50	48	56 (9)	4.5 (1.3)	140/76	+2.4/−0.1	38	45	...	0	100	2.0
PREVEND[19]	323	319	51 (11)	4.1 (1.0)	130/76	+1/+2	35	39	10 (>1.0)	3.3	4.3	4.0
BCAPS[5]	397	396	62 (5)	4.1 (0.9)	139/85	≈+1/?	55	31	100 (>1.2)	4.3	3.2	3.0
ELVA[6]	52	40	60 (10)	7.0 (2.1)	138/81	+3/0	49	27	79 (50%)	4	1	3.0
PREVENT[7]	...	...	57 (...)	3.6 (...)	129/79	+7/+4	20	25	...	100	...	3.0
MIDAS[8]	441	442	59 (9)	3.8 (0.7)	150/97	−3.5/0	22	20	100 (≥1.3)	4.1	...	3.0
VHAS[9]	232	224	54 (7)	3.9 (1.0)	168/102	−2/−0.4	48	18	40 (>1.5)	0	...	4.0
INSIGHT[10]	164	160	65 (6)	...	161/94	−1/0	50	27	34 (50%)	17	23	4.0
ELSA[11]	1012	1023	56 (8)	3.7 (1.0)	164/101	+0.2/−0.1	45	20	59 (≥1.3)	2.4	0	3.75
CELIMENE[12]	48	50	52 (9)	...	159/99	+4.2/+3.4	40	...	3 (...)	0	0	0.75
Roman[13]	28	22	51 (7)	...	150/94	−4/−4	26	...	...	0	0	0.5
PHYLLIS[20]	253	255	58 (7)	4.7 (0.5)	160/98	−0.5/+0.7	60	16	100 (1.3–4.0)	0	...	2.6
LAARS[14]	138	142	59 (9)	3.7 (0.9)	160/101	−0.5/−0.3	50	...	0 (>1.5)	0	...	2.0
DAPHNE[22]	39	41	59 (7)	4.5 (...)	163/100	−8/−1	0	46	...	100	0	3.0
Koshiyama[15]	11	11	68 (8)	...	...	...	55	...	0 (>2.0)	...	100	0.5
Topouchian[16]	23	23	53 (...)	...	158/99	≈0/−1	45	...	0 (≥2.0)	0	0	0.5
Pontremoli[17]	16	15	49 (7)	3.7 (1.1)	161/104	−3/−3	39	32	...	0	0	0.5
Stanton[18]	34	35	49 (11)	...	165/100	+1/−1	41	28	...	0	0	1.0
ELVERA[21]	85	81	67 (4)	3.9 (0.8)	175/93	0.8/1.9	45	41	...	0	...	2.0

SBP/DBP indicates systolic/diastolic blood pressure; LDL-C, serum LDL cholesterol; CV, cardiovascular. See figure legends and text for trial acronym expansions.

*Values are No. of patients randomized into the study except for PREVEND,[19] ELVA,[6] INSIGHT,[10] ELSA[11] and Roman,[13] in which only the characteristics of analyzed patients were given; †positive values indicate tighter blood pressure control on experimental treatment; ‡numbers are the percentage of patients with carotid plaques. The threshold intima-media thickness for diagnosis of plaques is given between parentheses; §values are mean duration of follow-up except for SECURE,[3] in which only median follow-up was reported.

effects on BP and lumen diameter were determined by subtracting the mean change in the experimental group from the corresponding mean change in the control group.

We ran statistical analyses using the SAS package, version 8.1 (SAS Institute). For mortality and cardiovascular events, we determined the relative benefit or risk of experimental versus control treatment from the odds ratios in stratified 2×2 contingency tables. We used StatXact for Windows (CYTEL Software Corp), version 4.0, to check the homogeneity of the odds ratios by Zelen test and to compute exact 95% CI.

Results

Characteristics of Trials and Patients

Our analysis included 22 studies[1–22] and 9138 subjects, of whom 8449 (92%) had been randomized in 17 double-blind trials and 689 (8%) in 5 studies with an open design (Table 1). In 15 trials,[2,3,5–14,16,19,21] the investigators excluded from analysis a proportion of the randomized patients (≈10%) who had incomplete data collection at randomization or during follow-up. Participants in 15 trials[1–4,6,7,9–13,17–19,21,22] had a broad range of carotid IMT at baseline, whereas the other studies exclusively recruited patients with[5,8,20] or without[14–16] plaques according to various definitions. In all[8–14,16–18,20–22] but 1[15] of the actively-controlled studies, the participants had to have systolic or diastolic hypertension. During follow-up, other antihypertensive drugs could be added to the randomized treatment to reach the target of BP.

In all trials, the major characteristics of the patients at baseline were similar between study groups. The mean age of the study subjects ranged from 49[17,18] to 68[15] years (Table 2). One trial included only patients with hypercholesterolemia.[6] The mean BPs at entry ranged from 129[7] to 175[21] mm Hg systolic and from 76[3,4,19] to 104[17] mm Hg diastolic. Mean follow-up duration was from 0.5[15–17] to 4.7[2] years.

Ultrasound Examination

In addition to the baseline measurement, carotid IMT was measured during follow-up once in 5 trials,[1,15–17,19] twice in 8 trials[2–5,12–14,21] and 3 times or more frequently in 9 trials (Table 3).[6–11,18,20,22] Carotid IMT was measured at both sides in 16 studies,[1–4,7–9,11,14–18,20–22] only at the right[5,6,10,12] or left[13,19] side in 6 studies, at both the near and far arterial walls in 7 studies,[1,3,4,7,8,20,22] or only at far wall in 15 trials.[2,5,9–19,21] Mean maximum IMT of multiple carotid segments, the mean of several random measurements, and the mean of the measurements over 1 carotid segment were taken as outcomes in 8,[1,3,7–9,11,20,21] 9,[4,12–19] and 5 trials,[2,5,6,10,22] respectively.

Antihypertensive Drugs Versus Placebo or No-Treatment

Altogether, the 8 trials comparing active treatment with placebo or no-treatment included 3329 subjects (Figure 1).

TABLE 3. Technical Aspects of Carotid IMT Measurements

			Scanning Protocol				Measurement of IMT	
Trial	Timeline, mo	Transducer (device), MHz	Tomographic Plane*	Artery	Wall	Length of segment(s), mm	Reading Protocol	Summarizing Protocol‡
Migdalis[1]	0, 12	7.5 (ATL UM4)	LT, TV	CBI, l, r	Far, near	8	Online	Mmax (C8+B4+I4)
PART-2[2]	0, 24, 48	10 (Acuson 128)	Orthogonal	C, l, r	Far	10	Offline	M over 1 segment (C2)
SECURE[3]	0, 18–26, 48–66	7.5 (Acuson), 10 (ATL UM9)	LT, circumferential	CBI, l, r	Far, near	10	Offline	Mmax (C4+B4+I4)
Hosomi[4]	0, 12, 24	7.5 (Aloka SSD-650, Toshiba SSH-160A)	LT	C, l, r	Far, near	10	Offline	M of 3 random readings (C4)
PREVEND[19]	0, 48	7.5 (Pie Medical Scanner 200)	LT	C, l	Far	10	Offline, automated	M of 3 readings (C1)
BCAPS[5]	0, 18, 36	7 (Acuson 128 CT)	LT	CB, r	Far	10	Offline, automated	M over 1 segment (C1), Mmax (B1)
ELVA[6]	0, 12, 24, 36	7 (Acuson 128 CT)	LT	CB, r	Far	10	Offline, automated	M over 1 segment (C1+B1)
PREVENT[7]	0, every 6 m	10 (Biosound phase 2)	LT, AP projections	CBI, l, r	Far, near	10	Offline	Mmax (C4+B4+I4)
MIDAS[8]	0, every 6 m	8 (Biosound 2000 II SA)	LT, AP projections	CBI, l, r	Far, near	10	Offline	Mmax (C4+B4+I4)
VHAS[9]	0, 3, yearly	7.5–8 (HP Sonos 1000, ATL UM9, Biosound 2000 II SA)	LT, multiple projections	CBI, l, r	Far	...	Offline	Mmax (C2+B2+I2 or C2+B2)
INSIGHT[10]	0, 4, yearly	5–10 (...)	LT, AP projections	C, r	Far	≥10	Offline, automated	M over 1 segment (C1)
ELSA[11]	0, yearly	8 (Biosound 2000 II SA)	LT	CB, l, r	Far	≈10	Offline, semi-automated	Mmax (C2+B2)
CELIMENE[12]	0, 5, 9	7.5 (Kontron Sigma 44)	LT, TV	C, r	Far	20 mm to B†	Offline, automated	M of several random readings (C1)
Roman[13]	0, 3, 6	7.0–7.5 (Biosound Genesis II)	LT	C, l,	Far	10 mm to B†	Offline	M of several random readings (C1)
PHYLLIS[20]	0, yearly	8 (Biosound 2000 II SA)	LT	CB, l, r	Far, near	...	Offline	Mmax (C4+B4)
LAARS[14]	0, 12, 24	7.5 (Kontron Sigma 44)	...	C, l, r	Far	10–15	Offline	M of 3 random readings (C1)§
DAPHNE[22]	0, 6, 12, 24, 36	7 (Acuson 128 CT)	LT	CBI, l, r	Far, near	10	Offline	M over 1 segment or Mmax (C4+B4+I4)
Koshiyama[15]	0, 6	7.5 (Logiq 500)	...	C, l, r	Far	20	Online	M of 1 max and 2 others 1 cm apart (C1)§
Topouchian[16]	0, 6	7.5 (Kontron Sigma 44)	LT, TV	C, l, r	Far	Middle and distal parts	Offline, automated	M of 3 readings (better image side, C1)
Pontremoli[17]	0, 24	10 (Diasonic Spectra)	LT, TV	C, l, r	Far	10	Online	M of 3 random readings (C2)
Stanton[18]	0, 3, 6, 12	7.5 (ATL UM4)	LT, ALP projections	C, l, r	Far	5–15	Offline	M of 3 random readings (C2)
ELVERA[21]	0, 12, 24	7 (Acuson 128)	LT	CBI, l, r	Far	...	Offline	Mmax (C2+B2+I2)

TV indicates transversal; LT, longitudinal; AP, anterior and posterior; ALP, anterior, lateral and posterior; C, common carotid artery; B, bifurcation; I, internal carotid artery; l, left side; r, right side; M, mean; Mmax, mean maximum IMT. See figure legends and text for trial acronym expansions.

*The longitudinal images were used in most studies. Several studies also captured transversal images; †a fixed section of the common carotid artery was used to measure IMT; ‡the No. of arterial segments used for the calculation of mean IMT or mean maximum IMT is given in the parentheses; §the side (left or right) with greater mean IMT was chosen. In Koshiyama's trial,[15] the investigators took the mean of the maximum IMT and 2 readings of sites, respectively, 1 cm downwards and 1 cm upwards from the site of maximum IMT.

Active antihypertensive treatment consisted of an ACE inhibitor in 5 trials (n=2090),[1–4,19] a β-blocker in 2 trials (n=862)[5,6] and a CCB in 1 trial (n=377; Table 1).[7] The weighted mean decrease in systolic pressure across the 8 trials was 6.4 mm Hg (95% CI, 2.2 to 10.5; $P=0.003$).

Mean IMT at baseline ranged from 691[1] to 1259 μm.[7] Across the 8 trials, we found significant heterogeneity mainly attributable to the large treatment effect in the Migdalis trial ($P=0.001$).[1] A random-effects model showed that active antihypertensive treatment significantly reduced the yearly increase in carotid IMT by 7 μm (95% CI, −14 to −2; $P=0.01$). The results of the Migdalis trial[1] also produced significant heterogeneity in the 5 ACE inhibitor trials ($P=0.003$).[1–4,19] The pooled effect size based on a random-effects model was similar to that in all trials, but did not reach statistical significance ($P=0.07$). The combined results of the β-blocker trials[5,6] were not statistically significant with borderline significant heterogeneity among individual trials ($P=0.05$).

New Drugs Versus Old Drugs

Among the 9 trials comparing new with old drug classes, the new antihypertensive drug was a CCB in 4 trials (n=3619),[8–11] an ACE inhibitor in 3 trials (n=640),[12,13,20] an angiotensin II receptor blocker in 1 trial (n=225)[14] and an α-blocker in 1 trial

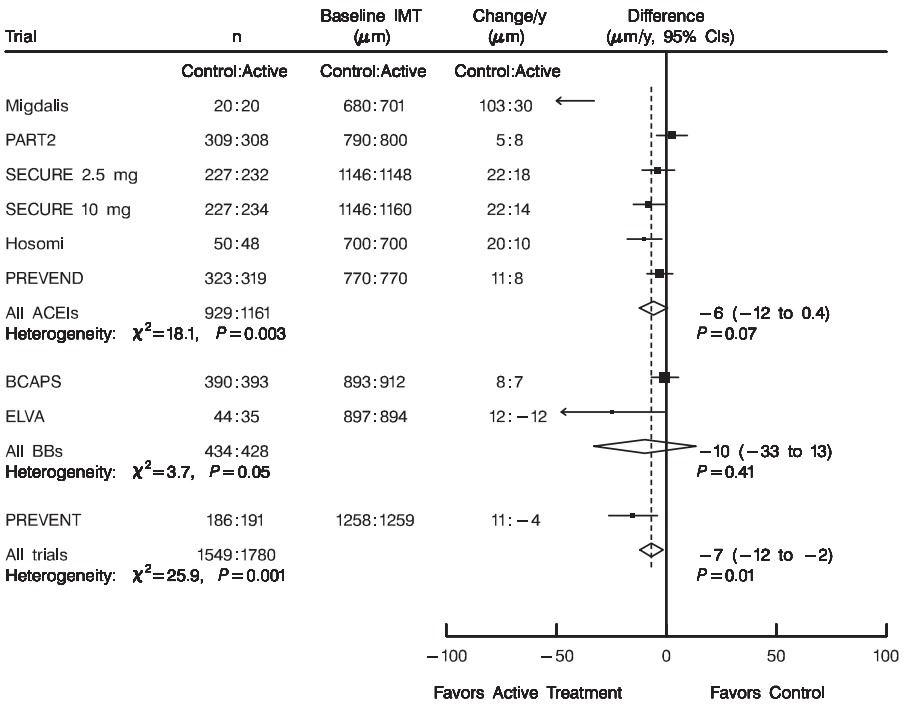

Figure 1. Effects of antihypertensive treatment on changes in carotid IMT compared with placebo or no-treatment. Solid squares represent the difference in individual trials between study groups (active minus placebo) in changes over follow-up in IMT and have a size proportional to the total number of analyzed patients. The 95% CIs for individual trials are denoted by lines and those for the pooled results by diamonds. Dotted line indicates the mean difference between randomized groups in all trials. BB and ACEIs indicate β-blockers and angiotensin-converting enzyme inhibitors, respectively. PART2 indicates Prevention of Atherosclerosis with Ramipril Trial[2]; SECURE, Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E[3]; PREVEND, the Prevention of Renal and Vascular ENdstage Disease intervention trial.[19]

(n=80; Table 1).[22] Sample sizes varied from 50[13] to 2035 patients (Figure 2).[11] The weighted mean decrease in systolic pressure across the 9 trials was 1.1 mm Hg (95% CI, −2.5 to 0.3; P=0.11).

Mean IMT at baseline ranged from 594[12] to 1410 μm.[22] There was no heterogeneity across these trials ($P \geq 0.19$). Compared with old drug classes, new hypertensive drugs significantly reduced the yearly increase in carotid IMT by 3 μm (95% CI, −5 to −0.3; P=0.01). This result mainly reflected the effect of CCBs[8–11] because overall ACE inhibitors were not different from old drug classes (P=0.19).[12,13,20]

CCBs Versus ACE Inhibitors

A total of 287 patients were included in 5 trials comparing ACE inhibitors with CCBs (Table 1).[15–18,21] The number of patients ranged from 22[15] to 126.[21] The weighted mean decrease in systolic pressure across the 5 trials was −0.1 mm Hg (95% CI, −3.5 to 3.4; P=0.97).

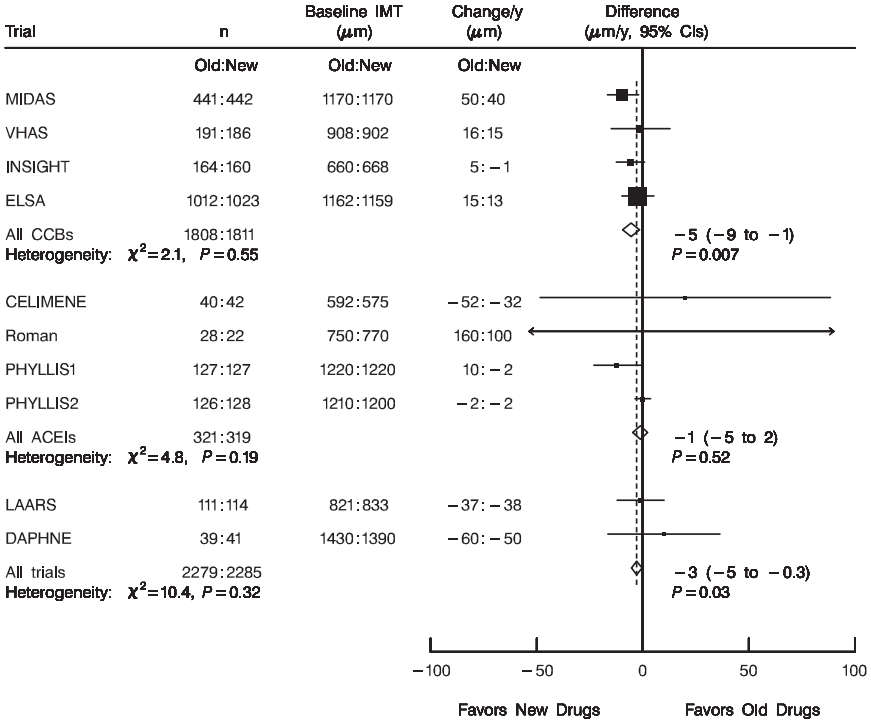

Figure 2. Effects of antihypertensive treatment on changes in carotid IMT in trials comparing old with new drugs. For further explanation, see Figure 1 legend. CCBs indicate calcium-channel blockers; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study[8]; VHAS, Verapamil in Hypertension and Atherosclerosis Study[9]; INSIGHT, International Nifedipine GITS Study–Intervention as a Goal for Hypertension Treatment: intima-media thickness substudy[10]; ELSA, European Lacidipine Study on Atherosclerosis[11]; CELIMENE, CELiprolol-induced regression of Intima-Media, compared with ENalapril, in Essential hypertensives[12]; PHYLLIS, the Plaque Hypertension Lipid-Lowering Italian Study[20]; PHYLLIS1, Fosinopril versus hydrochlorothiazide of the PHYLLIS trial in the absence of pravastatin[20]; PHYLLIS2, Fosinopril versus hydrochlorothiazide of the PHYLLIS trial in the presence of pravastatin[20]; LAARS, the Losartan vascular Regression Study[14]; DAPHNE, the Doxazosin Atherosclerosis Progression study in Hypertensives in the Netherlands.[22]

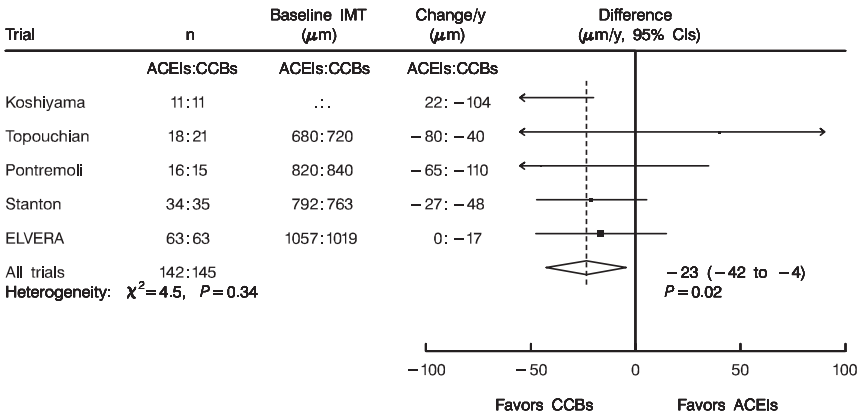

Figure 3. Effects of antihypertensive treatment on changes in carotid IMT in trials comparing CCBs versus ACEIs. For further explanation, see Figure 1. ELVERA indicates the Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (E/A Ration).[21]

Mean IMT at baseline ranged from 702[16] to 1038 μm (Figure 3).[21] No heterogeneity was noticed across the 5 trials (P=0.34). Compared with ACE inhibitors, CCBs significantly reduced the yearly increase in carotid IMT by 23 μm (95% CI, −42 to −4; P=0.02).

Meta-Regression Analysis

The BP difference during follow-up did not predict the treatment-induced difference in the yearly changes of carotid IMT (systolic, n=21; r=0.13; P=0.57 and diastolic, n=22; r=0.16; P=0.49). However, the treatment-induced differences in the yearly changes of carotid IMT correlated weakly and inversely with the differences in lumen diameter of the common carotid artery during follow-up (n=12; r=−0.49; P=0.10; Figure 4). This correlation became significant after further adjustment for mean systolic and diastolic pressures at entry (r=−0.73; P=0.02).

Evaluation of Publication Bias

The funnel plot showed a gap, indicating that few small studies with negative results had been published (Figure 5).

Cardiovascular Morbidity and Mortality

Five placebo-controlled trials[2,3,5,7,19,26] and 4 trials evaluating CCBs[8,9,11] or an ACE inhibitor[20] versus diuretics or a β-blocker reported morbidity and mortality results (Table 4). Because the trials were inadequately powered for hard outcomes, only the odds ratio for all fatal and nonfatal cardiovascular events in trials comparing active treatment with placebo reached statistical significance (P=0.007).

Discussion

The main finding of our meta-analysis was that treatment with BP-lowering drugs in high-risk patients with diabetes mellitus or coronary heart disease, irrespective of their background treatment, slightly reduced the progression of

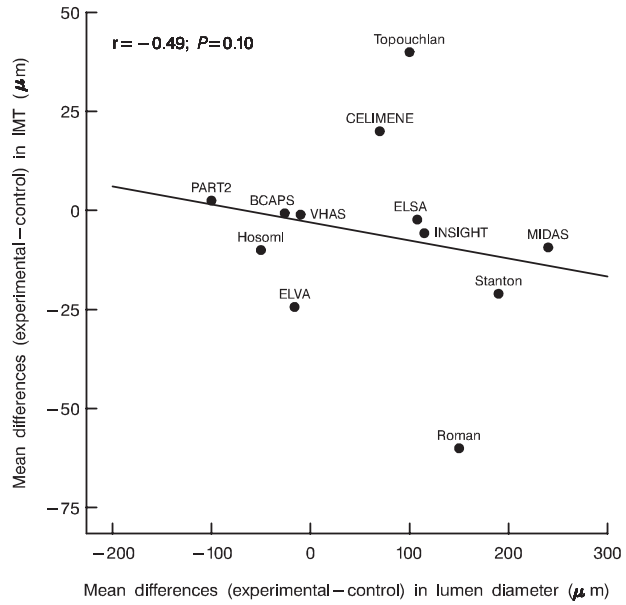

Figure 4. Relationship between the differences in the yearly changes of carotid IMT and the corresponding differences in lumen diameter of the common carotid artery. Differences (experimental minus control) were calculated by subtracting the mean change (follow-up minus baseline) in the control group from that in the experimental group. Negative values indicate a larger decrease in the experimental group than that in the control group. The regression line was weighted by the inverse of the variance of the individual differences in IMT. See other figure legends for trial expansions.

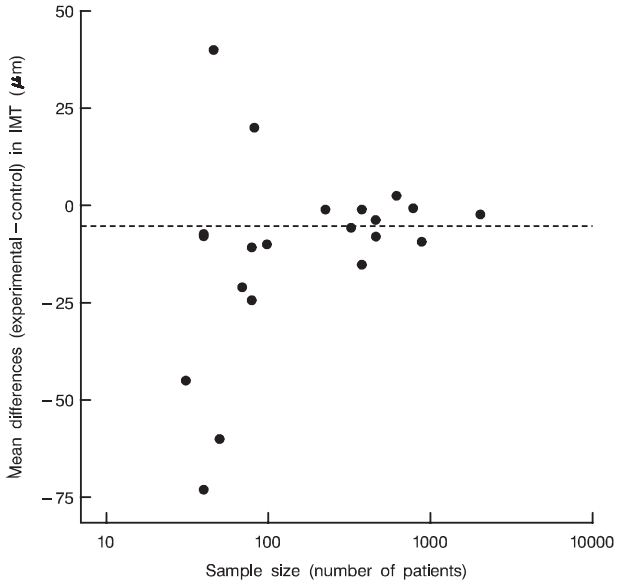

Figure 5. Funnel plot of the differences in the yearly changes of carotid IMT versus sample size. The horizontal axis is on a logarithmic scale. Dotted line indicates the mean difference in the yearly changes of carotid IMT across all studies combined.

TABLE 4. Pooled Estimates of Effects of Antihypertensive Drug Treatment on Mortality and Cardiovascular Events

	Antihypertensive Treatment vs Placebo*			CCBs or ACEIs vs Diuretics or β-Blockers†		
Event	No. of Events (treatment/placebo)	Odds Ratio (95% CI)	P	No. of Events (new drugs /old drugs)	Odds Ratio (95% CI)	P
Total mortality	31/44	0.69 (0.42–1.14)	0.13	23/30	0.76 (0.42–1.36)	0.39
Cardiovascular mortality	13/21	0.61 (0.28–1.30)	0.22	6/12	0.50 (0.15–1.44)	0.24
Fatal and nonfatal cardiovascular events	143/151	0.71 (0.55–0.92)	0.007	52/55	0.94 (0.63–1.40)	0.82
Fatal and nonfatal stroke	14/26	0.46 (0.13–1.67)	0.24	19/18	1.05 (0.52–2.13)	0.99
Fatal and nonfatal myocardial infarction plus sudden death	61/72	0.84 (0.58–1.21)	0.33	29/31	0.93 (0.54–1.60)	0.88

The Zelen test for homogeneity across trials was not significant for all end points ($P>0.20$), except for fatal and nonfatal stroke ($P=0.02$).

*The analyses included 5 trials (PART-2,[2] SECURE,[3] PREVEND,[19,26] BCAPS[5] and PREVENT[7]) for fatal and nonfatal cardiovascular events, 3 trials (PART-2,[2] BCAPS[3] and PREVENT[7]) for total mortality, fatal and nonfatal stroke, and fatal and nonfatal myocardial infarction plus sudden death, and 2 trials (PART-2[2] and PREVEND[19,26]) for cardiovascular mortality; †the analyses included 4 trials (MIDAS,[8] VHAS,[9] ELSA,[11] and PHYLLIS[20]) for fatal and nonfatal cardiovascular events, 3 trials (MIDAS,[8] VHAS,[9] and ELSA,[11]) for total mortality, fatal and nonfatal stroke, and fatal and nonfatal myocardial infarction plus sudden death, and 2 trials (VHAS[9] and ELSA[11]) for cardiovascular mortality.

arterial disease as reflected by carotid intima-media thickening. Furthermore, in the actively-controlled trials CCBs reduced the progression of carotid intima-media thickening more than diuretics, β-blockers or ACE inhibitors. The observed reductions in carotid IMT, though small, approximate to the mean yearly progression of carotid intima-media thickening in middle-aged and older adults.[27]

Among the trials which compared antihypertensive drug treatment with placebo or no-treatment, the point estimates for all 3 drug classes favored antihypertensive treatment. The Migdalis trial reported large decreases in BP (22/12 mm Hg) and IMT (73 μm/year), but is difficult to interpret because of its open design.[1] BP on randomized treatment might also explain the divergent results in 2 double-blind β-blocker trials.[5,6] Metoprolol compared with placebo lowered systolic pressure on average by 1 mm Hg in the β-Blockers Cholesterol-lowering Asymptomatic Plaque Study (BCAPS)[5] and 3 mm Hg in the Effect of Long-term treatment of metoprolol CR/XL on surrogate Variables for Atherosclerotic disease (ELVA) study.[6] A significant effect on the rate of progression of carotid intima-media thickening was only observed in ELVA.[6] Patient characteristics, in particular the presence of diabetes mellitus, may account for some of the differences among the trials comparing ACE inhibitors with placebo or no-treatment.[1–4,19]

In keeping with Fleckenstein's animal experiments,[28] several trials were mounted to test the hypothesis that calcium-channel blockade might be effective in slowing the progression of carotid atherosclerosis. Compared with no-treatment, the effect size tended to be larger in the PREVENT trial[7] than that in trials that tested ACE inhibitors[1–4,19] or β-blockers.[5,6] In the actively controlled trials, CCBs reduced carotid IMT more than diuretics,[8–10] a β-blocker[11] or ACE inhibitors.[15–18,21] In successive quantitative overviews,[29] we and other investigators demonstrated that CCBs compared with older drugs, including diuretics, β-blockers and their combination, and compared with ACE inhibitors, provided superior protection against stroke. Furthermore, using meta-regression, we additionally demonstrated that in hypertensive and high-risk patients BP-lowering rather than ancillary drug properties explained most of the cardiovascular protection conferred by antihypertensive drugs, but also that CCBs, independent of their BP-lowering activity, might have a small additional beneficial effect in the prevention of stroke.[28] Our current meta-analysis highlights one possible mechanism contributing to the differential effects of antihypertensive drugs on stroke prevention: that is, their influence on the progression of arterial disease at the level of the carotid arteries.

Differences in the progression of carotid IMT might be attributable to either functional or structural changes in the vessel wall, or both. However, it is difficult to differentiate these 2 mechanisms. Our current meta-regression analysis suggests that the treatment-induced differences in carotid IMT might at least in part be attributed to the corresponding differences in changes of lumen diameter. IMT is inversely related to lumen diameter. The reduction in carotid IMT in the patients treated with a CCB might therefore be attributable to a functional decrease by its vasodilatory effect and not necessarily to a structural decrease in intima-media cross-sectional area. This hypothesis is also supported by the observation of a larger effect in short-term studies[15–18] than in long-term trials.[7–11] Therefore, the clinical relevance of changes in carotid IMT as an intermediate outcome measure has to be further studied in trials with mortality and morbidity as end points.

In conclusion, compared with no-treatment, diuretics/β-blockers or ACE inhibitors, CCBs attenuate the rate of progression of carotid intima-media thickening. Whether these findings are attributable to functional changes through vasodilation without a structural decrease in cross-sectional area and whether these findings have implications for the long-term prevention of cardiovascular complications such as stroke, remain to be proven. In the prevention of carotid intima-media thickening, CCBs are more effective than ACE inhibitors, which in turn are more effective than placebo or no-treatment, but not more active than diuretics/β-blockers.

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Disclosures

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