Final Outcome Results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)

A Randomized Controlled Trial

Nemat O. Borhani, MD, MPH†; Michele Mercuri, MD, PhD; Patricia A. Borhani; Vardaman M. Buckalew, MD; Maria Canossa-Terris, MD; Albert A. Carr, MD; Tissa Kappagoda, MD, PhD; Michael V. Rocco, MD, MS; Harold W. Schnaper, MD; James R. Sowers, MD; M. Gene Bond, PhD

Objective.—To compare the rate of progression of mean maximum intimal-medial thickness (IMT) in carotid arteries, using quantitative B-mode ultrasound imaging, during antihypertensive therapy with isradipine vs hydrochlorothiazide.

Design.—Randomized, double-blind, positive-controlled trial.

Setting.—Nine medical center clinics.

Population.—A total of 883 patients with baseline mean±SD systolic and diastolic blood pressure (SBP and DBP, respectively) of 149.7±16.6 and 96.5±5.1 mm Hg, age of 58.5±8.5 years, and maximum IMT of 1.17±0.20 mm.

Interventions.—Twice daily doses of isradipine (2.5-5.0 mg) or hydrochlorothiazide (12.5-25 mg).

Main Outcome Measure (Primary End Point).—Rate of progression of mean maximum IMT in 12 carotid focal points over 3 years.

Results.—There was no difference in the rate of progression of mean maximum IMT between isradipine and hydrochlorothiazide over 3 years (P=.68). There was a higher incidence of major vascular events (eg, myocardial infarction, stroke, congestive heart failure, angina, and sudden death) in isradipine (n=25; 5.65%) vs hydrochlorothiazide (n=14; 3.17%) (P=.07), and a significant increase in nonmajor vascular events and procedures (eg, transient ischemic attack, dysrhythmia, aortic valve replacement, and femoral popliteal bypass graft) in isradipine (n=40; 9.05%) vs hydrochlorothiazide (n=23; 5.22%) (P=.02). At 6 months, mean DBP decreased by 13.0 mm Hg in both groups, and mean SBP decreased by 19.5 mm Hg in hydrochlorothiazide and 16.0 mm Hg in isradipine (P=.002); the difference in SBP between the 2 groups persisted throughout the study but did not explain the increased incidence of vascular events in patients treated with isradipine.

Conclusion.—The rate of progression of mean maximum IMT in carotid arteries, the surrogate end point in this study, did not differ between the 2 treatment groups. The increased incidence of vascular events in patients receiving isradipine compared with hydrochlorothiazide is of concern and should be studied further.

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HYPERTENSION CAUSES major changes in the arterial wall that predispose to the development of atherosclerosis.[1,2] Results of major randomized clinical trials of hypertension have demonstrated that treatment with diuretics and β-blockers reduces the risk of fatal and nonfatal stroke and coronary heart disease.[3-8] The impact of treatment with other agents, including calcium channel blockers, is less well studied.

Results of animal studies have demonstrated the antiatherogenic properties of isradipine, a dihydropyridine calcium antagonist used in the treatment of hypertension.[9-12] Similar findings have been reported with other calcium antagonists.[13]

For editorial comment see p 829.

Also, the utility of quantitative B-mode ultrasound imaging, a noninvasive technique, to measure intimal-medial thickness (IMT) of the arterial walls as a surrogate for assessing early atherosclerosis and the feasibility of its use in population studies has been demonstrated.[14-16] Thus, the objective of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) was to test the effect of isradipine compared with hydrochlorothiazide on the rate of progression in carotid artery IMT over 3 years, measured by quantitative B-mode ultrasound imaging in patients with sustained hypertension.

METHODS

A full description of the rationale and design of MIDAS has been published.[17-20] Briefly, MIDAS was a multicenter, randomized, double-blind, controlled clinical

From Department of Internal Medicine (Dr Borhani and Ms Borhani), and Division of Cardiovascular Medicine (Dr Kappagoda), School of Medicine, University of California at Davis; Department of Family and Community Medicine, School of Medicine, University of Nevada, Reno (Dr Borhani and Ms Borhani); Division of Vascular Ultrasound Research (Drs Bond and Mercuri), and Section of Nephrology, Department of Internal Medicine (Drs Buckalew and Rocco), The Bowman Gray School of Medicine, Winston-Salem, NC; Clinical Trials Unit, Miami (Fla) Heart Research Institute (Dr Canossa-Terris); Circulatory Disease Center, Augusta (Ga) Preventive Cardiology Inc (Dr Carr); Scientific Application Co Inc, Birmingham, Ala (Dr Schnaper); and Division of Endocrinology, Metabolism and Hypertension, Wayne State University, Detroit, Mich (Dr Sowers).

†Deceased.

Reprints: Vardaman M. Buckalew, Jr, MD, Section of Nephrology, Bowman Gray School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1053.

trial to compare the effect of 2 antihypertensive drugs, isradipine and hydrochlorothiazide, on the rate of change in IMT progression in the carotid arteries, as measured by quantitative B-mode ultrasound imaging, over a period of 3 years. Men and women 40 years of age or older with confirmed hypertension were recruited in 9 university-based clinical centers. Blood pressure (BP) was measured twice in the sitting position at 3 consecutive visits, using a standard sphygmomanometer. The average of these BPs was used to determine the presence of hypertension.[20] Only diastolic BP (DBP) was used to determine the presence of hypertension.[20] Hypertension was defined as an average DBP of from 90 to 115 mm Hg.

Inclusion criteria included documented sustained diastolic hypertension after completion of a 3- to 8-week placebo run-in period, during which all candidates were tested for compliance by using "the pill count method" (at least 80% compliance was the absolute requirement for eligibility); fasting levels of total cholesterol and low-density lipoprotein cholesterol of no more than 6.21 and 4.14 mmol/L (240 and 160 mg/dL), respectively; and presence of IMT in the carotid artery walls between 1.3 and 3.5 mm in the absence of ultrasonographic characteristics suggesting plaque complication (ie, mineralization or hemorrhage).[18]

Exclusion criteria included elevated levels of fasting total and low-density lipoprotein cholesterol (>6.21 and >4.14 mmol/L [240 and 160 mg/dL], respectively); elevated levels of blood glucose, creatinine, or liver enzymes; recent history (within 3 months) of stroke, myocardial infarction (MI), coronary bypass surgery, or angioplasty; contraindication to either study medication; and history of carotid endarterectomy, insulin-dependent diabetes, secondary hypertension, or hypothyroidism or hyperthyroidism.

A total of 18 800 potential candidates, identified through different strategies of recruitment (eg, mass mailing, population screening, or referrals by physicians in the catchment areas), signed informed consent forms to participate in the 3 screening visits and the placebo "washout" and assessment of compliance. Of this number, a total of 883 candidates met all eligibility criteria.

All eligible candidates signed another informed consent form to participate in the 3-year study and were randomized into 2 treatment groups: hydrochlorothiazide, 12.5 to 25 mg twice a day (n=441) or isradipine, 2.5 to 5.0 mg twice a day (n=442).[17,19,20] The randomization process was stratified and blocked by clinic to provide equal probability of assignment to either treatment group throughout the study. All randomized participants were followed up for 36 months, with follow-up visits every 2 months during the first year and every 3 months during the remaining 2 years. B-mode ultrasonography of carotid arteries was performed twice at baseline, twice at the final visit, and once every 6 months in the interim.

Baseline examination included complete medical history, BP measurement, electrocardiogram, and laboratory tests. During each follow-up visit, BP, electrocardiogram, laboratory tests, and compliance to assigned study medications were recorded. Also, during these visits new supplies of study medications were dispensed, and information on all illnesses, complaints, and hospitalizations was elicited and recorded. During the first 4 months, medications were titrated to achieve a predefined goal for DBP. The goal DBP was defined as a reduction of at least 10 mm Hg and a DBP of less than 90 mm Hg. However, for patients with baseline DBPs between 105 and 115 mm Hg, the goal DBP was set at less than 95 mm Hg.[17,19,20] If the DBP had not reached this goal during treatment with the highest dose of study medication allowed by the protocol, open-label enalapril, an angiotensin-converting enzyme inhibitor, was added at dosages of 2.5, 5.0, 7.5, or 10.0 mg twice per day to achieve the predetermined DBP goal. The level of systolic blood pressure (SBP) was recorded but was not considered a criterion for entry into the study, nor was it considered a requirement for initiating any change in study medication during the course of the trial.

B-mode Ultrasound

A standardized protocol for scanning and quantitative reading of B-mode ultrasound imaging examination of carotid arteries was used.[18,21] Sonographers and readers were trained and routinely tested and certified in these procedures. The carotid artery segments studied (distal 1.0 cm of the common carotid, carotid bifurcation, and proximal 1.0 cm of the internal carotid artery) were defined by 2 anatomical reference points (ie, origin of the bifurcation and position of the flow divider).[18] Multiple IMT measurements were made from individual frames of each of the 12 focal points of carotid artery walls. These focal points (near and far walls of the common carotid, carotid bifurcation, and internal carotid arteries bilaterally) have been described previously.[18-22] Briefly, they consisted of the following: (1) periadventitia-adventitia of the near-wall interface; (2) adventitia-media, near-wall interface; (3) intima-lumen, near-wall interface; (4) lumen-intima, far-wall interface; (5) media-adventitia, far-wall interface; and (6) adventitia-periadventitia, far-wall interface. All were measured bilaterally, for a total of 12 focal points.[18-22]

Ultrasound end point definitions were based on combined measurements of mean maximum IMTs, taking the linear distance between intima-lumen and media-adventitia interfaces. The single maximum IMT from each of the 12 focal points was used to calculate the mean maximum IMT.[18,19,22] Scans were evaluated and IMTs measured centrally at the Ultrasound Reading Center (URC), without knowledge of patients' randomization assignment.

Ultrasound Quality Assessment

A 20% random sample of participants who had ultrasound scans was selected every 6 months for repeat scanning; each was assigned a fictitious identification number, known only to the coordinating Operations Analysis Center (OAC). These selected participants signed a new informed consent form and had a scan repeated before they left the clinic. In addition, replicate scans were obtained in all participants at baseline and 36 months. These repeated scans with their fictitious identification numbers were sent to the URC (a total of 2647 replicate scans) and were read by the trained URC readers. The findings, like the findings of regular scans, were reported to the OAC. The OAC cross-sectionally monitored precision and reproducibility of these matched original and replicate studies.[21] The staff of the OAC were unblinded to the randomization assignments of participants and the masked identification of the repeat scans so that they could objectively monitor the performance of each center, including the URC, by randomization assignments. The OAC reported its findings on quality control at 6-month intervals to the policy and data monitoring committee. The investigators and the URC staff were also informed of the OAC findings, but without revelation of the randomization assignments.[21]

End Point Definitions

The primary end point was a comparison of the rate of progression in mean maximum IMT of 12 carotid focal points over 3 years in isradipine vs hydrochlorothiazide. Secondary end points were defined specifically for the purpose of identifying the effect, if any, on the specific segments of carotid artery. These end points were rate of progression in IMT of the following: (1) "normal" arterial walls, defined as the mean of those walls with IMTs less than 1.0 mm at baseline; (2) "borderline" walls with mean IMTs between 1.0 and 1.3 mm at baseline; (3) "diseased" walls with mean IMTs between 1.3 and 3.5 mm at baseline; (4) the 4 walls of the common carotid artery; (5) the 4 walls of the carotid bifurcation; (6) the 4

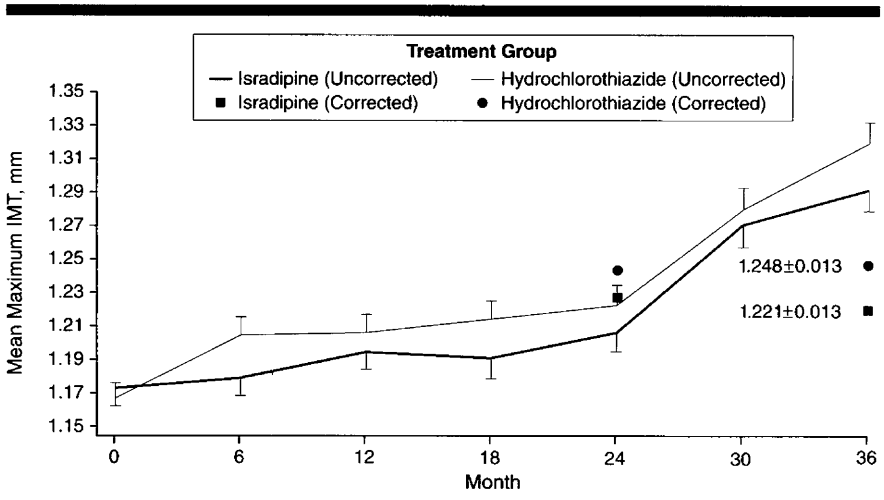
far walls of the common and bifurcation combined; (7) the single wall with the greatest maximum IMT at baseline; and (8) the single wall with the greatest maximum increase over the 36 months (identified retrospectively).

Clinical Events

All case-report forms were examined for evidence of any clinical events and adverse reactions. All reported clinical events were reviewed, adjudicated, and classified by the MIDAS Investigators' Morbidity and Mortality Committee, consisting of 6 clinicians, each from a different clinical center; all were blinded to the randomization assignments. At each MIDAS Investigators' semiannual meeting, this committee reviewed events that had resulted in hospitalization or a visit to the physician's office. Members of this committee were required to reach a unanimous decision, based on clinical judgment, on how each reported event should be classified. The classification choices available to the members of this committee were as follows: (1) any major vascular event, defined as stroke, MI, congestive heart failure (CHF), angina pectoris, and sudden death and other cardiovascular disease–related death; (2) any major vascular procedure, defined as endarterectomy, coronary artery bypass graft surgery, and angioplasty; (3) any major vascular events/procedures, defined as the combination of (1) and (2); and (4) any nonmajor vascular events/procedures, defined as transient ischemic attack, atrial fibrillation, premature ventricular contractions (PVCs), femoral/popliteal bypass graft, aortic valve replacement, and palpitation. The Morbidity and Mortality Committee had decided that for the purpose of analysis at the end of the study, only 1 major vascular event was to be counted for each randomized participant, using the following hierarchy to determine which of the "multiple" events in the same participant would be counted as the "official" reportable event: (1) death, (2) stroke, (3) MI, (4) CHF, and (5) angina pectoris, as documented by physicians' diagnosis or hospitalization (electrocardiographic changes, treadmill findings, or angiographic findings documenting the presence of ischemic heart disease).

Statistical Methods

Based on a study of 28 untreated hyperlipidemic men,[17,23] the pattern and the progression rate in IMT over 3 years in the hydrochlorothiazide treatment group was predicted to be linear between 0.15 and 0.20 mm/y. Isradipine was expected to slow the rate of this anticipated progression by approximately 30% to 40%. The power for detecting this expected difference between the hydrochlorothiazide and the isradipine groups was set at 90% with a 2-sided significance (α) level of .05 with P value of .05. These considerations determined the required sample size to be 800 participants to be followed up for 3 years. By the end of recruitment, 883 eligible participants were enrolled.



Cross-sectional measurement of the mean maximum intimal-medial thickness (IMT) of the 12 focal points in the carotid arteries overall, by clinic visit and treatment group. Horizontal bars indicate SE. Uncorrected points are those with evidence of drift in ultrasound reading over time; corrected points are those corrected for drift.

For the secondary end points (ie, difference in the progression rate of mean maximum IMT between isradipine and hydrochlorothiazide in different segments of carotid arteries) a P value of .01 was set a priori. Subsequently, a Bonferroni adjustment was made for multiple (n=8) comparisons, requiring P value of .00625 to achieve statistical significance.[24]

For the analysis of primary and secondary end points, a linear least-squares regression line was computed for each participant through all of the mean maximum IMT values at different time points (2 at baseline, 1 every 6 months, and 2 at 36 months). If the change was found to be linear, estimates of the mean slopes in the 2 treatment groups (weighted for possible missing visits) were to be compared as an estimate of rate of IMT progression. If a nonlinear change was identified, a nonlinear model was to be selected depending on the type of nonlinearity. A nonlinear relationship was noted between mean maximum IMT and time instead of the planned outcome (Figure). Therefore, a nonlinear model was selected[25] with 2 parameters, 1 estimating the progression rate of IMT for each group (drug × time effect) and a second estimating the average change from baseline of mean maximum IMT for each group at 6-month intervals (drug effect). The statistical significance of differences between the same parameters for each treatment group was tested, using generalized t statistics of the group data[24]; the models were fitted using restricted maximum likelihood.[26]

Group differences between baseline characteristics were assessed by t test. Longitudinal changes in BP and laboratory values were analyzed using analyses of covariance adjusted for baseline levels. Clinical events were compared between treatment groups, using life-table analyses and log-rank tests. All analyses were performed by the MIDAS OAC, using the intention-to-treat approach.

RESULTS

The baseline characteristics of the subjects are shown in Table 1.[22,27] The mean±SD age was 58.2±8.3 years in the isradipine group and 58.7±8.7 years in the hydrochlorothiazide group; 78% were male; and 72% were white, 22% African American, and 6% other ethnic groups.

Effects on IMT

No difference was seen in the rate of progression of IMT between the 2 treatment groups over 3 years (drug × time effect, P=.68) (Table 2). However, at 6 months after randomization, the mean±SD maximum IMT of the 12 focal points in the carotid arteries increased more in the hydrochlorothiazide group (0.035±0.007 mm) than in the isradipine group (0.008±0.007 mm), a difference that persisted but did not increase over the entire 3 years of the study (Figure). Thus, the average difference in IMT between the 2 treatment groups over 3 years was statistically significant (drug effect, P=.02) (Table 2), but there was no divergence in the slope of the progression (Figure).

Final 36-month ultrasound scans were obtained from 95% of all randomized participants. After the trial concluded, the OAC identified an upward drift in the reading process of the ultrasound scans between the 24- and 36-month visits. Therefore, a sample of scans from base-

Table 1.—Description of MIDAS Population at Baseline*

	Isradipine Group (n-442)	Hydrochlorothiazide Group (n=441)	Z of Difference	Both Groups Combined (N=883)
Demographics				
Age, y, %				
40-49	14.9	16.8	...	15.9
50-59	38.0	35.8	...	36.9
60-69	41.2	37.0	...	39.1
≥70	5.9	10.4	...	8.2
Mean (SD)	58.2 (8.3)	58.7 (8.7)	−0.85	58.5 (8.5)
Sex, % male	79.9	75.7	1.48	77.8
Race, %				
White	71.0	73.7	−0.88	72.4
African American	22.4	20.6	...	21.5
Other	6.3	5.7	...	6.1
Risk factors				
Systolic blood pressure, mean mm Hg (SD)	150.6 (16.8)	148.9 (16.4)	1.54	149.7 (16.6)
Diastolic blood pressure, mean mm Hg (SD)	96.7 (5.2)	96.2 (5.0)	1.33	96.5 (5.1)
Duration of hypertension, y, mean (SD) [median]	9.9 (8.9) [7]	10.2 (8.9) [8]	−0.45	10.1 (8.9) [8]
Cigarette smoking				
Former, %	37.6	40.0	−0.73	20.0
Current, %	19.0	21.0	...	38.8
Never, %	43.4	39.0	...	41.2
Pack-years, mean (SD) [median]	15.4 (22.1) [1.6]	17.0 (23.3) [4.5]	1.03	16.2 (22.7) [2.8]
Cholesterol, mean† mmol/L (SD) [mg/dL (SD)]				
Total	5.60 (0.73) [217 (28)]	5.58 (0.75) [216 (29)]	0.49	5.59 (0.74) [216 (29)]
Low-density lipoprotein	3.79 (0.69) [147 (27)]	3.77 (0.70) [146 (27)]	0.47	3.78 (0.70) [146 (27)]
High-density lipoprotein	1.22 (0.31) [47 (12)]	1.24 (0.34) [48 (13)]	−0.78	1.23 (0.33) [48 (13)]
Triglycerides, mean† mmol/L (SD) [mg/dL (SD)]	3.74 (1.81) [331 (160)]	3.64 (1.72) [322 (152)]	0.84	3.69 (1.77) [327 (157)]
Body mass index, mean kg/m^2 (SD)	27.9 (4.0)	27.6 (4.0)	0.93	27.8 (4.0)
Prior use of antihypertensive medications, %				
Diuretics	45.9	42.9	0.92	44.4
β-Blockers	18.1	18.6	−0.19	18.3
Angiotensin-converting enzyme inhibitors	20.6	18.8	0.66	19.7
Calcium antagonists	11.3	8.2	1.58	9.7
Not on any antihypertensives	22.4	24.5	−1.18	23.6
Prior history, %				
Myocardial infarction	1.4	2.5	−1.23	1.9
Angina	1.1	0.2	1.64	0.7
Coronary bypass	0.7	2.3	−1.96	1.5
Intimal-medial thickness, mm				
Mean† (SD) maximum among 12 walls	1.17 (0.21)	1.17 (0.19)	0.53	1.17 (0.20)
Single maximum among 12 walls	2.08 (0.54)	2.08 (0.52)	0.19	2.08 (0.53)
Mean† (SD) of 6 near walls	1.16 (0.25)	1.13 (0.23)	1.61	1.15 (0.24)
Mean† (SD) of 6 far walls	1.18 (0.25)	1.20 (0.25)	−0.81	1.19 (0.25)
Mean† (SD) of 4 common walls	0.98 (0.20)	0.98 (0.18)	−0.12	0.98 (0.19)
Mean† (SD) of 4 bifurcation walls	1.45 (0.34)	1.44 (0.29)	0.30	1.45 (0.32)
Mean† (SD) of 4 internal walls	1.09 (0.34)	1.07 (0.33)	1.12	1.08 (0.33)

*Adapted with permission.[22,27] MIDAS indicates Multicenter Isradipine Diuretic Atherosclerosis Study.
†Mean of 2 measurements before randomization.

line and 24-month and 36-month visits were reread independently by 4 trained and certified URC technicians who remained blinded to the original readings and the randomization assignments. Scans were chosen for rereading if they had been read by the same individual at 0 and 24 months and at 24 and 36 months. Comparing the second with the original readings indicated no significant drift at the 24-month visit ($P=.24$), but a significant upward drift at the 36-month visit ($P<.001$). However, the magnitude of this upward drift was the same in both treatment groups, and corrected mean maximum IMT scores did not change the relative differences in IMT progression between the 2 treatment groups. At the 36-month visit, the corrected readings were 1.221±0.013 mm and 1.248±0.013 mm in isradipine and hydrochlorothiazide, respectively (Figure).

The absolute difference in replicate scan readings in IMT, an estimate of total variability, was 0.12 mm. The mean arithmetic difference for baseline reproducibility for sonographers and readers was –0.003±0.005 mm, respectively.[21] These measures of interreader and intrareader variability are consistent with previous reports.[21,28]

For the secondary end points, there was no difference in IMT progression rate between the 2 treatment groups (drug × time effect, Table 2). However, as was the case for the primary end point, there was a trend in 3-year IMT average difference between the isradipine and the hydrochlorothiazide groups (drug effect), in favor of isradipine, some of which were statistically significant after Bonferroni adjustments for multiple comparisons (Table 2).

Because of the presence of the drug effect but no drug × time effect, the question arose as to whether the difference in IMT observed at 6 months might have been attributable to some effect of isradipine or hydrochlorothiazide on carotid size or lumen dimension. Thus, an additional post hoc analysis was performed in

Table 2.—Observed Changes in Mean Maximum IMT From Baseline To Three Years by Treatment Group*

Mean Maximum IMT	IMT Change From Baseline, mean±SE, mm		Difference in 3-y IMT Change [Isradipine−Hydrochlorothiazide], mm	P	
	Isradipine	Hydrochlorothiazide		Drug × Time Effect	Drug Effect
Overall of all 12 focal points of carotid arteries—primary end point	0.121±0.008	0.149±0.008	−0.028	.68	.02
Different segments of carotid arteries—secondary end points					
Normal segments	0.206±0.010	0.210±0.010	−0.004	.62	.45
Borderline segments	0.112±0.014	0.134±0.014	−0.022	.32	.94
Diseased segments	0.086±0.021	0.121±0.020	−0.035	.38	.02
Common segments	0.064±0.006	0.061±0.006	0.003	.11	.07
Bifurcation segments	0.154±0.014	0.208±0.014	−0.054	.71	.01
Far wall of common and bifurcation segments	0.178±0.011	0.200±0.011	−0.022	.13	<.001
Single maximum thickness identified at baseline	0.079±0.034	0.089±0.033	−0.010	.29	.12
Segment with greatest progression	0.837±0.031	0.856±0.032	−0.019	.92	.91

*For the overall 12 focal points, the 2-sided significance level was set, a priori, as $P \leq .05$. Per protocol, significance levels for secondary end points were set at $P \leq .01$. For the 8 different segments of carotid arteries the adjusted significance level, using Bonferroni convention, is $P = .006$. IMT indicates intimal-medial thickness.

a selected sample of 252 patients for whom baseline and 6-month scans were available. Eligibility included presence of an IMT greater than 1.3 mm in the distal common carotid artery and clear definition of the relevant focal points. The reader was blinded to treatment assignment and previous results. A total of 175 scans (isradipine=84, hydrochlorothiazide=91) were found suitable for reevaluation. The internal diameter (linear distance between the 2 lumen-intima interfaces) and external diameter (linear distance between the 2 adventitia-media interfaces) of the common carotid arteries were measured and compared statistically using the standard t test.[29] There was no significant difference between the 2 treatment groups at baseline, but at 6 months the hydrochlorothiazide group showed a significant decrease in carotid artery internal diameter (−0.13 mm; 95% confidence interval [CI], −0.22 to −0.04 mm), as well as external diameter (−0.13 mm; 95% CI, −0.22 to −0.04 mm), whereas in the isradipine group there was an increase in the internal diameter (+0.11 mm; 95% CI, 0.00 to +0.22 mm), but no change in the external diameter (+0.03 mm; 95% CI, −0.06 to +0.11 mm).

Effects on BP

At the 6-month visit, DBP in both groups had decreased by approximately 13 mm Hg from baseline, whereas SBP was reduced by 19.5 mm Hg in the hydrochlorothiazide group and 16.0 mm Hg in the isradipine group ($P = .002$). This difference between the 2 treatment groups persisted for the duration of the study.

Enalapril Use and Treatment Dropouts

During the course of MIDAS, 56% of participants assigned to isradipine and 54% of those assigned to hydrochlorothiazide remained on their initially assigned monotherapy (Table 3). At the final clinic visit, 25% of the isradipine group and 28% of the hydrochlorothiazide group were taking enalapril. Twenty percent of those on isradipine treatment and 18% of those on hydrochlorothiazide treatment had withdrawn from their respective study medications. The 3-year cumulative incidence of adverse reactions as the reason for discontinuing study medication was 9.3% in isradipine and 8.2% in hydrochlorothiazide.

Table 3.—Percentage of Participants on Monotherapy or Enalapril*

Follow-up Visit, mo	Isradipine Group (n=442), %			Hydrochlorothiazide Group (n=441), %		
	Monotherapy	On Enalapril†	Off Both Medications	Monotherapy	On Enalapril†	Off Both Medications
2	88.9	2.9	8.1	87.5	5.0	7.5
6	73.5	18.4	8.2	70.5	21.4	8.2
12	65.1	22.6	12.3	63.2	24.3	12.5
36	55.5	24.7	19.8	54.2	27.5	18.3

*No differences were statistically significant.
†Enalapril either added to study medications or used as monotherapy.

Clinical Events

After completion of the trial, when investigators were unblinded to the results on clinical events obtained by the Morbidity and Mortality Committee, concern was expressed as to whether objective criteria had been consistently applied in adjudication of clinical events, especially those classified as "hospitalized angina pectoris." Accordingly, an external ad hoc panel of 3 recognized authorities in the fields of cardiology and epidemiology was appointed. Using standard clinical definitions and the hierarchy described herein, this ad hoc committee independently reviewed and adjudicated selected clinical events while blinded to the randomization assignments of the participants. The final analysis of clinical events reported in this article is based on the classification of events reported by this ad hoc committee.

Morbid and fatal events based on the final classification of the independent panel of experts are presented in Table 4. Total numbers of events (fatal and nonfatal) were exactly the same in both groups (120 each). All-cause mortality was close to identical in both treatment groups (8 isradipine vs 9 hydrochlorothiazide). However, there were more reported cases of angina pectoris as documented by objective criteria during hospitalization in the isradipine group (11) than in the hydrochlorothiazide group (3) (relative risk [RR], 3.66; 95% CI, 1.03-13.02; $P = .03$). The incidence of major vascular events was higher in isradipine (25) than hydrochlorothiazide (14) (RR, 1.78; 95% CI, 0.94-3.38; $P = .07$). Also, the incidence of nonmajor events and procedures (eg, transient ischemic attack, dysrhythmia, PVCs, aortic valve replacement, and femoral/popliteal bypass grafts) was higher in isradipine (40) than in hydrochlorothiazide (23) (RR, 1.74; 95% CI, 1.06-2.85; $P = .02$). The incidence of vascular events and procedures was higher in isradipine (54) than in hydrochlorothiazide (33) (RR, 1.63; 95% CI, 1.08-2.47; $P = .02$).

The classification of clinical events by the external ad hoc panel of experts differed slightly from that of the original Morbidity and Mortality Committee. The independent panel's classification of major vascular events differed from the investigators' Morbidity and Mortality Committee as follows: isradipine group—1 less stroke, 1 more MI, and 2 less CHF; hydrochlorothiazide group—1 less MI, 1 less CHF, and 1 less angina pectoris. The RR

Table 4.—Morbid and Mortal Event Rates Through 36 Months by Treatment Groups*

Categories of Events	Isradipine Patients (n=442) No.	Isradipine Patients (n=442) No./100	Hydrochlorothiazide Patients (n=441) No.	Hydrochlorothiazide Patients (n=441) No./100	RR (95% CI)	P†
Any event (morbid/fatal)‡	120	27.0	120	27.0	1.00 (0.80-1.24)	.98
All-cause mortality	8	1.8	9	2.1	0.89 (0.35-2.28)	.81
Major vascular events						
Stroke	6	1.35	3	0.68	2.00 (0.50-7.93)	.32
Myocardial infarction	6	1.35	5	1.13	1.20 (0.37-3.89)	.77
Sudden death	2	0.45	2	0.45	1.00 (0.14-7.05)	>.99
Congestive heart failure	2	0.45	0	0.0	. . .	.16
Angina pectoris§	11	2.48	3	0.68	3.66 (1.03-13.02)	.03
Other cardiovascular disease death‖	1	0.22	1	0.22	1.00 (0.06-15.90)	>.99
Any major vascular events‡	25	5.65	14	3.17	1.78 (0.94-3.38)	.07
Major vascular procedures						
Endarterectomy	1	0.22	3	0.68	0.33 (0.04-3.19)	.32
CABG	6	1.35	6	1.35	1.00 (0.32-3.07)	.97
Coronary angioplasty	5	1.13	1	0.22	4.99 (0.59-42.53)	.10
Any major vascular procedure‡	11	2.48	10	2.27	1.10 (0.47-2.56)	.80
Major vascular events and procedures‡	30	6.78	19	4.31	1.58 (0.90-2.76)	.10
Other nonmajor events and procedures						
Cerebrovascular	10	2.26	6	1.37	1.66 (0.61-4.54)	.31
Cardiovascular	31	7.01	18	4.08	1.72 (0.98-3.03)	.055
Any other nonmajor events and procedures‡	40	9.05	23	5.22	1.74 (1.06-2.85)	.02
Any vascular events and procedures	54	12.21	33	7.48	1.63 (1.08-2.47)	.02
Cancer						
Fatal	4	0.90	5	1.13	0.80 (0.22-2.95)	.74
Nonfatal	9	2.04	15	3.40	0.60 (0.27-1.35)	.21
Any	13	2.94	20	4.53	0.65 (0.33-1.29)	.21
Other types of events and procedures						
Fatal¶	1	0.22	1	0.22	1.00 (0.07-15.90)	.99
Nonfatal	76	17.19	86	19.50	0.88 (0.67-1.17)	.38
Any other type of event and procedure‡	77	17.42	86	19.50	0.89 (0.67-1.18)	.42

*RR indicates relative risk; CI, confidence interval; and CABG, coronary artery bypass graft.
†Based on life table analysis, log rank statistics of the incidence of these events in the cohort over a 3-year period.
‡In all summary categories, patients who had experienced multiple events were counted only once.
§Defined as angina pectoris objectively documented in hospital.
‖For isradipine, cardiogenic shock during CABG; and for hydrochlorothiazide, ruptured aortic aneurysm.
¶For isradipine, motor vehicle crash; and for hydrochlorothiazide, anoxic brain death.

and P value for the group of major vascular events was essentially the same (RR=1.78, P=.07 for independent panel vs RR=1.80, P=.06 for investigators' Morbidity and Mortality Committee). The independent panel's classification of other nonmajor events and procedures differed from the investigators' Morbidity and Mortality Committee as follows: isradipine group—3 more cerebrovascular, 5 more cardiovascular; hydrochlorothiazide group—2 less cerebrovascular, 1 more cardiovascular. The RR and P value for the combined events was different (RR=1.74, P=.02 for independent panel vs RR=1.33, P=.26 for investigators' Morbidity and Mortality Committee).

Post hoc analysis was performed to determine whether higher SBP in the isradipine group might explain the difference in clinical events in the subjects with major vascular events (isradipine, n=25; hydrochlorothiazide, n=14). Although mean±SD baseline SBP was higher in the isradipine group (isradipine, 162.4±20.9 mm Hg; hydrochlorothiazide, 147.5±15.3 mm Hg), mean SBP within 90 days of the first event was in the normal range in both groups (isradipine, 139.4±16.4 mm Hg; hydrochlorothiazide, 127.1±10.7 mm Hg). Furthermore, the end point SBP was the same in both groups (isradipine, 133.4±18.1 mm Hg; hydrochlorothiazide, 130.0±12.2 mm Hg).

Adverse Reactions

Reported frequency of chest pain (0.7% in isradipine and 0.8% in hydrochlorothiazide), and other cardiovascular-related adverse reactions (3.0% in isradipine and 0.9% in hydrochlorothiazide) was similar in both groups. Only central nervous system adverse reactions were reported differently between the isradipine and hydrochlorothiazide groups (6.2% vs 4.4%, respectively). This was primarily attributable to more reports of headaches in the isradipine group than in the hydrochlorothiazide group. Overall, 183 participants in the isradipine group and 172 in the hydrochlorothiazide group reported at least 1 severe adverse reaction over the 36 months of the trial. With regard to specific symptoms within each organ system, there were 3 adverse reactions with different rates between the 2 groups: kidney stones—0.4% in isradipine vs 0.0% in hydrochlorothiazide; headache—2.2% in isradipine vs 1.1% in hydrochlorothiazide; and faintness—0.0% in isradipine vs 0.4% in hydrochlorothiazide. None of these differences were statistically significant.

COMMENT

Carotid IMT measured by B-mode ultrasound has been used extensively in population studies as a quantifiable surrogate for clinical atherosclerotic disease.[14-16,30,31] MIDAS was the first clinical trial in hypertension to use this measurement as a primary outcome (ie, primary end point). In this study, there was no difference in the rate of progression in mean maximum IMT over 3 years between the isradipine and hydrochlorothiazide groups. The rate of progression of IMT observed in MIDAS (0.03 mm/y, using the corrected 36-month value for IMT) was much slower than the rate observed in a small pilot study of 28 untreated hyperlipidemic patients used to calculate the sample size of MIDAS (0.15-0.20 mm/y).[17,22] This suggests that IMT progression rate may differ in different populations.

The objective of MIDAS was to determine the effects of isradipine and hydrochlorothiazide on carotid IMT as a surrogate for the effects of these antihypertensive drugs on the biological mechanisms of atherosclerosis. Of course, surrogate outcome measures should reflect the clinical outcome of interest to be useful. Although IMT progression rate was not different in MIDAS, the incidence of cardiovascular events was higher in the isradipine group than in the hydrochlorothiazide group. These findings cause concern even though the numbers of events were small and despite the fact that the study was not designed to detect a difference in clinical events between the 2 treatment groups. The reduction in mean DBP was similar over 3 years in the 2 treatment groups. However, SBP was not used to determine drug dosage and the isradipine group had a higher SBP throughout the treatment period. The difference in SBP did not, however, explain the observed difference in the incidence of vascular events between the 2 treatment groups.

It is possible that the finding of increased cardiovascular events in the isradipine group may have been attributable to chance, especially since multiple comparisons were made to test the statistical significance of the observed difference between the 2 groups. More important from a clinical point of view, however, is the possibility that isradipine may have actually been associated with more

events than hydrochlorothiazide. In this regard, these findings support the evidence from several case-control and cohort studies suggesting that some of the short-acting calcium antagonists may increase the risk of cardiovascular events, especially angina pectoris and acute MI.[32-36] Obviously, without the existence of a placebo group we cannot determine how many events would have occurred in the absence of either drug. However, ongoing clinical trials such as SHELL,[31] ELSA,[31] ALLHAT,[37] SYST-EUR,[38] and STOP-Hypertension-2[39] are prospectively comparing calcium channel blockers with other antihypertensive agents. These trials should provide further insight into the question of whether calcium channel blockers increase cardiovascular risk.

The MIDAS Collaborative Research Group: *Clinical Centers*—University of California at Davis: Tissa Kappagoda, MD, PhD; Nemat O. Borhani, MD, MPH (deceased); Patricia A. Borhani. University of Alabama at Birmingham and Baptist Health System: Robert A. Kreisberg, MD. Scientific Applications Co Inc: Harold W. Schnaper, MD; E. E. Eddleman, MD; Araceli Sweeney, PA; Patricia Wittig. Miami Heart Research Institute: Maria Canossa-Terris, MD; Angela Batcheller, MD; Sergio Medrano, MD; Oswaldo Sandoval, MD; Luis Rios, MD. Wayne State University: James R. Sowers, MD; Kathy Rice; Cathy Krempasky; Elizabeth Jones. Medical College of Georgia: Albert A. Carr, MD; Peggy Best, RN; Sue Converse. Bowman Gray School of Medicine, Department of Internal Medicine, Section on Nephrology: Vardaman M. Buckalew, MD; Michael V. Rocco, MD, MS; Vincent J. Canzanello, MD; Barbara S. Bearden, RN; Mary A. Boozer, LPN. University of Tennessee, School of Medicine and Berman Center for Clinical Research, Health Span Inc, University of Minnesota. *Ultrasound Reading Center*—Bowman Gray School of Medicine, Division of Vascular Ultrasound Research, Department of Neurobiology and Anatomy, Center for Medical Ultrasound: M. Gene Bond, PhD; Michele Mercuri, MD, PhD; Sharon Wilmoth. *Operations Analysis Center*—Bowman Gray School of Medicine, Department of Public Health Sciences.

The Ad Hoc External Expert Committee on the Classification of **Events:** Lawrence S. Cohen, MD (chair); Bertram Pitt, MD; Ronald J. Prineas, MD.

Policy Advisory Board: Jay N. Cohn, MD (chair); Lloyd D. Fisher, PhD; William Insull, Jr, MD; Walter M. Kirkendall, MD (deceased); Daniel H. O'Leary, MD.

Sandoz Research Institute: *Project Leaders*—Steven B. Brugger; James Fattu, MD, PhD; Leonard N. Gonasun, PhD; Howard Miller, MD (deceased); Susan Solar-Yohay, MS, MBA. *Preclinical Research*—John Heider, PhD; Robert Hof, MD; David Weinstein, PhD. *CRA/Site Monitoring*—Marie Conte; Ellen Halpin, RN; Kimberly Holmes, RN; Catherine Stork. *Statistical Analysis*—Mary Ellen Gibbons, MPH; Rachel Neuwirth, MS; Stephen Smeach, PhD. *Secretarial*—Barbara DeVenezia.

The following individuals participated in data gathering and analysis for MIDAS but elected to withdraw prior to completion of the manuscript. *Clinical Centers*—University of Tennessee, School of Medicine: William B. Applegate, MD; Bette Griffin, RN. Berman Center for Clinical Research, Health Span Inc, University of Minnesota: Richard H. Grimm, Jr, MD, PhD; John Flack MD, MPH; Tim Wilt, MD, MPH; Cathy Heuer, RN; Alpha Struck LPN. *Operations Analysis Center*—Bowman Gray School of Medicine, Department of Public Health Sciences: Curt D. Furberg, MD, PhD; Robert P. Byington, PhD; Mark A. Espeland, PhD; Timothy E. Craven, MSPH; Janine W. Sprinkle, MSPH; Beverly Spray, PhD; Sharon K. Wilmoth.

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