Isradipine in Prediabetic Hypertensive Subjects

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OBJECTIVE — Investigators from the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) previously reported that the isradipine group had a higher incidence of cardiovascular disease (CVD) events than the diuretic group. The ultimate objective of the analyses presented here was to assess how indices of glycemia (specifically, serum glucose, serum insulin, and HbA_{1c}) might have influenced the effects of the two agents on blood pressure control and CVD events.

RESEARCH DESIGN AND METHODS — Inclusion criteria included men and women ≥40 years of age with ultrasonographically confirmed carotid atherosclerosis and a diastolic blood pressure of >90 mmHg. Although insulin-dependent diabetic patients were excluded, the three glycemia indices had wide enough ranges to include patients who may be classified as prediabetic. A total of 883 patients were randomized either to the dihydropyridine calcium antagonist (CA) isradipine (2.5–5 mg twice a day) or to the diuretic hydrochlorothiazide (12.5–25 mg twice a day) and followed in double-blind fashion for 3 years.

RESULTS — Both treatment groups had achieved comparable control of diastolic blood pressure, and there were no statistically significant differences in any of the glycemia indices, either at baseline or during follow-up. However, the excess isradipine events were noted to be clustered among those patients with elevated baseline levels of HbA_{1c} who also experienced greater blood pressure reductions during follow-up.

CONCLUSIONS — The increased cardiovascular risk associated with dihydropyridine CAs in prediabetic patients may be an explanation for the overall CA debate.

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Individuals with coexistent diabetes and hypertension are at a substantially increased risk of cardiovascular disease (CVD) morbidity and mortality (1–3). It has been suggested that this relates to generalized atherosclerosis, coagulation and/or platelet endothelial dysfunction, and/or a greater propensity for the presence of unstable plaques in this population (1–3). A higher overall absolute risk may explain the greater absolute CVD reduction when diabetic patients are treated for CVD risk factors, such as hypertension (4). It may also explain a potential risk for therapeutic strategies that may affect CVD risk adversely. Evidence from recent trials suggests that long-term therapy with calcium antagonists (CAs) may increase CVD risk in individuals with coexistent diabetes and hypertension (5,6).

It is not known whether long-term use of CAs affects glucose metabolism in a nondiabetic population or whether the long-term clinical effects of CAs in hypertensive subjects are confounded by indices of impaired glucose metabolism. The Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), a 3-year randomized clinical trial of isradipine (a dihydropyridine CA) and the diuretic hydrochlorothiazide (HCTZ) in 883 hypertensive subjects with moderate intimal-medial thickening of the carotid arteries, lends itself to exploratory analysis. As part of the trial, fasting levels of serum glucose, serum insulin, and HbA_{1c} were determined at baseline and the annual follow-up visits.

It has been previously reported that the isradipine group had a higher incidence of cardiovascular events than the HCTZ group (7) and that the excess number of events were clustered among participants with elevated HbA_{1c} levels (8). The objectives of these further analyses of the MIDAS dataset were *1*) to determine the effect of isradipine on serum glucose, serum insulin, and HbA_{1c}; *2*) to assess the associations between each of the indices of glycemia and major CVD events by treatment (isradipine vs. HCTZ); *3*) to evaluate the associations between the indices of glycemia and blood pressure response by treatment; *4*) to describe the blood pressure response by treatment group for patients who suffered and did not suffer a major cardiovascular event during the trial; and *5*) to assess the interaction between the indices of glycemia, blood pressure reduction, and CVD event incidence by treatment group.

RESEARCH DESIGN AND METHODS

— A description of the design of MIDAS and its major results have been published elsewhere (7,9). In brief, MIDAS was a randomized double-blind clinical trial designed to compare the effects of isradipine and HCTZ on the progression of early carotid atherosclerosis, as determined by B-mode ultrasonography, in men and women ≥40 years of age with con-

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Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes Trial; CA, calcium antagonist; CVD, cardiovascular disease; dBP, diastolic blood pressure; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Trial; HCTZ, hydrochlorothiazide; HR, hazard risk ratio; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study; sBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Changes in mean levels of serum glucose, serum insulin, and HbA_{1c} between the baseline and 1-year examinations*

Glycemia index	Treatment group	*n*	Baseline	1-year	Absolute difference
Serum glucose (mg/dl)	Isradipine	442	101.4 ± 16.3	105.1 ± 19.2	3.8
	HCTZ	439	102.2 ± 16.9	106.9 ± 20.6	4.7
Serum insulin (μU/ml)	Isradipine	421	12.6 ± 11.9	14.5 ± 12.8	1.9
	HCTZ	423	11.3 ± 8.7	13.9 ± 9.3	2.6
HbA_{1c} (%)	Isradipine	440	6.7 ± 1.1	6.8 ± 0.8	0.1
	HCTZ	439	6.7 ± 1.1	6.9 ± 0.9	0.2

Data are means ± SD.

firmed hypertension. Inclusion criteria included ultrasonographically confirmed carotid atherosclerosis and a diastolic blood pressure (dBP) >90 mmHg on each of the last three visits of a placebo washout period. Exclusion criteria included LDL cholesterol >160 mg/dl, blood glucose >160 mg/dl, elevated levels of creatinine (>1.8 mg/dl) and liver enzymes (>3 times upper limit of normal), a recent history of a cardiovascular event or vascular procedure, and insulin-dependent diabetes.

A total of 883 patients were enrolled and randomized to HCTZ, 12.5–25 mg twice a day (n = 441), or to isradipine, 2.5–5 mg twice a day (n = 442). Randomization began in July 1988 and follow-up ended in December 1992. All patients were followed for up to 36 months. During the first 4 months after randomization, study medication was titrated in both groups to achieve a predefined goal for dBP. If goal pressure was not achieved, open-label enalapril was added in doses between 2.5 and 10 mg twice a day.

All reported major clinical events were reviewed, adjudicated, and classified by an external Morbidity and Mortality Committee that was blinded to the assigned treatment. The total incidence of major CVD events over the 3 years of follow-up was the clinical outcome of interest for both the trial and this report. This outcome was defined as the first fatal or nonfatal occurrence of a stroke, myocardial infarction, congestive heart failure, hospitalized angina, sudden death, or other cardiovascular death. Through the 3-year follow-up period, 39 individuals experienced a major CVD event.

Fasting blood was obtained at baseline and at the annual follow-up visits. The three indices of glycemia examined for this report were serum glucose, serum insulin, and HbA_{1c}. Because insulin-dependent diabetic patients were excluded from MIDAS, a higher value for any index identifies participants who are more likely to be prediabetic. HbA_{1c} was measured by an electrophoretic method. Baseline insulin was missing in 37 patients (3 with an event) and baseline HbA_{1c} was missing from 4 subjects (1 with an event).

Statistical methods

Means and standard deviations were computed to describe the three indices of glycemia. For each index separately, treatment group–specific proportional hazards regression models were developed to describe how well the index, as a continuous characteristic, predicted the incidence of major CVD events. Additional models were used to test whether there were treatment × index interactions in the prediction of events. Next, index-specific proportional hazards models were developed to test whether there were treatment group differences in events at various levels of the index. Adjusted risk ratios (controlling for age, smoking status, history of CVD, and baseline levels of systolic blood pressure [sBP], total cholesterol, and carotid intimal-medial thickness) were estimated for all models. The associations between treatment assignment and events were also examined by constructing two-way contingency tables for participants above and below the baseline (i.e., prerandomization) median levels for serum glucose, serum insulin, and HbA_{1c}. P values associated with these risk ratios were computed using log-rank tests from product-limit estimates of the time to major vascular event. The 1-year dBP and sBP responses to treatment were assessed using paired t tests, and the relationships among treatment assignment, 1-year blood pressure reduction, and the three glycemia indices were examined using analysis of covariance and proportional hazard models. "Greater dBP reduction" was defined as a reduction greater than the median of 14 mmHg and "high baseline HbA_{1c}" was defined as a value above the median of 6.6%.

Because these are post hoc exploratory analyses, the results should be interpreted cautiously. Nominal P values are presented as simple guides to the statistical significance. All analyses were performed using the intent-to-treat approach.

RESULTS — The baseline characteristics of the randomized participants and the main results of the trial have been previously reported (7,9), but they are briefly summarized here. The mean age of the MIDAS participants was 58 years, 78% were male, and 72% were white. The mean blood pressure at baseline was 150/97 mmHg. Almost 60% of the participants were either current (39%) or former (20%) smokers. The mean LDL cholesterol level was 146 mg/dl (3.78 mmol/l). Before randomization, 76% of the participants had been on an antihypertensive agent, most often a diuretic (44%). CAs had been used by 10% of the participants. Prior history of myocardial infarction was found in <2% of the participants. Overall, the two treatment groups were balanced for most characteristics at baseline. There was no treatment group difference in the 3-year progression of intimal-medial thickness, the primary outcome measure for the trial (7).

The mean (± SD) levels of the three indices of glycemia at baseline were: serum glucose 101.8 ± 19.9 mg/dl, serum insulin 12.0 ± 10.4 μU/l, and HbA_{1c} 6.7 ± 1.1%. Of the participants, 7% had a fasting glucose that was ≥126 mg/dl (7.0 mmol/l), which is the new threshold criterion for the provisional diagnosis of diabetes (10), and 35% had an HbA_{1c} >6.9%. The three indices were weakly, but positively, intercorrelated with the following observed correlation coefficients: 0.14 for glucose/insulin, 0.24 for glucose/HbA_{1c}, and 0.07 for serum insulin/HbA_{1c}. During the trial, 5 patients were placed on insulin and 29 on oral hypoglycemics; two suffered an event, one in each treatment group.

Effects of isradipine and HCTZ on the indices of glycemia

There were no statistically significant changes in fasting serum glucose, serum insulin, or HbA_{1c} between the baseline and 1-year examinations in either the isradipine- or HCTZ-treated groups (Table 1). For the isradipine group at baseline, the mean serum glucose, serum insulin, and HbA_{1c}

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Table 2—*Major CVD event rates over 36 months of follow-up by treatment group*

	Isradipine group	HCTZ group	HR	95% CI
n	442	441		
Stroke	6 (1.35)	3 (0.68)	2.00	0.50–7.93
Acute myocardial infarction	6 (1.35)	5 (1.13)	1.20	0.37–3.89
Sudden death	2 (0.45)	2 (0.45)	1.00	0.14–7.05
Congestive heart failure	2 (0.45)	0 (0.00)	—	—
Angina pectoris	11 (2.48)	3 (0.68)	3.66	1.03–13.02
Other CVD	1 (0.22)	1 (0.22)	1.00	0.06–15.90
Patients with any event	25 (5.65)	14 (3.17)	1.78	0.94–3.38

Data are *n* (%). Adapted from Borhani et al. (7).

levels were 101.4 mg/dl, 12.6 μU/l, and 6.7%, respectively, and at 1-year, they were 105.1 mg/dl, 14.5 μU/l, and 6.8%. At baseline, 95% of the isradipine participants had an HbA_{1c} value between 4.5 and 8.9%.

Indices of glycemia and major CVD events by treatment group assignment

Over the 3 years of follow-up, 25 patients in the isradipine group (5.7%) suffered a major CVD event, compared with 14 in the HCTZ group (3.2%) (7). The hazard risk ratio (HR) for this was 1.78, with 95% CI 0.94–3.38 (Table 2).

Of the three indices of glycemia, only HbA_{1c} was both predictive of a major CVD event and had a treatment group interaction with events. As previously reported, a statistically significant association between increasing levels of baseline HbA_{1c} and increasing risk of an event was observed in the isradipine-treated group ($P < 0.01$), but not in the HCTZ-treated group ($P = 0.39$) (8). The interaction *P* value for this difference between the treatment groups was 0.03. Figure 1 shows that the isradipine-to-HCTZ HR for having an event increases through the observed range of baseline HbA_{1c} values, with the lower bound of the 95% CI passing unity (i.e., HR = 1) at an HbA_{1c} of ~7%. Serum glucose and serum insulin had similar positive trends (not shown), although the 95% CI always included HR = 1.

The treatment group/event results in Table 3 are stratified by the baseline median values for the three glycemia indices. As when the characteristics were examined as continuous variables, the excess number of events in the isradipine group was mostly confined to those subgroups with the higher (prediabetic) levels of glucose, insulin, and HbA_{1c}. Thus, when the glucose values were stratified, the adjusted isradipine-to-HCTZ HR for the high group (>98 mg/dl) was 2.19, compared with 1.50 for the low group (≤98 mg/dl). Serum insulin showed an HR of 3.22 for the high stratum (>9.8 μU/l) and 1.25 for the low stratum. HbA_{1c} showed an HR of 2.71 for the high group (>6.6%) and 1.16 for the low stratum. Survival analyses (not shown) suggest a 1.5-year lag time before the separation of the event curves in the high HbA_{1c} stratum.

Indices of glycemia and blood pressure reduction by treatment group assignment

MIDAS was designed to achieve equivalent reductions in dBP in the two treatment groups. At the 6-month visit, the mean dBP reductions were equivalent (~13 mmHg), although the HCTZ group had a slightly greater mean reduction in sBP (19.5 vs. 16.0 mmHg). These trends were maintained throughout follow-up, so that the mean dBP reductions at the 1-year visit were again equivalent (14 mmHg), while the HCTZ group had a slightly greater reduction in sBP (17.5 vs. 20.2 mmHg)

Among the participants randomized to the HCTZ group, none of the three glycemia indices was associated with the 1-year reductions of either the dPB or sBP. Among the isradipine participants, however, both serum insulin and HbA_{1c} were negatively related to the 1-year reduction in sBP ($P = 0.06$ for insulin and $P = 0.01$ for HbA_{1c}), so that the higher (prediabetic) levels were associated with greater reductions

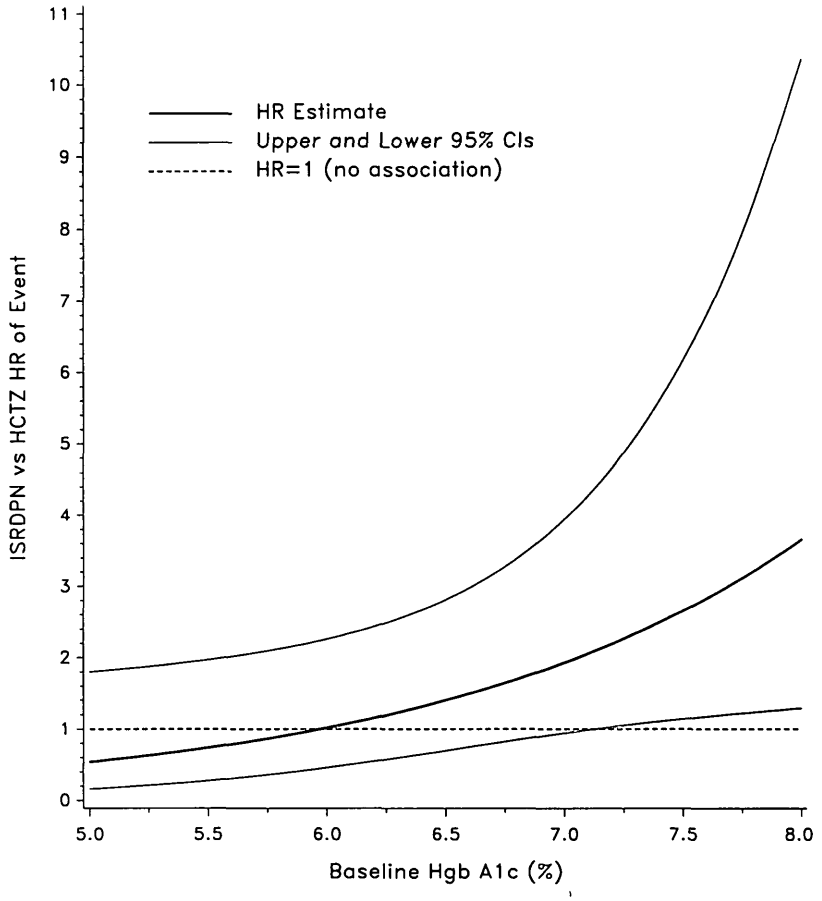

Figure 1—*HR of CVD events during follow-up for isradipine (ISRDPN) versus HCTZ groups by baseline level of HbA_{1c} (%). Adapted from Byington et al. (8).*

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in sBP. Similarly, HbA_{1c} was also negatively associated with the 1-year reduction in dBP in the isradipine group ($P = 0.01$), but not in the HCTZ group ($P = 0.33$). This is demonstrated in Fig. 2: over the range of HbA_{1c} values presented in the figure (5–8%), the dBP reductions would range from 13.1 to 15.9 mmHg for isradipine participants, but only from 14.0 to 14.9 mmHg for HCTZ participants.

Blood pressure reduction and the incidence of a major CVD event by treatment group assignment

With respect to events, Fig. 3*A* again shows that whereas both treatment groups experienced overall equivalent reductions in dBP, not all participant subgroups responded similarly. Among HCTZ group participants, the mean 1-year reductions in dBP were smaller in patients who suffered an event compared with those who did not: −9.4 vs. −14.6 mmHg for dBP ($P = 0.03$). There was a lesser difference for sBP: −19.2 vs. −21.4 mmHg ($P = 0.66$). However, the findings were the opposite of this among the isradipine participants. Those suffering a major CVD event in the isradipine group had greater blood pressure reductions than those who had no event: −19.1 vs. −14.4 mmHg for dBP ($P = 0.01$) and −28.9 vs. −18.6 mmHg for sBP ($P = 0.09$).

Interactions among indices of glycemia, blood pressure reduction, and the incidence of a major CVD event, by treatment group assignment

When the HbA_{1c}-stratified events in Table 3 were further stratified by the level of blood pressure reduction, a clustering of events is noted in the subgroup characterized as high HbA_{1c}/greater blood pressure reduction/isradipine. This is demonstrated in Fig. 4 for dBP, but was also observed for sBP (not shown). That is, the excess of events in the isradipine group is noted to be confined to those participants having both a high baseline HbA_{1c} value and a greater dBP reduction; neither characteristic alone was associated with an increase in risk.

To address the possibility that having an event during the first year may itself lower blood pressures, the 11 events occurring before the 1-year follow-up visit were next excluded from the analysis. The resulting pattern was virtually identical to that presented in Fig. 4. Similarly, given that 26% of the MIDAS participants were on open-labeled enalapril at the final clinic visit,

Table 3—*Adjusted treatment group differences in major CVD events, stratified by the median baseline values for serum glucose, serum insulin, and HbA_{1c}*

Glycemia index	Treatment group	Events/ cohort (%)	Adjusted HR	95% CI	*P* value for treatment × index interaction*
Serum glucose (mg/dl)					0.62
>98	Isradipine	14/214 (6.5)			
	HCTZ	7/230 (3.0)	2.19	0.89–5.52	
≤98	Isradipine	11/228 (4.8)			
	HCTZ	7/211 (3.3)	1.50	0.58–3.89	
Serum insulin (μU/ml)					0.53
>9.8	Isradipine	12/215 (5.6)			
	HCTZ	4/208 (1.9)	3.22	1.03–10.14	
≤9.8	Isradipine	11/207 (5.3)			
	HCTZ	9/216 (4.2)	1.25	0.51–3.08	
HbA_{1c} (%)					0.03
>6.6	Isradipine	15/199 (7.5)			
	HCTZ	6/216 (2.8)	2.71	1.05–7.03	
≤6.6	Isradipine	9/241 (3.7)			
	HCTZ	8/223 (3.6)	1.16	0.44–3.03	

HR is adjusted for age, smoking status, history of CVD, and baseline levels of sBP, total cholesterol, and carotid intimal-medial thickness. *The glycemia indices were treated as continuous variables in the treatment × index interaction analyses.

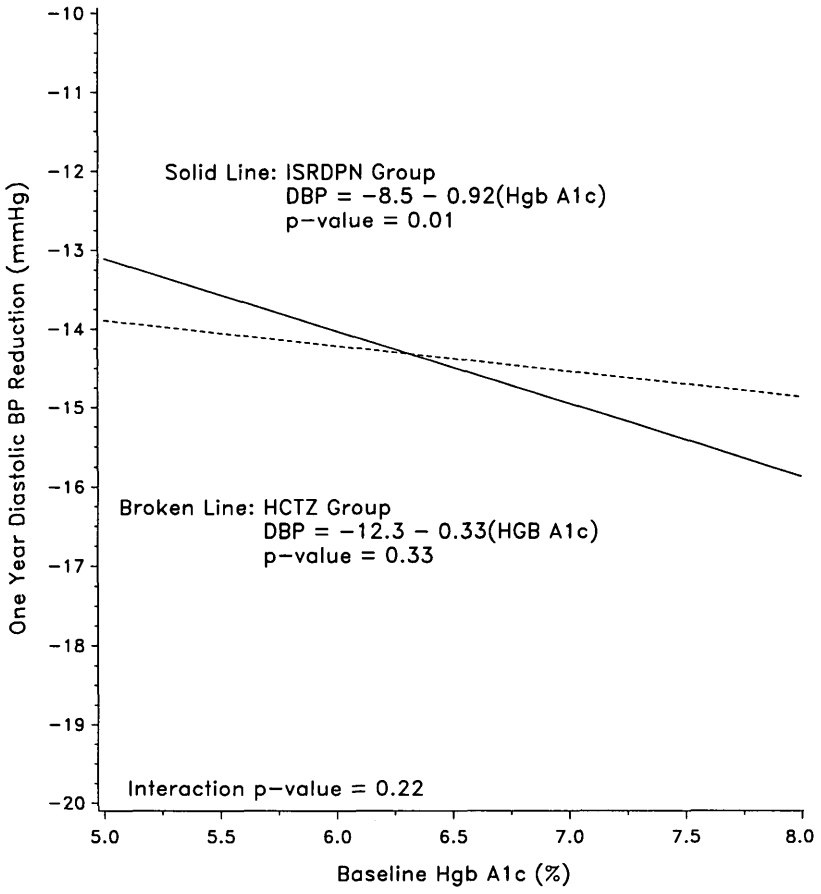

Figure 2—*Regression relationship between 1-year reduction in dBP and baseline HbA_{1c} by treatment group.*

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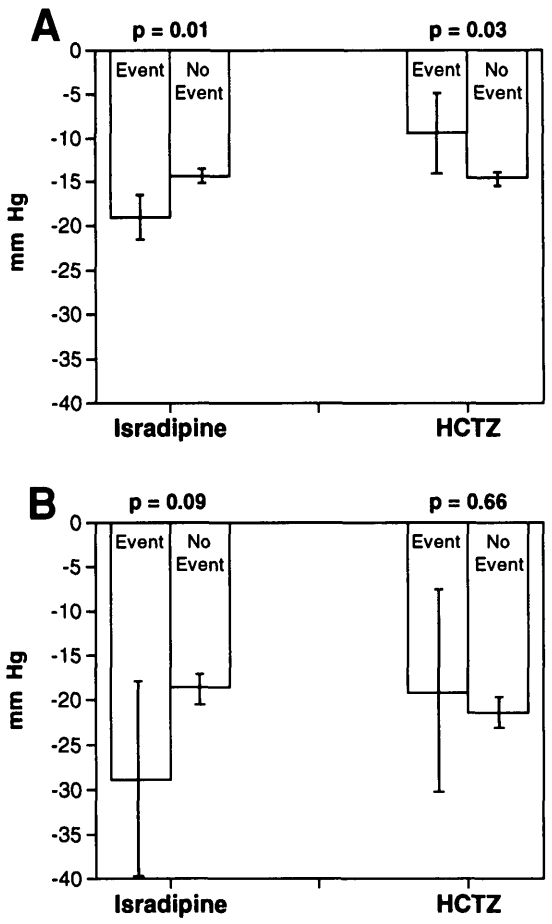

Figure 3—*Mean (and 95% CI) 1-year blood pressure reductions by treatment group and event status. A: dBP; B: sBP.*

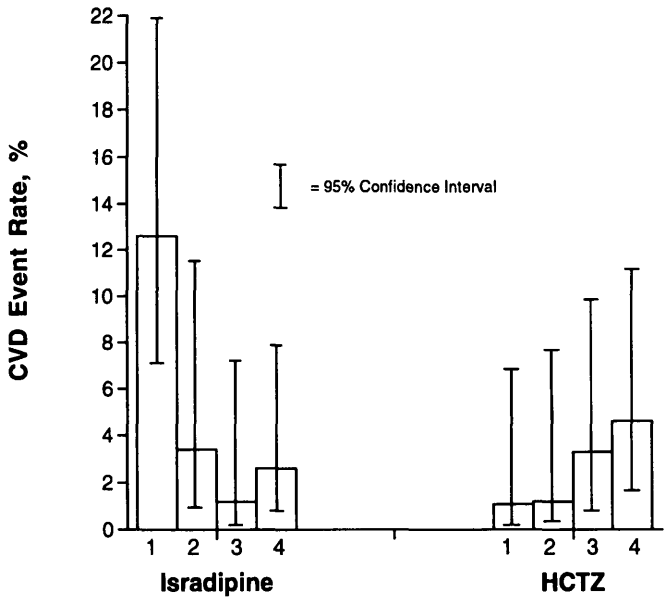

Figure 4—*CVD event rates by treatment group, baseline HbA_{1c}, and 1-year reduction in dBP. The four patient groups are distinguished as follows: 1) high HbA_{1c} (baseline >6.6%), greater decrease in dBP (>14 mmHg fall in dBP); 2) low HbA_{1c} (baseline ≤6.6%), greater decrease in dBP; 3) high HbA_{1c}, lesser decrease in dBP (≤14 mmHg fall in dBP); and 4) low HbA_{1c}, lesser decrease in dBP.*

another analysis was conducted excluding those participants who were on enalapril at any time during the first 2 years of follow-up. Again, the resulting pattern was virtually identical to that presented in Fig. 4.

Because HbA_{1c} was related to blood pressure reduction among the isradipine participants (Fig. 2), the mean blood pressure reductions were examined in each of the four isradipine HbA_{1c}/blood pressure reduction strata in Fig. 4. For participants with a dBP reduction >14 mmHg, the mean dBP reductions were 21 and 19 mmHg for participants with an HbA_{1c} >6.6% and ≤6.6%, respectively. For those with a reduction ≤14 mmHg, the mean dBP reduction was 9 mmHg for both HbA_{1c} levels. These findings indicate that the excess number of CVD events in the high HbA_{1c}/greater blood pressure reduction/isradipine subgroup is not due to a greater blood pressure reduction than that observed for the low HbA_{1c} /greater blood pressure reduction/isradipine subgroup.

These patterns are combined in Fig. 5. Whereas Fig. 1 illustrates that the isradipine-to-HCTZ HR increases with increasing levels of HbA_{1c}, Fig. 5, even with few events, refines this by demonstrating that the increased risk associated with isradipine use by people with elevated HbA_{1c} levels is dependent on the degree of dBP reduction: at greater levels of BP reduction, the excess number of events in the isradipine group is evident at lower levels of HbA_{1c}. For example, among patients with a 16-mmHg drop in dBP, the excess number of events in the isradipine group is apparent for patients with an HbA_{1c} between 6.8 and 7.4%. However, among patients with an 18.5-mmHg drop in dBP, the excess number of events in the isradipine group is apparent for patients with an HbA_{1c} between 6.4 and 6.8%.

CONCLUSIONS — It is well established that the cholesterol and phospholipid contents of cellular membranes are altered in diabetes (11). These alterations affect the binding of lipophilic drugs such as CAs. The lower cholesterol-to-phospholipid ratio in the membrane bilayer increases the partition coefficient for CAs, which can magnify their pharmacologic effects (12). It has also been reported that short-acting nifedipine impairs insulin secretion in humans (13) and exerts a hyperglycemic effect (14). A recent study reported a dose-dependent increase in HbA_{1c} with felodipine in sulfonylurea-treated hypertensive subjects with type 2 diabetes (15). Thus, there are

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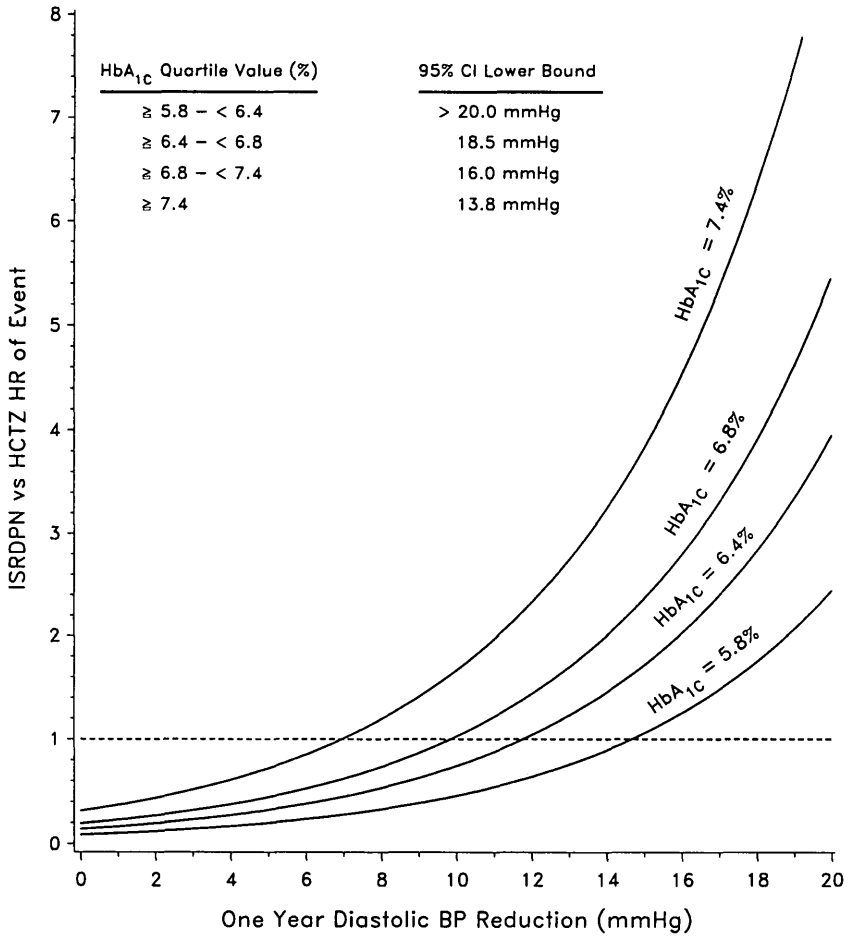

Figure 5—*HR of CVD events during follow-up for isradipine (ISRDPN) versus HCTZ groups by 1-year reduction in dBP and baseline level of HbA_{1c} (%).*

possible biological explanations for the observed findings from observational studies and clinical trials.

The exploratory analyses from MIDAS were stimulated by the findings from two recent randomized trials in diabetic hypertensive subjects, the Fosinopril Versus Amlodipine Cardiovascular Events Trial (FACET) (6) and the Appropriate Blood Pressure Control in Diabetes Trial (ABCD) (5). Both trials showed a much higher CVD event rate in the CA group when compared with a group treated with ACE inhibitors. Although insulin-dependent diabetic patients were excluded from enrollment in MIDAS, a large proportion of the randomized participants had elevated levels of serum glucose, serum insulin, and HbA_{1c}, permitting the identification of participants who were prediabetic. HbA_{1c}, which gave the most consistent results in these analyses, is actually the most sensitive measure of glycemic control because it measures the integration of control over a 3-month time period.

These MIDAS results are also supported by findings in observational studies. In 1997, Alderman et al. (16) reported from a case-comparison analysis that hypertensive patients who had had a cardiovascular event were almost four times more likely to have been on a short-acting CA, compared with matched hypertensive control subjects (adjusted odds ratio = 3.88 [95% CI 1.15–13.11], P = 0.03). Expanding on this in 1998, these investigators stratified the original analyses by history of diabetes and found that the excess risk appeared to be clustered among the diabetic patients: the odds ratio for a CVD event in patients taking any CA, compared with those taking other medications, was 6.85 (1.50–31.34) for diabetic patients, but only 1.35 (0.88–2.07) for nondiabetic subjects (17). Similarly, a case-comparison study of diabetic hypertensive subjects from the Group Health Cooperative of Puget Sound found that the risk of having had an MI was associated with CA use when compared with use of either a diuretic (odds ratio = 2.44 [1.09–5.26]) or an ACE inhibitor (odds ratio = 2.44 [1.00–5.88]) (18). With respect to prospective studies, investigators from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) reported that an observed excess of death attributable to CA use was significant only among patients with a history of diabetes (19). In that study, use of the CA nifedipine (compared with use of β-blockers) had for all-cause mortality a relative risk of 3.27 (1.40–7.62) for diabetic patients, but only 1.36 (0.78–2.39) for nondiabetic subjects. It has also been reported that a Swedish cohort study found that diabetic hypertensive subjects on a CA had a mortality rate twice that of similar patients on a β-blocker (20). We have previously reported that hypertensive subjects with impaired glucose metabolism (specifically, elevated HbA_{1c}) respond unfavorably to isradipine, compared with their response to a diuretic (8). The current analyses extend our original findings from MIDAS by demonstrating that it is actually the combination of impaired glucose metabolism and a greater than average blood pressure reduction that was associated with the excess of cardiovascular events in the isradipine group.

These findings are important in relation to the findings in FACET and ABCD. First, they extend the suggestion of an unfavorable effect of CA treatment in diabetic hypertensive subjects to hypertensive subjects with impaired glucose tolerance. Second, because the comparison group in MIDAS received a low-dose diuretic, while in FACET and ABCD the comparison groups received an ACE inhibitor, it is more likely that the observed differences in CVD event rates are due to an adverse action of CAs rather than a favorable effect of ACE inhibition. Common to all three trials was that the CA was a dihydropyridine. Isradipine (in MIDAS) is an intermediate-acting CA given twice a day, whereas amlodipine (in FACET) and nisoldipine (in ABCD) are long-acting CAs given once a day.

The benefit of antihypertensive treatment on CVD events is generally attributed to the lowering of elevated sBP and dBP. In MIDAS, HCTZ patients suffering an event had smaller reductions in blood pressure compared with patients who did not have an event. This expected result could reflect poor compliance and/or a more resistant blood pressure elevation, both plausible explanations for a cardiovascular event. However, the findings were opposite this

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among the isradipine participants: those experiencing CVD events had a significantly greater blood pressure reduction. Because the isradipine dose was standardized in MIDAS, a possible explanation for this paradox is that some hypertensive patients with impaired glucose tolerance are more susceptible to isradipine, which like other CAs, is lipophilic (21). The stronger binding of the drug to the cell membranes could magnify the blood pressure–lowering effect. Episodes of hypotension, especially during sleep, could trigger CVD events (22). Another explanation could also be that the blood pressure–lowering effect is an epiphenomenon unrelated to the apparent unfavorable effect on CVD risk.

This magnified pharmacologic effect due to a stronger binding to the cell membranes might have an effect similar to that of a high CA dose. Several studies have reported that the safety problems with CAs are strongly associated with high doses of the drugs. Thus, dose-response analyses in hypertensive populations have linked long-term use of high doses of short-acting CAs to an increased risk of myocardial infarction (23) and all cause mortality (19). The risk of mortality in survivors of an acute myocardial infarction was also associated with high doses of immediate-release nifedipine (24).

At the vascular level, the known blockade of apoptosis by CAs (25,26) may also be an explanation for the increased vascular event rates in individuals with impaired glucose tolerance. It has recently been reported that hyperglycemic conditions induce apoptosis in human umbilical endothelial cells (27). The authors of that report speculated that this induction in diabetes might represent a means by which severely damaged vascular cells are eliminated, thus permitting a delay in the development of vascular complications. If a CA blocks apoptosis, the development of vascular complications would not be delayed.

The reported observations of increased cardiovascular risk associated with CA use in diabetic or prediabetic patients may be the explanation for the overall CA debate. Further studies are required, but until more data are available, it seems prudent to restrict use of short- and long-acting dihydropyridine CAs in hypertensive patients with diabetes or impaired glucose tolerance. These patients ought to be treated with low-dose diuretics (preferably as a first-line drug) or with ACE inhibitors. The long-term safety of dihydropyridine CAs in nondiabetic subjects with normal glucose metabolism with hypertension or coronary heart disease has not been evaluated and, therefore, remains unknown.

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