Risk of Myocardial Infarction With Combination Antihypertensive Regimens Including a Dihydropyridine Calcium Channel Blocker in Hypertensive Diabetics

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ABSTRACT

OBJECTIVE: The primary objective of this study was to determine if there was an increased risk of myocardial infarction (MI) in a high-risk hypertensive diabetic managed care population receiving combination antihypertensive therapy including a dihydropyridine (DHP) calcium channel blocker (CCB).

METHODS: A retrospective, population-based, case-control study design was used to determine the risk of MI versus the prescribed antihypertensive drug regimen. During 1997-1999, 6,096 diabetics with hypertension were identified. After exclusions, there were 131 “high-risk” study patients who suffered an MI during the study period. These were compared to an equally matched sample. High-risk patients were defined as those with a medical history of previous MI, angina pectoris or ischemic heart disease, or those who had undergone a coronary artery bypass graft and/or angioplasty procedure. Patients were then assigned to Group I cases and controls (DHP use) and Group II cases and controls (no DHP use). Odds ratios (OR) and 95% confidence intervals (CI) were determined for the independent variables and antihypertensive drug regimens. Logistic regression analysis was used to model age, ethnicity, and potential risk factors to identify any differences among calcium channel blockers.

RESULTS: After adjusting for age and gender, the OR for an MI in patients on a combination DHP regimen was 0.52 (95% CI, 0.44, 1.29). The OR for other regimens ranged from 0.52 to 1.16, with no significant difference between antihypertensive drug classes. In comparison to nondihydropyridines (NDBPs), the OR for DHPs was 1.38 (95% CI, 0.54, 3.54), but it was determined to not be statistically different (P=0.5065).

CONCLUSION: No increase in risk of MI could be determined with the use of a combination antihypertensive regimen including a DHP CCB when compared to other antihypertensive drugs in a matched high-risk population of patients with hypertension and diabetes. Choice of antihypertensive drug regimen may be less important than strategies that focus on achieving optimal disease outcomes to reduce the incidence of MI and hospitalization and lower health care costs in this high-risk population in managed care.

KEYWORDS: Calcium channel blockers, Dihydropyridines, Nondihydropyridines, Myocardial infarction, Diabetes mellitus, Hypertension

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ORIGINAL RESEARCH

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in the United States. More than 30% of patients who suffer a myocardial infarction (MI) do not survive. Diabetic patients have an increase in the risk of coronary heart disease and MI mortality. Recent data suggest that even without a history of heart disease, type 2 diabetics have as high a risk for an MI as nondiabetics with a prior MI.1 Additional risk factors such as age, gender, obesity, smoking, hypertension, and hyperlipidemia can further increase this risk. More aggressive treatment of diabetes mellitus, hypertension, and hyperlipidemia is recommended.

It is estimated that there are more than 11 million diabetics with hypertension in the United States who often require combination drug therapy to control their blood pressure. Though an angiotensin converting enzyme inhibitor (ACEI) is considered the initial drug of choice in patients with diabetes mellitus and hypertension because of its nephroprotective effect, the calcium channel blockers (CCBs) are also recommended by the Joint National Committee VI and are used extensively in combination therapy because of their favorable metabolic side-effect profile.2 A concern about the safety of CCB agents in coronary heart disease has been the focus of recent clinical research. Several meta-analyses demonstrated a dose-related increase in MI risk with short-acting3 and possibly intermediate-acting dihydropyridine (DHPs).4

Follow-up studies have focused on assessing the risk of long-acting DHPs on adverse cardiovascular outcomes with mixed results. Alderman et al.3 found no increase in CV risk with long-acting CCBs in a matched case control study (adjusted odds ratio (OR) = 0.76, 95% confidence interval (CI), 0.41, 1.43). Two clinical studies in a hypertensive diabetic population suggest no adverse effects of DHPs, but perhaps even a beneficial one.5,6 One study4 and a meta-analysis12 suggest that aggressively lowering the blood pressure may be more important than the choice of the antihypertensive agent(s).

In contrast, 2 prospective, randomized controlled studies suggest that hypertensive type 2 diabetics given the newer long-acting CCBs may be at a higher risk of an MI compared to other antihypertensive medications.11,12 Pahor et al.13 completed a meta-analysis from 9 randomized clinical trials with an aggregate population of more than 27,000 hypertensive patients. After an average 2-year follow-up period, there was a 31% increase in the risk of MI with DHP CCBs compared to other antihypertensive agents. The average increase in MI risk in diabetics was 51%.
These are unexpected findings since CCBs have been shown to have a favorable effect on atherosclerosis and stroke, exclusive of their blood pressure-lowering effect.10,11 If there is an adverse CV effect with the DHPs, the mechanism is unknown but may be related to sympathetic activation caused by the reflex tachycardia. Are there different therapeutic effects on different CV risk factors? These disparate findings suggested the need to reevaluate the benefit versus risk of CCBs, specifically the DHPs, in hypertensive diabetics with coronary artery disease.

The primary objectives of the study were to (1) compare the risk of MI in high-risk type 2 diabetics receiving combination antihypertensive therapy with a DHP CCB versus other therapies for hypertension in a matched population of high-risk patients; and (2) assess the impact of such variables as age, gender, ethnicity, vital signs, laboratory tests, previous history of CV events, and concurrent medications on the relationship between CCBs and MI. A secondary objective was to compare the risk of MI between DHPs and nondihydropyridines (NDHPs).

Methods
This study followed a retrospective, case-control, matched analysis design. Data were collected from the membership, pharmacy dispensing, and claims database contained in the computerized Kaiser Permanente-Georgia (HMO) data warehouse. Information concerning ethnicity, smoking history, vital signs, and laboratory data was collected from patient chart review when available.

The primary outcome measurement was the incidence of MI. The null hypothesis for this study was that there was no difference in the incidence of MI in high-risk diabetic patients maintained on therapy with a combination antihypertensive regimen including a DHP CCB for hypertension compared to those patients on alternate antihypertensive treatment. Odds ratios and 95% CIs were computed. The null hypothesis was accepted if the OR and CIs were ≥1.0. Statistical significance was defined as a P value less than .05.

Patients with diabetes and hypertension were classified into cases with an MI (by ICD9 code 410) or matched controls without an MI diagnosis. The diagnosis of diabetes was consistent with criteria used by Health Plan Employer Data and Information Set (HEDIS) and by the HMO’s Diabetes Population Care Registry. Hypertension was defined by a minimum of 2 documented encounters and a minimum of 3 months of continuous use of any antihypertensive medications during the time that the member was also identified as having diabetes.

Inclusion criteria for the case-study patients was as follows: aged 30 to 75 years at the time of MI who were members of the HMO for a minimum of 6 months prior to the MI and had a diagnosis of both diabetes mellitus and hypertension (information was in the database) during the 3-year period from January 1, 1997, through December 31, 1999. Controls were identified from the database as patients aged 26 to 79 years as of December 31, 1999, with a diagnosis of diabetes mellitus and hypertension, but without an MI diagnosis during the study period.

Cases and controls were further divided into “high-risk” patients, defined by ICD9 code as all patients with a prior history of ischemic heart disease, angina pectoris, percutaneous transluminal coronary angioplasty, (PTCA) coronary artery bypass graft (CABG), or prior MI. We assumed that an adverse cardiovascular effect associated with a DHP medication regimen would most likely be seen in this population.

Controls were then matched to cases based on the enrollment eligibility of high-risk controls compared to the MI date of each case. For each case-MI date, a pool of controls was generated such that each possible control had to be enrolled in the HMO for the 6 months prior to the MI date. From this pool, one control patient was randomly selected without replacement and assigned the MI date as the index date. This process was repeated for each case. Index date is thus defined as the date of the MI for the cases and the assigned date for the matched controls. Controls were matched 1:1 with MI cases because of resource limitations on patient chart review.

The following patients were excluded from selection for cases and controls: patients with less than 6 months of continuous enrollment prior to the index date, patients treated for hypertension for less than 3 months prior to the index date, and noncompliance to prescribed treatment for hypertension. Patients were considered noncompliant if, according to the pharmacy dispensing records, their refill rate was less than 67% for any antihypertensive prescription.

All patients were then assigned to one of 2 arms of the study, based on their antihypertensive regimen: Group I cases and controls—which included any regimen (monotherapy or combination therapy) with a DHP; all DHPs were grouped in cases and controls—which included any regimen (monotherapy or combination therapy) with a DHP; all DHPs were grouped in cases and controls—to determine a class OR. Group II cases and controls—which included any other antihypertensive drug regimen that did not include DHPs such as diuretics, beta-blockers, ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), NDHPs, alpha adrenergic blockers, and clonidine. Although most patients were on combination therapy, the use of DHP was excluded from the Group II comparison group. NDHPs consisted of verapamil and diltiazem and were initially included in Group II.

Covariates for all matched cases and controls included age at the time of the event, gender, and medication use. Documentation was made separately for insulin therapy, oral hypoglycemics, estrogen replacement therapy, lipid-lowering therapy, and antiplatelet therapy (aspirin, ticlopidine, or clopidogrel). In order to better define disease control in the matched cases and controls, information from the patient medical record such as ethnicity, smoking status, vital signs (body mass index, systolic/diastolic blood pressures), and laboratory data (lipid profile, HbA1c, microalbuminuria) was collected for up to 12 months prior to the index date. Vital signs and laboratory data were averaged for statistical analysis.
Statistical analysis, utilizing SAS software, included determining the P values of potential covariables and an OR of having an MI among cases and controls on therapy with DHPs compared to other antihypertensive therapies. Contingency tables with chi-square analysis were computed on the covariables to determine the level of significance (P value) of any differences in the OR utilizing observed versus expected frequencies of the primary outcome, controlling for age and gender.

Mantel-Haenszel ORs adjusted for age and gender were used to measure the association between independent variables and the incidence of MI. A forward, step-wise, logistical regression model utilizing MI as a function of ethnicity, CV risk factors, and antihypertensive drug use was performed to test for independent risk factors as well as the OR of MI in DHP and NDHP cases and controls.

Results

From the Kaiser Permanente database, 10,399 patients (Figure 1) with a diagnosis of diabetes mellitus were identified for the 3-year study period. Of these, 6,096 (58.6%) were identified as having a diagnosis of hypertension. The initial data sample consisted of 299 patients (4.9%) with an MI diagnosis and 5,797 having a diagnosis of hypertension. The initial data sample consisted of 299 patients (4.9%) with an MI diagnosis and 5,797 controls who did not suffer an MI during the study period.

Of these, 6,096 (58.6%) were identified as having a diagnosis of hypertension. The initial data sample consisted of 299 patients (4.9%) with an MI diagnosis and 5,797 controls who did not suffer an MI during the study period.

Of this sample, 272 cases were considered “high-risk” by previously stated ICD9 criteria, and 961 controls were likewise considered “high-risk.”

After exclusions for drug noncompliance, 135 cases and 876 controls were identified. From the controls, 135 patients were randomly selected based on the index date of the MI of the matched case. Two patients from the cases and 2 patients from the controls were prescribed more than one CCB during the 3-month time frame prior to the index date and were excluded (along with their matched cases/controls) from further analysis, resulting in a matched-pair sample of 131 patients in each group.

For a high-risk population, the blood pressure, hemoglobin A1c, and lipid profile were reasonably well controlled among the cases and controls (Table 1). These values and other variables were converted to dichotomous variables for chi-square analysis. Insufficient sample size or missing data and/or charts eliminated smoking, microalbuminuria, antiplatelet drug, and hormone use from further analysis.

As seen in Table 2, there was a higher percentage of whites with an MI versus African Americans in the cases (P=0.011). As expected, there was a higher incidence of prior MI (P<.001), CABG (P<.001), and PTCA (P=0.004) among the cases. There was no statistical difference in other variables for the cases and controls, including the use of insulin, oral hypoglycemics, and lipid-lowering medication. In the univariate analysis, Group II cases were less likely than their controls to be on an NDHP (P=0.023). For statistical analyses, ARBs were combined with ACEIs, and clonidine and alpha-blockers were combined into an “other” category.

Of the 131 cases with MI, 35 patients were on combination therapy with some type of DHP (Group I). The Group I cases consisted of nifedipine (18 patients), lelodipine (8 patients), amlodipine (6 patients), isradipine (2 patients), and nicardipine (1 patient). Though considered an intermediate-acting DHP, isradipine was included in the cases and controls. Due to small sample size and patients on multiple DHPs, analysis of dose was not completed. As expected, few Group I cases (8.6%) were on monotherapy; 77.1% (n=27) were prescribed a beta-blocker (n=10), an ACEI (n=10), or both (n=7).

Of the Group I controls, 42 patients were on a DHP, including nifedipine (21 patients), lelodipine (13 patients), amlodipine (7 patients), and isradipine (1 patient). For the Group I controls, 11.9% (n=5) were on monotherapy; 71.4% (n=30) were prescribed a beta-blocker (n=6), an ACEI (n=16), or both (n=8).

There were 96 Group II cases and 89 Group II controls consisting of patients who were not taking a DHP within 3 months prior to the index date. For the Group II cases, 87.5% (n=84) were prescribed a beta-blocker (n=18), an ACEI (n=47), or both (n=19). For the Group II controls, 80.1% (n=72) were prescribed a beta-blocker (n=18), an ACEI (n=34), or both (n=20).

The ORs for the difference in variables and the risk of MI after adjusting for age and gender are listed in Table 3. As expected, the OR for an MI increases with the presence of a prior MI, PTCA, and/or CABG. The calculated ORs among the various antihyperten-

### TABLE 1

| Age, Gender, Ethnicity, Laboratory Data, and Vital Signs Among MI Cases and Controls |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Patient Demographics             | Cases           | Controls         |
| Age (years)                      | 58.3 (±9.1)     | 59.9 (±9.7)      |
| Males                           | 69%             | 63%             |
| Females                         | 31%             | 37%             |
| White                           | 68%             | 49%             |
| African American                | 29%             | 47%             |
| Clinical Characteristics         |                 |                 |
| BMI*                            | 31.7 (±5.9)     | 32.8 (±6.6)     |
| HgbA1c†                         | 8.6 (±2.3)      | 8.6 (±2.0)      |
| Total cholesterol‡              | 213.2 (±65.1)   | 213.9 (±48.7)   |
| HDL‡                           | 41.0 (±11.7)    | 44.8 (±12.8)    |
| LDL‡                           | 125.9 (±53.9)   | 122.4 (±42.2)   |
| SBP§                            | 134.8 (±17.2)   | 142.3 (±17.4)   |
| DBP§                            | 78.1 (±9.9)     | 81.5 (±9.5)     |

* Body mass index (BMI) values in kg/m2.
† HgbA1c values in %.
‡ Total cholesterol, HDL, LDL values in mg/dL.
§ Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values in mm Hg.
sive drug classes were not statistically significant and ranged from a low of 0.52 with NDHPs to a high of 1.16 with ACEIs. The OR of drug regimens containing a DHP was 0.75 (95% CI, 0.35, 1.62). No Group I or Group II antihypertensive drug class or combination appeared to increase the risk of MI.

A summary of the combination therapies for the cases and controls is listed in Table 4. To test for concurrent antihypertensive medications as a confounding variable, 2 x 2 contingency tables were developed for Group I and Group II cases and controls on beta-blockers, ACEIs, diuretics, and other antihypertensives. This analysis demonstrated that there was not a significant difference between groups on all combinations, at the 95% confidence level. Thus, these drugs, especially the beta-blockers and ACEIs, did not appear to attenuate the risk of recurrent MI among those patients on DHP combination therapy for their hypertension.

To test for multiple CV events as a confounding variable, 2 x 2 contingency tables were developed for Group I and Group II cases and controls for patients with prior MI plus additional CV events/risk, CABG, and/or PTCA (excluding MI), and ischemic heart disease (excluding MI, CABG, PTCA). These were chosen as surrogate markers for the extent of CV disease. As seen in Table 5, this analysis demonstrated that there were no differences between groups with various CV events and risks at the 95% confidence level.

A logistical regression model was then developed to test for differences between Group I DHP and Group II NDHP cases and controls. The results of the modeling are listed in Table 6. The model could not incorporate laboratory values or vital signs because of subset sample size. Variables that significantly increased the risk of an MI on a CCB included ethnicity (whites) and those patients with more than 2 CV risk factors. When compared to the NDHPs, the DHPs were less protective (OR 1.38, 95% CI, 0.54, 3.54), but the difference did not reach statistical significance.

**Discussion**

CCBs consume a high percentage of the antihypertensive drug budget of most managed care organizations. These medications are widely prescribed due to their convenient once-daily dosing, neutral effect on glucose and lipid profiles, relatively low incidence of side effects, and high efficacy in elderly and African American populations. Beta-blockers and ACEIs continue to be preferred drugs because of their cardioprotective and nephroprotective effects in patients with heart disease and diabetes. However, many patients need combination therapy to reach the aggressive blood pressure goals (<130/80 mm Hg) required for a high-risk diabetic hypertensive—is it safe to add a DHP CCB to a diuretic, an ACEI, or beta-blocker regimen?

Our results did not identify a significant difference in the incidence of MI in this high-risk population between DHP combination therapy and other antihypertensive drug regimens. These results are in agreement with some previous studies.\textsuperscript{3,4}
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addition, some studies\textsuperscript{11,12} have reported that patients receiving a DHP CCB may have an increased risk of MI. It is possible that the DHP MI cases may have had a shorter duration of hypertension or diabetes. The Group I DHP patients did not appear to have less severe CV disease compared to Group II (no DHP) patients on other antihypertensive drugs, but undetected differences in complex cases with more than one CV event and multiple combination antihypertensive therapy may have been present, i.e., one drug in the combination could offset the effects of another drug. The higher OR (1.16) detected for ACEIs may have been a surrogate marker for more advanced diabetes with renal complications.

In our study, NDHPs appear to be associated with a lower OR (0.54) than DHPs (0.75) though CIs overlapped, and the results did not reach statistical significance. Further comparative analysis of this group of patients in a larger sample is necessary. Unexpectedly, white patients were more likely to suffer an MI on a CCB than African American patients, based upon the results of the logistical regression analysis. Ethnic differences should be further explored in future studies.

The strengths of the study were (1) both study and control populations were well matched by eligibility criteria and comparable by age, gender, vital signs, and biochemical laboratory tests; (2) cases and controls were well controlled in terms of control of their diabetes, hypertension, and hyperlipidemia; and (3) compliance was assessed by checking pharmacy dispensing records, thereby increasing the reliability of determining whether the case and control groups were taking the prescribed antihypertensive medication(s).

\textbf{Limitations}

The limitations of our study are (1) the retrospective case-control design limits control of all covariables, and the sample size limits power; (2) most patients were on combination therapy and, therefore, the OR is reported in “marginal” as opposed to “absolute” terms, though no differences were noted on combination therapies; (3) the duration of drug exposure was variable from a minimum period of 3 months, and the effect of dose was not analyzed; and (4) there were both missing charts and data for variables such as ethnicity, smoking status, vital signs, and laboratory tests. For example, in 37 MI cases (and 48 controls), ethnicity could not be determined, thus it is possible that a disproportionate amount of minorities may have been in the missing data.

An unexpected finding was that almost 6 times as many

\textbf{TABLE 4} Number of Patients on Combination Antihypertensive Therapy* in Group I (DHP Exposure) Cases and Controls Versus Group II (No DHP Exposure) Cases and Controls

<table>
<thead>
<tr>
<th>Medication</th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Nondihydropyridines</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>ACEIs</td>
<td>10</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Diuretics</td>
<td>15</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Others†</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

* Other drugs include clonidine and alpha adrenergic blockers.

\textbf{TABLE 5} Number of Patients With Major Cardiovascular Events in Group I (DHP Exposure) Cases and Controls Versus Group II (No DHP Exposure) Cases and Controls

<table>
<thead>
<tr>
<th>CV Event/Risk</th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Prior MI+*</td>
<td>13</td>
<td>9</td>
<td>48</td>
</tr>
<tr>
<td>CABG and/or PTCA†</td>
<td>10</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Ischemic heart disease‡</td>
<td>9</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

* Includes MI plus CABG and/or PTCA and/or ischemic heart disease.
† Excludes MI.
‡ Excludes MI, CABG, PTCA.
high-risk “case” patients with an MI were excluded from the analysis (137 of 272, or 50.4%) due to noncompliance compared to “control” patients (85 of 961, or 8.8%) who did not suffer an MI (Figure 1). This suggests that identifying reasons for noncompliance (lack of patient education, high cost, side effects) and keeping high-risk patients out of the hospital should become a high priority for a managed care organization.

Strategies to assure patient education and compliance may be important pharmacy initiatives in such a high-risk population.

While an increase in CV risk was not identified with the DHP CCBs in our study, it is possible that this class of agents may increase the long-term risk of diabetic complications by increasing proteinuria. Results from 2 recent studies suggest that ACEIs are much more nephroprotective than DHPs in both hypertension and diabetes. A comparison of the safety and long-term efficacy of CCBs with lower-cost alternatives remains an important issue for managed care organizations. The recently released results of the National Heart, Lung, and Blood Institute-funded Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial study may provide the necessary evidence-based medicine to address this important issue.

**Conclusion**

Combination therapy with a DHP CCB did not appear to have a deleterious effect on increasing the risk of an MI in a high-risk diabetic, hypertensive population. Further research in prospective, randomized, double-blind clinical trials with more patients is needed to determine if monotherapy or combination therapy with the various CCBs are safe and cost effective for long-term use. Strategies should continue to be focused on achieving optimal disease outcomes and maximizing patient compliance to more effectively reduce the incidence of MI and hospitalization and lower health care costs.

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