Patterns of Antihypertensive Therapy Among Patients with Diabetes

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BACKGROUND: Hypertension is extremely prevalent in patients with diabetes. Limited data exist on whether patterns of antihypertensive use in this population are consistent with evidence-based practice guidelines.

OBJECTIVE: To evaluate utilization patterns of antihypertensive agents and blood pressure (BP) control among diabetic patients with hypertension.

DESIGN: Retrospective cohort study.

PATIENTS/PARTICIPANTS: In all, 9,975 patients with diabetes and hypertension as of March 2001 from an outpatient medical center of the Department of Veterans Affairs.

MEASURES: Proportions of use of 6 different antihypertensive drug classes were compared for all patients receiving 1, 2, 3, or 4 or more drugs, and separately among patients with and without coronary artery disease (CAD). Blood pressure control (< 130/85 mmHg) was compared for untreated patients, those on monotherapy, and patients on multidrug regimens.

RESULTS: Over 60% of patients were receiving angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB), followed by diuretics (38.1%), calcium channel blockers (35.3%) and β-blockers (28.5%) with 19.1% of patients untreated. Patients on monotherapy were mostly receiving ACEI/ARB (59.5%). The majority (70.7%) of treated patients were on multidrug regimens. In patients with CAD, β-blocker and ACEI/ARB use was higher, and 70.5% of patients on single-drug regimens received either ACEI/ARB or β-blockers. The proportions of patients not on medications, on monotherapy, or multidrug regimens achieving BP control were 23.4%, 27.4%, and 24.9%, respectively.

CONCLUSIONS: Patterns of anti-hypertensive therapy were generally consistent with evidence-based practice guidelines. Areas of improvement include increasing ACEI/ARB and diuretic use, decreasing the number of untreated patients, and increasing the proportion of patients with controlled BP in this population.

KEY WORDS: hypertension control; diabetes; multidrug regimens; prescribing patterns; evidence base.
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Hypertension affects about 60% of patients with type 2 diabetes.[1] Serious cardiovascular events are more than twice as likely in patients with diabetes and hypertension than either disease alone.[2] The benefits of tight blood pressure (BP) control in patients with diabetes exceed the benefits of tight glycemic control and extend to the prevention of both macrovascular and microvascular complications.[3] However, studies consistently demonstrate that most diabetic patients do not achieve recommended levels of BP control, and the majority have a BP of > 140/90 mmHg.[4–6]

Appropriate use of anti-hypertensive agents may improve BP control and reduce complications in patients with diabetes. Evidence also supports the need for using multiple anti-hypertensive agents rather than monotherapy to achieve target BP control and greater renoprotection.[7] In addition, more recent data from The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) highlight the frequent need to use multidrug regimens to treat BP to target levels, especially in this population.[8]

Studies have shown that the use of angiotensin-converting enzyme inhibitors (ACEI) can prevent the progression of renal damage and delay progression to end-stage renal disease in addition to lowering BP.[7] Thus, it has been suggested that all diabetic patients with BP greater than 130/80 mm Hg should begin ACEI treatment unless contraindicated.[7] In addition to ACEI, Joint National Committee (JNC) VI guidelines also recommended diuretics or calcium channel blockers as preferred therapies and the use of multiple medications to lower BP to the target 130/85 mmHg. For patients with CAD, the preferred medications according to JNC VI are β-blockers.

There are limited data in the literature regarding practitioners' choices of anti-hypertensive therapies for a patient with diabetes in single- and multiple-drug regimens. Therefore, we undertook a database study to evaluate treatment patterns in a Department of Veterans Affairs (VA) cohort of diabetic patients with hypertension. Our objectives were:

(1) To evaluate the utilization of ACEI or angiotensin receptor blockers (ARBs) and other preferred anti-hypertensive therapies based on the JNC VI guidelines as agents to treat diabetic hypertension,
(2) To compare utilization of antihypertensive therapies especially ACEI/ARB and β-blockers for diabetic patients with and without CAD, and
(3) To assess BP control in this population.

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METHODS

Study Site and Subjects

We conducted this study at one of the largest medical centers of the VA. The VA is the country's largest equal access, comprehensive, integrated health care system comprised of 163 hospitals, and more than 850 outpatient and community-based clinics. The provision of medical care has been structured around a primary care model since the mid-1990s. Pharmacotherapy is managed by a formulary, and during the time of our study, angiotensin receptor blockers were restricted by the VA. VA physicians are expected to follow VA guidelines for the treatment of hypertension, which are evidence based and published by the Office of Quality and Performance. Practitioners at this site were a combination of primary care staff physicians (about 35), allied health professionals (about 15), sub-specialists who staffed primary care clinics part time (about 20), and general medicine residents (a rotating group of about 110). About a third of the primary care physicians and all of the sub-specialists had an academic affiliation.

We used the computerized medical record to obtain diagnostic information (International Classification of Diseases, Clinical Modification, 9th Revision (ICD-9-CM) codes), demographic information, laboratory test results, vital signs, and prescription drug use from pharmacy dispensing records. Data were collected retrospectively for the period October 1, 1998 to March 1, 2001. All inpatients and outpatients of the parent tertiary care facility as well as all outpatients from the subsidiary clinics in the surrounding catchment area were screened. All data were transferred over the VA intranet from the regional network data warehouse computer system to the study team for analysis. All aspects of the study protocol, including access to and use of the computerized patient clinical information, was authorized by the local Institutional Review Board (IRB) and VA research review committee.

Inclusion and Exclusion Criteria

Patients were identified for inclusion in the study based on previous research, described in detail elsewhere.[9,10] Briefly, all patients seen from October 1, 1998 to March 1, 2001 were screened and classified as having hypertension and diabetes based on a combination of diagnoses, clinical parameters, and prescription drug information.

Patients were classified as having hypertension if they met any of the following 5 criteria:

(1) At least 2 outpatient visit diagnoses of hypertension; or
(2) At least 1 prescription of antihypertensive drug plus at least 1 outpatient diagnosis of hypertension; or
(3) At least 1 prescription of antihypertensive drug plus at least 1 elevated BP; or
(4) At least 2 elevated BP measurement plus one outpatient diagnosis of hypertension; or
(5) At least 2 elevated BP measurements.

- Elevated BP was defined as greater than or equal to130/85 mmHg, according to the sixth report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[11]

Patients were identified with diabetes if they met any of the following 4 criteria:

(1) At least 2 outpatient visit diagnoses of diabetes; or
(2) At least 1 inpatient diagnosis of diabetes; or
(3) At least 1 prescription of anti-diabetic drug or monitoring supply; or
(4) At least 1 elevated HbA1C level.

- Elevated HbA1C for purposes of screening was 6.5%.

To better study the use of ACEI specifically for diabetes, patients with any record of an inpatient or outpatient diagnosis of chronic heart failure (CHF) were excluded (ICD-9-CM codes 398.91, 428, 428.0, 428.1, and 428.9).

Treatment Patterns

We used computerized pharmacy records to identify prescription fills of any anti-hypertensive drugs (β-blockers, calcium channel blockers, other antihypertensives, thiazide diuretics, loop diuretics, ACEI, ARB, and α-blockers) between the time period November 1, 2000 and March 1, 2001. We narrowed our time frame to this 4-month period to determine a point-prevalence estimate of the proportion of patients on drugs at the end of our study period. We used a 4-month period to ensure capture of 90-day fills prior to March 1. The number of antihypertensive drugs being prescribed was tabulated. We classified patients with any prescriptions for ACEI or ARB as ACEI/ARB users and classified patients with any prescriptions for thiazide or loop diuretics as diuretic users. The proportion of use of these antihypertensive drug classes, among patients with 1, 2, 3, or 4 or more drugs, was tabulated for all patients.

Analysis

We present the patterns of use of antihypertensive drugs among all patients overall, and in sub-groups of patients on 1, 2, 3, or 4 or more drugs. We compared the proportions of drug class use among patients with and without CAD (ICD-9-CM codes 413.9, 414.0, 414.8, 414.9, 429.2, V45.81, and V45.82), and further compared the proportion of patients at BP control among patients not receiving medication, on monotherapy, and on multi-drug regimens. Patients with BP below 130/85 mmHg were classified as having BP control. Patients with missing BP measurements or above this level were classified as not having BP control. Differences in proportions were tested in pairwise comparisons by the normal approximation to the binomial. Because of the relatively large sample sizes and multiple comparisons being made, we adjusted the type I α level for each test comparing drug classes to 0.0028 to achieve statistical significance. Blood pressure comparisons were made at an α level of 0.05.

RESULTS

There were 9,975 patients who met the inclusion criteria for hypertension and diabetes and did not have chronic heart failure. The average age (SD) was 61.2 (11.5) years old and almost 97% were male. Approximately 49% were white, 26.9% were African American, and 8.5% were Hispanic. Race was classified as unknown in 15.7% of patients. Slightly more than one-third of the patients (34.4%) had coronary artery disease.

Overall, 1,909 (19.1%) patients were receiving no drugs from these anti-hypertensive drug classes, 2,363 patients (23.7%) were receiving 1 drug, 2,390 patients (24.0%) were receiving 2 drugs, 1,796 patients (18.0%) were receiving 3 drugs, and 1,517 patients (15.2%) were receiving 4 or more drugs.

Table 1. Patterns of Use of Anti-Hypertensive Drugs Among Patients with Single- Versus Multidrug Hypertension

Drug class, *N* (%)	Overall *N*=9,975 (100.0%)	No Drugs *n*=1,909 (19.1%)	1 Drug *n*=2,363 (23.7%)	2 Drugs *n*=2,390 (24.0%)	3 Drugs *n*=1,796 (18.0%)	4 or More Drugs *n*=1,517 (15.2%)
ACE inhibitors or angiotensin II Inhibitors	6,167 (62.2)	–	1,406 (59.5)	1,817 (76.0)	1,538 (85.6)	1,406 (92.7)
Thiazide or loop diuretics	3,805 (38.1)	–	221 (9.4)	953 (39.9)	1,265 (70.4)	1,366 (90.0)
β-blockers	2,846 (28.5)	–	271 (11.5)	691 (28.9)	815 (45.4)	1,069 (70.5)
Calcium channel blockers	3,518 (35.3)	–	265 (11.2)	857 (35.9)	1,080 (60.1)	1,316 (86.8)
Other antihypertensives	958 (9.6)	–	41 (1.7)	88 (3.7)	212 (11.8)	617 (40.7)
α-blockers	1,512 (15.2)	–	156 (6.6)	351 (14.7)	389 (21.7)	616 (40.6)

Note: Percentages of individual drug classes are given within columns: overall, and by number of drugs in regimen.
ACE, angiotensin-converting enzyme.

Therefore, a total of 5,703 patients (57.2% of all and 70.7% of pharmacologically treated patients) were on a multiple-drug regimen.

Most patients were receiving ACEI or ARB (62.2%), followed by diuretics (38.1%), calcium channel blockers (35.3%), and then β-blockers (28.5%) (see Table 1). This was the same pattern observed separately among patients on 2, 3, or 4 or more drugs, where ACEI/ARB use ranged from 76.0% to 92.7%, and diuretic use ranged from 39.9% to 90.0%. Patients on monotherapy were mostly receiving ACEI/ARB (59.5%). α-blocker use ranged from 6.6% in patients on monotherapy to 40.6% in patients receiving 4 or more medications. Use of other antihypertensives, which include methyldopa, reserpine, clonidine, hydralazine, and minoxidil, ranged from 1.7% in patients on monotherapy to 40.7% among patients receiving 4 or more medications.

Use of all drug classes was higher overall ($P<.0001$) among patients with CAD compared with patients without CAD (see Table 2). β-blocker use was higher ($P<.0001$) for patients with CAD on monotherapy and for patients on multidrug regimens, and 70.5% of patients on single drug regimens received either ACEI/ARB or β-blockers. Among patients without CAD, use of ACEI/ARB was higher for patients on monotherapy ($P<.0001$) than in patients with CAD.

Blood pressure control overall was 25.2%: 23.4% among untreated patients, 27.4% in patients on monotherapy, and 24.9% in patients receiving multidrug regimens. None of these proportions were statistically significantly different from each other.

DISCUSSION

We studied patterns of antihypertensive use in patients with diabetes and hypertension, without CHF, to evaluate whether they were consistent with evidence-based practice guidelines. Although our study revealed that 19% of patients were not on any antihypertensives, a substantial majority of treated patients in all drug regimens received ACEI or ARBs. Overall ACEI/ARB and β-blocker use was higher in those with CAD compared with patients without CAD. Either β-blocker or ACEI/ARB was used in a majority (70.5%) of those with CAD as single drug therapy. A large proportion of treated patients (70.7%) were being prescribed multidrug regimens, reflecting the pattern observed in several previous trials. In these regimens, the most common drug class prescribed was ACEI/ARB (83.5%) followed by diuretics (62.8%), both agents recommended by the JNC VI. Our findings indicate that medication use was mostly consistent with evidence-based practice guidelines to treat hypertension in patients with diabetes, including the JNC VI guidelines. There was, however, room for improvement in prescribing, especially in the untreated group.

In 2001, evidence from several trials and meta-analysis clearly suggested that ACE inhibitors are better than any other class of antihypertensives in protecting against progressive renal damage.[7,12–15] Evidence from the HOPE trial also suggested their cardiovascular protection benefit.[16] The cost–benefit ratio of starting every diabetic patient on an ACEI has been shown to be favorable in a previous VA study.[17] Thus, the choice of a single-line agent based on evidence at the time of

Table 2. Patterns of Use of Antihypertensive Drugs Among Patients with and Without CAD

Drug class, *N* (%)	Among Patients with CAD (CAD)†			Among Patients Without CAD (No CAD)‡		
	Overall *N*=3437 (100.0)	1 Drug *n*=586 (17.0)	2 or More Drugs *n*=2,610 (75.9)	Overall *n*=6,538 (100.0)	1 Drug *n*=1,777 (27.2)	2 or More Drugs *n*=3,093 (47.3)
ACE inhibitors or angiotensin II inhibitors	2,432 (70.8)*	247 (42.2)	2,185 (83.7)	3,770 (57.7)	1,162 (65.4)*	2,608 (84.3)
Thiazide or loop diuretics	1,638 (47.6)*	52 (8.9)	1,586 (60.8)	2,167 (33.2)	169 (9.5)	1,998 (64.6)
β-blockers	1,783 (51.9)*	166 (28.3)*	1617 (61.9)*	1063 (16.3)	105 (5.9)	958 (31.0)
Calcium channel blockers	1,581 (46.0)*	79 (13.5)	1,502 (57.5)	1,937 (29.6)	186 (10.5)	1,751 (56.6)
Other antihypertensives	392 (11.4)*	11 (1.9)	381 (14.6)	566 (8.6)	30 (1.7)	536 (17.3)
α-blockers	681 (19.8)*	31 (5.3)	650 (24.9)	831 (12.7)	125 (7.0)	706 (22.8)

Notes: Percentages of individual drug classes are given within columns: overall, and by number of drugs in regimen.
**Statistically significantly greater percentage (P<.0001) than corresponding drug class in comparisons of patients with CAD to similar regimen in patients without CAD.*
†241 (7.0%) patients diagnosed with CAD were on no antihypertensive drugs.
‡1,668 (25.5%) of patients without CAD were on no antihypertensive drugs.
ACE, angiotensin-converting enzyme. CAD, coronary artery disease.

our study was clearly an ACEI. Although the use of ARBs was minimal due to restrictions on the VA formulary in 2000 to 2001, we combined their use with ACEI for analysis. In single-drug regimens, ACEI/ARB were the most commonly used drugs (about 60%). More than 80% of these patients were either on ACEI/ARB, a diuretic, or a calcium channel blocker, all preferred agents according to the JNC VI guidelines (although the use of calcium channel blockers in this population became controversial a few years after the guidelines were published).

To further examine the utilization of antihypertensives, we evaluated patients with and without CAD. The rationale for this was that many patients with diabetes also have CAD, and may instead be on β-blockers. As expected, ACEI/ARB use as single agents was lower in those with CAD, although their overall use was higher as compared with those without CAD. Use of β-blockers was higher in those with CAD in both single- and multidrug regimens. Either β-blocker or ACEI/ARB was used in the majority (70%) of those with CAD as single-drug therapy. Although the prescribing in CAD was not perfect, the data suggested that it was fairly consistent with evidence-based practice guidelines.

Berlowitz et al.[18] have shown worse BP control in patients with diabetes and less intensive anti-hypertensive medication therapy. Use of multiple drugs in combinations is being increasingly recognized as critical to control hypertension in patients with diabetes. In our study, a majority of pharmacologically treated patients (70.7%) were on 2 or more drugs to control BP, consistent with what has been seen in several trials and literature.[7,8] After ACEI/ARBs, diuretics were the next most prescribed class of drugs in such regimens. Diuretics offer both cardiovascular[19] and renal protection,[20–22] do not increase risk for diabetes,[23] and their safety and beneficial effects in this population are well established. They were recommended by JNC VI as one of the preferred therapies in this population. This utilization was consistent with evidence-based practice guidelines, although with potential room for improvement in the post-ALLHAT era. A relatively high proportion of α-blocker prescriptions could be partly explained by the high prevalence of benign prostatic hyperplasia in our predominantly male population. Additionally, α-blocker use could be explained by the JNC VI recommendations and the fact that reviews in the 1990s often focused on the potential lipid benefits from these drugs.

We found overall BP control ($<130/85$) to be 25.2 %. This is reflective of control seen at baseline in ALLHAT,[24] where only 27% of patients had BP $<140/90$ at initial enrollment, despite 90% treatment rates. Obviously, BP control is multifactorial, with factors such as age, comorbidity, and patient adherence to medication regimens affecting this outcome, and our study does not attempt to examine these. Interestingly, the control rate did not differ much across the regimens.

There is an abundance of literature from previous trials about underutilization of ACEI for CHF,[27] but the data with diabetes are limited. A recent analysis from the National Health and Nutrition Examination Survey (NHANES) revealed that in elderly diabetics, only 39.2% were taking an ACEI or ARB.[28] Our figures are more encouraging. A small study analyzing ACEI use in a hypertensive Medicaid population showed that even though their use increased from 1994 to 1998, it remained less than optimal.[29] A VA study carried out in 1997 showed overall use of ACEI in diabetics to be 65% but did not analyze their use as in single-drug regimens.[30] A mail survey-based study showed that ACEI were prescribed to 84% of diabetic patients as initial therapy.[31] Our study corroborates some of these latter findings, and in addition provides an insight into their use in single-drug regimens. Two international studies with small samples of hypertensive diabetic patients have shown prescribing patterns to differ from the guidelines.[32,33]

Our study has several strengths. We have a large sample of patients with both diseases. The study had the advantage of assessing actual prescriptions dispensed and was able to assess the prescription volume for a given class and characterize specific prescribing for patients, for example, percentage of patients on multidrug regimen taking a diuretic or those on monotherapy for ACEI. Our algorithm to define patients is based on previous published work,[9,10] and combines information from diagnostic, pharmacy, and laboratory test results and vital signs so as not to rely on any single source of information. The use of HbA1C tests to identify patients with diabetes may be controversial to some; however, this value has been used in other studies,[34] and we used this measure in combination with the other information, and less than 3% of all patients ($n=285$) were identified based on this test alone.

Interpretation of our results must be considered along with recognition of several limitations of our study. First, our study is retrospective and was conducted at 1 tertiary care hospital. In addition, because of the predominantly male population of our patients, the results cannot be generalized to women. Because our database required prescriptions to be filled within the VA system, prescriptions filled in the private sector could not be accounted for. However, because the medication co-pay was only $2 in the VA at the time of our study, we do not believe this to be a significant potential bias. We also did not analyze individual medical records to look for contraindications to specific drugs. The rates of withdrawal of ACEI due to adverse effects or patient choice are between 10% and 20%.[25,26] Also, about 5% of our population had a Cr ≥ 2.0 mg/dL, which may have been a deterrant for some physicians to use ACEI/ARB at the time of our study. Based on this information, we estimated that a large majority of patients, but probably not all, were at least put on an ACEI/ARB as a trial. This estimate is limited because we did not perform chart review or a time trend analysis. In addition, we did not have the breakdown of the number of specific anti-hypertensive prescriptions written by individual physicians. Finally, as in all studies of prevalence of pharmaceutical use based on computerized dispensing records, the estimates presented are a balance of physician prescribing intent reflected in the actual fill patterns of patients.

In conclusion, our findings suggest that in our diabetic hypertensive population, ACEI/ARB use was found in a large proportion of treated patients and was consistent with evidence-based practice guidelines. The majority (70.7%) of treated patients were on multidrug regimens. Anti-hypertensive use in multidrug regimens was generally consistent with JNC VI guidelines, those being the current guidelines at the time of our study. However, there remains potential room for improvement in drug utilization and a critical need for better BP control. Further research is needed to qualify how utilization and control rates compare outside the VA setting, and to determine specific patient and provider factors associated with variation in prescribing patterns and BP control. Continued research

efforts to understand poor BP control despite good pharmacological treatment are needed.

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