Adherence to Antihypertensive Medications and Cardiovascular Morbidity Among Newly Diagnosed Hypertensive Patients

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Background—Nonadherence to antihypertensive treatment is a common problem in cardiovascular prevention and may influence prognosis. We explored predictors of adherence to antihypertensive treatment and the association of adherence with acute cardiovascular events.

Methods and Results—Using data obtained from 400 Italian primary care physicians providing information to the Health Search/Thales Database, we selected 18,806 newly diagnosed hypertensive patients ≥35 years of age during the years 2000 to 2001. Subjects included were newly treated for hypertension and initially free of cardiovascular diseases. Patient adherence was subdivided a priori into 3 categories—high (proportion of days covered, ≥80%), intermediate (proportion of days covered, 40% to 79%), and low (proportion of days covered, ≤40%)—and compared with the long-term occurrence of acute cardiovascular events through the use of multivariable models adjusted for demographic factors, comorbidities, and concomitant drug use. At baseline (ie, 6 months after index diagnosis), 8.1%, 40.5%, and 51.4% of patients were classified as having high, intermediate, and low adherence levels, respectively. Multiple drug treatment (odds ratio, 1.62; 95% CI, 1.43 to 1.83), dyslipidemia (odds ratio, 1.52; 95% CI, 1.24 to 1.87), diabetes mellitus (odds ratio, 1.40; 95% CI, 1.15 to 1.71), obesity (odds ratio, 1.50; 95% CI, 1.26 to 1.78), and antihypertensive combination therapy (odds ratio, 1.29; 95% CI, 1.15 to 1.45) were significantly (P<0.001) associated with high adherence to antihypertensive treatment. Compared with their low-adherence counterparts, only high adherers reported a significantly decreased risk of acute cardiovascular events (hazard ratio, 0.62; 95% CI, 0.40 to 0.96; P=0.032).

Conclusions—The long-term reduction of acute cardiovascular events associated with high adherence to antihypertensive treatment underscores its importance in assessments of the beneficial effects of evidence-based therapies in the population. An effort focused on early antihypertensive treatment initiation and adherence is likely to provide major benefits. (Circulation. 2009;120:1598-1605.)

Key Words: antihypertensive agents ■ cardiovascular diseases ■ cohort studies ■ medication adherence ■ prevention

High blood pressure (BP) is one of the most preventable causes of cardiovascular disease morbidity and mortality.1 The use of antihypertensive drug therapy (AHT) has been shown to reduce the risk of stroke and coronary heart disease by an estimated 34% and 21%, respectively, in long-term randomized controlled trials (RCTs).2,3 Generally, AHT should be maintained indefinitely. However, findings in clinical practice have raised concerns about the high extent of undertreatment and nonadherence to AHT, which hampers the effectiveness of these medications. In RCTs, antihypertensive drug discontinuation rates range from 5% to 10% per year, and rates up to 50% to 60% after 6 months have been reported in actual practice.4,5

Adherence to AHT has been associated with improved BP, decreased hospitalization rates, and lower medical care costs.3,6 A recent cohort study7 has also confirmed that the long-term survival advantages associated with improved adherence to AHT after acute myocardial infarction (AMI) appear to be class specific and correlated positively in a
AHT and its association with concurrent drug use, comorbidities, and cardiovascular risk factors. Furthermore, we assessed the impact of adherence on the incidence of CVE among newly diagnosed hypertensive patients.

Methods

Sources of Data
We obtained information from the Health Search/Thales Database, an Italian general practice registry that comprises data given by computer-based patient records of a selected group of primary care physicians (PCPs) distributed across Italy. They voluntarily agreed to collect patient information and to attend specified training courses for data entry.

The Health Search/Thales Database contains patient demographic details that are linked through the use of an encrypted patient code with medical records (diagnoses, tests, and results), drug prescription information (medication name, date of filled prescription, and number of days' supply), prevention records, hospital admission, and date of death. To be considered for participation in epidemiological studies, PCPs should meet “up-to-standard” quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, and years of recording.

A number of comparative studies have been published confirming the research validity of the Health Search/Thales Database in conducting studies on the observed outcomes.10 When this study was initiated, 400 PCPs homogeneously distributed across all Italian areas, covering a patient population of 521,214, reached the up-to-standard quality criteria.

Cohort Definition
We identified all subjects ≥35 years of age who were diagnosed with hypertension (International Classification of Diseases, 9th revision, clinical modification [ICD-9-CM] codes 401 through 404.x and 437.2) during the years 2000 to 2001 and were newly treated with at least one of the possible antihypertensive drugs (ie, diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin-2 receptor blockers) in the 90 days after index diagnosis. Patients were considered newly treated if they had not taken any AHT 6 months before the index diagnosis. Patients included in the study cohort were registered with one of the participating PCPs for at least 1 year before entry into the study and survived at least 1 year after index diagnosis.

We excluded any patient who had been diagnosed with coronary heart disease (codes 410 through 414.x), cerebrovascular disorders (codes 430 through 438.x), or congestive heart failure (code 428.x); subjects who had been hospitalized for coronary artery bypass surgery or coronary angioplasty, and those recovered in a cardiological ward before index diagnosis. To avoid the tendency of PCPs to diagnose and treat hypertension as an early manifestation of major cardiovascular outcome. The aim of the present study was to describe adherence to AHT and its association with concurrent drug use, comorbidities, and cardiovascular risk factors. Furthermore, we assessed the impact of adherence on the incidence of CVE among newly diagnosed hypertensive patients.

Assessment of Adherence
Adherence to AHT, defined as the extent to which patients followed their antihypertensive medication schedules as prescribed by their PCPs, was estimated by calculating the proportion of days on which a patient had pills available during the follow-up (proportion of days covered [PDC]). The follow-up period was separated into 180-day intervals, and within each interval, the PDC corresponded to the total number of days’ supply of medication dispensed divided by the length of the corresponding follow-up and multiplied by 100. The number of days supplied by each prescription was calculated by dividing the total amount of active drug in each prescription by the recommended defined daily dose. Prescriptions filled before the beginning of each interval could contribute if the days supplied extended into the interval period. Prescriptions filled at any point after the start of the interval contributed days from the date dispensed forward.

Consistent with data in the literature, patients were classified into the following adherence levels: high (PDC ≥80%), intermediate (PDC, 40% to 79%), or low (PDC ≤40%). They were further classified into single therapy if taking 1 antihypertensive drug class or combination therapy if multiple-pill medications such as angiotensin-converting enzyme inhibitors and calcium channel blockers or a fixed-dose combination therapy (ie, angiotensin-converting enzyme inhibitors plus diuretics) was prescribed for >50% of days during each time interval.

Acute Cardiovascular Events
The onset of any acute CVE was ascertained through the physician’s coded diagnosis during follow-up. A CVE was defined as a composite end point of first-ever acute coronary syndromes such as AMI (codes 410.x and 411.x) and angina pectoris (code 413.x) or cerebrovascular events such as acute stroke (codes 430 through 432.x, 433.01, and 436.x) and transient ischemic attack (code 435.x). The reliability of the coded diagnoses was assessed by manual review of the “free text” electronic medical charts. Validation procedures were performed by the use of encoded medical problems, which primarily allowed us to confirm the occurrence of an acute event (ie, “acute,” “sudden,” “heart attack,” “stroke,” “hemorrhage,” “recovery,” “hospital”) leading to angina/transient ischemic attack (ie, “ischemic,” “oclusion,” “obstruction,” “stenosis,” “transient”) or AMI/stroke (“infarct,” “necrosis”).

Cardiovascular Risk and Comorbidity
To control for global cardiovascular risk, we identified most of the documented variables potentially associated with coronary heart disease and stroke.14 They included age, gender, familiar history of cardiovascular disease, BP values (calculated as the average between the last 2 separate measurements over the 12 months before the index diagnosis), and obesity (body mass index ≥30 kg/m² last available value for the 12 months before the index diagnosis) or ICD-9-CM code 278.0). Coexisting illnesses were ascertained from physician ever-recorded diagnosis and medication use. We used a previously validated approach15 to identify diabetes mellitus on the basis of PCP diagnosis (codes 250.x, excluding 250.x1 and 250.x2) and ≥1 antihyperglycemic medications. Dyslipidemia was based on PCP diagnosis (code 272.x) and receipt of lipid-lowering therapy.16 We also identified arrhythmias (code 427.x) and peripheral vascular diseases (code 443.9), cancer (codes 140 through 199.x, 200 through 208.x), and chronic respiratory diseases (codes 490 through 496.x). Drug information was used to assign prior and follow-up receipt of relevant medications, including antihyperglycemic agents, anti-thrombotics, cardiac glycosides, lipid-lowering agents, antihypertensives, corticosteroids, thyroid therapy, nonsteroidal anti-inflammatory drugs, and antidepressants, for each eligible person.
Statistical Analysis
To analyze differences in baseline characteristics across adherence levels, we tested for linear trends using a $\chi^2$ test (categorical variables) or linear regression models (continuous variables) when appropriate. Multivariable logistic regression models, adjusting for all baseline factors, were constructed to examine predictors of high adherence to AHT.

The relationship between adherence and incident CVE was examined by constructing multivariable Cox proportional-hazards models. To adjust for potential confounders, we included age, gender, baseline concomitant medical treatment, comorbidity, obesity, family history of cardiovascular diseases, BP values, and hospitalization for the 12 months before the index diagnosis (Table 1). In addition, we considered cardiovascular risk factors and concurrent drug use as time-dependent covariates in the model to adjust for global cardiovascular risk during follow-up (model 1). Adherence to AHT was assessed at 2 different time windows: at baseline and during follow-up. At baseline, AHT was determined during the first 6 months after the index diagnosis and evaluated on the basis of an intention-to-treat approach. During follow-up, AHT was treated as a

Table 1. Characteristics of Newly Diagnosed Hypertensive Patients According to Baseline Adherence to AHT

<table>
<thead>
<tr>
<th>Adherence Levels*</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>9666 (51.4)</td>
<td>7624 (40.5)</td>
<td>1516 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62.0 (12.4)</td>
<td>61.9 (11.9)</td>
<td>61.3 (11.6)</td>
<td>0.089</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>5787 (59.9)</td>
<td>4384 (57.5)</td>
<td>800 (52.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Concurrent drug use, n (%)*
- Antihyperglycemic drugs: 741 (7.7) 794 (10.4) 200 (13.2) <0.001
- Antithrombotics: 1047 (10.8) 1136 (14.9) 267 (17.6) <0.001
- Lipid-modifying agents: 763 (7.9) 815 (10.7) 177 (11.7) <0.001
- Antiarrhythmics: 148 (1.5) 110 (1.4) 19 (1.3) 0.678
- Corticosteroids: 484 (5.0) 365 (4.8) 100 (6.6) 0.013
- Thyroid therapy: 406 (4.2) 325 (4.3) 73 (4.8) 0.544
- NSAIDs: 2757 (28.5) 2347 (30.8) 491 (32.4) <0.001
- Antidepressant drugs: 5787 (6.0) 579 (7.6) 127 (8.5) 0.207

Concurrent medications, mean, n (SD)*
- Diabetes mellitus: 915 (9.5) 890 (11.7) 208 (13.7) <0.001
- Arrhythmias: 295 (3.1) 332 (4.4) 66 (4.4) <0.001
- Peripheral vascular diseases: 300 (3.1) 280 (3.7) 73 (4.8) 0.002
- Dyslipidemia: 1048 (10.8) 979 (12.8) 221 (14.6) <0.001
- Cancer: 657 (6.8) 541 (7.1) 115 (7.6) 0.469
- Respiratory illness: 716 (7.4) 544 (7.1) 129 (8.5) 0.174
- Obesity‡: 806 (8.3) 786 (10.3) 193 (12.7) <0.001

Comorbidity at index diagnosis, n (%)
- Diabetes mellitus‡: 915 (9.5) 890 (11.7) 208 (13.7) <0.001
- Arrhythmias: 295 (3.1) 332 (4.4) 66 (4.4) <0.001
- Peripheral vascular diseases: 300 (3.1) 280 (3.7) 73 (4.8) 0.002
- Dyslipidemia: 1048 (10.8) 979 (12.8) 221 (14.6) <0.001
- Cancer: 657 (6.8) 541 (7.1) 115 (7.6) 0.469
- Respiratory illness: 716 (7.4) 544 (7.1) 129 (8.5) 0.174
- Obesity‡: 806 (8.3) 786 (10.3) 193 (12.7) <0.001

Family history of cardiovascular diseases
- Diabetes mellitus‡: 915 (9.5) 890 (11.7) 208 (13.7) <0.001
- Arrhythmias: 295 (3.1) 332 (4.4) 66 (4.4) <0.001
- Peripheral vascular diseases: 300 (3.1) 280 (3.7) 73 (4.8) 0.002
- Dyslipidemia: 1048 (10.8) 979 (12.8) 221 (14.6) <0.001
- Cancer: 657 (6.8) 541 (7.1) 115 (7.6) 0.469
- Respiratory illness: 716 (7.4) 544 (7.1) 129 (8.5) 0.174
- Obesity‡: 806 (8.3) 786 (10.3) 193 (12.7) <0.001

BP, mean (SD), mm Hg
- Systolic: 145.2 (17.8) 143.9 (17.1) 144.2 (17.5) <0.001
- Diastolic: 86.3 (9.9) 85.2 (9.5) 85.5 (9.4) <0.001

BP categories, n (%)*
- High normal: 2293 (39.6) 2293 (42.7) 478 (42.6)
- Mild: 1849 (31.9) 1858 (34.6) 376 (33.3)
- Moderate: 1182 (20.4) 854 (15.9) 178 (15.8)
- Severe: 464 (8.0) 357 (6.7) 89 (7.9)

Patients with hospital recovery, n (%)*
- High normal: 2293 (39.6) 2293 (42.7) 478 (42.6)
- Mild: 1849 (31.9) 1858 (34.6) 376 (33.3)
- Moderate: 1182 (20.4) 854 (15.9) 178 (15.8)
- Severe: 464 (8.0) 357 (6.7) 89 (7.9)

Antihypertensive drug use with 1-pill regimen or multiple-pill combinations, n (%)
- High normal: 2293 (39.6) 2293 (42.7) 478 (42.6)
- Mild: 1849 (31.9) 1858 (34.6) 376 (33.3)
- Moderate: 1182 (20.4) 854 (15.9) 178 (15.8)
- Severe: 464 (8.0) 357 (6.7) 89 (7.9)

NSAIDs indicates nonsteroidal anti-inflammatory drugs.
*Adherence was defined as the PDC: high (PDC ≥80%), intermediate (PDC, 40% to 79%), or low (PDC <40%).
†Six months before the index diagnosis.
‡ICD-9-CM code 278.0 or body mass index ≥30 kg/m².
§High normal, 130 to 139/85 to 99 mm Hg; mild hypertension, 140 to 159/90 to 99 mm Hg; moderate hypertension, 160 to 179/100 to 109 mm Hg; severe hypertension, ≥180/≥110 mm Hg. Of 18 806 patients, 6535 (34.7%) did not record BP values at baseline.
||Twelve months before the index diagnosis.
time-dependent covariate in which each patient could contribute to any adherence level within any 180-day interval.

As an observational study of clinical practice, concerns exist about treatment selection bias. Adjusted estimates were therefore weighted by the inverse estimated propensity scores in an additional Cox proportional-hazards regression model of adherence effect (model 2). We developed 2 propensity score models to weight for adherence selection: high versus low adherence and intermediate versus low adherence.

Multivariable selection of risk factors was done by a stepwise procedure after adjustment for age and gender. The best model chosen by the stepwise procedure was confirmed by testing a range of related models with the Akaike information criterion. Because of the hierarchical structure of the variables, all statistical models accounted for the clustering of registered patients within each regional health authority.

Several sensitivity analyses were performed to ensure the consistency of our primary analysis in the presence of potential biases. Statistical significance was defined as a 2-tailed value of \( P \leq 0.05 \).

Estimates of treatment effects, 95% confidence intervals (CIs), and probability values were generated with STATA software, version 10.1 (STATA Corp, College Station, Tex).

Results

After applying the inclusion and exclusion criteria, from 25,763 hypertensive patients newly diagnosed by PCPs during 2000 to 2001, we selected 18,806 patients (73.0%) with a mean age at entry of 62 years, 41.6% of whom were male, and 27.5% of whom had at least 1 cardiovascular risk factor.

Determinants of Adherence

At baseline, 9666 (51.4%), 7624 (40.5%), and 1516 (8.1%) patients were classified as having low, intermediate, and high adherence, respectively. At the end of the follow-up, 1196 low and 1637 intermediate adherers switched to high adherence. Of 1516 baseline high adherers, 43.5% maintained the same category, whereas 31.0% and 25.5% switched to intermediate and low adherence, respectively. Overall, 18.8% of patients ended their follow-up with high adherence levels, whereas the proportion of intermediate and low adherers was 32.3% and 48.9%, respectively (the Figure).

Table 1 illustrates baseline characteristics of hypertensive patient according to 6 months of adherence to AHT. After adjustment for relevant baseline factors (Table 2), older patients (odds ratio [OR], 0.76; 95% CI, 0.68 to 0.86) and women (OR, 0.72; 95% CI, 0.65 to 0.86) were less likely to exhibit high adherence. The risk of being a high adherer increased in the presence of concurrent treatment with \( \geq 5 \) medications (OR, 1.62; 95% CI, 1.43 to 1.83), antithrombotics (OR, 1.54; 95% CI, 1.31 to 1.80), and combination AHT (OR, 1.29; 95% CI, 1.15 to 1.45). Overall, most of the documented cardiovascular risk factors (ie, diabetes mellitus, dyslipidemia, and obesity) had significant \( P < 0.001 \) associations with high adherence to AHT.

Impact of Adherence on Cardiovascular Events

During the follow-up (mean±SD, 4.6±1.2 years per patient), a total of 1018 patients (12.1 per 1000 person-years) were censored because they transferred from their PCPs, and 541 patients (6.4 per 1000 person-years) died. The crude incidence rates of acute CVEs were 7.4, 8.4, and 7.5 per 1000 person-years for low, intermediate, and high adherers, respectively.

Table 3 illustrates that the adjusted relationship between adherence and CVE (ie, model 1) followed a dose-response gradient, although not statistically significant among intermediate adherers. Although the direction of the association was similar, additional weighting for inverse propensity scores estimates (ie, model 2) reduced the magnitude of association between high adherence and the risk of acute CVE (hazard ratio [HR], 0.62; 95% CI, 0.40 to 0.96), whereas the HR among those with intermediate adherence remained similar (HR, 0.86; 95% CI, 0.71 to 1.03). After weighting by the inverse estimated propensity scores for high adherence selection, significant associations were reported for the following covariates: antithrombotic use (HR, 0.50; 95% CI, 0.37 to 0.67), diabetes mellitus (HR, 2.38; 95% CI, 1.56 to 3.63), and dyslipidemia (HR, 1.39; 95% CI, 1.11 to 1.73). No significant association was reported for combination AHT.

Sensitivity Analysis

To ensure that our method did not introduce a survival bias, we re-estimated the association between adherence to AHT and CVEs among subjects without any major cardiovascular outcomes for at least 90 and 365 days after the index diagnosis. We also stratified the patient population according
to the presence of at least 2 cardiovascular risk factors to ensure that any relationship between adherence and CVE also applied to various risk groups. Although the observed associations did not always achieve statistical significance because of sample size, subgroup analyses yielded trends consistently shown in the primary analysis.

**Discussion**

The main finding of the present study is that high adherence to AHT is associated with a 38% decreased risk of CVEs compared with lower adherence. This result is similar in magnitude to results presented in recent meta-analyses of placebo-controlled trials, which reported a nearly 30% relative risk reduction of major CVEs achieved with different antihypertensive drugs. The methods we applied to assess the relationship between baseline adherence to AHT and incident CVEs adapt 1 principle of the design of RCTs (ie, intention-to-treat analysis). Studies from the United Kingdom, Canada, and the Netherlands have in fact demonstrated that discontinuation rates are likely to be higher during the first year of follow-up but are more likely to remain rather stable thereafter for the long term.

The benefits of BP lowering may partially explain the decreased risk of CVEs among high adherers. During follow-up, we observed similar reductions of BP levels across the adherence groups (see the online-only Data Supplement), in accordance with an RCT documenting substantial benefit of various antihypertensive drugs even when BP reductions are small. Additional explanation is provided by several recent studies that have suggested that early and rapid achievement of BP control with various antihypertensive drugs was associated with significant benefits for subsequent CVEs. Indeed, in hypertension, BP variability increases with increasing BP levels, and there is evidence that its magnitude correlates closely with target-organ damage and with the incidence of CVE independently of absolute BP levels. Therefore, any antihypertensive drug capable of providing smooth 24-hour BP control might confer additional target-organ protection.

Consistent with previous research, patients at higher risk for adverse health outcomes, expressed as being treated with ≥5 medications, and those with higher baseline cardiovascular risk showed stronger associations with high adherence to AHT. Patients with severe clinical conditions are in fact

### Table 2. Crude and Multivariable Analyses of the Association of Patient Baseline Characteristics With Corresponding 6-Month High Adherence Level

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>Crude*</th>
<th>Adjusted†</th>
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<tbody>
<tr>
<td></td>
<td>High vs Low Adherence</td>
<td>P</td>
<td>High vs Low Adherence</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>. . .</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>. . .</td>
<td>0.76 (0.68–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>. . .</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>. . .</td>
<td>0.72 (0.65–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent drug use‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>1.85 (1.59–2.16)</td>
<td>&lt;0.001</td>
<td>1.54 (1.31–1.80)</td>
</tr>
<tr>
<td>Concurrent medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.79 (1.59–2.02)</td>
<td>&lt;0.001</td>
<td>1.62 (1.43–1.83)</td>
</tr>
<tr>
<td>≥5</td>
<td>1.65 (1.36–1.99)</td>
<td>&lt;0.001</td>
<td>1.40 (1.15–1.71)</td>
</tr>
<tr>
<td>Comorbidity at index diagnosis§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.56 (1.18–2.06)</td>
<td>0.022</td>
<td>1.37 (1.03–1.82)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>1.60 (1.22–2.09)</td>
<td>0.012</td>
<td>1.32 (1.00–1.75)</td>
</tr>
<tr>
<td>Peripheral vascular diseases</td>
<td>1.68 (1.37–2.05)</td>
<td>&lt;0.001</td>
<td>1.52 (1.24–1.87)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.61 (1.35–1.91)</td>
<td>&lt;0.001</td>
<td>1.50 (1.26–1.78)</td>
</tr>
<tr>
<td>Obesity§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.41 (1.12–1.78)</td>
<td>0.003</td>
<td>1.40 (1.10–1.77)</td>
</tr>
<tr>
<td>Family history of cardiovascular diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.29 (1.15–1.45)</td>
<td>&lt;0.001</td>
<td>1.29 (1.15–1.45)</td>
</tr>
</tbody>
</table>

*Age- and gender-adjusted.†Adjusted for all variables included in the table and clustering by regional health authority.‡Nonusers as reference.§Absence of disease as reference.
Table 3. Multivariable Analysis of the Association of Patient Characteristics With First-Ever Acute Cardiovascular Event Estimated by Cox Proportional-Hazards Models

<table>
<thead>
<tr>
<th>Adherence Within 6 mo After Diagnosis</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (PDC &lt;40%)</td>
<td>1.00</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Intermediate (PDC, 40% to 79%)</td>
<td>0.87 (0.73−1.03)</td>
<td>0.117</td>
</tr>
<tr>
<td>High (PDC ≥80%)</td>
<td>0.50 (0.35−0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (PDC &lt;40%)</td>
<td>1.00</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Intermediate (PDC, 40% to 79%)</td>
<td>0.86 (0.71−1.03)</td>
<td>0.109</td>
</tr>
<tr>
<td>High (PDC ≥80%)</td>
<td>0.62 (0.40−0.96)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

A total of 659 CVEs were considered in the models.

*All models were adjusted for clustering by regional health authority.
†Model 1: adjusted for age, gender, use of antithrombotics, ≥5 concurrent medications, presence of diabetes mellitus, dyslipidemia, and prior hospitalization.
‡Model 2: model 1 additionally weighted by the inverse estimated propensity scores.
§P values for the overall comparison between models with and without adherence to AHT using the log-likelihood ratio test.

more aware of being at higher risk and therefore are more willing to follow a therapeutic regimen. The small proportion of baseline high-risk patients might therefore explain the considerable suboptimal adherence to AHT encountered in our study. Conversely, the improved adherence observed during follow-up might be due to an increased cardiovascular risk among the study sample. This hypothesis has been confirmed in a recent study from the Netherlands that revealed that the hospitalization for cardiovascular disease (OR, 2.20; 95% CI, 1.84 to 2.63) and, to a lesser extent, the prescribing of cardiovascular comediations (OR, 1.25; 95% CI, 1.11 to 1.40) were each independently associated with initiation of antihypertensive treatment after temporary discontinuation. However, several trials of AHT have demonstrated that, despite intense BP lowering, the incidence of CVEs remains much higher in high-risk hypertensive patients than in hypertensive patients with initial lower risk. This evidence suggests that some of the major cardiovascular risk changes may be difficult to reverse and that restricting AHT to high-risk patients may be a strategy that is far from optimal.

The use of combination AHT has not reduced the incidence of CVEs per se. This finding might be explained by the low proportion of cardiovascular risk factors observed in our sample. In fact, combination therapy has been found to be more effective in diabetic, renal, and high-risk patients, whereas no conclusive evidence has been reported among hypertensive patients at lower risk. However, we observed improved adherence (>30%) associated with combination therapy compared with monotherapy. This result may support a recent statement from the European Society of Hypertension and European Society of Cardiology guidelines, which argued that the use of low-dose combinations favors compliance because of the smaller side effects compared with full-dose monotherapy and that BP targets may be reached earlier than with monotherapy.

Previous researches have assessed the relationship between survival and adherence to antihypertensive, lipid-lowering, and antihyperglycemic drugs among patients discharged from hospitals with coronary heart disease, congestive heart failure, or diabetes mellitus. To the best of our knowledge, this is one of the first studies to investigate the effect of adherence to AHT on the occurrence of first-ever major CVE. Another recent study explored the effect of early discontinuation of AHT on the risk of first-ever AMI and stroke. Nonpersistent antihypertensive use was associated with a 15% and 28% increased risk of AMI and stroke, respectively. However, although discontinuation to AHT is common, 50% of patients are likely to reinitiate treatment within 1 year. This certainly demonstrates that compliance with AHT is a dynamic factor that needs to be evaluated far beyond the simple treatment withdrawal.

Limitations

Our study has several noteworthy limitations. First, we confirmed the recorded diagnosis against medical charts, thus decreasing the likelihood of including false positives. However, the completeness of the ICD-9-CM coding might be questioned. Several studies have in fact estimated a sensitivity ranging from 60% to 80% for AMI diagnosis and the likelihood of ascertainment bias for stroke diagnosis because of the high case fatality rate. The potential misclassification, however, is unlikely to be differential among the adherence groups.

Second, our inability to track the time-varying global cardiovascular risk for each patient might have limited the comprehensiveness of risk adjustment. Nonetheless, our analyses have been adjusted for many factors, including most of the documented variables generally used to validate cardiovascular prediction scores such as BP, familiar history of cardiovascular disease, diabetes mellitus, dyslipidemia, and obesity. Finally, because the allocation of patients into different adherence groups was not randomized, it might have produced a resulting imbalance in the underlying cardiovascular risk profile, and comparison among treatment groups can generate biased results. However, we excluded from analysis patients without any antihypertensive treatment, thus removing 1 source of selection bias. A propensity score method was also used to control for the baseline differences observed across the adherence groups. Sensitivity analyses that stratified patient population according to various cardiovascular risk groups confirmed the robustness of our findings.

Conclusions

The real-world results from the present study indicate that high adherence to antihypertensive medication is associated with a relevant decrease in CVEs in the context of the primary prevention of cardiovascular diseases. These findings emphasize the need to optimize earlier and appropriate treatment strategies to maximize the beneficial effects of evidence-based therapies even among lower-risk hypertensive patients. Therefore, a systematic effort to improve the adherence to AHT is likely to provide major long-term benefits.
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Disclosures

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References


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**CLINICAL PERSPECTIVE**

It is important for clinicians to pay greater attention to early treatment initiation and adherence to antihypertensive medications because adherence is a key factor determining the success of preventive measures for cardiovascular risk reduction. Restricting appropriate treatment to only high-risk patients may be far from optimal because some of the major cardiovascular risk factors might be difficult to reverse. Educational strategies and interventions involving both health professionals and patients, which should focus on simplification of dosing regimens and patient trust in their physicians, might improve patient motivation to take prescribed medication.
Adherence to Antihypertensive Medications and Cardiovascular Morbidity Among Newly Diagnosed Hypertensive Patients

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**Supplemental table 1.** Mean Systolic Blood Pressure levels (mm/Hg) during follow-up (stratified by six-months time units), according to baseline adherence to antihypertensive therapy.

<table>
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<tr>
<th>Time units (six months)</th>
<th>Baseline adherence levels</th>
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