Better Medication Adherence Associated with Reduced Risk of Stroke and Death

Bailey JE, Wan JY, Tang J, Ghani MA, Cushman WC. Antihypertensive medication adherence, ambulatory visits, and risk of stroke and death. J Gen Intern Med 25:495–503.

Study Overview

Objective. To determine if antihypertensive medication refill adherence, ambulatory visits, and type of antihypertensive medication are associated with decreased stroke and death for community-dwelling patients with hypertension.

Design. Retrospective cohort study.

Setting and participants. The study included all patients with chronic medication-treated hypertension enrolled in Tennessee's Medicaid program (TennCare) during the period 1994–2000. Each enrollee was assigned to a primary care provider and had pharmacy benefits with no copayments. The cohort of patients was defined as all noninstitutionalized people with continuous Medicaid eligibility (> 320 days/year) for at least 3 years. They had to be 18 to 64 years old, not on Medicare, have a diagnosis of hypertension, and receive at least 1 antihypertensive medication prescription for the 2 baseline years. Exclusion criteria included dying or having a stroke during the baseline period.

Main outcome measures. The key outcome measures were time to stroke and time to death (all-cause mortality determined according to vital records). Stroke was defined using ICD-9 codes. Antihypertensive medication refill adherence was calculated using pharmacy records; specifically, medication refill adherence (MRA) was defined as the percentage of eligible prescription days with filled medications. Demographic and comorbidity variables were included as independent variables to control for confounding in the main analysis models. Prespecified baseline comorbidity variables included obesity, diabetes, mental illness, substance abuse, and hypercholesterolemia. Follow-up period comorbidity variables, calculated for every 6 months prior to event or to study conclusion, included congestive heart failure, atrial fibrillation, transient ischemic attack, myocardial infarction, and Charlson index of multiple comorbidity. Health care utilization patterns were defined as ambulatory visits per year, emergency visits per year, hospital visits per year, and hospital days per year. They were evaluated using administrative data linked to vital records during the 2-year baseline run-in period and 1- to 5-year follow-up period. The investigators used Cox regression modeling to determine multivariate associations (hazard ratios) with time to event (stroke and death). They also classified subjects as adherent or not based on a MRA cutoff value of 80%. Kaplan-Meier survival curves were calculated based on this binary variable.

Main results. The investigators included a total of 49,479 subjects (mean age, 48.5 years) followed for an average period of 4.7 years (including 2-year baseline period). Over a total of 133,593 person-years of follow-up, 619 strokes (1.25%) and 2051 deaths (4.15%) occurred. Mean MRA was 67%, ranging from 3% to 100%. Baseline antihypertensive MRA was associated with decreased multivariate hazards of stroke (hazard ratio [HR], 0.91 [95% confidence interval {CI}, 0.86–0.97 for each 15% increase in adherence]). Medication adherence in the follow-up period was associated with decreased hazards of stroke (HR, 0.92 [CI, 0.87–0.96]) and death (HR, 0.93 [CI, 0.90–0.96]). Baseline ambulatory visits were also associated with decreased death (HR, 0.99 [CI, 0.98–1.00]; $P < 0.05$). All 4 major classes of antihypertensive agents (thiazide diuretic, ACE inhibitors, calcium channel blockers, and beta blockers) were associated with mortality reduction ($P < 0.05$). However, only thiazide-type diuretic use was also associated with decreased stroke (HR, 0.89 [CI, 0.85–0.93]). Using the predefined 80% MRA cutoff to define adherence, 39.4% of patients were adherent in this study. The adjusted Kaplan-Meier survival curves showed that ≥ 80% baseline refill adherence was associated with better 5-year estimated survival than < 80% refill adherence for death ($P < 0.001$) and for a combined outcome of stroke or death ($P < 0.001$). The adjusted survival curves for stroke, however, were not significantly different ($P = 0.262$). Based on the survival model, the absolute difference in survival probability for death at 5 years was 0.5% between the adherent and nonadherent groups.

Conclusion. A low rate (less than 40%) of antihypertensive medication adherence existed in a statewide Medicaid population. Both ambulatory visits and antihypertensive medication adherence were associated with reduced mortality.

Increasing adherence to daily antihypertensive medications by 15% (1 extra pill per week) reduced the hazard of stroke by 8% to 9% and death by 7%.

Commentary

Numerous clinical trials show that a variety of hypertension medications reduce stroke and overall cardiovascular events. Fewer effectiveness studies in real-world settings document the impact of medication use on reducing cardiovascular events. While many studies have documented a relationship between adherence and intermediate outcomes such as blood pressure control [1], only a few previous studies show a relationship between adherence and major clinical outcomes [2,3].

This study sought to determine in a large administrative database whether medication adherence measured through claims data is associated with stroke and death in a population of Medicaid patients. The investigators found that low adherence is an important risk factor for major outcomes and death in patients with hypertension. Each 15% increase in adherence was associated with an 8% to 9% reduction in stroke and 7% reduction in hazard of death (number needed to treat [NNT] of 344 to prevent 1 death in 2.7 years). By comparison, the NNT for statin therapy to prevent 1 death in 5 years in patients with 2 or more cardiovascular risk factors is over 500 [4]. Based on their findings, the authors of this study estimate that over 200,000 lives could be saved in the United States over 5 years by increasing hypertension medication adherence to over 80%. Finally, the authors intriguingly found that increased ambulatory visits were associated with a small but statistically significant reduction in mortality for patients with hypertension, even after controlling for a wide variety of demographic, clinical, care utilization, and adherence variables. This finding is notable given that previous studies of chronic disease patients did not find a protective effect for ambulatory visits [5], though the work of Barbara Starfield and others has documented the population-level mortality benefits of regular access to a primary care physician [6].

A number of limitations to this study exist. First, the use of administrative claims data has inherent well-known limitations. Claims data are constructed for billing purposes, not research, and the lack of directly measured verifiable clinical data is a drawback. Second, the authors used a claims-based measure of adherence (MRA) that was not directly verifiable. The measure simply calculated the number of days for which a patient had a prescription refilled, not whether or not they actually took their medication or whether their blood pressure was affected. Nonetheless, this measure has been used widely in previous research studies with good effect. Third, the generalizability of the findings is limited by the fact that the time period of measurement was over a decade ago (hypertensive medication use has changed since then) and limited to 1 southern U.S. state (Tennessee). Finally, the use of multiple measures of comorbidity and medication adherence introduced the possibility of statistical collinearity in the multivariate models. Collinearity does not negate the main findings but can statistically dilute the strength of the associations, leading to a possible underestimation of the actual association.

Applications for Clinical Practice

Medication adherence, as measured through relatively straightforward and obtainable claims data, was associated with risk of stroke and death in a cohort of hypertensive patients enrolled in Medicaid. Given the significant associations between adherence and mortality or major cardiovascular outcomes, as well as frequent physician underestimation of patient adherence, what are potential interventions for measuring and improving adherence at the point of primary care? At least 3 interventions exist that can harness the potential of health information exchanges to improve adherence through real-time adherence data feedback [7]. Specifically, reporting medication adherence levels (MRA) through electronic health record dashboards at the point of care can help providers to identify and counsel nonadherent patients as well as uncover barriers to medication use. Second, use of nonphysician team members to track adherence through chronic disease registries, such as those used in the patient-centered medical home model, can enable population-based management of hypertensive patients with proactive staff outreach [8]. Third, computer-generated reminders can be sent directly to patients by mail or through personal health records online to promote improved adherence through increased patient engagement.

—Review by Asaf Bitton, MD, MPH

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