PREDICTORS AND CONSEQUENCES OF NONADHERENCE TO ANTIHYPERTENSIVE MEDICATION

by

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ABSTRACT OF THE DISSERTATION

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ABSTRACT

Context: Nonadherence to antihypertensive therapy attributes to uncontrolled blood pressure. This may worsen the severity of hypertension and ultimately increase health care costs. This underlines the importance of identifying predictors and consequences of nonadherence to antihypertensive therapy.

Objectives: (I) To empirically determine the length of gap between antihypertensive prescription refills that predicts long term prescription discontinuation. This gap can be used to define antihypertensive medication nonadherence. (II) To examine predictors of nonadherence and (III) To evaluate the role of nonadherence on rates of hospitalization and emergency room visits.

Design, settings and subjects: For Objectives I and II, retrospective cohort designs were employed on 51,615 subjects enrolled in a large United States pharmacy benefit manager during Jan 1st 2003 and May 31st 2006. Subjects were included if they had $\geq$ 2 prescriptions of antihypertensive medication, were new users and were $\geq$ 30

years. For Objective III, a cross-sectional design was employed on 9,945 subjects aged 30-64 years continuously enrolled in New Jersey Medicaid between Jan 1999 and Dec 2001. For Objective I, Receiver Operating Characteristics (ROC) analysis was performed using maximum gap in anti hypertensive therapy as a predictor of long term treatment discontinuation. For Objective II, time to nonadherence was analyzed with the use of Cox Proportional Hazard Regression model. For Objective III, Log-Linear Regression analysis was utilized to estimate the risk of health care utilization associated with nonadherence

Results: For Objective I, ROC analysis generated a C-statistic of 0.87. The cut-off value for maximum gap between refills that optimized sensitivity (0.81) and specificity (0.79) was 75 days. For Objective II, region of the country in which the subjects resided and subjects living in a census block with high percentage of African American population and low levels of income were found to be significant predictors of nonadherence. Subjects who were treated by cardiologists and younger physicians also had improved adherence. Objective III showed that subjects who were nonadherent to antihypertensive therapy had significantly higher rates of hospitalizations as well as emergency visits.

Conclusion: Timely corrective interventions to improve adherence will have significant impact on the cost-effectiveness in the treatment of hypertension.

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INTRODUCTION

Burden of the Disease: High blood pressure (HBP) is defined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥ 90 mm Hg. HBP is the most common primary diagnosis in physicians office in the United States (1) and about 1 in 3 American adults suffer from it (2). The direct costs (cost of physicians and other professionals, hospital and nursing home services, cost of medications, home health care and other medical durables) and indirect cost (lost productivity resulting from morbidity and mortality) of HBP in the United States for 2006 is estimated at $63.5 billion (1). The risk of cardiovascular disease, a major consequence of HBP, doubles with each increment of 20/10 mmHg in blood pressure (1). On the other hand, a 12- to 13-point reduction in HBP can reduce heart attack by 21%, stroke by 37% and all deaths from cardiovascular disease by 25% (3). These statistics highlight the importance of effective control of HBP.

Disparities: The prevalence of HBP in African Americans in the United States is among the highest in the world regardless of gender and educational status. Compared with whites, African Americans develop HBP earlier in life and average blood pressures among African Americans are much higher than whites even after accounting for the effect of age. As a result, HBP-related morbidity and mortality is higher in African Americans (4; 5). Research has shown that blood pressure control rate (an index that is related to the development of HBP-associated morbidity and mortality) varies with race/ethnicity. In the 1999-2000 NHANES data, rates of blood pressure control were lower in Mexican Americans (17.7 percent) compared with non-Hispanic (NH) whites (33.4 percent) and NH African Americans (28.1 percent) (6).

The occurrence of HBP has also been demonstrated to vary across age and gender. The prevalence of hypertension increases in a monotonic pattern with advancing age (6). Men are more likely than women to have HBP before the age 45. From ages 45–54, the percentage of women with HPB is slightly higher, and for age ≥55a much higher percentage of women have HBP than men (7).

The Southeastern part of the U.S. has witnessed the highest death rates from circulatory disease (8) and residents of the South experience the highest rates of hospitalization due to chronic heart failure and stroke, common sequelae of HBP (9). It has also been reported that Southern-born African-Americans had highest age-specific mortality rates from hypertension-related diseases and the mortality rates remained high even when Southern-born African-Americans migrated to other regions of the USA (10).

Treatment: Pharmacotherapy is the main treatment modality for HBP. According to the JNC 7 guidelines, for *uncomplicated hypertension* (i.e. *stage I hypertension* defined as systolic blood pressure of 140–159 or diastolic blood pressure of 90–99 mmHg and *stage II hypertension* defined as systolic blood pressure >160 or diastolic blood pressure >100 mmHg), thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes such as, angiotensin converting enzyme inhibitor (ACEI); angiotensin receptor blocker (ARB) ; beta blocker (BB); or calcium channel blocker (CCB). Compelling indications involve high-risk conditions that can be direct sequelae of hypertension (heart failure, ischemic heart disease, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes, high coronary disease risk). For compelling indications, two or more antihypertensive medications will be required to achieve targeted BP control of <140/90 mmHg. For

subjects with compelling indications such as diabetes and chronic kidney disease, the goal of BP control is even lower (<130/80 mmHg) (1).

Treatment nonadherence: Antihypertensive treatment effectiveness poses a much greater challenge than treatment efficacy that is achieved under controlled conditions (clinical trials). According to National Health and Nutrition Examination Survey (NHANES) 1999-2000 data, current blood pressure control rates of 36%, though an improvement over the previous decades, are still far below the Healthy People 2010 goal of 50% (6). The full benefit of medications that have been tested for their efficacy in clinical trials will be achieved only if subjects follow their prescribed treatment regimens reasonably closely (11). With an average estimated rate of about 50% (12-13) nonadherence has become a recognized public health problem.

Several methods have been suggested to study medication adherence behaviors ranging from patient and physician surveys to microprocessor-chip technologies on medicine containers (14). These techniques may prove to be useful for assessing compliance (how well a patient follows physician orders over a designated time frame). On the other hand, persistence (how long a patient remains on therapy) is better assessed by prescription refill patterns over a longer period of time. Pharmaceutical claims databases have become a common source of information to study persistence in recent years. While an analysis of prescription refill pattern over a longer period of time does not confirm the actual ingestion of a pill by a patient, it is realistic to assume that subjects would continue to refill with the intention to use the medication. However, measuring persistency with the use of refills records have gain popularity because it is reasonable and inexpensive way of obtaining information regarding adherence to prescribed

medication for a large group of subjects. Moreover, adherence measured without patient awareness increases accuracy of the estimates by eliminating recall bias and Hawthorne effect. Finally, adherence measured from claims databases has been shown to have a 75% to 85% concordance with patient self-reported compliance in a variety of therapeutic areas (15-21). Analysis of claims data can provide an estimate of adherence as the number of days on which the patient possesses an adequate supply of medication as that is the number of days upon which the patient would be able to comply with the treatment regimen (22). The amount of medication dispensed when the prescription is filled is expressed as the number of days supply; this is used to determine whether the patient has mediation available for use on any given day (23).

A recent review of medication compliance studies measuring refilling persistency identified the following three methods to characterize persistency when analyzing claims data (24): (i) Persistency as a Function of Medication Possession Ratio (MPR); this measure assesses the availability of medication (proportion of days covered) over multiple refill intervals. For antihypertensive medication, subjects with a predetermined cut-off value of 80% or more is usually classified as either persistent or nonpersistent (25-34). Others have analyzed MPR as a continuous variable (35). (ii) Persistency as a Function of Medication Availability at a Fixed Point in Time; this method measures medication possession at a single refill interval. This measure categorizes subjects as either persistent or non persistent often ignoring the timing and gaps between other refills in antihypertensive medication (36-39) and fails to capture information on large refill gaps and is unresponsive to changes in refill behavior, and (iii) Persistency as a Function of the Gaps between Refills; this measure quantifies the gaps between prescription refills

over multiple refill intervals and allows its use as a continuous or dichotomous measure. In this approach, grace period (permissible gap) is allowed for refill. The grace period starts at the end of supply of the previous prescription and this permissible period is arbitrarily determined by the investigator. The latter method has been considered superior than others because it has an advantage of identifying nonadherent subjects for intervention once they exceed the permissible gap. Moreover, with this approach, a time to event (survival) analysis can be used to study predictors and consequences of nonadherence (24).

While *persistency as a function of the gaps between refills* is considered a better approach to characterize nonadherence, numerous studies have examined treatment persistence using this method without the use of a uniform definition of permissible gap. Permissible gaps that are used in the literature are arbitrary and are solely based on the discretion of the investigator. Gap in these studies ranges from 15 -120 days; typically half to three times the duration of the preceding prescription (40-48). However, none of these studies have established empirically the validity of this cut-off value for determination of permissible gap. Establishing an appropriate length of the permissible gap is essential in studying persistency of antihypertensive medications in order to address this important public health problem.

Risk factors of nonadherence: A number of reports have identified predictors such as age, gender and antihypertensive drug class to be associated with nonadherence in subjects with hypertension (49-62). But there is limited data in the literature examining the association between socio-economic correlates and antihypertensive treatment nonadherence. Examination of additional predictors of nonadherence will further help

gather baseline information to target specific population subgroups that are at increased risk. Nonadherence may worsen disease severity, leading to increased utilization of medical care services (63-69) and therefore increase in overall health care costs. Evaluating the relationship between medication nonadherence and health care utilization becomes imperative in order to decrease economic burden associated with nonadherence This is perhaps more important for communities that disproportionately experience cardiovascular morbidity and mortality associated with HBP. All these factors merely underscore the need for research in this area.

Employer based pharmacy benefit data as well as data from Medicaid beneficiaries provide unique opportunities to study persistency as well as predictors and consequences of medication nonadherence because studies done with the use of these databases minimizes the role of access to medical insurance which is difficult to control in other settings. Therefore, the *broad goal* of the dissertation is to examine predictors of nonadherence to antihypertensive medication and to determine the impact of nonadherence to antihypertensive medications on rates of health services utilization after empirically determining a cut-off value between prescription refills to define treatment nonadherence.

Specific Objectives:

1. To empirically establish a gap between prescription refills among antihypertensive therapy users that predicts long term discontinuation.
2. To examine variations in the rates of antihypertensive medication adherence by characteristics of census block (% African Americans, income, adjusted for household size), region of the country, physician's characteristics (specialty, age and gender) and by type of drug dispensing (mail order vs. retail order).
3. To determine if nonadherence to antihypertensive medications is associated with higher use of health services in particular, hospitalizations and emergency room visits.

The 3 Objectives are addressed herein as in the form of 3 papers to follow.

REFERENCES

1. Chobanian AV, Bakris GL, African American HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003; 289:2560-72.
2. American Heart Association. Heart Disease and Stroke Statistics – 2006 Update. Dallas, Texas: American Heart Association; 2006. Available at: http://www.americanheart.org. Accessed May 10, 2006
3. The Centers for Disease Control and Prevention, 2006. Available at: http://www.cdc.gov/DHDSP/library/moving_into_action/science.htm. Accessed June 2, 2006
4. Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, et al. 2000. Trends and disparities in coronary heart disease, stroke and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 102:3137–3147.
5. Williams DR. 1999. Race, socioeconomic status and health. Ann NY Acad Sci. 896:173–188.
6. Hajjar I, Kotchen TA.Trends in Prevalence, Awareness, Treatment, and Control of hypertension in the United States, 1988-2000 JAMA 2003; 290:199-206.
7. Health, United States, 2005, CDC/NCHS. Available at http://www.cdc.gov/nchs/data/hus/hus05.pdf . Accessed May 19, 2006
8. Cooper ES. Cardiovascular diseases and stroke in African Americans: a call for action. J Natl Med Assoc. 1993; 85:97-100.
9. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. Circulation. 2005 15; 111:1233-41.
10. Schneider D, Greenberg MR, Lu LL. Region of birth and mortality from circulatory diseases among African American Americans. Am J Public Health. 1997; 87:800-4.
11. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353:487-97.
12. Nichol MB, Venturini F, Sung JCY. A critical evaluation of the methodology of the literature on medication compliance. *Ann Pharmacother*.1999; 33:531–540.
13. Schlenk EA, Burke LE, Rand C. Behavioral strategies to improve medication-taking compliance. In: Burke LE, Ockene IS, eds. *Compliancein Healthcare and Research*. Armonk, NY: Futura Publishing Co; 2001:57–70.
14. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989; 261: 3273-3277.
15. Erickson SR, Coombs JH, Kirking DM, Azimi AR.Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother*. 2001; 35:997-1003.
16. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*.1997; 50(5): 619–625.
17. Heerdink ER, Leufkens HG, Koppedraaijer C, Bakker A. Information on drug use in the elderly: a comparison of pharmacy, general-practitioner and patient data. *Pharm World Sci* 1995; 17(1): 20–24.

18. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. J *Am Geriatr Soc* 1991; 39(11): 1079–1084.
19. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. *Pharm World Sci* 1999; 21(5): 217–220.
20. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. *Br J Clin Pharmacol* 1998; 45(6): 591–595.
21. Curtis JR, Westfall AO, Allison J, Freeman A, Kovac SH, Saag KG. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users. *Pharmacoepidemiol Drug Saf.* 2006 Oct;
22. Dezii CM.Persistence with drug therapy: a practical approach using administrative claims data. Manag Care. 2001; 10:42-5.
23. Day D.Use of pharmacy claims databases to determine rates of medication adherence. Adv Ther. 2003; 20:164-76.
24. Sikka R, Xia F, Aubert RE. Estimating Medication Persistency Using Administrative Claims Data. *Am J Manag Care* 2005; 11: 449-457.
25. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. *Am J Public Health*. 1996; 86:1805-8.
26. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. Am J Hypertens. 1997;10: 697-704.
27. Rizzo JA, Simons WR.Variations in compliance among hypertensive patients by drug class: implications for health care costs. Clin Ther.1997; 19:1446-57
28. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo JP. Assessing compliance to antihypertensive medications using computer-based pharmacy records. Med Care. 1997; 35:1164-70.
29. Okano GJ, Rascati KL, Wilson JP, Remund DD, Grabenstein JD, Brixner DI. Patterns of antihypertensive use among patients in the US Department of Defense database initially prescribed an angiotensin-converting enzyme inhibitor or calcium channel blocker. Clin Ther. 1997; 19:1433-45.
30. Ren XS, Kazis LE, Lee A, Zhang H, Miller DR Identifying patient and physician characteristics that affect compliance with antihypertensive medications. J Clin Pharm Ther. 2002; 27:47-56.
31. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. The association between compliance with antihypertensive drugs and modification of antihypertensive drug regimen. J Hypertens. 2004; 22:1831-7.
32. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J.Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med. 2002; 17:504-11.
33. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005 23; 165:1147-52.

34. Poluzzi E, Strahinja P, Vargiu A, Chiabrando G, Silvani MC, Motola D, et al.Initial treatment of hypertension and adherence to therapy in general practice in Italy. Eur J Clin Pharmacol. 2005 ;61:603-9
35. Roe CM, Motheral BR, Teitelbaum F, Rich MW Angiotensin-converting enzyme inhibitor compliance and dosing among patients with heart failure. Am Heart J. 1999; 138:818-25.
36. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther. 1998; 20:671-81.
37. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ. 1999; 160:41-6.
38. Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ.Four-Year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other artihypertensive drug classes. Clin Ther. 2001; 23:1999-2010.
39. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. Am Heart J. 2006; 151:185-91.
40. Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. *Can J Cardiol* 2000; 16: 1109-1117.
41. Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens*. 2002; 16:569-75.
42. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J Manag Care Pharm*. 2003; 9:424-9.
43. Perreault S, Lamarre D, Blais L, Dragomir A, Berbiche D, Lalonde L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Ann Pharmacother*. 2005; 39:1401-8.
44. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF, Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. *Pharmacoepidemiol Drug Saf.* 2005; 14:795-803.
45. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. *J Hypertens*. 2005; 23:2093-100.
46. Bourgault C, Senecal M, Brisson M, Marentette MA, Gregoire JP. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. *J Hum Hypertens.* 2005 Aug;19(8):607-13,
47. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG.Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *J Hypertens*. 2006 Jun; 24(6):1021-2.
48. Morgan SG, Yan L. Persistence with hypertension treatment among community-dwelling BC seniors. *Can J Clin Pharmacol*. 2004 Fall; 11(2):e267-73.
49. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. *Am J Public Health*. 1996; 86:1805-8.
50. Balkrishnan R. Predictors of medication adherence in the elderly. *Clinical Therapeutics*. (1998) 20: 764-71.

51. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *J Natl Med Assoc.* 2003 Jan; 95:17-27.
52. Degli Esposti E, Sturani A, Di Martino M, Falasca P, NoviMV, Baio G, et al. Long-term persistence with antihypertensive drugs in new patients. J Hum Hypertens 2002; 16: 439–444.
53. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. Am J Hypertens 1997; 10:697–704.
54. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med. 2007 Jan; 120(1):26-32.
55. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ 1999; 160: 41–46.
56. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther*. 1998; 20:671-81.
57. Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clin Ther.*1997; 19:1446-1457.
58. Fletcher AE, Bulpitt CJ, Chase DM, et al. Quality of life with three antihypertensive treatments-cilazapril, atenolol, nifedipine. *Hypertension.* 1992; 19:499-507.
59. Bulpitt CJ, Connor M, Schulte M, Fletcher AE. Bisoprolol and nifedipine retard in elderly hypertensive patients: effect on quality of life. *J Hum Hypertens.* 2000; 14:205-212.
60. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. *Can J Cardiol*. 2002 Jun; 18:649-56.
61. Juncos L. Patient compliance and angiotensin converting enzyme inhibitors in hypertension. *J Cardiovasc Pharmacol*. 1990; 15:S22-S25.
62. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med*. 2005 May 23; 165(10):1147-52.
63. Sclar DA, Skaer TL, Chin A, Okamoto MP, Gill MA. Utility of a transdermal delivery system for antihypertensive therapy. Part 2. *Am J Med.* 1991; 91:57S-60S.
64. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA. Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clin Ther.* 1991; 13:489-495.
65. Skaer TL, Sclar DA, Robison LM, Markowski DJ, Won JK.Effect of pharmaceutical formulation for diltiazem on health care expenditures for hypertension. *Clin Ther.* 1993 Sep-Oct; 15(5):905-11.
66. Schlenk EA, Burke LE, Rand C. Behavioral strategies to improve medication-taking compliance. In: Burke LE, Ockene IS, eds. *Compliance in Healthcare and Research*. Armonk, NY: Futura Publishing Co; 2001:57–70.
67. Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *Am J Med*. 1997; 102:43– 49.
68. Skaer TL, Sclar DA, Robison LM, Chin A, Gill MA, Okamoto MP, Nakahiro RK.Effect of pharmaceutical formulation for antihypertensive therapy on health service utilization. *Clin The*r. 1993 Jul-Aug;15(4):715-25

69. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005 Jun; 43(6):521-30.

LENGTH OF GAP IN PRESCRIPTION REFILLS THAT PREDICTS LONG-TERM TREATMENT DISCONTINUATION AMONG HYPERTENSIVE SUBJECTS

by

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ABSTRACT OF MANUSCRIPT 1 OF 3

LENGTH OF GAP IN PRESCRIPTION REFILLS THAT PREDICTS LONG-TERM TREATMENT DISCONTINUATION AMONG HYPERTENSIVE SUBJECTS

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ABSTRACT

Context: Numerous studies have examined treatment persistence using persistency as a function of the gaps between refills method, without a uniform definition of permissible gap. Standardization of the definition of permissible gap is essential because this nonuniform definition makes comparison of study results across different settings virtually impossible.

Objective: The aim of this study was to determine an empirically derived cut-off value between anti hypertensive prescription refills that predicts long-term discontinuation.

Design, settings and subjects : A retrospective cohort study of newly diagnosed hypertensive subjects aged $\geq$30 years during the period between Jan 1st 2003 to May 31st 2006 was conducted using a large pharmacy benefit manager database in the United States. Descriptive analysis was used to characterize the study population. Receiver Operating Characteristics (ROC) analysis was performed using maximum gap in therapy as a predictor of treatment discontinuation (binary outcome). The C-statistic which is

analogous to area under the curve was used to compare overall performance of the ROC model.

Main Outcome Measure: The outcome of the study was discontinuation of antihypertensive therapy. A subject was defined to have discontinued if there were no prescription claims during an entire 6-month follow-up period for any of the antihypertensive drug classes under study.

Results: For this study 51,615 subjects with 477,820 pharmacy records were analyzed. ROC analysis of maximum prescription gap in antihypertensive therapy during the observation period predicting treatment discontinuation generated a C-statistic (area under the curve) of 0.87. The cut-off value for maximum gap between refills that optimized sensitivity and specificity was calculated to be 75 days. Sensitivity and specificity for this cut-off were estimated to be 0.81 and 0.79 respectively.

Conclusions: Subjects who had medication supply gaps of $\geq$75 days were more likely to discontinue their treatment long term. This 75 days treatment gap can be used to define permissible gaps in antihypertensive therapy users. This methodology can also be used to determine cut-off value of permissible gap for other chronic conditions. A standard definition of persistency obtained this way will permit comparisons of studies across different settings.

LENGTH OF GAP IN PRESCRIPTION REFILLS THAT PREDICTS LONG-TERM TREATMENT DISCONTINUATION AMONG HYPERTENSIVE SUBJECTS

Introduction:

Medication adherence is taking medications correctly and on time, i.e. subjects follow mutually agreeable instructions prescribed by a healthcare provider (1). There are various ways of measuring medication adherence including, electronic monitoring, determination of serum drug levels and assessment of physiologic drug effects. These methods are often difficult to use because they are not only expensive but also require time and effort. This is especially true for pharmacoepidemiologic studies that often entail large study populations. For these studies, pharmaceutical claims databases are relatively easy and inexpensive resource as they can provide otherwise unobtainable information about the pattern and timing of drug exposure (2). Moreover, studies that have attempted to validate adherence measured from pharmacy refill records have found 75% to 90% concordance with patient self-reported adherence in a variety of therapeutic areas; making them a reliable alternative to measure compliance (3-9).

Persistency has been defined as a method of assessing medication adherence for subjects on chronic therapy by capturing the number of days they fail to fill their prescriptions during an observation period (10-14). The literature has not been consistent in the definition of persistency. As a result, direct comparisons among persistency studies have been difficult. Sclar and colleagues (1991) provided the first uniform methodology and definition for estimating persistency using pharmacy claims data (15-16). Later Steiner et al. (1997) developed a typology of methods for assessing refill

adherence (persistency) (1). Recently, Sikka and his associates reviewed the literature in detail and suggested three methods of measuring adherence (17). (i) Persistency as a function of the medication possession ratio: defined as the sum of the days of supply of medication, divided by number of days between the first fill and the last refill, including the duration of the last refill (proportion of days covered). Common cut-off for classifying a subject as persistent is $\geq$80% medication possession ratio (MPR). (ii) Persistency as a function of medication availability at a fixed point in time: in this method, a subject is defined as persistent if he/she has a current prescription on a prespecified date, for example, one year after the initial prescription. (iii) Persistency as a function of the gap between refills: in this approach, permissible gap that starts at the end of supply of the previous prescription is allowed between refills. A subject is considered to be persistent with therapy at all times until he/she exceeds the permissible gap.

Sikka and associates identified some of the weaknesses of using the MPR and persistency as a function of medication availability at a fixed point of time method (17). The MPR method fails to provide information on the timeliness and consistency of refilling. Moreover, since MPR is a proportion, it is largely dependent on the denominator (number of days observed) and subjects with shorter lengths of follow-up are more likely than those with longer lengths of follow-up to have high persistency. Persistency as a function of medication availability at a fixed point in time eliminates important periods of stoppage of therapy and gives same credit to individuals who take medications regularly for longer periods of time with that of individuals who may have stopped for prolonged periods. On the other hand, the method of persistency as a function of the gaps between refills has the advantage of identifying nonadherent subjects

for intervention once they exceed the permissible gap. Moreover, with this approach, a time to event (survival) analysis can be used to study predictors and consequences of nonadherence.

Numerous studies have examined treatment persistence using persistency as a function of the gaps between refills without a uniform definition of permissible gap. For e.g., the allowable gap for hypertension ranges from 15 -120 days; gaps often ranging from half to three times the duration of the previous prescription (18-26). However, none of these studies have empirically established the validity of these cut-off values for determination of permissible gap. Standardization of the definition of permissible gap is essential because this nonuniform definition makes comparison of study results across different settings very difficult.

Using a large pharmaceutical claims database in the United States that included subjects on antihypertensive therapy, the aim of this study was to determine a cutoff value between prescription refills that could be used to define permissible gaps in therapy. It was hypothesized that identification of maximum number of days that subjects remain without antihypertensive therapy during an observation period that corresponds to long term discontinuation in subsequent follow-up, will be one way to establish an empirically derived permissible gap between prescription refills. The findings will contribute to methods of measurements of persistency in the literature and help inform interventions to reduce the burden of disease in the population.

Materials and Methods

Data source: The data used for this study is from a de-identified pharmacy claims database of a large pharmacy benefits manager in the US providing benefits for more than 55 million lives. The database represents a stratified random sample of 2.5 million plan participants that were continuously eligible from 1st Jan 2003 to 31st Dec 2004 (please see *appendix* for more information regarding the construction of this sample). The sample was constructed by proportionally sampling on strata of age, sex and geographic region. Region was defined using the 9 geographic regions described by the Census Bureau (see *appendix*) (27). Please see Figure 1 for subject selection flowchart for this study.

Study design: For this study, a retrospective cohort design was employed.

Study subjects: The initial sample of 2.5 million subjects was continuously eligible for 24 months. In order to have sufficient observation and follow-up time, additional 17 months of continuously eligibility was extended to these subjects. Therefore, a continuously eligible subject's information for 41 months between Jan 1st 2003 to May 31st 2006 was obtained. This reduced the sample size from 2.5 million to 1.2 million (Figure 1). A final inclusion criteria of retaining only new users of antihypertensive therapy subjects $\geq$30 years, who had at least two prescriptions of antihypertensive medications yielded a sample size of 51,615 for the analysis (Figure 1). Existing users were excluded from the analysis because may represent a group of subjects that are already adherent to antihypertensive medication.

Measurements: During the study period, four non overlapping measurement calendar periods were defined (Figure 2): (i) Targeting period; (ii) Look back period; (iii)

Observation period; and (iv) Follow-up period. The *targeting period* runs for 12 months from July 1st 2003 to June 30th 2004 and was primarily used to identify the index prescription date of each subject. The *look back period* starts on the index prescription date and goes back 6 months. This period served to identify subjects new to therapy. Subjects that had no claims of any antihypertensive drugs during the entire 6 months prior to the index prescription date were designated as subjects who were new to therapy (new users) and were retained in the analysis. These subjects formed the cohort and observed for subsequent 1 year period (o*bservation period*) starting from the index prescription date. The refilling behavior of each subject was determined during this observation period. Finally, a *follow-up period* that runs for 6 months subsequent to the end of the observation period of each subject was determined. This period was used to establish whether or not a subject discontinued his/her antihypertensive therapy.

Outcome variable: The outcome of the study was discontinuation of antihypertensive therapy during the follow-up period. A subject was considered to have discontinued if there were no prescription claims during the entire 6-month follow-up period for any of the antihypertensive drug classes under study.

Explanatory variable: The predictor variable for treatment discontinuation was the largest number of days without antihypertensive medication (maximum refill gap) during the 1 year observation period. Maximum gap was determined by first establishing an observation period for each subject in the study cohort. The period from start date (index date) to an end date (365 days from the index date) formed the observation period. Refill information of more than 12-months was truncated at the end date for all subjects. Length of gap between each prescription refills was then determined with the use of 'new

service date' and 'end of supply of the previous refill' variables between medication claims in the observation period. A gap was defined as absence of prescription claims for any of the antihypertensive drug classes under study. Length of maximum gap during the 1 year observation period was measured as a continuous variable and used as a predictor for this analysis. For the purpose of this analysis change in medication class did not constitute a treatment gap as long as a patient continues to refill an antihypertensive medication.

Other variables: Patient's age, gender, antihypertensive drug class, method of drug dispensing (mail order pharmacy versus retail order pharmacy), drug type (generic drug, single source brand drug or multi source brand drug) and regions of the United States during the initiation of antihypertensive therapy were other variables examined. Age was categorized into 12 non overlapping categories from 30 to 85+ with 5 year increments. The drug classes include thiazide diuretics; angiotensin converting enzyme inhibitor; angiotensin receptor blocker; beta blocker; calcium channel blocker; combination therapy (two or more monotherapy in conjunction) and miscellaneous antihypertensives (alpha/beta adrenergic blocking agents, loop and potassium sparing diuretics etc).

Statistical analysis: Descriptive analysis was used to characterize the study population. Receiver Operating Characteristics (ROC) analysis was performed using maximum gap in therapy as a predictor of treatment discontinuation (binary outcome). The C-statistic which is analogous to the area under the curve was used to compare overall performances of the ROC model (28). The Maximum gap cut point that minimizes misclassification error (false positive and false negative) was then determined

to predict long-term discontinuation of antihypertensive drugs. The study was approved by the Institutional Review Board of the University of Medicine and Dentistry at New Jersey. All the statistical analyses were performed using SAS for Windows, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina).

Results:

A total of 51,615 subjects who were new to antihypertensive therapy were examined in the analysis. Table 1 displays the characteristics of the study population during treatment initiation. Study subjects had a mean age of 56.6 years (SD 13.4; median 55 years) and were slightly more likely to be female. Approximately 54% of the population was between the age ranges of 45-65 years. Angiotensin converting enzyme inhibitors were the most commonly prescribed initial antihypertensive agent followed by beta blockers and diuretics. About 19% of subjects had filled a mail order prescription during treatment initiation and approximately half of the subjects filled a generic antihypertensive medication. Subjects residing in the Middle and South Atlantic regions of the US had larger representation in the study sample.

During the 6 months follow up period, 9,396 (18%) subjects discontinued antihypertensive therapy. Table 2 shows the proportion of subjects who discontinued therapy according to patient characteristics at therapy initiation. Discontinuation was most commonly observed in the age group between 30-45 years (23-31%). Subjects who started on angiotensin converting enzyme inhibitors or angiotensin receptor blockers were less likely to discontinue after a year on therapy than on other antihypertensive monotherapies such as beta blockers, calcium channel blockers and diuretics. About 10%

of subjects started on more than one course of antihypertensive drug class on their index prescription date (multiple scripts). These subjects had the lowest rate of discontinuation among all antihypertensive prescriptions users. Mail pharmacy users were less likely to discontinue to antihypertensive therapy.

ROC analysis of maximum prescription gap in antihypertensive therapy during the observation period predicting treatment discontinuation generated a C-statistic (area under the curve) of 0.87 (Figure 3). The cut-off value for maximum gap between refills that optimized sensitivity and specificity was computed to be 75 days. Sensitivity and specificity for this cut-off were estimated to be 0.81 and 0.79.

Discussion:

Subjects who remain without filling their prescription for >75 days are more likely to discontinue their treatment long term. This paper contributes to methods of measurements of persistency as this is the first study establishing empirical cut-points for gaps in therapy of antihypertensive prescription refills that predicts long-term prescription treatment discontinuation. The 75 days treatment gap can be used to define permissible gaps in antihypertensive therapy users. This empirically derived cut-off value of prescription gap between refills will enhance the standardization of persistency antihypertensive medication users and will permit comparison of studies on persistency across different settings.

Discontinuation was defined as absence of any prescription of antihypertensive therapy during a 6-month follow-up period following the completion of 1 year

observation from initiation of therapy. This 6 months follow-up period was based on clinical trial findings that have shown that the benefit of antihypertensive treatment on morbidity (myocardial infarction, congestive heart failure, stroke, transient ischemic attacks etc.) and mortality of hypertension begins as early as six months to one year post randomization (29-37). A sensitivity analysis was performed by extending the follow up period from 6 months to 11 months (maximum additional available data on all subjects) for definition of the outcome (discontinuation) but did not find any difference in the maximum gap cut-off point.

Maximum gap during the observation period was selected as predictor of long term discontinuation after considering other gaps such as mean gap, median gap and total gap. In order to calculate these other gap measures each subject would have to be followed for an entire observation period which would not be feasible in the real world. Moreover, when these measures were used as predictors of long term discontinuation the C-statistics was low except for total gap (see *appendix* for ROC curves using these measures as predictors of discontinuation, respectively). Maximum gap was the only single measure of observation that could be easily identified and targeted for consulting.

For this study 51,615 subjects with 477,820 pharmacy records were analyzed. Although it would be premature to generalize the study findings to other chronic conditions that require long term treatment, a preliminary analysis on a population on oral hypoglycemic drugs (diabetics) produced similar findings, suggesting that the study findings may be generalizable (38). This study has important clinical and public health implications. With the wealth of data on large number of subjects that pharmacy benefit

managers serve, the findings of this study can be used to create 'disease management programs' that can notify health care providers when subjects are nonadherent. Targeting nonadherent subjects will not only help to improve patient outcomes but might contain medical costs that are attributable to uncontrolled hypertension.

In order to determine the final gap cut-off value between prescription refills, a number of possible values for maximum gap in therapy derived from the ROC curve was considered: (i) 90 days (sensitivity=.76; specificity =.83). (ii) 75 days (sensitivity=.81; specificity =.79). This gap cut point had similar sensitivity and specificity. (iii) 50 days (sensitivity= .87; specificity =.70). This cut-off gave a high sensitivity but a lower specificity (increased the false positive rates). (iv) 30 days (sensitivity= .92; specificity =.57). This cut-off gave further increased the sensitivity but at the expense of lowering specificity. A gap such as (v) 15 days (sensitivity=.95; specificity =.50) has 50% false positive rate. Establishing a cut-off value which has higher false positive rates (low specificity) will require unnecessary resource utilization in subjects who are actually adherent to therapy. As a result, a gap that minimized the overall number of misclassification errors (false positives as well as false negative) appeared to be the best choice for defining cut-off value for maximum gap. The gap that optimized both sensitivity and specificity to predict for long-term treatment discontinuation was estimated to be 75 days. This gap was used as final cut-off value for defining permissible gap in antihypertensive therapy.

On the basis of the study findings, studies that have used shorter permissible gap (i.e. <75 days) in the literature for antihypertensive medication users provide a stricter

definition of persistency and decreases the number of individuals classified as persistent (overestimation of non persistence), whereas studies with permissible gap of ≥75 days provides a less stringent definition and increases the number of individuals classified as persistent (underestimation of non persistence).

The study has several limitations. First, filling of antihypertensive prescription does not translate into consumption of medication. Additionally, patients were considered to be on therapy as long as they were continuing to take any class of antihypertensive medication between refills. Based on these two assumptions, 75 day permissible gap cut-point could be conservative and people in the real world may even have greater gaps than what is described in this paper. Secondly, early prescription refills (drug stockpiling) were also seen in this database. Adjustments on refill gap were made by decreasing the length of subsequent gaps (credit for stockpiling) if a subject stockpiles an antihypertensive prescription which has the same National Drug Code (NDC) as the previous antihypertensive script. This approach assumed that as long as the NDC of the two prescriptions are the same, the stockpiling was done to consume those dosages at some point in time. However, a vast majority of subjects did not get recognition for their stockpiling behavior because of this strict criterion. Finally, it was not possible to distinguish subjects who discontinue their drug on a prescriber's advice. Though the number is likely to be very small, this may have lead to misclassification of subjects who were classified as discontinued in this study. It is however noteworthy, that the study has many strengths. It is a large population based study and the data is complete and accurate. There is avoidance of recall bias and Hawthorne effect that occurs when adherence is measured by patient's self reports.

In conclusion, 75 days of complete absence of therapy is the empirically derived cut-off value that will define non-persistence among antihypertensive subjects. An uniform definition of permissible gap will not only standardize the way adherence is determined, but will also enable comparisons of study findings across different setting possible. Furthermore, this methodology can be borrowed to determine permissible gap cut-off point for other chronic conditions and allow a standard definition of nonadherence as well.

REFERENCES

1. Cramer JA. Effect of partial compliance on cardiovascular medication effectiveness. *Heart*. 2002 Aug; 88(2):203-6.
2. Steiner JF, Prochazka AVThe assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997 Jan; 50(1):105-16.
3. Erickson SR, Coombs JH, Kirking DM, Azimi AR.Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother.* 2001; 35:997-1003.
4. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*.1997; 50(5): 619–625.
5. Heerdink ER, Leufkens HG, Koppedraaijer C, Bakker A. Information on drug use in the elderly: a comparison of pharmacy, general-practitioner and patient data. *Pharm World Sci* 1995; 17(1): 20–24.
6. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. J *Am Geriatr Soc* 1991; 39(11): 1079–1084.
7. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. *Pharm World Sci* 1999; 21(5): 217–220.
8. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. *Br J Clin Pharmacol* 1998; 45(6): 591–595.
9. Curtis JR, Westfall AO, Allison J, Freeman A, Kovac SH, Saag KG. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users. *Pharmacoepidemiol Drug Saf.* 2006 Oct; 15(10):710-8.
10. Urquhart J. Some economic consequences of noncompliance. *Curr HypertensRep.* 2001; 3:473-480.17. Dezii CM. Persistency with drug therapy: a practical approach using administrative claims data. *Manag Care.* 2001; 10(2):42-45.
11. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Longterm persistence in use of statin therapy in elderly patients. *JAMA.* 2002; 288:455-461.
12. Gerth WC. Compliance and persistence with newer antihypertensive agents. *Curr Hypertens Rep.* 2002; 4:424-433.
13. Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther.* 2003; 25:2307-2335.
14. Dezii CM. Persistency with drug therapy: a practical approach using administrative claims data. *Manag Care.* 2001; 10(2):42-45.
15. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA. Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clin Ther.* 1991; 13:489-495.
16. Sclar DA, Skaer TL, Chin A, Okamoto MP, Gill MA. Utility of a transdermal delivery system for antihypertensive therapy. Part 2. *Am J Med.* 1991; 91:57S-60S.
17. Sikka R, Xia F, Aubert RE. Estimating Medication Persistency Using Administrative Claims Data. *Am J Manag Care* 2005; 11: 449-457.
18. Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. *Can J Cardiol* 2000; 16: 1109-1117.

19. Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens*. 2002; 16:569-75.
20. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J Manag Care Pharm*. 2003; 9:424-9.
21. Perreault S, Lamarre D, Blais L, Dragomir A, Berbiche D, Lalonde L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Ann Pharmacother*. 2005; 39:1401-8.
22. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF, Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. *Pharmacoepidemiol Drug Saf*. 2005; 14:795-803.
23. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. *J Hypertens*. 2005; 23:2093-100.
24. Bourgault C, Senecal M, Brisson M, Marentette MA, Gregoire JP. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. *J Hum Hypertens.* 2005 Aug;19(8):607-13,
25. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG.Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *J Hypertens*. 2006 Jun; 24(6):1021-2.
26. Morgan SG, Yan L. Persistence with hypertension treatment among community-dwelling BC seniors. *Can J Clin Pharmacol*. 2004 Fall; 11(2):e267-73.
27. United States Census Bureau. Available at http://www.census.gov/geo/www/us_regdiv.pdf. Assessed on 19th June 2006.
28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristics (ROC) curve. *Radiology*. 1982; 143:29–36.
29. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F. Mortality and morbidity results from the European Working Party on High BloodPressure in the Elderly trial. *Lancet*. 1985; 1:1349–1354.
30. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA*. 1979; 242:2562–2571.
31. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program, II: mortality by race-sex and age. *JAMA*. 1979; 242:2572–2577.
32. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program, III: reduction in stroke incidence among persons with high blood pressure. *JAMA*. 1982; 247:633–638.
33. The effect of treatment on mortality in “mild” hypertension: results of the Hypertension Detection and Follow-up Program. *N Engl J Med*. 1982; 307:976–980.
34. Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA*. 1974; 229:409–418.

35. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992; 304:405–412.
36. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA*. 1967; 202:1028–1034.
37. Effects of treatment on morbidity in hypertension, II: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA*. 1970; 213:1143–1152.
38. Sikka R, Levin RJ, Aubert RE. "Predicting Diabetes Medication Discontinuation from Pharmacy Claims Data". American Diabetes Association 64th Annual Meeting and Scientific Sessions. Orlando, June 4-8, 2004.

Figure 1: Study selection flowchart

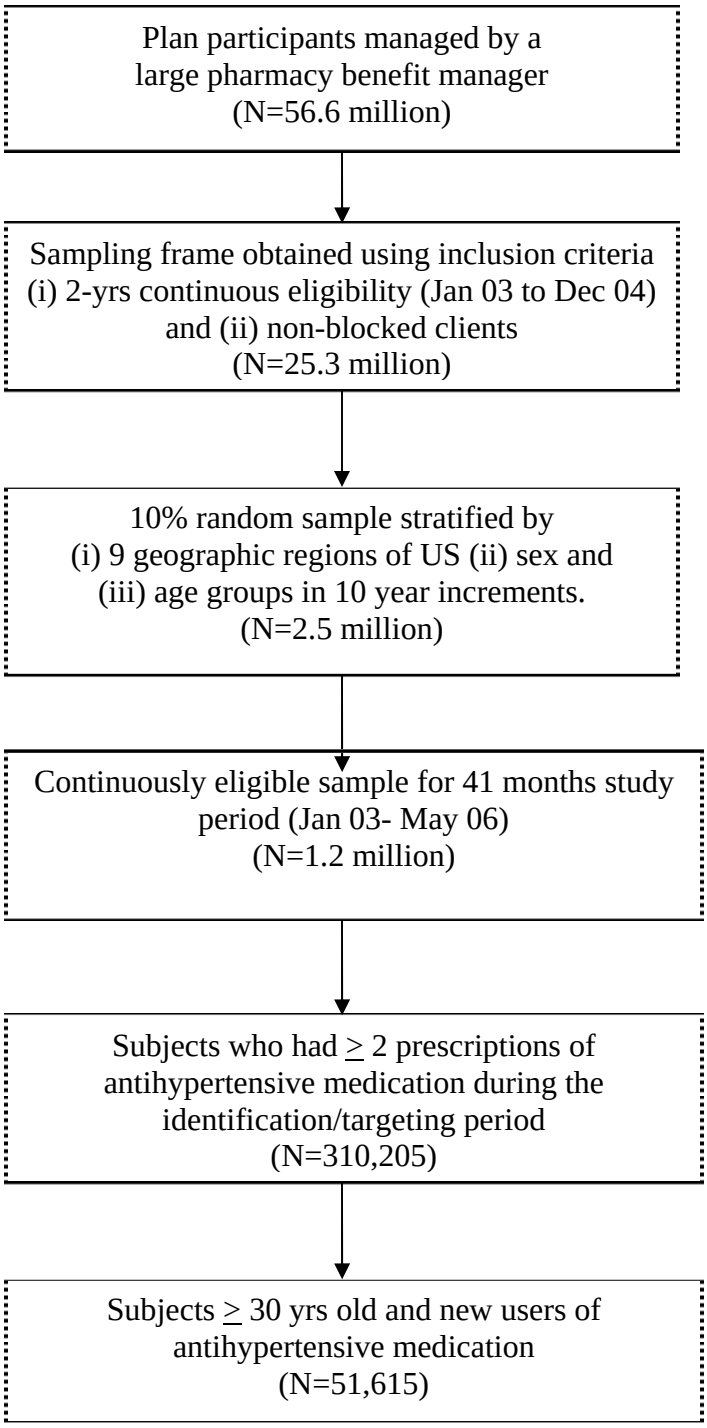


Fig 2: Definitions of measurements during the study period.

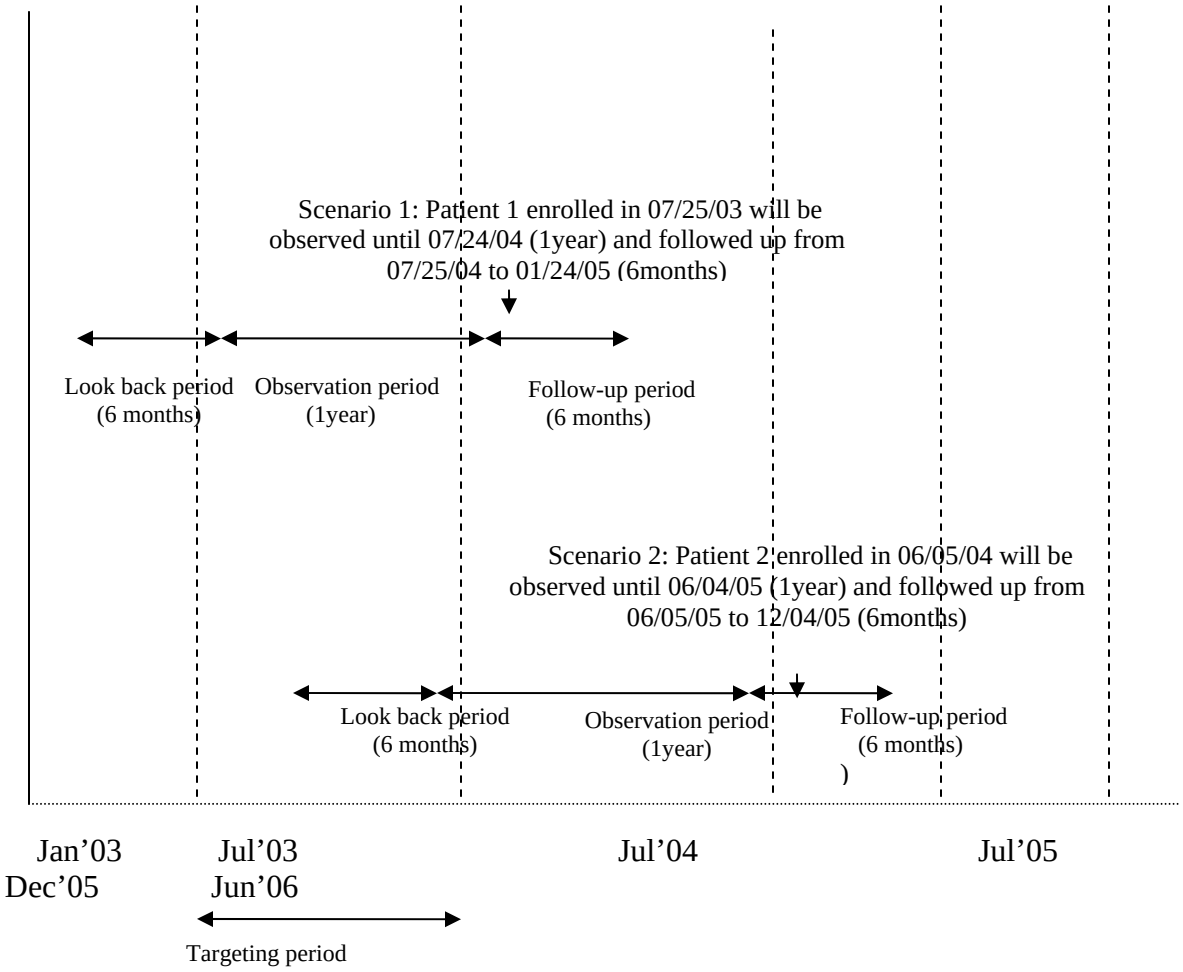


Table1: Descriptive characteristics of the study population at initiation of therapy: Large Pharmacy Benefit Manager Database, United States (N=51,615), 2003-2005

Characteristics	%
Age (yrs)	
30-34	3.47
35-39	5.87
40-44	9.66
45-49	13.6
50-54	15.35
55-59	14.76
60-64	10.34
65-69	7.55
70-74	7.16
75-79	6.05
80-84	4.0
≥85	2.17
Gender	
Female	52.5
Anti Hypertensive Drug Classes	
Diuretics	14.55
Angiotensin Converting Enzyme Inhibitor	21.08
Beta Blocker	18.29
Calcium Channel Blocker	8.20
Angiotensin Receptor Antagonists	14.13
Combined Pill	8.91
Combination Therapy*	10.26
Other Anti Hypertensive Therapy**	4.60
Method of Drug Dispensing	
Retail Order Pharmacy	81.12
Mail Order Pharmacy	18.88
Nine Regions of United States	
East North Central	14.75
East South Central	5.71
Middle Atlantic	18.25
Mountain	5.42
New England	3.5
Pacific	10.24
South Atlantic	22.48
West North Central	5.27
West South Central	14.36

* Combination therapy: (two or more monotherapy in conjunction)

**Other antihypertensive therapy: Alpha/beta adrenergic blocking agents, loop/potassium Sparing diuretics etc.

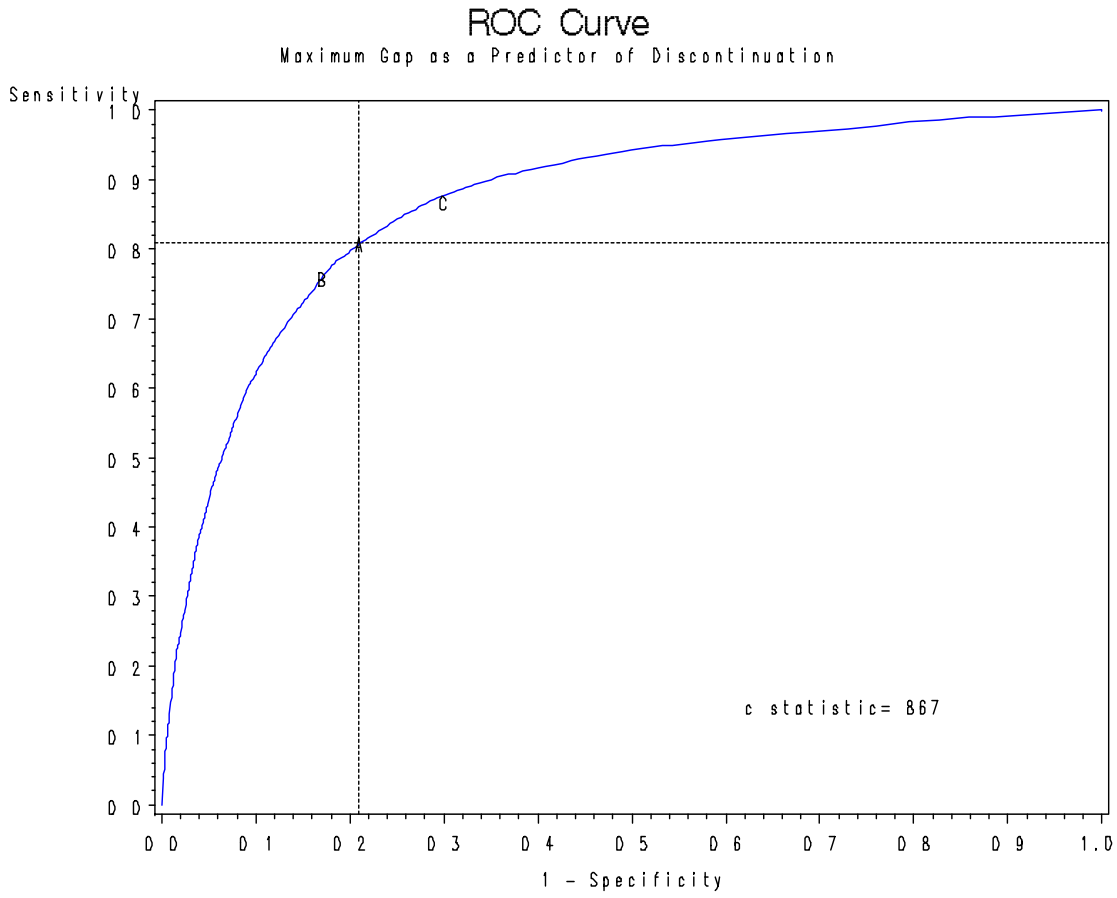
Table 2: Percent discontinued to antihypertensive therapy according to subject characteristics: Large Pharmacy Benefit Manager Database, United States (N=51,615), 2003-2005

Characteristics	% discontinued (N=9,396)
Age (yrs)	
30-34	31.30
35-39	25.66
40-44	22.94
45-49	19.59
50-54	17.95
55-59	15.18
60-64	14.14
65-69	14.45
70-74	14.70
75-79	16.70
80-84	18.11
≥85	18.09
Gender	
Female	18.58
Male	17.79
Anti Hypertensive Drug Classes	
Diuretics	26.21
Angiotensin Converting Enzyme Inhibitor	15.20
Beta Blocker	19.73
Calcium Channel Blocker	18.65
Angiotensin Receptor Antagonists	13.16
Combined Pill*	20.19
Combination Therapy**	12.41
Other Anti Hypertensive Therapy	21.89
Method of Drug Dispensing	
Retail Order Pharmacy	21.48
Mail Order Pharmacy	11.55
Nine Regions	
East North Central	17.90
East South Central	18.45
Middle Atlantic	18.07
Mountain	18.39
New England	16.44
Pacific	17.84
South Atlantic	18.75
West North Central	16.69
West South Central	18.91

* Combination therapy: (two or more monotherapy in conjunction)

**Other antihypertensive therapy: Alpha/beta adrenergic blocking agents, loop/potassium Sparing diuretics, etc.

Fig 3: Receiver operating characteristics curve of maximum gap as predictor of long term discontinuation (C statistic= 0.867).



A= 75 days (sensitivity=.81; specificity =.79)
B= 90 days (sensitivity=.76; specificity =.83)
C= 50 days (sensitivity= .87; specificity =.70)

PREDICTORS OF NONADHERENCE TO ANTIHYPERTENSIVE THERAPY: ANALYSIS OF A LARGE PHARMACY BENEFIT MANAGER DATABASE IN THE UNITED STATES

by

PUZA P. SHARMA

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Doctoral Program of the University of Medicine and Dentistry of New Jersey

School of Public Health

Written under the direction of

Kitaw Demissie, MD, PhD

ABSTRACT OF MANUSCRIPT 2 OF 3

PREDICTORS OF NONADHERENCE TO ANTIHYPERTENSIVE THERAPY: ANALYSIS OF A LARGE PHARMACY BENEFIT MANAGER DATABASE IN THE UNITED STATES

Dissertation Director

Kitaw Demissie, MD, PhD

ABSTRACT

Context: Although highly effective antihypertensive drugs are currently available for the treatment of hypertension, high blood pressure remains poorly controlled in many subjects, for the most part due to nonadherence to antihypertensive therapy. This underlines the importance of identifying factors associated with nonadherence to antihypertensive therapy so that relevant interventions can be directed to subjects that are at highest risk of nonadherence.

Objective: To examine predictors of nonadherence to antihypertensive medication.

Design, settings and subjects: A retrospective cohort analysis of newly diagnosed continuously eligible hypertensive subjects, aged ≥30 years between Jan 1st 2003 to May 31st 2006 was conducted among plan participants of a large US pharmacy benefit manager. Time to nonadherence was analyzed as the number of days from the index date

of prescription to the date of the first failure (gap $\geq$ 75 days) to renew antihypertensive medications with the use of Cox Proportional Hazard Regression model.

Outcome Measure: Main outcome measure was time to nonadherence. A subject was defined as nonadherent (outcome) if there was a gap of $\geq$ 75 days between prescription refills during the observation period. A prescription gap of 75 days or more was chosen as a cut-off point for nonadherence because this cut-off point predicted long term prescription discontinuation in my previous study.

Results: For this study 51,615 subjects with 477,820 pharmacy records was analyzed. Region of the country in which the subjects resided and subjects living in a census block with high percentage of African American population and low levels of income (adjusted for family size), were found to be significant predictors of nonadherence.. The analysis also showed that subjects who were treated by a cardiologist and younger physician and subjects who used mail order pharmacy as a dispensing channel had lower levels of nonadherence.

Conclusions: These results show that nonadherence occurs disproportionately among different subgroups of the population and suggests the possibility of targeting education and other interventions to address this problem.

PREDICTORS OF NONADHERENCE TO ANTIHYPERTENSIVE THERAPY: ANALYSIS OF A LARGE PHARMACY BENEFIT MANAGER DATABASE IN THE UNITED STATES

Introduction:

High blood pressure affects approximately 60 million Americans (1 in 3 adults) and about 1 billion people worldwide (1-3). United States estimates for direct and indirect cost of high blood pressure for 2006 was $63.5 billion. The cost for stroke, coronary heart disease and heart failure, which are important consequences of hypertension, was estimated at $230 billion during the same year (4).

Although highly effective antihypertensive drugs are currently available for the treatment of hypertension, high blood pressure remains poorly controlled in many subjects, for the most part due to nonadherence to antihypertensive therapy (5-8). According to the National Health and Nutrition Examination Survey (NHANES), during 1999-2000, hypertension was controlled only in 36% of hypertensives. Although this figure marks a significant improvement from previous decades, it is still far below the Healthy People 2010 goal of 50%. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (9) concluded that cardiovascular disease risk doubles for each increment of 20/10 mmHg in blood pressure. On the other hand, reduction of blood pressure by 12- to 13-points is associated with lowering the risk of heart attacks by as much as 20%, strokes by a third and all deaths from cardiovascular disease by 25% (10). These data underline the importance of identifying factors associated with nonadherence to antihypertensive

therapy so that specific population subgroups that disproportionately experience cardiovascular morbidity and mortality associated with noncompliance can be targeted.

A number of reports have identified factors such as age, gender and antihypertensive drug class to be associated with nonadherence in subjects with hypertension (11-24). But there is limited date in the literature examining the association of socio-economic correlates on antihypertensive treatment nonadherence. Using a large pharmacy benefit manager database that is representative of the US population, the aim of this study was to examine the association of socio economic correlates on nonadherence to antihypertensive therapy.

Materials and Methods

Data source: The data used for this study is from a de-identified pharmacy claims database of a large pharmacy benefits manager providing benefits for more than 55 million lives all over the United States. The database represents a stratified random sample of plan participants that were continuously eligible from 1st Jan 2003 to 31st Dec 2004 (24 months). The sample was constructed by proportionally sampling on age, sex and geographic region. Region is defined using the 9 geographic regions described by the U.S. Census Bureau (25). Figure 1 shows study subject flowchart.

Study design: For this study, a retrospective cohort design was employed.

Study subjects: In order to fulfill the data requirements for this study the stratified random sample of 24 months were followed for an additional 17 months. Therefore, a continuously eligible subject's information for 41 months between Jan 1st 2003 to May 31st 2006 was obtained. This reduced the sample size from 2.5 million to 1.2 million

(Figure 1). Final inclusion criteria retaining only new users of antihypertensive therapy who were ≥30 years and had ≥ 2 prescriptions of antihypertensive medications yielded a sample size of 51,615 for the analysis (Figure 1). Existing users were excluded from the analysis because may represent a group of subjects that are already adherent to antihypertensive medication.

Measurements: During the study period, three nonoverlapping measurement calendar periods were defined (Figure 2): (i) Targeting period (ii) Look back period and (iii) Observation period. The *targeting period* runs for 12 months from July 1st 2003 to June 30th 2004 and was primarily used to identify the index prescription date of each subject. The *look back period* starts on the index prescription date and goes back 6 months. This period served to identify subjects new to therapy. Subjects that had no claims of any antihypertensive drugs during the entire 6 months prior to the index prescription date were designated as subjects who were new to therapy (new users) and were retained in the analysis. These subjects formed the cohort for a subsequent observation period of 1 year (o*bservation period*) starting from the index prescription date. The refilling behavior of each subject was determined during this observation period.

Outcome variable: A subject was defined as nonadherent (outcome) if there was a gap between prescription refills of ≥ 75 days during the observation period. A prescription gap of 75 days or more was chosen as a cut-off point for nonadherence because this cut-off point predicted long term prescription discontinuation in my previous study (26).

In order to calculate gap between refills, at first, the start date (index date) and end date (365 days from the index date) of prescription was defined to establish each subject's observation period. The end of supply of each prescription was calculated with the use of "service date" and "days supply" variables. Length of gap between each prescription refills was then determined with the use of 'end of supply of the previous prescription' and service date of subsequent prescription. A gap was defined as absence of prescription claims for all of the antihypertensive drug classes under study.

Explanatory variables: African American race and income (adjusted for family size) as measured from each subject's census block group, and region of the U.S. in which the subjects resided, were the main predictor variables in the study. Information on race and income was inferred from the census block subject's area of residence. The utility of area-based measures of race (% African American, % Hispanic, etc.) and other socio demographic variables in epidemiologic studies has been examined previously (27;28) and have been found to correlate well with information that is obtained at the individual patient level. Regions of the U.S. proposed by the Census Bureau (25) namely: North East, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific States were used as one of the predictors of nonadherence.

The 9 digit zip code of the study subject's place of residence available in the database was used to identify the census block in which each subject resided using EASI Analytic Software (29). Please see *appendix* for more information about the software. The Block Group file was developed using the latest Topologically Integrated Geographic Encoding and Referencing (TIGER) files. These files created by the Census

Bureau are publicly available and updated periodically (30). The TIGER files are a digital database of geographic features, such as roads, railroads, rivers, lakes, legal boundaries, census statistical boundaries, etc. covering the entire U.S. The database contains information about these features such as their location in latitude and longitude, the name, the type of feature, address ranges for most streets, the geographic relationship to other features, and other related information.

The detailed information in the TIGER files permitted the conversion of each subject's 9 digit zip code to the census block they belonged. These census blocks represent geostatistical neighborhoods that contain households with relatively homogeneous economic and social living conditions. Once a census block is assigned, the percentage of residents who are African American together with median household income and average household size in a particular block is ascribed to each individual. Percent African American obtained hereby was divided into four groups for the analysis. Group 1 (%African American <0.5%), Group 2 (%African American 0.5% -20%), Group 3 (%African American 20% -80%) and Group 4 (%African American > 80%). A socio economic status variable was also created by taking the ratio of median household income and average number of individuals in the household (income *adequacy*). This continuous income adequacy variable was grouped based on quintiles for the analysis.

Other variables that were considered either as potential confounders or as independent variables were age, gender, physician characteristics (physician's specialty, age and gender), dollar copay amount, comorbidity, dispensing channel (mail order versus retail pharmacy) and antihypertensive drug class. Age was categorized into twelve nonoverlapping categories from 30 to 85+ for descriptive analysis with 5 year

increments. In a subsequent model, age was modeled as a continuous variable. Physicians' specialty was characterized into five groups namely: cardiologists, family medicine, general practice, internal medicine and others. Age of the physicians were characterized into four groups (<40, 40-49, 50-59 and ≥60 yrs). A subject was defined to be a mail order pharmacy user if he/she obtained ≥75% prescriptions through a mail dispensing channel during the observation period.

The antihypertensive drug classes include: thiazide diuretics; angiotensin converting enzyme inhibitor; angiotensin receptor blocker; beta blocker; calcium channel blocker; combination drugs, combination therapy (two or more monotherapy in conjunction) and other antihypertensive (alpha/beta adrenergic blocking agents, loop/potassium sparing diuretics, other antihypertensive etc). The average dollar copay amount per prescription per individual during the observation period was calculated and was used as a confounder for the analysis. Comorbidity scores (chronic disease score) of each individual were calculated based on the number of drugs dispensed in their pharmacy claims during the one year observation period using the same methodology that was originally developed by Von Korff *et al* (31). For this purpose, a regression model was utilized to estimate parameters associated with each disease condition (represented by the use of selected medication classes on the claims database) with total drug cost as the outcome. Each subject's score represents the sum of all weights derived from integer weights given to each disease category. The resulting continuous score was stratified into six groups of increasing order for the analysis. The summary measure of an individual's burden of chronic disease score was tested among two independent datasets for validation.

Statistical analysis: The distribution of gap ≥ 75 days between prescription refills by subject's characteristics at treatment initiation was described. Time to nonadherence was analyzed as the number of days from the index date of prescription to the date of the first failure (gap ≥ 75 days) with the use of Cox Proportional Hazard Regression model. Statistical significance was defined as alpha < .05. Cox Snell residuals method was used for checking model assumptions. The study was approved by the Institutional Review Board of the University of Medicine and Dentistry in New Jersey. All the statistical analyses were performed using SAS for Windows, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina).

Results:

A total of 51,615 new users of antihypertensive therapy were examined. Mean age of the subjects was 56.6 years (SD 13.4; median 55) and females slightly outnumbered males (53%). Approximately 54% of the population was between the age ranges of 45-65 years. Seventy five percent of the subjects had filled a retail prescription as opposed to a mail order prescription. The South Atlantic region of the United States accounted for the largest number of subjects on antihypertensive medication (22.5%), followed by Middle Atlantic region (18.3%) and East North Central region (14.7%). The New England region had the least representation (3.5%). Angiotensin converting enzyme inhibitors were the most commonly prescribed initial agent accounting for twenty one percent of the first prescriptions followed by beta blockers (18.3%) and diuretics (14.6%).

Percent nonadherent to antihypertensive therapy by characteristics of the study population during the first year of treatment is summarized in Table1 and Table 2. Nonadherence was most commonly observed in the age group between 30-45 years. With increasing age, nonadherence decreased linearly. Female gender and East and West South Central and South Atlantic regions had higher rates of nonadherence. Subjects residing in a census block which had a higher percentage of African American population and lower income (adjusted for family size) had greater gap between prescription refills.

Mail pharmacy users had higher levels of adherence as compared to retail pharmacy users. Subject's who used mail order prescriptions were more likely to be older (>50 years). Subjects residing in the East South Central region in the US had the highest representation in the sample. Mail users were also more likely to have higher chronic disease score and were less likely to reside in an area with greater percentage of African American population (data not shown). All other characteristics were similar to subjects that used a retail script. Some subjects started on more than one course of treatment on their index prescription date (combination drugs). These subjects had the lowest levels of nonadherence. With increasing comorbidity, adherence rates of hypertension increased in a dose dependent manner. Subjects who were treated by cardiologists and by younger physicians, also showed improved adherence.

The results of the crude analysis were confirmed by the adjusted estimates from the Cox Proportional Hazards Regression model (Table 3). Cox Snell residuals method was used for checking model assumptions was satisfied (given by a linear plot). Please see *appendix* for graph. Subjects who resided in an area which had the lowest percent of

African American population (referent group) were most likely to be adherent to therapy. The rates of nonadherence increased steadily when proportion of African American in which the subjects resided increased. Subjects residing in East and West South Central, South Central and Middle Atlantic regions of the United States had significantly higher rates of nonadherence as compared with the New England region.

Compared to the subjects who resided in an area with a high level of income (adjusted to family size), subjects who resided in an area of low level of income adequacy had higher likelihood of failure to adhere. The mail pharmacy dispensing channel, compared to the retail pharmacy dispensing channel, was significantly associated with better adherence to antihypertensive therapy after adjusting for all other predictors in the model. Ninety six percent of mail order pharmacy users and 82% of retail order pharmacy users continued the same type of drug dispensing channel at 180 days. Among physician variables, subjects who were treated by a cardiologist were most likely to be adherent than subjects who were treated by internists and family medicine practitioners. The results remained unchanged when subjects were stratified by single drug use versus multiple drug use (data not shown). Subjects who were treated by a physician $\geq$ 60 yrs were less likely to be adherent as compared to the youngest age group of the physicians (<40 yrs). Physician's gender did not predict treatment nonadherence. There was a strong correlation between subject's physician specialty on index date and at 90 and 180 days. For example, among the subjects treated by a cardiologist on the index date, 93% and 81% continued to be treated by a cardiologist at 90 days and at 180 days, respectively.

Table 3 also reports independent effects of the additional variables that were considered as secondary predictors in the study. Adherence improved with increasing age. With every five year increment in age, nonadherence decreased by four percent. Male gender had improved levels of adherence and the inverse relationship between comorbidity and adherence was confirmed in the adjusted model. Antihypertensive monotherapies did not show any significant difference in adherence rates as compared to angiotensin receptor blocking agents (referent group). Subjects on combination drugs however, had lower rates of nonadherence than the referent group. On the other hand, combined pill users were found to have higher levels of nonadherence. Subjects who started on diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers, combined pill and combination therapy on the index date were 91%, 96%, 98%, 94%, 96%, 95% and 91% likely to continue the same at 90 days, respectively. The likelihood of continuing on the same class of antihypertensive drug at 180 days after initiation of therapy was diuretics (75%), angiotensin converting enzyme inhibitors (84%), angiotensin receptor blockers (90%), calcium channel blockers (80%), beta blockers (84%), combined pill (82%) and combination therapy (76%).

Discussion:

This large population based study comprising of 51,615 study subjects with 477,820 pharmacy records found that region of the country in which the subjects resided and subjects living in a census block with high percentage of African American population and low levels of income (adjusted for family size), were found to be

significant predictors of nonadherence. Subjects that are treated by cardiologists and younger physicians were more likely to be adherent to antihypertensive medications. Finally, subjects who used a mail order pharmacy to obtain their medications were also seen to have greater levels to adherence.

It is well known that African American as compared to whites have increased rates of hypertension regardless of gender and educational status (9). The finding that subjects living in census tract with high representation of African American are less likely to adhere to antihypertensive therapy is consistent with a handful of studies that have reported increased rates of nonadherence to antihypertensive medication among African Americans (11, 16 32-34). While all but one study analyzed data on a select group of hypertensive subjects (Medicaid and veterans), the remaining study was conducted at a single site primary care center at an urban, county health system. Additionally, subjects residing in an area of low levels of income (adjusted for household size) were also found to be an independent predictor of nonadherence as compared to subjects residing in areas of high income areas. Possibly greater representation of African American population in the areas of low income could explain some of the high levels of nonadherence.

My results showed that subjects that resided in regions of the U.S. that is reported to have the high concentration of African American population (i.e. East and West South Central and South Atlantic region) had highest rates of nonadherence. These regions are collectively referred to as the South region of the U.S. (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West

Virginia) by the Census Bureau where the concentration of African Americans in the South region as high as 55% (35). The National Heart, Lung and Blood Institute has defined most of the states in the South region as the "Stroke belt" (Alabama, Arkansas, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia and Indiana) where the adjusted stroke mortality rates in the stroke belt are more than ten percent higher than the U.S. average (36-38). Excess stroke among hypertensive subjects has been attributed to the under treatment of hypertension (39; 40), and nonadherence could explain some of the excess statistics in these areas.

The literature is scarce in examining the association between physician's characteristics and nonadherence among hypertensive population. A study conducted in the Netherlands (41) found higher adherence rates among subjects treated by cardiologists, a finding similar to ours. Possible explanations for improved adherence among cardiologists treated subjects' could be that subjects may give more weight to the advice of cardiologists than primary care physicians. Alternately, subjects going to cardiologists may be sicker and as a result perceive the importance of adherence to medication more seriously. The study findings were similar to another study on physician's gender and age (42). The reason for increased nonadherence among older physicians remains to be determined.

To knowledge, there has been only one study that examined the association between mail order pharmacy usage and medication adherence. Similar to this study finding, improved adherence were found among individuals who used mail order pharmacy (43). The most likely mechanism of improved adherence among mail pharmacy users is perhaps the prevention of monthly gaps which is likely to occur if

refills are not obtained in a timely manner. It has been found that the dispensing error rate (error caused by dispensing a drug other than the prescribed drug) for mail order pharmacy is substantially lower than retail pharmacy users (44). Since hypertension is a chronic condition often necessitating life long medication use, use of mail order dispensing channel could not only reduce morbidity and mortality associated with medication errors but also decrease rates of nonadherence that could be related to trips to the pharmacy to collect medication due to other competing demands of the patient.

Increasing age was found to improve adherence. This is supported by the finding that increasing comorbidity (that is seen with older subjects) leads to improved adherence. Increasing comorbidity has been associated with improved adherence in literature (15; 33). It could be possible that subjects with more comorbid conditions and therefore use multiple drugs, may more likely be convinced that they need treatment and consume their drugs regularly. They may also be more likely to be older subjects; as a result, understand the importance to taking care of their individual health than the younger counterparts. Advanced age was found to be associated with improved adherence to antihypertensive therapy in the literature (10; 33) but the association between adherence and gender has been inconclusive (10;15; 45-48). Combined pill users were also more likely to be nonadherent. This finding contrasts a previous study that found decreased levels of adherence with the use of combination drugs versus a combined pill (49). The findings on drug class require caution because prescription claims data is not ideal for examining such associations. The actual reason as to why subjects switch from one drug class to the other cannot be determined with the use of

prescription claims. Controlled settings or prospective cohort studies are ideal to arrive at such conclusions.

There are two common ways of examining adherence from prescription claims database namely (i) persistency as a function of the medication possession ratio (MPR) and (ii) persistency as a function of the gaps between refills. MPR is defined as the sum of the days of supply of medication divided by number of days between the first fill and the last refill, including the duration of the last refill (i.e. proportion of days covered). Although the medication possession ratio method provides insight into the availability of medication, it does not provide information on the timeliness and consistency of refilling. As a result it has the danger of biasing results with subjects with shorter lengths of follow-up more likely to have high persistence compared with those with longer lengths of follow-up. In the gap between refills approach, permissible gap (gaps assumed to be secondary to patient noncompliance) that starts at the end of supply of the previous prescription is allowed between refills. A subject is considered to be persistent with therapy at all times until he/she exceeds the permissible gap. This method has been considered to provide the best assessment of refill compliance it has the advantage of identifying nonadherent subjects for intervention once they exceed the permissible gap. Moreover, with this approach, a time to event (survival) analysis can be used to study predictors and consequences of nonadherence (50).

Numerous studies examined treatment nonadherence with the use of claims data without a uniform definition of permissible gap between refills (51-59). My previous validation study (26) was designed to standardize the definition of permissible gap so that comparisons of study results across different settings become possible. A 75 day gap cut-

off point provided the best prediction of long-term prescription antihypertensive discontinuation of the study subjects. This gap cut-off point was used to define nonadherence in this paper.

This study has limitations. First, adherence defined by the use of drugs in hand does not give information as whether subjects are actually consuming the medications. However, studies that have attempted to validate compliance measured from pharmacy refill records have found 75% to 90% concordance with patient self-reported compliance in a variety of therapeutic areas; making them a reliable alternative to measure compliance (60-65). Second, lack of diagnosis codes for hypertension may have led to certain misclassification of subjects in our study. However, a subject was defined to be hypertensive if he/she had at least two prescriptions of antihypertensive medication during the targeting period. Additionally, subjects <30 years and all subjects taking drugs primarily for benign prostrate hypertrophy were excluded. This study has many strength as well. It is population based. The data is complete and accurate. There is avoidance of recall bias that occurs when adherence is measured by patient's self reports.

In conclusion, independent of other determinants, greater degree of nonadherence was seen amongst subjects residing in neighborhood with high proportion of African American residents and with low household income. Subjects residing in the Southern region of the United States also were least likely to be adherent. Strategies to improve adherence should focus on subjects from disadvantaged backgrounds.

REFERENCES

1. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995; 25:305-13.
2. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003; 290:199-206.
3. World Health Report 2002: Reducing risks, promoting healthy life. Geneva, Switzerland: World Health Organization. 2002. Available at: http://www.who.int/whr/2002/.Accessed Dec 10, 2006
4. American Heart Association. Heart Disease and Stroke Statistics – 2006 Update. Dallas, Texas: American Heart Association; 2006. Available at: http://www.americanheart.org/statistics. Accessed Dec 18, 2006.
5. Hershey JC, Morton BG, Davis JB, Reichgott MJ. Patient compliance with antihypertensive medication. *Am J Public Health* 1980; 70:1081-9.
6. Lücher TF, Vetter H, Siegenthaler W, Vetter W. Compliance in hypertension: facts and concepts. *J Hypertens* 1985; 3:3-9.
7. Bittar N. Maintaining long-term control of blood pressure: the role of improved compliance. *Clin Cardiol* 1995; 18:312- 6.
8. Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. J Manag Care Pharm. 2006 Apr; 12(3):239-45.
9. Chobanian AV, Bakris GL, African American HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003; 289:2560-72.
10. The Centers for Disease Control and Prevention, 2006. Available at: http://www.cdc.gov/DHDSP/library/movingintoaction/science.htm. Accessed June 2, 2006.
11. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. *Am J Public Health*. 1996; 86:1805-8.
12. Balkrishnan R. Predictors of medication adherence in the elderly. *Clinical Therapeutics*. (1998) 20: 764-71.
13. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *J Natl Med Assoc.* 2003 Jan; 95:17-27.
14. Degli Esposti E, Sturani A, Di Martino M, Falasca P, NoviMV, Baio G, et al. Long-term persistence with antihypertensive drugs in new patients. J Hum Hypertens 2002; 16: 439–444.
15. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. Am J Hypertens 1997; 10:697–704.
16. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med. 2007 Jan; 120(1):26-32.
17. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ 1999; 160: 41–46.

18. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther*. 1998; 20:671-81.
19. Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clin Ther*.1997; 19:1446-1457.
20. Fletcher AE, Bulpitt CJ, Chase DM, et al. Quality of life with three antihypertensive treatments-cilazapril, atenolol, nifedipine. *Hypertension.* 1992; 19:499-507.
21. Bulpitt CJ, Connor M, Schulte M, Fletcher AE. Bisoprolol and nifedipine retard in elderly hypertensive patients: effect on quality of life. *J Hum Hypertens.* 2000; 14:205-212.
22. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. *Can J Cardiol*. 2002 Jun; 18:649-56.
23. Juncos L. Patient compliance and angiotensin converting enzyme inhibitors in hypertension. *J Cardiovasc Pharmacol*. 1990; 15:S22-S25.
24. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med*. 2005 May 23; 165(10):1147-52.
25. http://www.census.gov/geo/www/us_regdiv.pdf
26. Sharma PP et al. Length of Gap in Prescription Refills that Predicts Long-Term Treatment Discontinuation among Hypertensive Patients. Objective1 of this dissertation.
27. Demissie K, Hanley JA, Menzies D, Joseph L, Ernst P. Agreement in measuring socioeconomic status: area-based versus individual measures. *Chronic Dis Can* 2000; 21: 1-7.
28. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health* 1992; 82: 703-710.
29. Easy Analytic Software, Inc. (EASI). Available at: http://www.easidemographics.com/.
30. Topologically Integrated Geographic Encoding and Referencing system. Available at: http://www.census.gov/geo/www/tiger/index.html. Accessed Oct 15, 2006
31. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992; 45:197–203.
32. Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. *Pharmacotherapy*. 2006 Apr; 26(4):483-92.
33. Sharkness CM, Snow DA. The patient's view of hypertension and compliance. Am *J Prev Med.* 1992; 8:141-146.
34. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *J Natl Med Assoc*. 2003 Jan; 95(1):17-27.
35. United States Census Bureau. Available at: http://www.census.gov/prod/2003pubs/p20-541.pdf. Accessed Jan 15, 2007.
36. National Heart, Lung, and Blood Institute. *Data Fact Sheet: The Stroke Belt: Stroke Mortality by Race and Sex*. Bethesda, Md: National Heart, Lung, and Blood Institute; 1989.
37. Hall WD, Ferrario CM, Moore MA, et al. Hypertension-related morbidity and mortality in the southeastern United States. *Am J Med Sci.* 1997;313:195-209

38. Perry HM, Roccella EJ. Conference report on stroke mortality in the southeastern United States. *Hypertension.* 1998;31:1206-1215
39. Klungel OH, Stricker BH, Paes AH, Seidell JC, Bakker A, Voko Z, Breteler MM, Anthonius de Boer. Excess stroke among hypertensive men and women attributable to undertreatment of hypertension. *Stroke.* 1999 Jul; 30(7):1312-8.
40. Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Blood pressure control and risk of stroke: a population-based prospective cohort study. *Stroke.* 2005 Apr; 36(4):725-30.
41. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens*. 2005 Nov;23(11):2101-7.
42. Ren XS, Kazis LE, Lee A, Zhang H, Miller DR. Identifying patient and physician characteristics that affect compliance with antihypertensive medications. *J Clin Pharm Ther*. 2002 Feb;27(1):47-56.
43. Gross R, Zhang Y, Grossberg R. Medication refill logistics and refill adherence in HIV. *Pharmacoepidemiol Drug Saf*. 2005 Nov;14(11):789-93.
44. Teagarden JR, Nagle B, Aubert RE, Wasdyke C, Courtney P, Epstein RS. Dispensing error rate in a highly automated mail-service pharmacy practice. *Pharmacotherapy*. 2005 Nov; 25(11):1629-35.
45. Degli Esposti L, Degli Esposti E, Valpiani G, et al. A retrospective, population-based analysis of persistence with antihypertensive drug therapy in primary care practice in Italy. *Clin Ther*. 2002;24(8):1347-1357
46. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ. 1999; 160:31-7.
47. Degli Esposti E, Sturani A, Di Martino M, et al. Long-term persistence with antihypertensive drugs in new patients. *J Hum Hypertens*. 2002; 16(6):439-444.
48. Dezii CM. A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. Manag Care. 2000 Sep;9(9 Suppl):2-6
49. Sikka R, Xia F, Aubert RE. Estimating Medication Persistency Using Administrative Claims Data. *Am J Manag Care* 2005; 11: 449-457.
50. Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. *Can J Cardiol* 2000; 16: 1109-1117.
51. Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens*. 2002; 16:569-75.
52. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J Manag Care Pharm*. 2003; 9:424-9.
53. Perreault S, Lamarre D, Blais L, Dragomir A, Berbiche D, Lalonde L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Ann Pharmacother*. 2005; 39:1401-8.
54. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF, Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. *Pharmacoepidemiol Drug Saf*. 2005; 14:795-803.
55. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. *J Hypertens*. 2005; 23:2093-100.

56. Bourgault C, Senecal M, Brisson M, Marentette MA, Gregoire JP. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. *J Hum Hypertens.* 2005 Aug;19(8):607-13,
57. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG.Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *J Hypertens*. 2006 Jun; 24(6):1021-2.
58. Morgan SG, Yan L. Persistence with hypertension treatment among community-dwelling BC seniors. *Can J Clin Pharmacol*. 2004 Fall; 11(2):e267-73.
59. Erickson SR, Coombs JH, Kirking DM, Azimi AR.Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother.* 2001; 35:997-1003.
60. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*.1997; 50(5): 619–625.
61. Heerdink ER, Leufkens HG, Koppedraaijer C, Bakker A. Information on drug use in the elderly: a comparison of pharmacy, general-practitioner and patient data. *Pharm World Sci* 1995; 17(1): 20–24.
62. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. J *Am Geriatr Soc* 1991; 39(11): 1079–1084.
63. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. *Pharm World Sci* 1999; 21(5): 217–220.
64. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. *Br J Clin Pharmacol* 1998; 45(6): 591–595.
65. Curtis JR, Westfall AO, Allison J, Freeman A, Kovac SH, Saag KG. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users. *Pharmacoepidemiol Drug Saf.* 2006 Oct; 15(10):710-8.

Figure 1: Study selection flowchart

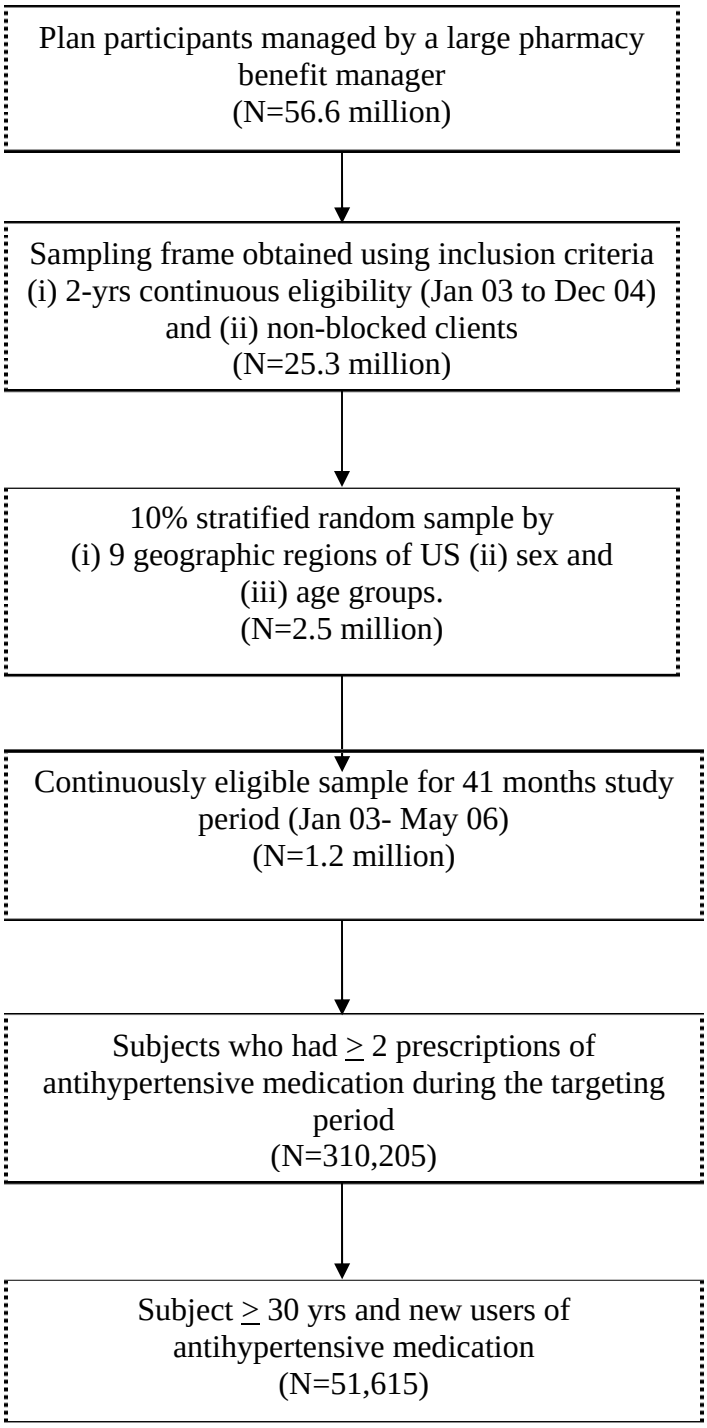

Fig 2: Definitions of measurements during the study period.

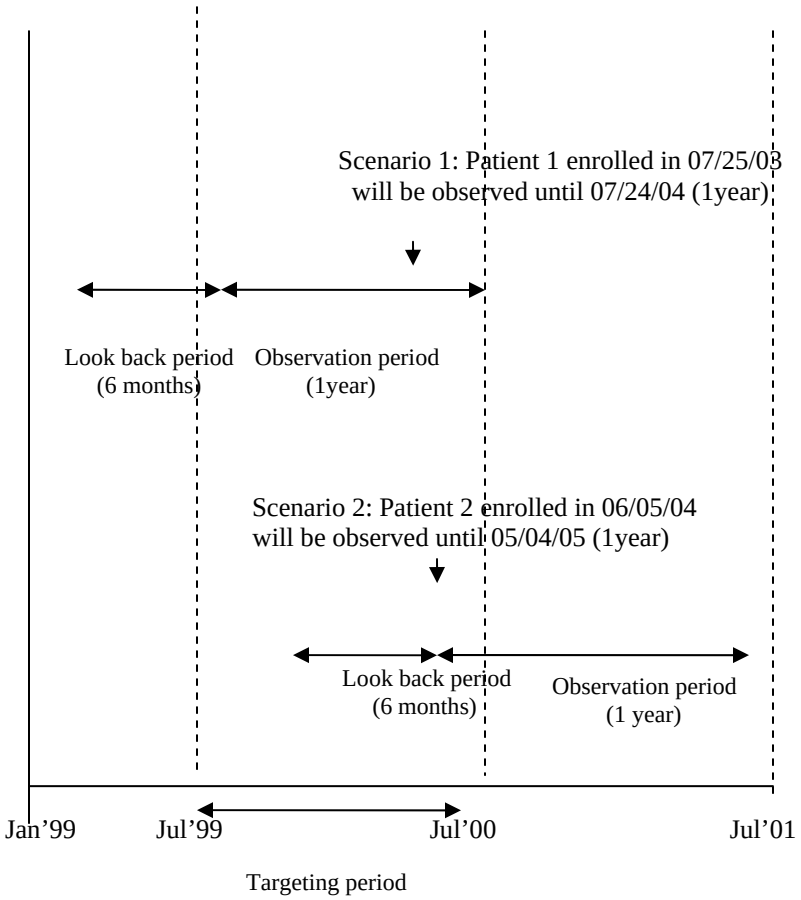

Table I: Socio demographic characteristics of the study population by length of gap ≥ 75 days: Large Pharmacy Benefit Manager Database, United States (N=51,615), 2003-2005

Characteristics	*non complaint (% gap ≥75 days)*
Age in years	
30-<35 (n=1,789)	48.91
35-<40 (n=3,032)	41.92
40-<45 (n=4,988)	38.23
45-<50 (n=7,018)	34.43
50-<55 (n=7,924)	31.75
55-<60 (n=7,617)	28.19
60-<65 (n=5,339)	26.73
65-<70 (n=3,896)	26.87
70-<75 (n=3,694)	27.42
75-<80 (n=3,125)	29.95
80-<85 (n=2,071)	31.39
>85 (n=1,122)	28.88
Gender	
Female (n=27,096)	33.56
Male (n=24,519)	30.32
Nine Regions of United States	
East North Central (n=7,615)	29.52
East South Central (n=2,948)	33.31
Middle Atlantic (n= 9,421)	32.14
Mountain (n=2,800)	32.64
New England (n=1,807)	28.72
Pacific (n= 5,286)	30.12
South Atlantic (n=11,604)	33.96
West North Central (n=2,721)	28.08
West South Central (n=7,413)	34.28
African American Race *	
Group1 (n=10,167)	29.60
Group 2 (n=29,128)	31.40
Group 3 (n=4,624)	37.48
Group 4 (n=1,282)	38.92
Missing (n=6,414)	33.41
Income Adequacy ($)**	
0-<30,909 (n=8,875)	35.43
30,909-41039 (n=8,883)	33.48
41039<53845 (n=9,509)	30.81
53845<73131 (n=8,251)	29.41
>73131 (n=8,883)	29.79
Missing (n=7,214)	33.38

* African American Race: Group1 (% African American <0.5%), Group2 (% African American 0.5% - 20%), Group3 (% African American 20% -80%), and Group4 (% African American > 80%).

** Income adequacy (median household income/average # of individuals in the household): the groups were based on the quintiles of the variable.

Table 2: Other characteristics of the study population by length of gap ≥ 75 days: Large Pharmacy Benefit Manager Database, United States (N=51,615), 2003-2005

Characteristics	*non complaint (% gap ≥75 days)*
Method of Drug Dispensing	
Retail (n= 38,715)	35.3
Mail (n= 12,900)	22.2
Physicians specialty	
Cardiologists (n=4,770)	27.97
Family Medicine (n=15,587)	30.95
General Practice (n=1,440)	33.96
Internal Medicine (n=15,453)	29.70
Other (n=14,365)	36.84
Physicians gender	
Male (n=35,577)	31.49
Female (n=7,761)	32.29
Missing (n=8,277)	34.07
Physicians age	
<40 (n=7,055)	30.40
40-<50 (n=15,264)	31.58
50-<60 (n=15,000)	31.55
≥60 (n=5,845)	33.41
Missing (n=8,451)	34.07
Anti hypertensive drug class	
Diuretics (n=4,999)	35.19
ACE Inhibitor (n=10,878)	27.67
Beta Blocker (n=9,438)	33.09
Calcium Channel Blocker (n=4,231)	32.90
Angiotensin receptor antagonists (n=7,293)	27.99
Combined pill (n=4,596)	36.36
Combination Therapy (5,317) *	25.71
Other antihypertensive therapy (n=4,859) **	44.54
Cormorbity (CDS score) *	
0-<10 (n=15,510)	37.27
10-<20 (n=15,557)	29.52
20<30 (n=11,117)	26.86
30-<50 (n=7,455)	25.30
>50 (n=1,976)	26.72

* Combination therapy: (two or more monotherapy in conjunction)

**Other antihypertensive therapy: Alpha/beta adrenergic blocking agents, loop/potassium Sparing diuretics, etc.

Table3: Cox Proportional Hazard regression model results: Large Pharmacy Benefit Manager Database, United States (N=51,615), 2003-2005

Characteristics	*Hazard Ratio*	*(95%CI)*
African American Race *		
Group1 (n=10,167)	1.00	-
Group 2 (n=29,128)	1.10	1.03-1.16
Group 3 (n=4,624)	1.31	1.21-1.43
Group 4 (n=1,282)	1.34	1.18-1.53
Missing (n=6,414)	1.19	0.98-1.45
Income Adequacy ($)**		
0-<30,909	1.20	1.04-1.22
30,909-41039	1.06	0.99-1.15
41039<53845	0.99	0.92-1.07
53845<73131	0.97	0.90-1.05
>73131	1.00	-
Missing	1.12	0.71-1.77
Nine Regions of United States		
East North Central	1.01	0.88-1.16
East South Central	1.27	1.10-1.48
Middle Atlantic	1.18	1.04-1.35
Mountain	1.16	0.99-1.35
New England	1.00	-
Pacific	1.06	0.92-1.22
South Atlantic	1.21	1.06-1.38
West North Central	1.00	0.85-1.17
West South Central	1.22	1.07-1.40
Method of Drug Dispensing		
Retail	1.00	-
Mail	0.85	0.80-0.90
Age in years	0.98	0.97-.99
Gender		
Male	0.83	0.80-.0.87
Physicians specialty		
Cardiologists	1.00	-
Family Medicine	1.11	1.02-1.21
General Practice	1.09	0.94-1.26
Internal Medicine	1.10	1.00-1.19
Other	1.27	1.16-1.40
Physicians gender		
Male	1.00	-
Female	0.95	0.90-1.01
Missing	0.92	0.84-1.01

Physicians age		
<40	1.00	-
40-<50	1.01	0.94-1.08
50-<60	1.05	0.98-1.13
≥60	1.12	1.07-1.26
Missing	1.09	0.77-1.54
Anti hypertensive drug class		
Diuretics	1.09	0.99-1.20
ACE Inhibitor	0.96	0.89-1.04
Beta Blocker	1.06	0.98-1.15
Calcium Channel Blocker	1.08	0.98-1.19
Angiotensin Receptor Anagonists	1.00	-
Combined Pill	1.27	1.16-1.39
Combination Therapy***	0.87	0.78-0.96
Misc Antihypertensive****	1.53	1.40-1.67
Cormorbity (CDS score)		
0-<10	1.00	-
10-<20	0.78	0.74-0.82
20<30	0.75	0.70-0.79
30-<50	0.67	0.63-0.72
>50	0.67	0.54-0.75

* African American Race: Group1 (% African American <0.5%) Group2 (% African American 0.5% - 20%) Group3 (% African American 20% -80%) and Group4 (% African American > 80%).

** Income adequacy (median household income/average # of individuals in the household): the groups were based on the quintiles of the variable.

*** Combination therapy: (two or more monotherapy in conjunction)

**** Other antihypertensive therapy: Alpha/beta adrenergic blocking agents, loop/potassium sparing diuretics, etc.

***** All analysis adjusted for the confounding effect of all other independent variables.

IMPACT OF MEDICATION NONADHERENCE ON RATES OF HOSPITALIZATION AND EMERGENCY ROOM VISITS IN NEW JERSEY MEDICAID DATABASE

by

PUZA P. SHARMA

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Doctoral Program of the University of Medicine and Dentistry of New Jersey

School of Public Health

Written under the direction of

Kitaw Demissie, MD, PhD

ABSTRACT OF MANUSCRIPT 3 OF 3

IMPACT OF MEDICATION NONADHERENCE ON RATES OF HOSPITALIZATION AND EMERGENCY ROOM VISITS IN NEW JERSEY MEDICAID DATABASE

Dissertation Director

Kitaw Demissie, MD, PhD

ABSTRACT

Context: Nonadherence to antihypertensive may worsen disease severity, leading to increased utilization of health care utilization. This may further increase the burden of this highly prevalent condition by increasing the overall health care costs.

Objective: The objective of this study is to evaluate the impact of medication nonadherence on rates of hospitalization and emergency room visits.

Design, settings and subjects : A retrospective cohort observation of 9,945 subjects aged 30-64 years who were continuously enrolled for medical and prescription benefit plans in New Jersey Medicaid from Jan 1999 through Dec 2001 and who had $\geq$ 2 prescription claims for antihypertensive drugs during the first 6 months of the study was identified. Drug utilization was measured during the entire study period after patient identification (index prescription). A subject was defined as nonadherent (exposure) if there was a gap of $\geq$ 75 days between prescription refills during the observation period.

A log-linear regression analysis was utilized to estimate the risk of health care utilizations (hospitalization and emergency room visits) between the nonadherent vs. adherent groups while controlling for age, sex, race and number of comorbid conditions.

Outcome measures: The primary outcome measures were (i) All cause hospitalizations and emergency room visits and (ii) Cardiovascular-specific hospitalizations and emergency room visits, expressed as counts.

Results: The unadjusted relative risk for *all-cause emergency room visits* was 2 times more in the nonadherent group than the adherent group [RR 2.0, (95% CI 1.96, 2.03)] whereas the adjusted model showed 67% increased risk of emergency room visits in subjects who were nonadherent to antihypertensive therapy [RR 1.67, (95% CI 1.63, 1.69)]. For the *cardiovascular-specific emergency room visits,* the unadjusted relative risk was 87% greater in the nonadherent group than the adherent group [RR 1.87, (95% CI 1.63, 2.10)] and for the adjusted model, nonadherent subjects were found to have 70% increased risk of cardiovascular-specific emergency room visits [RR 1.70, (95% CI 1.57, 2.05)]. The nonadherent group than the adherent group were twice more likely to be a risk for *all-cause hospitalizations* in the unadjusted model [RR 2.01, (95% CI 1.95, 2.08)]. The results did not change when potential confounders were accounted for in the adjusted model [RR 1.97, (95% CI 1.91, 2.04)]. For *cardiovascular-specific hospitalizations,* the unadjusted model showed 50% increased risk in the nonadherent group than the adherent group [RR 1.5, (95% CI 1.28, 1.80)]. In this analysis also, the results remained unchanged in the adjusted model [RR 1.5, (95% CI 1.2, 1.83)].

Conclusion: In conclusion, timely corrective interventions to improve adherence will significantly reduce health care costs associated with increased health care utilization.

IMPACT OF MEDICATION NONADHERENCE ON RATES OF HOSPITALIZATION AND EMERGENCY ROOM VISITS IN NEW JERSEY MEDICAID DATABASE

Introduction:

Pharmacotherapy has demonstrated to decrease morbidity and mortality and has become the main modality for the management of hypertension (1). In order to realize the therapeutic and economic benefits of antihypertensive drugs established in clinical trails, subjects are required to be adherent to their prescribed therapy (2). However, treatment effectiveness poses a much greater challenge than treatment efficacy that is achieved under controlled conditions. With an average estimated rate of nonadherence of about 50% antihypertensive medication (3; 4), nonadherence has become a recognized public health problem. Over 30% of hypertensives discontinue after a year on therapy (5) and only one third of those who remain under therapy take enough medication to control their blood pressure (6)

Nonadherence may worsen disease severity, leading to an increased utilization of medical care services (7-16) leading to increase in the overall health care costs. This study evaluates the relationship between medication nonadherence and health care utilization, in particular, hospitalizations and emergency room visits, in a large population based cohort of New Jersey Medicaid enrollees who had benefits for prescription drugs as well as medical services.

Materials and Methods:

Data source: The New Jersey Medicaid Data System for the years 1999 through 2001 was utilized for the analysis. Medicaid provides health insurance for 12.9% of the New Jersey population. The Medicaid data gives detailed individual level information on prescription medications which can be linked to demographic characteristics of subjects and healthcare providers. The dataset provides information on healthcare utilization (out-patient visits, emergency room visits, hospitalizations and frequency and dose of medication use). The Medicaid Analytic eXtract File (MAX) provided by the Centers for Medicare and Medicaid Services (CMS) was used for the analysis. MAX files has five parts,namely (1) the Personal Summary File; (2) the Inpatient File, (3) Other services record File, (4) the Drug File and (5) Long Term Care File. *The Personal Summary File* contains patient-level information on date of birth, age, date of death, gender, race, county code (FIPS), zip code, and social security number. *The inpatient file* contains hospitalization claims with admission dates, primary and secondary medical diagnosis codes according the ninth revision of the International Classification of Disease (ICD-9), procedure codes (ICD-9) and provider IDs. *The outpatient file* contains medical claims information on date of service, type of service, primary and secondary diagnosis codes, procedure code, and drug code for injections provided in the outpatient setting. *The drug file* contains information on type of drug, number of days supplied, date of prescription, date filled, quantity of drug, drug code information, National Drug Code (NDC) number reflecting brand name and drug form, generic versus brand name, number of units dispensed, and strength. Medicaid data are probably the most reliable and valid data source for information on drug use, making the Medicaid drug file very attractive (17).

This is because prescription drugs are a benefit for all Medicaid clients and out-of-system use is rare. Also, medications are included in the database regardless of the number of different pharmacies used. The Medicaid drug file has been validated against primary source of data (e.g., Medical and pharmacy records) and the agreement was found to be extremely high. Furthermore, the use of Medicaid data to identify drug use is believed to have the advantage of being more comprehensive than either patient recall or physician's prescribing records.

Study subjects: Subjects were identified for the study if they had the following (i) continuous medical and drug benefit eligibility through the New Jersey Medicaid during the period between Jan 1999 through Dec 2001(3 years), (ii) were users of at least two prescriptions of antihypertensive medications during the first six months of the study period and (iii) were $\geq$ 30 years old. Subjects who were $\geq$65 yrs of age and were dual eligibles for Mediciad and Medicare benefits were excluded. After this exclusion 9,945 subjects remained for the analysis (Figure 1).

Measurements: Subjects who had two or more prescriptions of antihypertensive medication in the first six months formed the study cohort. Subjects were observed from the index prescription date till the end of the study period (Dec 31st 2001). The refilling behavior of each subject during the observation period was determined in order to distinguish subjects as adherent versus not. During the same period, the number of hospitalizations and emergency rooms visits was quantified for each subject.

A subject was considered nonadherent if there was a gap between prescription refills of $\geq$ 75 days during the observation period. A prescription gap $\geq$ 75 days was

chosen as a cut-off value was found to predict long term prescription discontinuation in my previous study (5).

In order to calculate gap between refills, at first, the start date (index date) and end date (31st Dec 2001) of prescription was defined to establish each subject's observation period. The end of supply of each prescription was calculated with the use of "service date" and "days supply" variables. Length of gap between each prescription refills was then determined with the use of 'end of supply of the previous prescription' and service date of subsequent prescription. A gap was defined as absence of prescription claims for all of the antihypertensive drug classes under study. The drug classes include: thiazide diuretics, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker, combination pills and miscellaneous antihypertensives such as alpha/beta adrenergic blocking agents, loop and potassium sparing diuretics etc.

Outcome Measures: The primary outcome measures were (i) All cause hospitalizations and emergency room visits and (ii) Cardiovascular-specific hospitalizations and emergency room visits, expressed as counts. Cardiovascular-specific hospitalizations include diagnosis of essential hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal disease, subarachnoid hemorrhage, intracerebral hemorrhage, nontraumatic epidural hemorrhage, nontraumatic subdural hemorrhage, unspecified intracranial hemorrhage, hypertensive encephalopathy, and hypertensive retinopathy.

Statistical Analysis: Descriptive analysis was used to characterize the study population. Log-linear regression analysis was conducted to estimate the risk of hospitalization and emergency room visit associated with nonadherence after controlling for age, sex, race and number of comorbid conditions. The total number of comorbid conditions for each individual was counted and was grouped as follows: Group 1 (number of comorbid condition=0), Group 2 (number of comorbid condition=1), Group 3 (number of comorbid condition=2&3), Group 4 (number of comorbid condition=4&5) and Group 5 (number of comorbid condition=6&7). Statistical significance was defined as $P = 0.05$. The study was approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey. All the statistical analyses were performed using SAS for Windows, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina).

Results:

A total of 9,945 subjects who were on antihypertensive therapy in the analysis were examined. Table 1 displays the characteristics of the study population during treatment initiation. Subjects had a mean age of 50 years (SD 8.6; median 52 years). All subjects had at least 2.5 years of observation (mean 2.9 years, max 3yrs, median 2.9 yrs, and SD 33.9 days). Approximately three quarters (73%) of the population were females. African American race and 55-60 years age-group had the highest representation in the sample. Fifty one percent of the study sample had either zero or one comorbid condition. The mean number of *all-cause* hospitalization and emergency room visits in the observation period was 1.5 and 5 respectively whereas the mean number of

cardiovascular-specific hospitalization and emergency room visits in the observation period was 0.6 and .1 respectively.

Table 2 displays the characteristics of the study population by their adherence status. Overall, 37 % of the sample was nonadherent to antihypertensive therapy during the observation period. Subjects who were nonadherent were younger and more likely to be females. Within the race variable, white race had the highest percent of adherent subjects, while African Americans had the highest percent of nonadherent subjects in the sample. With increasing comorbidity, the rates of nonadherence was found to decrease linearly i.e. subjects with the highest number of comorbid conditions had the lowest rates of nonadherence.

Results of the log-linear regression model are shown in Table 3. These estimates represent relative risks of hospitalizations and emergency room visits comparing adherent and nonadherent groups, with and without adjustment of covariates. Subjects who were nonadherent to antihypertensive therapy were more than 50% likely to have higher rates health care utilization in all models (statistically significant). The unadjusted relative risk for *all-cause emergency room visits* was two times more in the nonadherent group than the adherent group. The adjusted model showed 67% increased risk of emergency room visits in subjects who were nonadherent to antihypertensive therapy. For the *cardiovascular-specific emergency room visits* the unadjusted relative risk of was 87% greater in the nonadherent group than the adherent group. For the adjusted model, subjects who were nonadherent to antihypertensive therapy were found to have 70% increased risk of cardiovascular-specific emergency room visits.

The nonadherent group than the adherent group were twice more likely to be at risk for *all-cause hospitalizations* in the unadjusted model. The results did not change when potential confounders were accounted for in the adjusted model. For *cardiovascular-specific hospitalizations*, the unadjusted model showed 50 % more risk in the nonadherent group than the adherent group. In this analysis also, the results remained unchanged in the adjusted model.

Another approach was used to analyze the study subjects. In this approach, refilling behavior of each subject was determined during the first year after index prescription (*observation period)*. An 18 month *follow-up period* subsequent to the end of each subject's observation period was used to identify number of hospitalizations and emergency rooms visits for both adherent as well as nonadherent subjects. Please see *appendix* for results from this approach.

Discussion:

Subjects who are nonadherent to antihypertensive therapy were significantly more likely to have higher rates of hospitalizations and emergency room visits for *all-cause* as well as *cardiovascular-specific* hospitalizations. In the literature few studies that have examined the relationship between antihypertensive medication nonadherence and health care resource utilization have arrived at similar conclusion (13-16). While Sokol et al. (13) used a similar method like this study to examine the impact of nonadherence on all-cause and cardiovascular specific rates of hospitalization, the study did not control for race in the adjusted model. Race was also not controlled for in the study conducted by Chen et al. (14). Additionally, continuous coverage eligibility for the entire study period

was not a criterion during subject selection for this study (14). Maronde andcollegues, examined the association of nonadherence to antihypertensive therapy and hospital readmissions and found that the hospital readmitted group had significantly higher levels of nonadherence than those who were not readmitted (15). In a large study conducted in a public health care system in Indianapolis, nonadherence of antihypertensive medication in subjects with complicated hypertension was significantly associated with higher rates of hospitalization (16). My study examined the impact of antihypertensive medication nonadherence and hospitalization as well as emergency visits in addition to in a Medicaid population that were <65 years of age. Emergency visits were not accounted for as an outcome in any of the above studies. In spite of some differences, this consistent finding of increased health care utilizations among nonadherent subjects across different settings underscores the importance of effective health policy and public health actions to improve medication adherence that will help decrease the cost burden of the disease in the population.

The study is population based. There is also avoidance of Hawthorne effect as well as recall bias that occurs when adherence is measured by patient's self reports. The study also has limitations. First, the observational nature of the study may limit drawing a cause-effect inference due to insufficient information on temporality. In other words, it is difficult to be sure whether the hospitalizations/emergency visits or nonadherence came before the other. Utilization of existing users of antihypertensive drug in this study design, however, may have ensured that these subjects have been on antihypertensive therapy for a prolonged period of time before the analysis began. As a result, the observed rates hospitalizations as well as emergency room visits probably reflects the

collective effects of nonadherence that is sustained over a much longer period of time. This study can therefore provide a good estimation of the consequences of nonadherence to antihypertensive therapy that is likely to been seen if subjects are followed longitudinally over time. Conducting a prospective study on the other hand, may require subjects to be followed for an extended period of time in order to observe events. This is not only expensive and time consuming but may also be difficult to carry out especially when it entails a large study population.

Secondly, adherence defined by the use of drugs in hand does not give information as whether subjects are actually consuming the medications. However, studies that have attempted to validate compliance measured from pharmacy refill records have found 75% to 90% concordance with patient self-reported compliance in a variety of therapeutic areas; making them a reliable alternative to measure compliance (18-24). Thirdly, ICD-9 codes on medical claims that was used to measure hospitalization-specific and emergency room visits may not accurately or completely reflect the patient's diagnosis. However, these inaccuracies should not be differential among adherent versus nonadherent group.

A subanalysis was conducted in order to assess whether difference in the penetration rates of Medicaid Managed care over the three year period could impact rates of hospitalization utilization observed over the different time-periods. For this analysis, only a subset of subjects that had either a hospitalization or emergency room visit in the observation period was considered. Rates of hospitalization or emergency room visit of these subjects in the follow-up period were then compared. The mean and median rates of hospitalization or emergency room visits during the observation period remained very

comparable to the mean and median rates of hospitalization or emergency room visits in the follow-up period indicating that the penetration rates of Medicaid Managed care over the three year period did not impact reporting of health care utilization in the study sample.

In conclusion, timely corrective interventions to improve adherence will significantly reduce health care costs associated with increased health care utilization.

REFERENCES

1. Chobanian AV, Bakris GL, African American HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003; 289:2560-72.
2. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353:487-97.
3. Nichol MB, Venturini F, Sung JCY. A critical evaluation of the methodology of the literature on medication compliance. *Ann Pharmacother*.1999; 33:531–540.
4. Schlenk EA, Burke LE, Rand C. Behavioral strategies to improve medication-taking compliance. In: Burke LE, Ockene IS, eds. *Compliance in Healthcare and Research.* Armonk, NY: Futura Publishing Co; 2001:57–70.
5. Sharma PP et al. Length of Gap in Prescription Refills that Predicts Long-Term Treatment Discontinuation among Hypertensive Patients. Objective 1 this dissertation.
6. Eraker SA, Kirscht JP, Becker MH.Understanding and improving patient compliance. Ann Intern Med. 1984 Feb; 100(2):258-68.
7. Sclar DA, Skaer TL, Chin A, Okamoto MP, Gill MA. Utility of a transdermal delivery system for antihypertensive therapy. Part 2. *Am J Med.* 1991; 91:57S-60S.
8. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA. Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clin Ther.* 1991; 13:489-495.
9. Skaer TL, Sclar DA, Robison LM, Markowski DJ, Won JK.Effect of pharmaceutical formulation for diltiazem on health care expenditures for hypertension. *Clin Ther.* 1993 Sep-Oct;15(5):905-11.
10. Schlenk EA, Burke LE, Rand C. Behavioral strategies to improve medication-taking compliance. In: Burke LE, Ockene IS, eds. *Compliance in Healthcare and Research.* Armonk, NY: Futura Publishing Co; 2001:57–70.
11. Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *Am J Med*. 1997; 102:43– 49.
12. Skaer TL, Sclar DA, Robison LM, Chin A, Gill MA, Okamoto MP, Nakahiro RK.Effect of pharmaceutical formulation for antihypertensive therapy on health service utilization. *Clin The*r. 1993 Jul-Aug;15(4):715-25
13. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005 Jun; 43(6):521-30.
14. Chen GJ, Smith RD, Ferrario CM.Association between antihypertensive agent use and hospital admissions in a managed care population. *Am J Med Sci*. 2004 Jun; 327(6):310-4.
15. Maronde RF, Chan LS, Larsen FJ, Strandberg LR, Laventurier MF, Sullivan SR.Underutilization of antihypertensive drugs and associated hospitalization. Med Care. 1989 Dec;27(12):1159-66.
16. Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD. Association of refill adherence and health care use among adults with hypertension in an urban health care system. Pharmacotherapy. 2006 Jun; 26(6):779-89.
17. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol. 1989 Apr; 129(4):837-49.

18. Erickson SR, Coombs JH, Kirking DM, Azimi AR.Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother.* 2001; 35:997-1003.
19. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*.1997; 50(5): 619–625.
20. Heerdink ER, Leufkens HG, Koppedraaijer C, Bakker A. Information on drug use in the elderly: a comparison of pharmacy, general-practitioner and patient data. *Pharm World Sci* 1995; 17(1): 20–24.
21. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. J *Am Geriatr Soc* 1991; 39(11): 1079–1084.
22. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. *Pharm World Sci* 1999; 21(5): 217–220.
23. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. *Br J Clin Pharmacol* 1998; 45(6): 591–595.
24. Curtis JR, Westfall AO, Allison J, Freeman A, Kovac SH, Saag KG. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users. *Pharmacoepidemiol Drug Saf.* 2006 Oct; 15(10):710-8.

Figure 1: Study selection flowchart

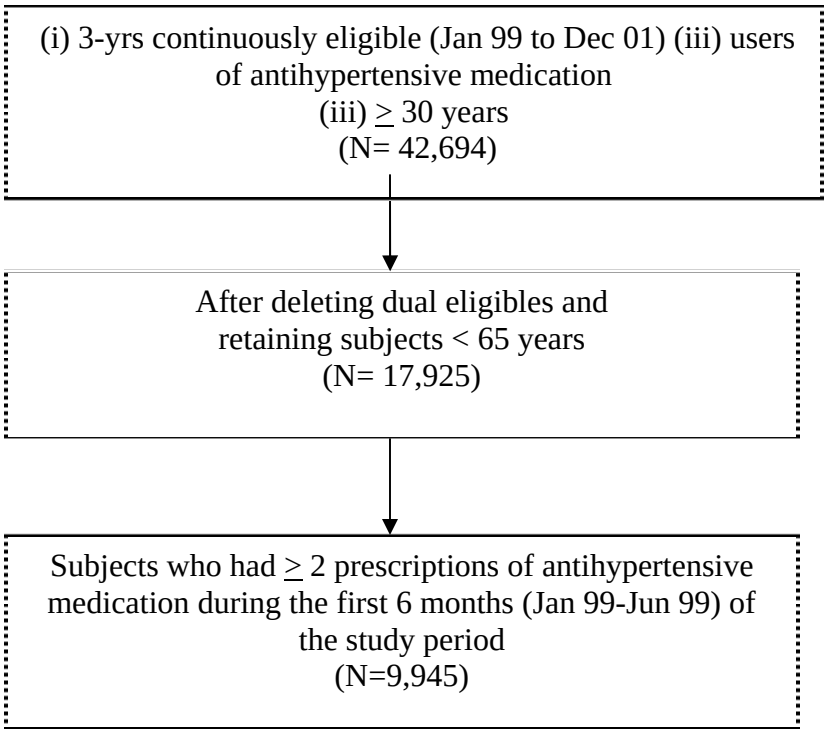


Table1: Characteristics of the population: New Jersey, Medicaid, United States (N=9,945), 1999-2001

Age in years	
Mean (SD)	50.3 (8.6)
Median(Inter quartile range)	52(14)
Characteristic	*%*
Age-group in years	
30-34	5.3
35-39	8.9
40-44	12.2
45-49	15.6
50-54	18.5
55-59	25.1
60-64	14.5
Gender	
Female	72.9
Race	
White	34.4
African American	36.9
Hispanic	7.5
Other/unknown	21.2
Number of comorbid conditions	
0	28.3
1	22.4
2-3	15.3
4-5	19.7
6-7	14.3
	Number of utilization
Hospitalization visits in the observation period	
All cause	
Mean	1.5
Median (SD)	0 (2.9)
Cardiovacular specific	
Mean	0.06
Median (SD)	0 (0.2)
Emergency visits in the observation period	
All cause	
Mean	4.9
Median (SD)	2.0 (14.9)
Cardiovascular specific	
Mean	0.1
Median (SD)	0 (0.4)

Table2: Characteristics of the population according to their adherence status: New Jersey, Medicaid, United States (N=9,945) 1999-2001

Characteristics	% nonadherent (gap ≥ 75 days) (N=3,707)	% adherent (gap <75 days) (N=6,238)
Age-group in yrs		
30-35	6.5	4.5
35-40	11.6	7.2
40-45	14.8	10.7
45-50	17.4	14.5
50-55	16.9	19.4
55-60	21.5	27.3
60-65	16.5	16.5
Gender		
Female	75.8	71.1
Male	24.2	28.9
Race		
White	29.5	37.3
African American	39.5	35.4
Hispanic	10.4	5.7
Other/unknown	20.6	21.6
Number of comorbid conditions		
0	31.7	26.3
1	23.6	21.7
2-3	14.7	15.7
4-5	18.3	20.5
6-7	11.7	15.7

Table3: Log-linear regression model results: New Jersey, Medicaid, United States (N=9,945) 1999-2001

Characteristics	*Unadjusted RR (CI)*	Adjusted RR(CI)
Emergency Room Visits		
Model type:		
All cause	2.0 (1.96-2.03)	1.67(1.63-1.69)
Cardiovascular specific	1.85(1.63-2.10)	1.7(1.57-2.05)
Hospitalizations		
Model type:		
All cause	2.01(1.95-2.08)	1.97(1.91-2.04)
Cardiovascular specific	1.5 (1.28-1.80)	1.5 (1.2-1.83)

Note: Adjusted risk ratios were obtained after controlling for the effects of age, race, gender and number of comorbid conditions.

CONCLUSION

With an average estimated rate of nonadherence of about 50%, nonadherence to antihypertensive medication has become a recognized public health problem. This may not only attribute to a large fraction of uncontrolled blood pressure, but may also worsen disease severity, leading to increased health care utilizations and subsequently increasing the overall health care costs. This underlines the importance of identifying predictors as well as consequences of nonadherence to antihypertensive therapy so that relevant interventions can be directed to nonadherent subjects in a timely manner.

Consequently, in this dissertation, the following was investigated with the use of large population based databases: (i) determination of an empirically derived cut-off value between prescription refills that could be used to define permissible gaps in antihypertensive therapy; (ii) examination of predictors of nonadherence to antihypertensive medication and (iii) evaluating the role of medication nonadherence on rates of hospitalization and emergency room visits.

ROC analysis of maximum prescription gap in antihypertensive therapy during the observation period that predicted long-term treatment discontinuation generated a C-statistic (area under the curve) of 0.87. The cut-off value for maximum gap between refills that optimized sensitivity and specificity (minimizes misclassification errors) was calculated to be 75 days (sensitivity=.81, specificity=.79).

Additionally, independent of other determinants, region of the country in which the subjects resided and subjects living in a census block with high percentage of African American population and low levels of income (adjusted for family size), were found to

be significant predictors of nonadherence. The analysis also showed that subjects who were treated by a cardiologist and younger physician and subjects who used mail order pharmacy as a dispensing channel, had lower levels of nonadherence. Finally, subjects who were nonadherent to antihypertensive therapy were > 50% likely to have higher rates of *all-cause* and *cardiovascular-specific* hospitalizations as well as emergency visits (statistically significant) both in the adjusted as well as the unadjusted models.

The findings of the dissertation have important clinical as well as public health implications. First, with the wealth of data on large number of subjects that pharmacy benefit managers covers, the results of Objective I can be used to create 'disease management programs' that can rapidly inform health care providers of those subjects who exceed the 75 days gap in antihypertensive therapy and as a result are at high risk of discontinuation. Health care provider can subsequently contact these subjects and provide them with appropriate counseling. Targeting subjects who are at risk of discontinuation will help not only to improve patient outcomes but also contain medical costs that are attributable to hypertension. Second, the methodology used in Objective I can be extended to determine permissible gap cut-off point for other chronic conditions such as diabetes, asthma, depression, etc. A uniform definition of permissible gap of all chronic conditions obtained this way will not only standardize the way adherence is determined for each condition, but also enable comparisons of study findings across different settings possible.

Cut-off for permissible gap determination however will depend on the chronic condition in question. Lowering the permissible gap cut-off point would increase

sensitivity at the expense of specificity (false positives). Researchers should weigh in whether the penalty for missing cases (false negatives) is greater than identifying subjects who are falsely labeled as nonadherent (false positives) in determining the cut-off value for a condition in question. Establishing a cut-off point for any condition which has a higher false positive rates (high sensitivity and low specificity) will require unnecessary resource utilization in subjects who are actually adherent to therapy.

Third, as observed in the results of Objective II, while targeting interventions to improve adherence, one should consider that certain subgroups of subjects are more likely to be nonadherent to antihypertensive therapy than others. Emphasis should be given to the population subgroups that are more at likely to disproportionately experience cardiovascular mortality and morbidity. Giving more educational emphasis to these population subgroups on the value of their drug therapy and motivating behavior changes will help improve adherence and thereby decrease the burden of hypertension in the population.

Lastly, increased risk of hospitalization and emergency room visits seen amongst nonadherent subjects as shown by the results of Objective III, could be responsible for a large component of health care costs. Improving adherence can provide a net economic return by cost savings observed at higher levels of adherence. Timely corrective interventions will have significant impact upon the quality and cost-effectiveness of health care delivery.

BIBLIOGRAPHY

APPENDIX

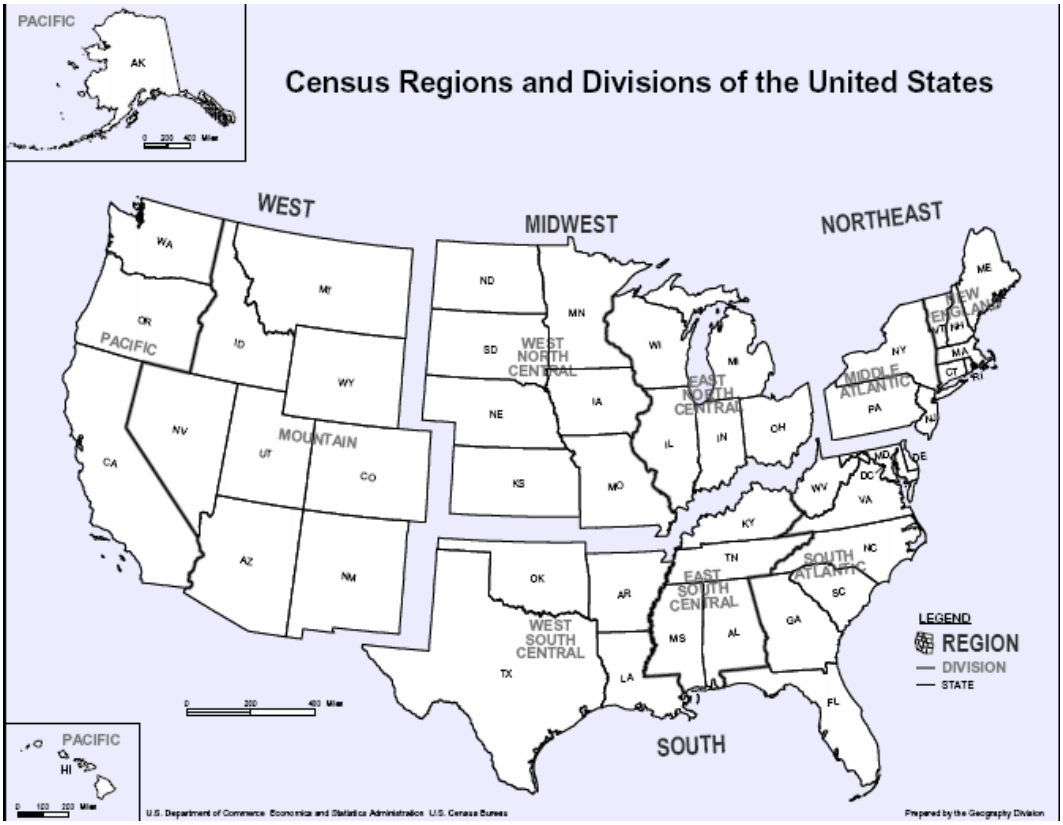
Construction of the Research Probability Sample Data System of a Large Pharmacy Benefit Manager in the United States.

The research probability sample used in Objectives I and II is a stratified random sample of plan participants and their prescription drug claims from a large pharmacy benefit manager in the United States. This pharmacy benefit manager manages prescription drug benefits of more than 55 million people (approximately 20% of the US population). The system maintains 3-year rolling claim records which are updated every 15 days. The data system contain information on service date, National Drug Code (NDC), pill strength, pill dose, quantity dispensed, route of administration code (e.g. oral), formulary indicator, days supply, quantity, an indicator of new versus refill, drug name, drug class, drug strength, etc. Furthermore, demographic information such as age, gender and zip codes are available for plan participants and can easily be linked to the claims file using unique auto generated identification number. Prescribing physician specialty (e.g., generalist, internist, cardiologist etc) is available for approximately 70-80% of providers. The records of about 20-25% of these subjects are not readily usable for research purposes (blocked clients).

The research probability sample data system is a 10% stratified random sample of unique subjects (covered lives) with a total of about 2.5 million unique eligible (covered lives). This large sample is easy to process for analysis purposes without compromising the generalizability of findings to the broader population. The sampling frame for the probability sample was derived using the following inclusion/exclusion criteria: (i) subjects (covered lives) must have 2-years continuous eligibility (Jan, 2003 - Dec, 2004);

(ii) subjects must be from non-blocked clients and (iii) subjects must have complete eligibility information such as on gender, age and region of the country. The sampling frame consists of approximately about 25.3 million unique subjects. The probability sample is constructed in two stages. At first, a 10% stratified random sample of unique subjects (covered lives) is selected from the sampling frame. Stratification is done by the 9 geographic regions defined by the National Center for Health Statistics (North East, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific States), sex and age groups (0, 1-4, 5-17, 18-44, 45-64, 65-74, 75-84 and 85+). In the second stage all prescription drug claims corresponding to the selected patient identifiers during the two year period (Jan 2003 – Dec 2004) are captured.

Nine regions of the United States as defined by the Census Bureau



Region I: Northeast
New England
Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont
Middle Atlantic
New Jersey, New York and Pennsylvania

Region 2: Midwest
East North Central
Indiana, Illinois, Michigan, Ohio and Wisconsin
West North Central
Iowa, Nebraska, Kansas, North Dakota, Minnesota, South Dakota and Missouri

Region 3: South

South Atlantic

Delaware, District of Columbia,Florida,Georgia,Maryland, North Carolina, South Carolina, Virginia and West Virginia

East South Central

Alabama, Kentucky, Mississippi and Tennessee

West South Central

Arkansas, Louisiana, Oklahoma and Texas

Region 4: West

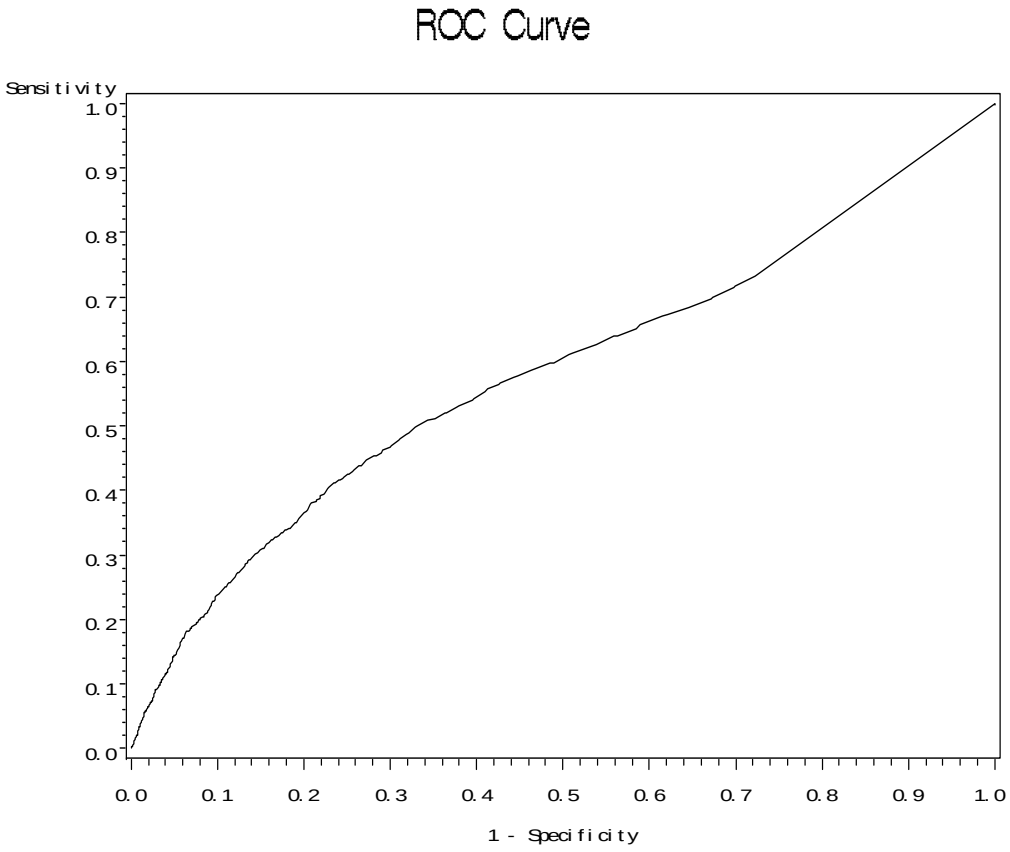
Mountain

Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming,

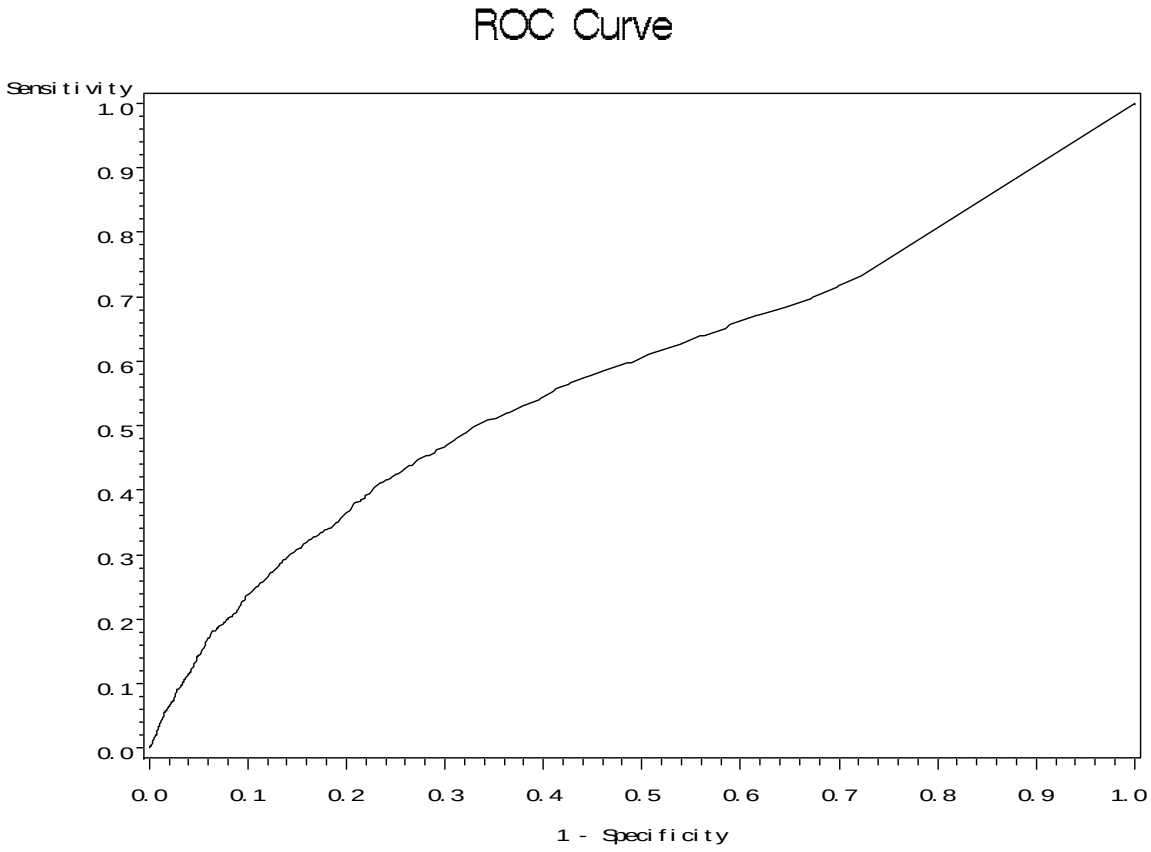
Pacific

Alaska, California, Hawaii, Oregon and Washington.

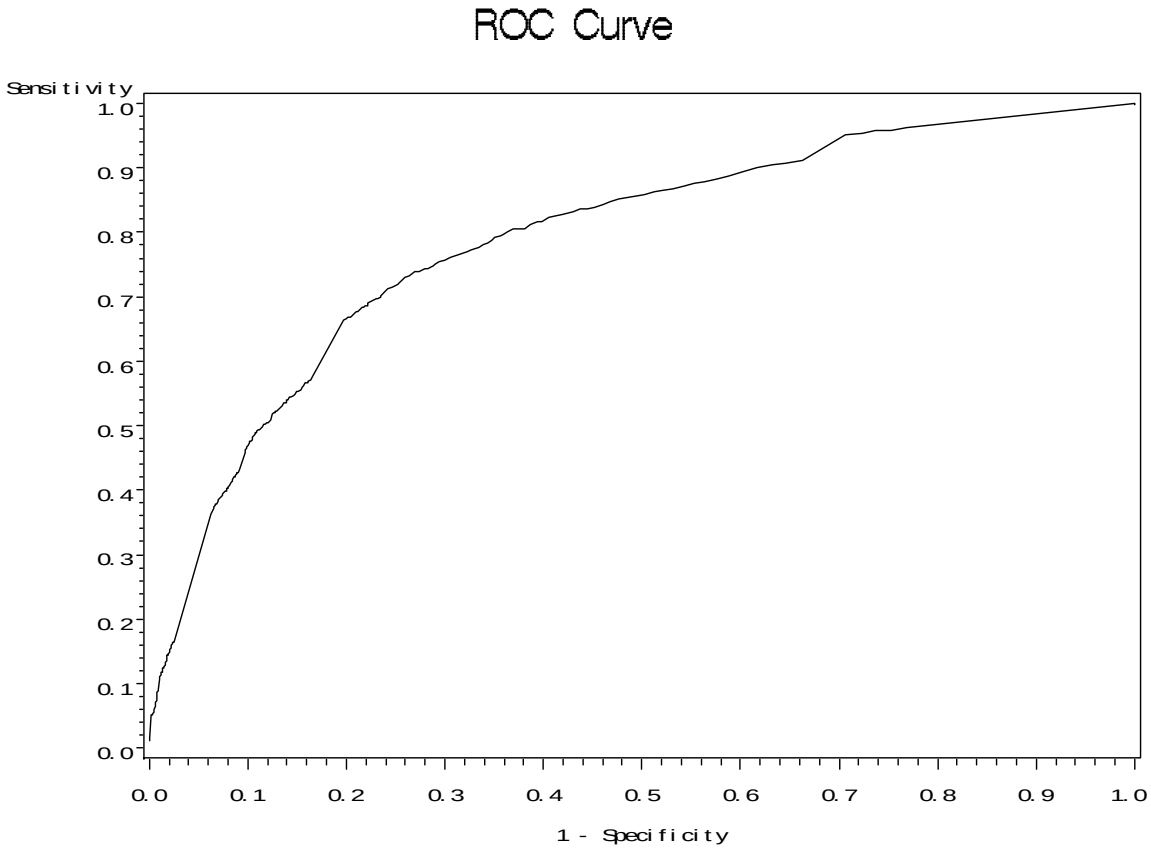
Receiver operating characteristics curve of *median gap* as predictor of long term discontinuation (C statistic= 0.59).



Receiver operating characteristics curve of *mean gap* as predictor of long term discontinuation (C statistic= 0.64).



Receiver operating characteristics curve of *total gap* as predictor of long term discontinuation (C statistic= 0.79).



The Right Site ® – executive edition software of EASI was used to identify each subject's census block.

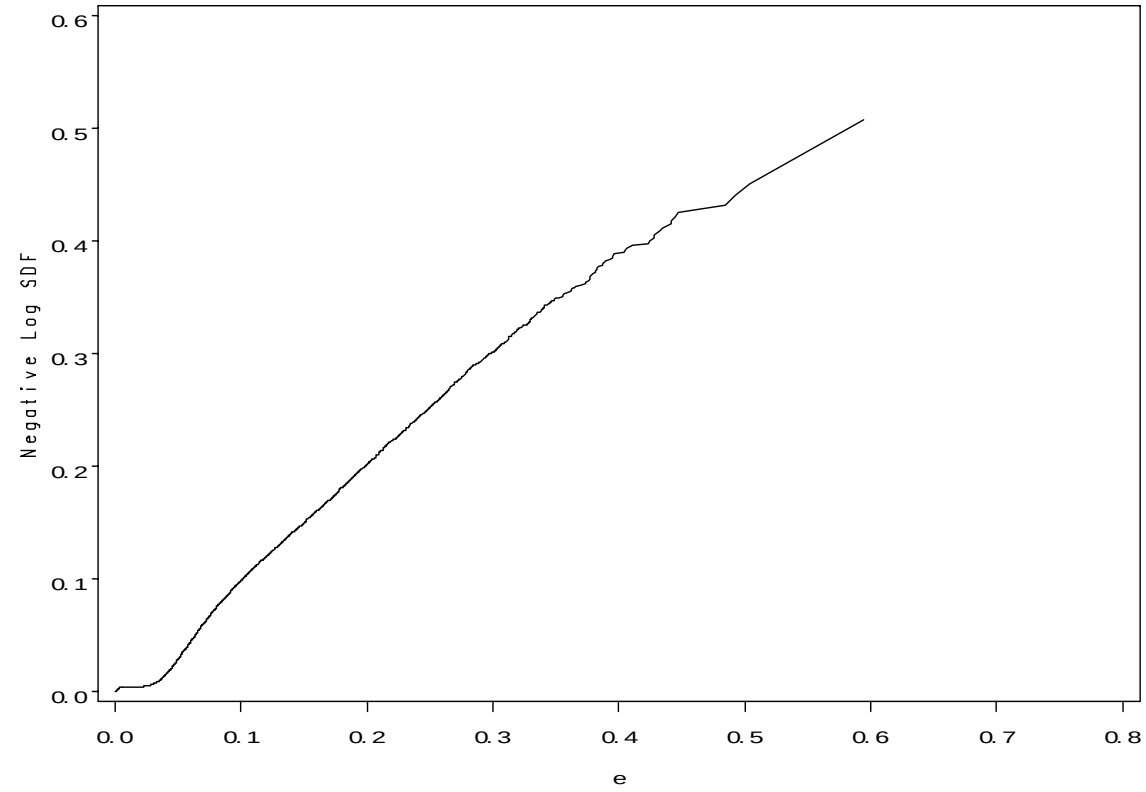
EASI is a New York based independent developer and marketer of demographic data/ software. The Right Site ® – executive edition software of EASI was used for the analysis. The ZIP Plus 4's of each study subject's usual place of residence available in the pharmacy benefit manager data was used to identify the census block groups in which each subject resides with the help of the software. Census block groups represent census geostatistical neighborhoods that contain households with relatively homogeneous economic and social living conditions. The boundaries of these areas have been drawn along recognizable divisions between neighborhoods by the United States Census Bureau to create units that are as homogeneous as possible in socio-economic terms. Once a census block group is assigned from the place of residence to an individual, socio-economic variables and race is ascribed to each subject as percent race (white/African American/Asian/other); percent ethnicity (hispanic/nonhispanic) and other socio demographic characteristics.

The following are the steps used by EASI to create ZIP Plus 4 (ZIP+4) and Block Group mailable households in order to update the demographic and economic characteristics for the United States. At first, EASI develops a split Block Group file and a plurality file of these matches using the latest TIGER file. This determines which Block Group (primary) each ZIP+4 should be assigned to. The TIGER files give directly about 85% of the matches of the correct ZIP+4 to the Block Groups in this way. For the remaining 15% balance of the ZIP+4s a distance formula is calculated to identify which Block Group is the closest to each ZIP+4. A subjective factor is assigned to each ZIP+4

based upon the possible other Block Groups that are almost as close as the closest ZIP+4. For this paper, the most current (2006) census block socio demographic measures from the census bureau were used.

EASI makes numerous checks for internal and external consistency in their estimates. There are 3 types of checks that are rigorously reviewed. These include; census internal consistency, controlling updates to definitions of estimates, and correcting for, or preventing, rounding errors, especially in small geographies.

Objective 2: Test for model assumption: Cox Snell residual plot



ALTERNATIVE APPROACH FOR EXAMINING THE IMPACT OF MEDICATION NONADHERENCE ON RATES OF HOSPITALIZATION AND EMERGENCY ROOM VISITS

Another approach was used to examine the impact of medication nonadherence on rates of hospitalization and emergency room visits. In this approach, refilling behavior of each subject was determined during the first year after index prescription (*observation period)*. An 18 month *follow-up period* subsequent to the end of each subject's observation period was used to identify number of hospitalizations and emergency rooms visits for both adherent as well as nonadherent subjects (Fig).

The mean number of all-cause hospitalization and emergency room visits in the follow-up period was 0.8 (median 0; SD 1.7) and 0.7 (median 1; SD 9.8) respectively, whereas the mean number of cardiovascular-specific hospitalization and emergency room visits in the follow-up period was 0.05 (median 0; SD 0.3) and 0.05 (median 0; SD 0.27) respectively. Since the risk of emergency room visits as well as hospitalizations may be correlated during the observation and follow up period, in addition to the confounders that were considered in the first approach, rates of hospitalizations and emergency room visits during the observation period (baseline) were also controlled for in the log-linear regression model.

Results of the log-linear regression model are shown in Table. The unadjusted relative risk for *all-cause emergency room visits* was significantly higher in the nonadherent group than the adherent group, but there was no difference between the two

groups in the adjusted model. Although the unadjusted relative risk and adjusted relative risk of *cardiovascular-specific emergency room visits* was higher in the nonadherent group than the adherent group, the confidence intervals failed to reach statistical significance. The nonadherent group in both the unadjusted as well as the adjusted model showed significantly increased risk for *all-cause hospitalizations* than the adherent group. Although the *cardiovascular-specific hospitalizations* risk was higher in the unadjusted as well as the adjusted models in the nonadherent group than in the adherent group, the confidence intervals failed to reach statistical significance.

This approach has the advantage of preventing bias due to reverse causality. Even though the point estimates (RR) for hospitalizations and emergency room visits for nonadherent subjects were consistently higher than adherent subjects in almost all models, the confidence intervals failed to reach significance in almost half of the models. This reason for this may be due to relatively short follow-up of subjects (18 months) which may result in insufficient number of events (health care utilizations) in order to see a cause-effect relationship.

Fig: Definitions of measurements during the study period.

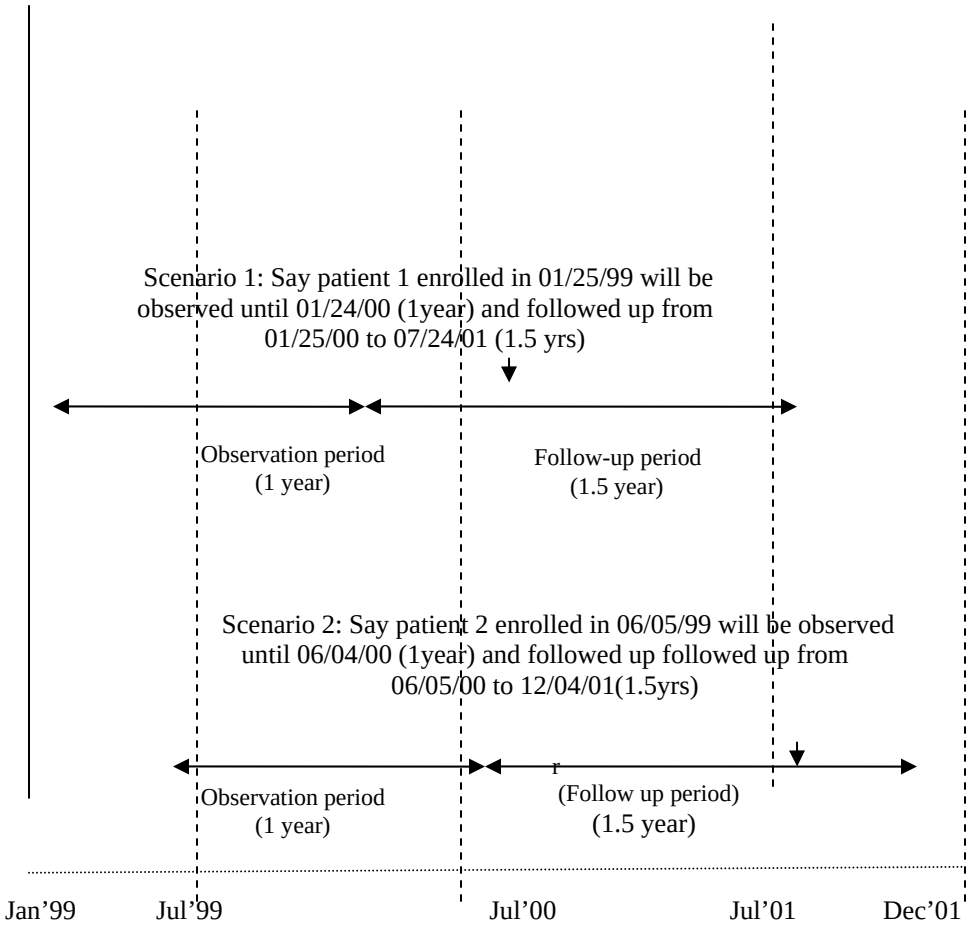


Table: Log-linear regression model results showing nonadherence as predictor of hospitalizations and emergency room visits. New Jersey, Medicaid, United States (N=9,945), 1999-2001.

Characteristics	*Unadjusted RR (CI)*	Adjusted RR(CI)
Emergency Room Visits		
Model type:		
All cause	1.10 (1.07-1.12)	0.98 (0.96-1.01)
Hypertension specific	1.09 (0.89-1.34)	1.11 (0.90, 1.36)
Hospitalizations		
Model type:		
All cause	1.07 (1.01-1.13)	1.12 (1.06-1.17)
Hypertension specific	1.03 (0.83, 1.29)	1.11 (0.89, 1.38)

Note: Adjusted risk ratios were obtained after controlling for the effects of age, race, gender, number of comorbid conditions and number of emergency room visits as well as hospitalizations in the observation period.

Curriculum Vitae

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Publications

1. Junaid I, Paz R, Salihu HM, **Sharma PP** Aliyu ZY. Pseudo-Meig's syndrome with multiple synchronous benign and malignant pelvic tumors. Archives of Gynecology and Obstetrics 2005; Sep 1;1-4
2. Salihu HM, Garces I, **Sharma PP**, Kristensen S, Ananth CV, Kirby RS. Stillbirth and infant mortality among Hispanic singletons, twins and triplets in the United States. Obstetrics & Gynecology 2005; 106:789-796.
3. Salihu HM, Emusu D, **Sharma PP** ,Aliyu ZY, Oyelese Y, Druschel CM, Kirby RS. Parity effect on preterm birth and growth outcomes among omphalocele-affected infants. European Journal of Obstetrics and Gynecology & Reproductive Biology 2006 Sep-Oct; 128(1-2):91-6.
4. Salihu HM, **Sharma PP**, Kristensen S, Blot C, Alio AP, Ananth CV, Kirby RS. Risk of stillbirth following a cesarean section: African American-white disparity. Obstetrics & Gynecology. 2006 Feb;107(2 Pt 1):383-90
5. **Sharma PP**, Salihu HM, Oyelese Y, Ananth CV, Kirby RS. Is race a determinant of stillbirth recurrence? Obstetrics & Gynecology 2006 Feb; 107(2 Pt 1):391-7.
6. Salihu HM, **Sharma PP** ,Ekundayo OJ, Kristensen S, , Badewa AP, Kirby RS, Alexander GR. Childhood pregnancy (10-14 years old) and risk of stillbirth in singletons and twins. Journal of Pediatrics. 2006 Apr; 148(4):522-6.
7. **Sharma PP**, Salihu HM. Very low maternal age (10-14) and stillbirth phenotypes. Archives of Gynecology and Obstetrics 2006 Apr; 274(1):19-20.
8. Salihu HM, **Sharma PP**, Aliyu MH, Kristensen S, Grimes-Dennis J, Kirby RS, Smulina J. Is small for gestational age a marker of future fetal survival in utero? Obstetrics & Gynecology 2006 Apr; 107(4):851-6.
9. Salihu HM, Bagchi S and **Sharma PP**. A novel method of quantifying birth weight discordance in quadruplets. American Journal of Perinatology. 2006 May; 23(4):223-8.
10. Salihu HM, **Sharma PP**, Peters S. Twinning and risk for stillbirth subtypes in pediatric mothers. Twin Research and Human Genetics. 2006 Oct; 9(5):673-6.
11. **Sharma PP**, Salihu HM, Kirby RS. Stillbirth recurrence in a population of relatively low risk mothers. Pediatric and Perinatal Epidemiology. 2007 Jul; 21 (s1):24 July 2007.