ORIGINAL ARTICLE

Overestimation of the effects of adherence on outcomes: a case study in healthy user bias and hypertension

Joanne LaFleur,[1,2] Richard E Nelson,[2,3] Brian C Sauer,[2,3] Jonathan R Nebeker[4]

[1]Department of Pharmacotherapy, University of Utah, Salt Lake City, UT, USA
[2]Informatics, Decision Enhancement, and Surveillance (IDEAS) Center, VA Salt Lake City Health Care System, Salt Lake City, UT, USA
[3]Department of Medicine, University of Utah, Salt Lake City, UT, USA
[4]Geriatrics Research, Education, and Clinical Center, VA Salt Lake City Health Care System, Salt Lake City, UT, USA

Correspondence to
Joanne LaFleur, Assistant Professor, Department of Pharmacotherapy, University of Utah, 30 S. 2000 East, Room 258, Salt Lake City, Utah, 84112, USA;
joanne.lafleur@pharm.utah.edu

Accepted 2 April 2011
Published Online First 17 May 2011

ABSTRACT

Background The healthy user bias is usually overlooked as an explanation in studies in which a strong association is found between poor patient medication adherence and worse disease outcomes. Such studies are increasing in frequency across disease states and influence clinical practice. Adherence to antihypertensive medications was studied to illustrate confounding in such studies.

Methods Using data from veterans with hypertension starting antihypertensive treatment, causal models were developed that predicted the risks of hospitalisation, myocardial infarction (MI) and death associated with poor adherence (<80%) while adjusting for patient demographics, baseline disease severity and disease comorbidity. In a second set of otherwise identical models, adjustment was made for time-varying blood pressure (BP), thus controlling for adherence effects that were mediated through the main pharmacological effects of the drugs. It was hypothesised that the second set of models would reveal a positive association between poor adherence and adverse disease outcomes that is largely explained by unmeasured confounders, including health-related behaviours.

Results The models that did not adjust for time-varying BP levels showed that patients with poor adherence had statistically significantly increased risks of 3.7% for hospitalisation, 28.1% for MI and 23.3% for death. These estimates exceed the benefits of these drugs demonstrated by clinical trials. When controlling for time-varying BP, the increased risks were similar (3.4% for hospitalisation, 27.7% for MI and 23.4% for death). The findings were consistent across a range of adherence thresholds (50–90%) and when allowing disease status variables to vary.

Conclusions The associations between poor adherence and outcomes are largely independent of the pharmacological effects of the drugs on BP control as well as commonly measured patient covariates. This finding suggests that even carefully designed observational adherence studies using rich clinical data are impossibly confounded and probably overestimate the true magnitude of the effect. Clinical practice guidelines based on reported adherence effects should be reconsidered.

BACKGROUND

Observational studies attempting to show increased risks of adverse outcomes due to poor adherence are becoming increasingly popular across a wide range of disease states.[1–10] These types of studies are often used to support decisions in clinical care. For example, three observational studies that showed increased risks of death, myocardial infarction (MI) and stent thrombosis in patients who discontinued thienopyridine therapy following stent placement[11–13] prompted a new clinical guideline recommending that the duration of antiplatelet therapy be extended following stent placement.[14] In hypertension, reported effect sizes of low versus high adherence include a 15–194% increased risk of any-cause hospitalisation,[15–18] 43% increased risk of cardiovascular hospitalisation,[18] 15–61% increased risk of acute cardiovascular disease events[3 19] and 50–74% increased risk of death.[17 20] This is in contrast to intention-to-treat results of clinical trials where patients who took antihypertensive medications versus no exposure experienced no statistically significant effect on hospitalisation, only 11–30% decreased risk of cardiovascular events and only 11–17% decreased risk of death.[21] When we examine the inference that imperfect adherence to antihypertensive agents could put patients at greater risk than no exposure at all, it suggests that the causal effect of adherence on outcomes is overestimated in these observational studies. Consequently, decisions to change care recommendations may be misguided.

One potential explanation for the overestimation in such studies is the 'healthy user' hypothesis,[22] which suggests that adherence to pharmacotherapy may be a surrogate marker for other important health-related behaviours, as illustrated in figure 1. This bias has been proposed as an explanation for the now outmoded belief that hormone replacement therapy could protect postmenopausal women from cardiovascular disease events,[23] the supposed effect of lipid-modifying therapy on preventing hip fractures[24] and an apparent protective benefit of statins in community-acquired pneumonia.[25] Perhaps the most compelling evidence of the healthy user effect comes from a meta-analysis showing decreased mortality in clinical trial patients who were adherent to placebo compared with those who were non-adherent to placebo.[26] In most studies, including adherence studies, healthy user bias is overlooked as a potential explanation for findings.

A study was undertaken to explore the role of healthy user effects in these types of studies. We used the best available methods and secondary observational data to create causal models for the associations between poor patient adherence to antihypertensive medications and three outcomes

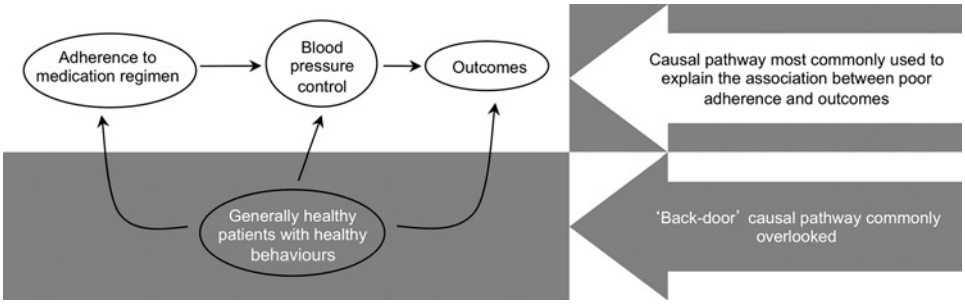

Figure 1 Directed acyclic graph illustrating 'healthy user' bias. The unshaded portion of the drawing shows the indirect causal effect of medication adherence on outcomes that is mediated through blood pressure control. Better medication adherence improves blood pressure control, which in turn decreases risks of death, hospitalisation, myocardial infarctions, and other outcomes. Conversely, worse medication adherence leads to worse blood pressure control and to increased risks for those outcomes. There is no direct effect of adherence on outcomes that is independent of the pharmacologic effects of the drug. The shaded portion of the drawing shows that other healthy behaviours, such as following instructions about exercise, diet and other medications, quitting smoking, getting recommended cancer screenings, etc., are associated with adherence, blood pressure control, and outcomes. If healthy patient behaviours are uncontrolled in an analysis, this "healthy user" pathway confounds the relationship between adherence and outcomes.

including MI, any-cause hospitalisation and death. We then contrasted two versions of these models—those that adjusted for time-varying blood pressure (BP) levels and those that did not. We theorised that adjusting out the indirect effects of adherence on outcomes that were mediated through effects on BP—while also adjusting for patient demographics, disease severity and comorbid conditions—would show that unmeasured confounding was present since there is no plausible explanation for direct effects of adherence on these outcomes.

METHODS

Study design and patients

A cohort design was used to study the risks of any-cause hospitalisation, MI and any-cause death in a nationally representative sample of veterans from six regions of the USA (Northwest, Southwest, West, Midwest, Northeast and Southeast). From these data we randomly sampled 100 000 patients who (1) had received one of five antihypertensive classes considered by the JNC-7 to be cardioprotective and first-line[27] (ie, thiazide diuretics, ACE inhibitors, angiotensin receptor blockers, β-blockers and calcium channel blockers) between 1 October 2002 and 31 December 2004; (2) were at least 18 years old on the index date (the date of the first prescription for an antihypertensive agent); and (3) had no prescription for an antihypertensive agent in the year prior to the index date. Patients were then excluded if they did not have at least one BP reading on or before the index date and at least one during the follow-up period.

Sample size was determined by calculating the number of observations needed to avoid over-fitting predictive multivariable models using the heuristic that 10 events were required for each covariate. From a similar analysis conducted using data from a subset of veterans in our western region,[28] we knew that we might have up to 50 levels of covariates in our final models, meaning that we would need at least 500 events. From the same data, we also calculated that the rarest of our three endpoints of interest (MI) occurred in about two patients per 1000 person-years with an average follow-up time of 4.1 years, suggesting we would need approximately 65 000 patients to avoid over-fitting. We also estimated that we would exclude about 25% of our cohort because of a lack of baseline and follow-up BP measures and determined that randomly sampling 100 000 patients would yield enough patients to avoid over-fitting.

Independent variables

The primary independent variable was adherence to antihypertensive medications, which was calculated using a cumulative measure of medication availability (CMA).[29] The CMA was based on pharmacy refill data from the VA's Decision Support System datasets and was calculated as the sum of days on which medications were available in the numerator divided by the number of days between the first fill and the last day of supply dispensed with the last fill of an antihypertensive therapy in the denominator. The CMA was dichotomised at an adherence threshold of 80%, with patients whose ratio was ≥0.8 considered adherent and patients whose ratio was <0.8 considered non-adherent. The adherence measure was calculated for all five classes of antihypertensive medications together; if patients switched between classes they were considered to be adherent as long as their overall adherence ratio for antihypertensive medications was ≥0.8. Adherence was treated as cumulative and time-varying; ratios were calculated for each quarter following the initiation of treatment and updated at each subsequent quarter. Adherence was lagged so that cumulative adherence in each quarter predicted events in the subsequent quarter until patient censorship.

Confounding was handled by direct adjustment for other independent variables. These were selected based on their known or theoretical associations with the outcomes of interest and their availability in the dataset. Covariates included sociodemographic characteristics (sex, marital status and socioeconomic status (SES)); disease severity (baseline BP and levels of ischaemic disease); and comorbid conditions (chronic obstructive pulmonary disorder, diabetes, cancer, psychological disorders, physical disabilities, smoking disorder, sleep apnoea and thyroid disorder). Covariates were obtained using vital signs from the VA's Corporate Data Warehouse; labs, diagnosis codes and procedure codes from the VA's Medical SAS datasets (inpatient and outpatient records so named because they are kept in SAS format); and pharmacy refill data from VA's Decision Support System datasets. The primary models included only baseline adjustment for each of these covariates.

Outcomes

The outcomes of interest were any-cause hospitalisation, MI and any-cause death. Any-cause hospitalisation information was captured from the inpatient files of the Medical SAS datasets. MI was identified from inpatient and outpatient files from Medical SAS datasets using the ICD-9 codes 410.01 (acute MI of the anterolateral wall, initial episode of care), 410.11 (acute MI of other anterolateral wall, initial episode of care) and 410.21 (acute MI of inferolateral wall, initial episode of care). The occurrence of death was identified using the Beneficiary Identification Records Locator Subsystem death file kept by the VA

Benefits Administration which contains information on veterans known to be deceased. The file is updated weekly by matching with the Social Security Administration Death Master File. The file is also updated when a hospital, cemetery, relative or acquaintance of a veteran reports a veteran's death.

Statistical analysis

Descriptive statistics were used to characterise the baseline demographic data of the cohort. Univariate and multivariable Cox proportional hazards models with time-varying exposures were used to measure the association between independent variables and each outcome. Multivariable models were constructed by reviewing the literature and considering the causal mechanisms for variables that can potentially confound the relationships of interest, regardless of whether the associations were found to be statistically significant in this dataset.

We developed models that incorporated all of the available variables that would theoretically be expected to be important for unmasking the relationship between patient adherence to antihypertensive medications and hospitalisation, MI or death. For each endpoint we contrasted two models that were identical in all respects except that one did not adjust for time-varying BP level and one did. By adjusting for time-varying BP, we were essentially blocking the pathway between adherence and outcomes that is mediated through the pharmacological effects of the drug. We theorised that any association that remained after blocking that pathway must be mediated through other pathways. Because we had also adjusted for patient demographics, disease severity and comorbidity in both sets of models, the remaining pathways must be limited and must include unmeasured healthy behaviours.

All models included baseline BP so the analyses controlled for the follow-up level of BP in addition to the changes. In the models that adjusted for time-varying BP as an explanatory variable, follow-up BPs were coded as five categorical variables: low (diastolic ≤70), normal (systolic <120 and diastolic and >70 but <80); pre-hypertension (systolic 120–139 or diastolic 80–89); stage 1 hypertension (systolic 140–159 or diastolic 90–99); and stage 2 hypertension (systolic ≥160 or diastolic ≥100). Patients were censored at the occurrence of an event, in the quarter following discontinuation of the drug, or 31 December 2007, whichever occurred first. All statistical tests were performed using Stata SE V.10 and SAS V.9.

Sensitivity analyses

In accordance with guidelines from the International Society for Pharmacoeconomics and Outcomes Research,[30] multiple alternative adherence thresholds were evaluated in sensitivity analyses including 50%, 60%, 70% and 90%. Sensitivity analyses were also conducted that (1) did not allow BP control to vary over time (ie, BP was coded as the hypertension level at the end of the entire follow-up period); (2) allowed other explanatory variables to vary over time, with patients contributing person-time to different levels of each covariate on a quarterly basis if their conditions changed over time; and (3) excluded the days supplied with the last fill from both the numerator and the denominator for the calculation of the adherence ratio, since the algorithm we used assumes 100% adherence in that interval. Time-varying independent variables were lagged by one quarter so that the statistical analysis captured the effect of patient characteristics on outcomes in the subsequent quarter. By lagging these variables we avoided the situation in which a change in disease status that occurred at the end of a quarter predicted an event that occurred earlier in the same quarter.

RESULTS

Patients and blood pressure readings in the follow-up period

Of 100 000 randomly sampled veterans who met our inclusion criteria, a total of 80 359 had at least one BP recorded at baseline and in the follow-up period. Of these, 4475 were excluded because of missing zip codes (from which the SES index was calculated), leaving 75 884 patients in the final analysis. Baseline demographic characteristics for the cohort are summarised in table 1. The mean age of the veterans was 65.7 years and they were predominantly male (96.7%). By definition, patients were approximately evenly distributed among quartiles of SES index categories, an index based on several demographic variables obtained by linking the zip code with 2000 census data.[31] The mean (SD) number of post-index BPs per patient was 30.2 (62.2); in each quarter each patient had a mean of 2.1–5.0 BP observations. The mean (SD) change from baseline for systolic BPs in each quarter following the index date ranged from −3.05 (25.2) mm Hg in the first quarter to −15.7 (30.0) mm Hg in the penultimate quarter for systolic BP and from −1.8 (14.8) mm Hg in the first quarter to −8.9 (16.0) mm Hg in the last quarter for diastolic BP.

Outcomes

A total of 14 315 patients in our study cohort had a hospitalisation, 1063 had an MI and 1132 died between the index date and discontinuation of the index regimen over an average follow-up time of 3.2–3.5 years. This corresponds to incidence rates of 61.4 hospitalisations, 4.0 MIs and 4.2 deaths per 1000 person-years. Table 2 shows a summary of the risks for each outcome associated with poor adherence to antihypertensive medications for the two models in the base case as well as sensitivity analyses. In the first set of models (those that did not control for time-varying BP levels), a cumulative adherence ratio of <80% was associated with a 3.7% increased risk of hospitalisation (95% CI 1.01 to 1.07), a 28.1% increased risk of MI (95% CI 1.08 to 1.52) and a 23.3% increased risk of death (95% CI 1.06 to 1.43) compared with patients with good adherence, while adjusting for baseline demographics, disease severity and comorbidity. When also controlling for time-varying BP, the magnitude of the association between poor adherence and each outcome was very similar. In this second set of models, poor adherence was associated with a 3.4% increased risk of hospitalisation (95% CI 1.00 to 1.07), a 27.7% increased risk of MI (95% CI 1.08 to 1.52) and a 23.4% increased risk of death (95% CI 1.06 to 1.44). Sensitivity analyses consistently showed similar results.

DISCUSSION

Our findings support the conclusion that much of the association between poor adherence and worse outcomes is mediated through a pathway other than the pharmacological effects of antihypertensive medications on BP. Similar to the findings of other researchers,[3 15–19] we showed a substantial increase in the risk of MI (28%) and death (23%) associated with poor adherence to antihypertensive agents over an average follow-up of more than 3 years. Counter to intuition, this difference was present whether or not we controlled for time-varying BP, a finding that was consistently reproduced in all sensitivity analyses. If a considerable amount of the association between poor adherence to antihypertensive medications and patient outcomes was mediated through the pharmacological action pathway illustrated in the unshaded area of figure 1, then we would have observed a considerable difference between the models that did and did not adjust for time-varying BP. Instead, our results are consistent with the hypothesis that most of this

Table 1 Descriptive statistics of the cohort at baseline

	All patients (N = 75 884)		Adherent (CMA ≥0.80) at the end of observation (N = 24 650)		Non-adherent (CMA <0.80) at the end of observation (N = 51 234)	
	Frequency	%	Frequency	%	Frequency	%
Age (years)						
0–50	6493	8.6	1759	7.14	4734	9.24
50–54	7101	9.4	2355	9.55	4746	9.26
55–59	11 746	15.5	4188	16.99	7558	14.75
60–64	8768	11.6	3157	12.81	5611	10.95
65–69	9755	12.9	3532	14.33	6223	12.15
70–74	11 781	15.5	4029	16.34	7752	15.13
75–79	10 863	14.3	3310	13.43	7553	14.74
80+	9378	12.4	2320	9.41	7057	13.77
Number of hospitalisations in year prior to index						
0	69 450	91.52	22 937	93.05	46 513	90.79
1	4534	5.97	1272	5.16	3262	6.37
2	1222	1.61	306	1.24	916	1.79
3	386	0.51	93	0.38	293	0.57
4	172	0.23	32	0.13	140	0.27
5	60	0.08	9	0.04	51	0.10
≥6	60	0.08	1	0.00	59	0.11
Body mass index (kg/m^2)						
Underweight (<18.5)	1766	2.33	473	1.92	1293	2.52
Normal weight (18.5–24.9)	12 668	16.69	3288	13.34	9380	18.31
Overweight (25–29.9)	28 544	37.62	9329	37.85	19 215	37.50
Obese (30–34.9)	20 276	26.72	7133	28.94	13 143	25.65
Extremely obese (35+)	12 630	16.64	4427	17.96	8203	16.01
Sex						
Female	2527	3.3	770	3.12	1757	3.43
Male	73 357	96.67	23 880	96.88	49 477	96.57
SES index*						
Highest quartile	18 033	23.76	5857	23.76	12 176	23.77
2nd quartile	16 117	21.24	5411	21.95	10 706	20.90
3rd quartile	19 162	25.25	6387	25.91	12 775	24.93
Lowest quartile	22 572	29.75	6995	28.38	15 577	30.40
Baseline blood pressure						
Normal (SBP <120 and DBP <80)	6235	8.22	1897	7.70	4338	8.47
Prehypertension (120≤SBP<140 or 80≤DBP<90)	39 321	51.82	13 046	52.92	26 275	51.28
Stage I hypertension (140≤SBP<160 or 90≤DBP<100)	22 718	29.94	7339	29.77	15 379	30.02
Stage II hypertension (SBP ≥160 or DBP ≥100)	7610	10.03	2368	9.61	5242	10.23
COPD						
No COPD	63 505	83.69	21 148	85.79	42 357	82.67
Treated COPD	7688	10.13	2122	8.61	5566	10.86
Untreated COPD	4691	6.18	1380	5.60	3311	6.46
Diabetes						
No diabetes	48 947	64.50	15 487	62.83	33 460	65.31
Controlled diabetes (A1c ≤7)						
Treated with oral medications and no complications†	8293	10.93	2883	11.70	5410	10.56
Treated with oral medications and with complications†	828	1.09	280	1.14	548	1.07
Treated with insulin and no complications†	2139	2.82	679	2.75	1460	2.85
Treated with insulin and with complications†	766	1.01	222	0.90	544	1.06
Uncontrolled diabetes (A1c >7)						
Treated with oral medications and no complications†	5042	6.64	1804	7.32	3238	6.32
Treated with oral medications and with complications†	770	1.01	291	1.18	479	0.93
Treated with insulin and no complications†	2818	3.71	908	3.68	1910	3.73
Treated with insulin and with complications†	1409	1.86	455	1.85	954	1.86

Continued

Table 1 Continued

	All patients (N = 75 884)		Adherent (CMA ≥0.80) at the end of observation (N = 24 650)		Non-adherent (CMA <0.80) at the end of observation (N = 51 234)	
	Frequency	%	Frequency	%	Frequency	%
Untreated and no complications†	4590	6.05	1568	6.36	3022	5.90
Ischaemic heart disease						
No ischaemic heart disease‡						
No risk factors§ and no antihyperlipidaemia medications	19 869	26.18	5833	23.66	14 036	27.40
No risk factors§ and with antihyperlipidaemia medications	21 240	27.99	7606	30.86	13 634	26.61
Risk factors§ present and no hyperlipidaemia medications	6420	8.46	2101	8.52	4319	8.43
Ischaemic heart disease‡						
Treated with hyperlipidaemia medications	20 766	27.37	7098	28.80	13 668	26.68
Untreated with hyperlipidaemia medications	7589	10.00	2012	8.16	5577	10.89
Cancer						
No cancer diagnosis or treatment	61 056	80.46	19 894	80.71	41 162	80.34
Cancer diagnosis or treatment	14 828	19.54	4756	19.29	10 072	19.66
Psychiatric disorders						
No psychiatric disorders and no psychiatric treatment	37 151	48.96	12 431	50.43	24 720	48.25
Treated psychiatric disorders	4029	5.31	1188	4.82	2841	5.55
Untreated psychiatric disorders	34 704	45.73	11 031	44.75	23 673	46.21
Disability						
No disability diagnosis	54 881	72.32	17 661	71.65	37 220	72.65
Disability diagnosis	21 003	27.68	6989	28.35	14 014	27.35
Sleep apnoea						
No sleep apnoea diagnosis	72 192	95.13	23 361	94.77	48 831	95.31
Sleep apnoea diagnosis	3692	4.87	1289	5.23	2403	4.69
Thyroid disorder						
No thyroid disorder or treatment	69 781	91.96	22 742	92.26	47 039	91.81
Treated thyroid disorder	5139	6.77	1605	6.51	3534	6.90
Untreated thyroid disorder	964	1.27	303	1.23	661	1.29

*SES, socioeconomic status categories were defined by linking on zip code with United States 2000 census data and were constructed from variables for median annual household income, percentage below poverty level, percentage of households receiving Social Security income, percentage of households on public assistance, median home value, percentage of owner-occupied homes, median home construction year, percentage room occupancy of ≤1 person, population density, percentage managerial occupations, percentage unemployed, percentage with some high school or less and percentage of single parent households.
†Diabetes complications included ketoacidosis, coma, renal manifestations, ophthalmic manifestations, neurological manifestations and peripheral circulatory disorders.
‡Ischaemic heart disease includes diagnoses for coronary artery disease, myocardial infarction, angina, peripheral vascular disease and cardiovascular disease.
§Ischaemic heart disease risk factors included diagnoses of hyperlipidaemia or dyslipidaemia, or low-density lipoprotein cholesterol >160.
A1c, haemoglobin A1c; CMA, medication adherence ratio (cumulative measure of medication availability); COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

association is independent of the pharmacological actions of the drug on BP and must have other causes, such as the 'healthy user' pathway illustrated in the shaded area of figure 1.

The problem we illustrate here is conceptually similar to the problem of reporting 'per-protocol' or 'as-treated' analyses versus 'intention-to-treat' (ITT) analyses in the clinical trial literature. Essentially, it has been repeatedly shown that non-adherent patients in randomised controlled trials (RCTs) have worse outcomes and that it is both biologically implausible and contradicted by the results of ITT analyses to suppose that this usually strong association is a treatment effect.[32–34] This conclusion has resulted in a CONSORT (Consolidated Standards of Reporting Trials) guideline that discourages exclusive reporting of per-protocol analyses in RCT publications.[35] Adherence studies are analogous to per-protocol analyses in which patient characteristics determine both the extent to which patients will experience the exposure and their degree of risk for adverse outcomes, resulting in highly confounded effect estimates.

We considered a variety of alternative observational methods that might avoid the confounding that we demonstrated: First, similar causal models developed using logistic regression have the same structural confounding shown in figure 1. Second, the case crossover design and other within-subject designs are able automatically to address time-invariant confounding. These methods have been developed to evaluate the acute effects of intermittent exposure, but their use is not as well understood under time-varying treatment and cumulative effects of drug exposures.[36 37] Moreover, they are not suited to the adherence problem because a strong and probably untenable assumption must be made that other important healthy user factors do not covary with adherence. Third, instrumental variables may be useful to minimise unmeasured confounders, but there are no known instruments that are useful for adherence studies in the observational setting. Finally, newer techniques such as marginal structure models and inverse probability weighting may be better at capturing both the exposure and the measured confounders by treating the exposure and covariates as processes that evolve over time, but they do not adequately control for unmeasured patient confounders. It is most likely that the only way to assess the causal effect of adherence on outcomes is in the RCT setting and with the use of instrumental variables and

Table 2 Risk of events associated with poor adherence

	Without time-varying BP*		With time-varying BP†	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Any-cause hospitalisation				
CMA ≥0.50 vs <0.50	1.081 (1.032 to 1.123)	0.0003	1.076 (1.037 to 1.128)	0.0007
CMA ≥0.60 vs <0.60	1.062 (1.017 to 1.099)	0.0021	1.058 (1.022 to 1.104)	0.0046
CMA ≥0.70 vs <0.70	1.060 (1.022 to 1.094)	0.0007	1.057 (1.025 to 1.097)	0.0012
CMA ≥0.80 vs <0.80	1.037 (1.006 to 1.069)	0.0204	1.034 (1.003 to 1.066)	0.0302
CMA ≥0.90 vs <0.90	1.022 (0.993 to 1.050)	0.1191	1.021 (0.994 to 1.051)	0.1434
Non-time-varying‡	1.444 (1.356 to 1.537)	<0.0001	1.429 (1.342 to 1.521)	<0.0001
All time-varying§	1.049 (1.018 to 1.082)	0.0021	1.047 (1.015 to 1.079)	0.0034
Censored at last fill¶	1.032 (1.001 to 1.065)	0.043	1.030 (0.999 to 1.063)	0.059
Myocardial infarction				
CMA ≥0.50 vs <0.50	1.616 (1.304 to 2.002)	<0.0001	1.603 (1.293 to 1.987)	<0.0001
CMA ≥0.60 vs <0.60	1.534 (1.255 to 1.876)	<0.0001	1.525 (1.247 to 1.866)	<0.0001
CMA ≥0.70 vs <0.70	1.332 (1.101 to 1.612)	0.0032	1.326 (1.095 to 1.605)	0.0038
CMA ≥0.80 vs <0.80	1.281 (1.079 to 1.522)	0.0047	1.277 (1.075 to 1.516)	0.0054
CMA ≥0.90 vs <0.90	1.141 (0.973 to 1.339)	0.1052	1.142 (0.974 to 1.340)	0.1022
Non-time-varying‡	1.539 (1.258 to 1.883)	<0.0001	1.532 (1.258 to 1.883)	<0.0001
All time-varying§	1.381 (1.161 to 1.642)	0.0003	1.375 (1.156 to 1.635)	0.0003
Censored at last fill¶	1.301 (1.093 to 1.550)	0.003	1.298 (1.090 to 1.546)	0.003
Death				
CMA ≥0.50 vs <0.50	1.398 (1.160 to 1.685)	0.0004	1.402 (1.163 to 1.689)	0.0004
CMA ≥0.60 vs <0.60	1.307 (1.095 to 1.561)	0.0030	1.308 (1.095 to 1.562)	0.0030
CMA ≥0.70 vs <0.70	1.203 (1.016 to 1.424)	0.0317	1.209 (1.020 to 1.433)	0.0287
CMA ≥0.80 vs <0.80	1.233 (1.061 to 1.433)	0.0062	1.234 (1.06 to 1.436)	0.0066
CMA ≥0.90 vs <0.90	1.160 (1.008 to 1.334)	0.0377	1.163 (1.010 to 1.340)	0.0357
Non-time-varying‡	1.857 (1.581 to 2.182)	<0.0001	1.857 (1.580 to 2.182)	<0.0001
All time-varying§	1.403 (1.211 to 1.624)	<0.0001	1.399 (1.207 to 1.623)	<0.0001
Censored at last fill¶	1.262 (1.076 to 1.480)	0.004	1.261 (1.073 to 1.481)	0.005

*Model was adjusted for baseline demographics (age, sex, socieoeconomic index); disease severity (baseline BP categorised as normal, pre-hypertension, hypertension; levels of ischaemic disease categorised as no ischaemic disease and no hyperlipidaemia and no cardiovascular disease risk factors, no ischaemic disease and treated hyperlipidaemia and no cardiovascular disease risk factors, no ischaemic disease and untreated hyperlipidaemia and cardiovascular disease risk factors, ischaemic disease and treated hyperlipidaemia, ischaemic disease and untreated hyperlipidaemia); comorbid conditions (body mass index categorised as underweight, normal weight, overweight, obese; chronic obstructive pulmonary disease; diabetes categorised as no diabetes, controlled diabetes without treatment and no complications, controlled diabetes with oral antidiabetics and complications, uncontrolled diabetes with oral antidiabetics and no complications, uncontrolled diabetes with oral antidiabetics and complications, controlled diabetes with insulin and no complications, controlled diabetes with insulin and complications, uncontrolled diabetes with insulin and no complications, uncontrolled diabetes with insulin and complications, untreated uncontrolled diabetes with no complications, untreated uncontrolled diabetes with complications; cancer diagnosis or treatment; psychiatric disorder categorised as none, treated psychiatric disorders, untreated psychiatric disorders; sleep apnoea; thyroid disorder categorised as none, treated thyroid disorder, untreated thyroid disorder); and number of hospitalisations in the pre-index period.

†Model was adjusted for all covariates listed for Model * plus time-varying on-treatment quarterly BP level categorised as low (DBP ≤70), normal (SBP <120 and 70<DBP<80), prehypertension (120≤SBP<140 or 80≤DBP<90), stage I hypertension (140≤SBP<160 or 90≤DBP<100) and stage II hypertension (SBP ≥160 or DBP ≥100).

‡Model was adjusted for all baseline covariates listed for Model * plus non-time-varying BP level in the follow-up period; CMA threshold was <0.80 for non-adherent and ≥0.80 for adherent.

§Model was adjusted for all baseline covariates listed in Models * and ‡; all covariates were allowed to vary over time, with patients contributing to different levels of each covariate as disease status changed in the follow-up period; CMA threshold was <0.80 for non-adherent and ≥0.80 for adherent.

¶Model was adjusted for all baseline covariates listed in * above; the adherence ratio was calculated as the sum of days on which medication was available divided by the difference in days between the first and last fill, excluding the days supplied with the last fill.

CMA, medication adherence ratio (cumulative measure of medication availability); DBP, diastolic blood pressure; BP, blood pressure; HR, hazards ratio; SBP, systolic blood pressure.

nested structural models,[38–40] methods that do not directly apply to the observational setting.

We were surprised that the association between poor adherence and risk of hospitalisation did not change discernibly between analyses with and without time-varying BP. This finding was consistently reproduced throughout all of the sensitivity analyses. Upon examination of our data, we theorised that this lack of difference could be explained by a possible floor effect. The mean decrease in BP from baseline was greater among non-adherent patients by about 3 mm Hg in every quarter. The adherent patients, whose BPs were lower at baseline, could not experience reductions of the same magnitude as the non-adherent patients because their lower baseline BP afforded less room to improve. Nonetheless, the fact that we saw a consistent decrease in BP in both groups suggests that the antihypertensive medications did have a clinical effect on the patients.

A central question for our analysis is whether or not it is valid to assume that BP reduction mediates the effects of antihypertensive agents on outcomes. There is strong clinical trial evidence that antihypertensives both reduce BP and prevent the outcomes of interest,[21] but it is difficult to show a strong causal link between BP and outcomes. Vittenhoff recommends that three conditions should be present for concluding a variable is a mediator: (1) the predictor of interest (adherence) predicts the mediator (BP); (2) the mediator predicts the outcome (MI, hospitalisation or death) in a model controlling for the predictor of interest; and (3) adding the mediator to a multivariable model for the outcome attenuates the association for the predictor of interest.[41] The first condition is difficult to show in the

observational setting because of the unmeasured confounding that we highlight here. However, the matter is really a question of dose-response: poorly adherent patients are exposed to lower doses on average than adherent patients. We can infer from phase 2 clinical trials that higher levels of exposure are associated with greater reductions in BP than lower levels,[42–46] thus meeting the first condition. When we examined our data for the presence of the second condition we found that, indeed, patients whose treated BP level was in the normal range had a lower risk of events than patients with high treated BP levels, when adjusting for adherence. The third condition—that the addition of the mediator to a multivariable analysis attenuates the estimated coefficient for the predictor of interest—was also met, but the magnitude of the difference was very small. We contend that it was small because most of the effect appears to be mediated through other pathways, including the healthy user pathway illustrated in figure 1.

There could be other explanations for our findings. One could be that all of the pharmacological effects on outcomes are mediated through other direct effects of the drugs that are independent of changes in BP. For example, ACE inhibitors have renal protective effects in patients with diabetes,[47 48] and β blockers after MI improve outcomes in ways that are not mediated through BP.[49] The magnitudes of the associations between these direct effects and outcomes of interest are not well quantified, but it would be highly speculative to conclude that these alternative effects would overshadow the effects mediated through BP. Second, adherent patients may differ systematically from non-adherent patients in their access and utilisation of care outside the VA. In that case, VA-based outcomes such as hospitalisation and MI would be captured preferentially in one group, which could potentially overwhelm the effects of BP drugs in our models. However, this effect would not be present for the death outcome, which is reported by the Social Security Administration and is not dependent on a patient's care source. The fact that our results for the death endpoint are consistent with the other two endpoints suggests that differential identification of the outcomes is not driving our findings.

Limitations of the study

This analysis has some limitations. By introducing follow-up BP into the models we may have introduced a new type of confounding—uncontrolled common causes of both BP level and outcome risk—that is not present in analyses directly relating outcomes to adherence. Some of these causes—those that relate to behavioural factors—are included in figure 1; others may be independent of healthy user characteristics. For example, we could postulate a whole host of genetic or environmental factors that lead both to high BP and worse outcomes as well as low BP and better outcomes. Since this might result in many patients with good adherence having high BPs and worse outcomes as well as many others with bad adherence having low BPs and good outcomes, then the overall analysis when pooling these patient types within the two exposure categories would have the effect of attenuating the treatment effect in the models where we adjust for BP. Thus, our results are robust to this issue. Moreover, there may be known confounders that are not adequately measured in our data. For example, although we are able to adjust for diagnoses such as angina (a marker of disease severity), the data afford us little insight into symptom frequency, which would have improved discrimination of baseline severity. However, this latter is a limitation of all such secondary database studies.

CONCLUSIONS

We found that the associations between poor adherence to antihypertensive medications and outcomes such as hospitalisation, MI and death are largely independent of the pharmacological effects of these drugs on BP control while adjusting for patient demographics, disease severity and comorbidity. This suggests that other unmeasured confounders must explain most of the association between patient medication adherence and outcomes. Using the current array of epidemiological methods, observational studies that attempt to assess the effect of adherence on outcomes are impossibly confounded by healthy user bias and are likely to overestimate or misidentify any effect.

Acknowledgements The authors thank Dr Tom Greene for his thoughtful comments on drafts of this paper and Kristin Knippenberg for her careful editorial assistance. The authors would like to acknowledge the Agency for Healthcare Research and Quality (AHRQ) for a career development award supporting Joanne LaFleur (5K08HS018582), the National Cancer Institute for it's support of Richard E. Nelson (1KM1CA156723), and the VA's Health Services Research and Development (HSR&D) office for a career development award supporting Brian C Sauer.

Funding This project was supported by the Veterans Affairs (VA) Geriatric Research, Education, and Clinical Center (GRECC), the University of Utah Primary Care Research Center Scholarship and Novartis Pharmaceuticals.

Competing interests JL has support from the United States (US) Veterans Affairs (VA) Geriatric Research, Education, and Clinical Center (GRECC), the University of Utah Primary Care Research Center Scholarship and Novartis Pharmaceuticals for the submitted work. JL, REN, BCS and JRN have no relationships with any other companies that might have an interest in the submitted work in the previous 3 years or any non-financial interests that may be relevant to the submitted work. Their spouses, partners, or children have no financial relationships that might be relevant to the submitted work.

Ethics approval This study was conducted with the approval of the University of Utah Institutional Review Board and Salt Lake City Veterans Affairs Office of Research and Development.

Contributors All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Ho PM,** Peterson ED, Wang L, *et al*. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008;**299**:532—9.
2. **Hood KK,** Peterson CM, Rohan JM, *et al*. Association between adherence and glycemic control in pediatric type 1 diabetes: a meta-analysis. *Pediatrics* 2009;**124**: e1171—9.
3. **Mazzaglia G,** Ambrosioni E, Alacqua M, *et al*. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009;**120**:1598—605.
4. **Nachega JB,** Leisegang R, Bishai D, *et al*. Association of antiretroviral therapy adherence and health care costs. *Ann Intern Med* 2010;**152**:18—25.
5. **Perreault S,** Dragomir A, White M, *et al*. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. *J Intern Med* 2009;**266**:207—18.
6. **Perreault S,** Ellia L, Dragomir A, *et al*. Effect of statin adherence on cerebrovascular disease in primary prevention. *Am J Med* 2009;**122**:647—55.
7. **Pinsky BW,** Takemoto SK, Lentine KL, *et al*. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant* 2009;**9**:2597—606.
8. **Salas M,** Hughes D, Zuluaga A, *et al*. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. *Value Health* 2009;**12**:915—22.
9. **Shalev V,** Chodick G, Silber H, *et al*. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 2009;**169**:260—8.
10. **Siris ES,** Selby PL, Saag KG, *et al*. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009;**122**:S3—13.
11. **Iakovou I,** Schmidt T, Bonizzoni E, *et al*. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126—30.
12. **Spertus JA,** Kettelkamp R, Vance C, *et al*. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006;**113**:2803—9.
13. **Eisenstein EL,** Anstrom KJ, Kong DF, *et al*. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;**297**:159—68.

14. **Grines CL,** Bonow RO, Casey DE Jr, *et al*. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007;**115**:813—18.
15. **Stroupe KT,** Teal EY, Tu W, *et al*. Association of refill adherence and health care use among adults with hypertension in an urban health care system. *Pharmacotherapy* 2006;**26**:779—89.
16. **Sun SX,** Ye X, Lee KY, *et al*. Retrospective claims database analysis to determine relationship between renin-angiotensin system agents, rehospitalization, and health care costs in patients with heart failure or myocardial infarction. *Clin Ther* 2008; (30 Pt 2):2217—27.
17. **Ho PM,** Rumsfeld JS, Masoudi FA, *et al*. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836—41.
18. **Wu PH,** Yang CY, Yao ZL, *et al*. Relationship of blood pressure control and hospitalization risk to medication adherence among patients with hypertension in Taiwan. *Am J Hypertens* 2010;**23**:155—60.
19. **Breekveldt-Postma NS,** Penning-van Beest FJ, Siiskonen SJ, *et al*. The effect of discontinuation of antihypertensives on the risk of acute myocardial infarction and stroke. *Curr Med Res Opin* 2008;**24**:121—7.
20. **Ho PM,** Magid DJ, Shetterly SM, *et al*. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J* 2008;**155**:772—9.
21. **Wright JM,** Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev* 2009;(3):CD001841.
22. **Brookhart MA,** Patrick AR, Dormuth C, *et al*. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol* 2007;**166**:348—54.
23. **Humphrey LL,** Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med* 2002;**137**:273—84.
24. **Ray WA,** Daugherty JR, Griffin MR. Lipid-lowering agents and the risk of hip fracture in a Medicaid population. *Inj Prev* 2002;**8**:276—9.
25. **Majumdar SR,** McAlister FA, Eurich DT, *et al*. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* 2006;**333**:999.
26. **Simpson SH,** Eurich DT, Majumdar SR, *et al*. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;**333**:15.
27. **National Heart Lung and Blood Institute.** The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC7). 2003. http://www.nhlbi.nih.gov/guidelines/hypertension/ (accessed 15 Dec 2008).
28. **LaFleur J,** Nelson RE, Sauer BS, *et al*. Any-cause hospitalization outcomes associated with poor patient adherence to antihypertensives. *2nd International Conference on Fixed Combination in the Treatment of Hypertension, Dyslipidemia, and Diabetes Mellitus*. Valencia, Spain,10-12 December 2009.
29. **Steiner JF,** Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105—16.
30. **Peterson AM,** Nau DP, Cramer JA, *et al*. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007;**10**:3—12.
31. **Blanc PD,** Yen IH, Chen H, *et al*. Area-level socio-economic status and health status among adults with asthma and rhinitis. *Eur Respir J* 2006;**27**:85—94.
32. **Peduzzi P,** Wittes J, Detre K, *et al*. Analysis as-randomized and the problem of non-adherence: an example from the Veterans Affairs Randomized Trial of Coronary Artery Bypass Surgery. *Stat Med* 1993;**12**:1185—95.
33. **Greene T,** Daugirdas J, Depner T, *et al*. Association of achieved dialysis dose with mortality in the hemodialysis study: an example of "dose-targeting bias". *J Am Soc Nephrol* 2005;**16**:3371—80.
34. **Peduzzi P,** Detre K, Wittes J, *et al*. Intent-to-treat analysis and the problem of crossovers. An example from the Veterans Administration coronary bypass surgery study. *J Thorac Cardiovasc Surg* 1991;**101**:481—7.
35. **Moher D,** Hopewell S, Schulz KF, *et al*. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.
36. **Maclure M.** The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;**133**:144—53.
37. **Maclure M,** Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000;**21**:193—221.
38. **Imbens GW,** Rubin DB. Bayesian inference for causal effects in randomized experiments with noncompliance. *Ann Stat* 1997;**25**:305—27.
39. **Joffe MM,** Brensinger C. Weighting in instrumental variables and G-estimation. *Stat Med* 2003;**22**:1285—303.
40. **Goetghebeur E,** Stijn V. Structural mean models for compliance analysis in randomized clinical trials and the impact of errors on measures of exposure. *Stat Methods Med Res* 2005;**14**:397—415.
41. **Vittinghoff E,** Glidden D, Shiboski S, *et al*. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. New York: Springer, 2005:95—8.
42. **Curry RC Jr,** Schwartz KM, Urban PL. Atenolol and chlorthalidone therapy for hypertension: a double-blind comparison. *S Med J* 1988;**81**:1401—6, 11.
43. **Gavras HP,** Salerno CM. The angiotensin II type 1 receptor blocker losartan in clinical practice: a review. *Clin Ther* 1996;**18**:1058—67.
44. **Giles TD,** Robinson TD. Effects of olmesartan medoxomil on systolic blood pressure and pulse pressure in the management of hypertension. *Am J Hypertens* 2004;**17**:690—5.
45. **Black HR,** Bakris GL, Weber MA, *et al*. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. *J Clin Hypertens (Greenwich)* 2007;**9**:760—9.
46. **Heran BS,** Wong MM, Heran IK, *et al*. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev* 2008;(4):CD003822.
47. **Lewis EJ,** Hunsicker LG, Bain RP, *et al*. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**:1456—62.
48. **Ravid M,** Savin H, Jutrin I, *et al*. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;**118**:577—81.
49. **Freemantle N,** Cleland J, Young P, *et al*. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;**318**:1730—7.

Heart

Overestimation of the effects of adherence on outcomes: a case study in healthy user bias and hypertension

Joanne LaFleur, Richard E Nelson, Brian C Sauer and Jonathan R Nebeker

Heart 2011 97: 1862-1869 originally published online May 17, 2011
doi: 10.1136/hrt.2011.223289