Patient Preference and Adherence

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ORIGINAL RESEARCH

Assessment of Medication Adherence Using Pharmacy Data Before and After Percutaneous Coronary Intervention

Seifu M Abera[1,2], Colin O'Donnell[3], Taufiq Salahuddin[1,2], Krishna Prabhu[4], Carol E Simons[1], P Michael Ho[5,6], Stephen W Waldo[3,5,6], Jacob A Doll[1–3]

[1]Section of Cardiology, VA Puget Sound Health Care System, Seattle, WA, USA; [2]Department of Medicine, University of Washington, Seattle, WA, USA; [3]Department of Veterans Affairs Clinical Assessment, Reporting, and Tracking Program, VHA Office of Quality and Patient Safety, Washington, DC, USA; [4]Hennepin County Medical Center, Minneapolis, MN, USA; [5]Rocky Mountain Regional VA Medical Center, Aurora, CO, USA; [6]Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Correspondence: Jacob A Doll, VA Puget Sound Health Care System, 1660 S. Columbian Way, S111-CARDIO, Seattle, WA, 98108, USA, Tel +1 206-277-6199, Fax +1 206-764-2257, Email jdoll@uw.edu

Objective: Adherence to anti-platelet medications is critical following coronary stenting, but prior studies indicate that clinician assessment and patient self-assessment of adherence are poorly correlated with future medication-taking behavior. We therefore sought to determine if integrated pharmacy data can be used to identify patients at high risk of non-adherence after percutaneous coronary interventions (PCI).

Methods: Using Veteran Affairs (VA) Clinical Assessment, Reporting, and Tracking (CART) data linked with pharmacy records, we assessed adherence to cardiovascular medications from 2012 to 2018. Adherence was defined as the proportion of days covered (PDC) ≥ 0.80. We assessed the association of pre-PCI adherence with post-PCI adherence to $P2Y_{12}$ inhibitors and clinical outcomes using logistic regression and Cox proportional hazard models, respectively.

Results: Among 56,357 patients, 66.0% filled at least 1 cardiovascular medication within VA for the year prior to PCI and were evaluable for adherence. Pre-PCI non-adherence was 20.7%, and non-adherent patients were more likely to be younger and present non-electively. Non-adherent patients were less likely to adhere to $P2Y_{12}$ inhibitor therapy after PCI (Adjusted OR 0.45 C.I. 0.41–0.46), compared with adherent patients, and had a higher adjusted risk of mortality (HR 1.17 C.I. 1.03–1.33).

Conclusion: Adherence to cardiovascular medications prior to PCI can be assessed for most patients using pharmacy data, and past adherence is associated with future adherence and mortality after PCI. Use of integrated pharmacy data to identify high-risk patients could improve outcomes and cost-effectiveness of adherence interventions.

Plain Language Summary: Why was the study done?: Non-adherence to anti-platelet medications is common following coronary stenting procedures and is associated with worse outcomes, but predicting non-adherence is challenging.

What did the researchers do and find?: The researchers examined pharmacy fill-based adherence assessments before and after stenting procedures. Pharmacy data can provide adherence estimates for most patients receiving percutaneous coronary intervention, and these estimates are associated with downstream medication-taking behavior and clinical outcomes.

What do the results mean?: Health systems should seek to integrate pharmacy-based adherence estimates into routine care for patients with cardiovascular disease. Identification and targeting of patients at high-risk for non-adherence may improve the impact and cost-effectiveness of future research and health policy interventions aimed at improving adherence.

Keywords: percutaneous coronary intervention, medication adherence

Introduction

Non-adherence to cardiovascular medications is common and is associated with adverse outcomes and higher healthcare costs.[1–3] Adherence is particularly important for anti-platelet medications after percutaneous coronary intervention (PCI,

Received: 18 July 2023
Accepted: 29 September 2023
Published: 3 November 2023

also known as coronary stenting), since non-adherence may lead to stent thrombosis, myocardial infarction (MI), and death.[4,5] Hospitals and clinicians therefore invest significant resources in patient education and other interventions to promote adherence;[6] however, these interventions may be costly, and non-adherence rates remain unacceptably high. Randomized trials have identified some effective strategies, but large improvements in adherence are uncommon and even fewer interventions alter clinical outcomes.[7,8]

The impact and cost-effectiveness of interventions may be improved if health systems can identify patients at high risk for non-adherence. Unfortunately, clinicians are poor at assessing adherence,[9] and patient self-report is often unreliable,[10] highlighting the need for objective measures of adherence. The use of pharmacy fills for assessing adherence is well described,[11,12] and prior studies have demonstrated the utility of pharmacy data for predicting future medication-taking behavior.[13–15] There are increasing opportunities to integrate pharmacy data into electronic health systems,[16,17] but it is unknown if these technological investments will improve patient care. The potential role of pharmacy fills data for adherence risk prediction must be further investigated.

We therefore examined pre- and post-procedural adherence among patients treated with PCI in Veterans Affairs (VA) hospitals, the largest health system in the United States, which includes an integrated pharmacy system. We hypothesized that most patients would have an evaluable cardiovascular medication adherence history, that prior adherence to cardiovascular medications would be associated with post-PCI adherence, and that non-adherent patients would have worse clinical outcomes.

Methods

The VA Clinical Assessment, Reporting, and Tracking (CART) Program is a national quality and safety program for invasive cardiovascular procedures with universal participation by VA catheterization laboratories. Clinicians prospectively document patient characteristics and procedural details using standardized definitions derived from the National Cardiovascular Data Registry (NCDR). The VA CART Program has been previously described, including methods for ensuring data accuracy.[18,19] We linked the demographic, clinical, and procedural data from CART with VA pharmacy records for four cardiovascular medication classes: statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), and $P2Y_{12}$ inhibitors. Aspirin usage is not consistently captured by VA pharmacy records because of a high rate of over-the-counter purchase, and so was not included in this analysis.

We examined 56,357 patients receiving PCI at a VA hospital from Jan 1, 2012 and Dec 31, 2018. Of these, 37,164 patients (66.0%) filled at least one cardiovascular medication (from any of the 4 classes listed above) for at least one year prior to the procedure and were therefore eligible for pre-PCI adherence assessment. Of these, 33,705 (90.7% of patients with pre-PCI adherence assessment) also had at least 1 year of pharmacy fill data for a $P2Y_{12}$ inhibitor after PCI (Supplementary Figure).

To assess pre-procedure adherence, we calculated a proportion of days covered (PDC) for each of the eligible medication classes, defined as the ratio of the number of days the patient had medication on hand over the evaluative period. A PDC of 0.8 or greater was considered adherent.[12] Days spent as an inpatient were not counted in the numerator or denominator. For patients on more than one class of medication prior to PCI, the highest of the individually calculated PDC values was used to classify overall pre-procedure adherence. An additional 6-month window was added to the 1-year pre-procedure evaluative period (18 months total) to capture supply on hand. Adherence to a $P2Y_{12}$ inhibitor after PCI was calculated similarly over a 1-year period. Any $P2Y_{12}$ inhibitor supply prior to PCI was accounted for when assessing post-PCI PDC.

In addition, we assessed clinical outcomes within 1 year of PCI. Death was assessed using VA mortality files. Readmission for myocardial infarction, stroke, and revascularization (PCI or CABG) were assessed using ICD and CPT codes (Supplementary Methods).

Statistical Analysis

We compared baseline demographic, clinical, and presentation characteristics among patients who were adherent vs non-adherent in the one year prior to presentation, using binomial test of proportions for categorical variables and Student's t-tests for continuous variables.

To assess the association of pre-procedure adherence with post-procedure $P2Y_{12}$ adherence, an initial logistic regression with 54 candidate covariates was performed (Supplementary Methods). We then performed one elimination step to remove any covariate with a p-value < 0.1, leaving 26 covariates: age, race, heart failure (HF), hypertension, hyperlipidemia, prior myocardial infarction (MI), prior PCI, prior valve surgery, prior stroke/transient ischemic attack, peripheral arterial disease (PAD), dialysis status, sleep apnea, atrial fibrillation, deep vein thrombosis, prior cancer diagnosis, anxiety, depression, post-traumatic stress disorder (PTSD), current or former smoker, current or former alcohol abuse, illicit drug abuse, procedural status (elective, urgent, emergent, salvage), cardiogenic shock, diastolic blood pressure, high-density lipoprotein (HDL), and pre-procedure adherence. This final model had a c-statistic of 0.64 (Supplementary Methods). Exclusion of pre-procedural adherence from the model resulted in a c-statistic of 0.60.

Next, we assessed the association of pre-procedural adherence with death and the clinical composites death/MI/stroke and death/MI/stroke/revascularization within 1 year. We used a Cox proportional hazards models adjusting for the following covariates, selected a priori as potentially unbalanced between the groups or associated with the clinical outcomes: age, race, sex, body mass index (BMI), body surface area (BSA), HF, hypertension, hyperlipidemia, diabetes, prior MI, prior cardiac catheterization, prior PCI, prior coronary artery bypass graft surgery (CABG), prior valve surgery, prior PCI, prior stroke/transient ischemic attack, PAD, chronic lung disease, chronic kidney disease, dialysis status, prior renal transplant, sleep apnea, atrial fibrillation, deep vein thrombosis, prior cancer diagnosis, liver disease, anxiety, depression, post-traumatic stress disorder, current or former smoker, current or former alcohol abuse, illicit drug abuse, family history of coronary artery disease, ST-segment elevation MI presentation, procedural status (elective, urgent, emergent, salvage), cardiogenic shock, cardiac arrest, surgical turn down, blood pressure, creatinine, total cholesterol, low-density lipoprotein (LDL), and HDL. Patients who died were censored on the date of death and PDC was calculated from the time of PCI to the date of censoring. We then assessed the association of post-PCI adherence with clinical outcomes using the same methodology.

This analysis was approved by the VA Puget Sound Health Care System Institutional Review Board (IRB#01733). Analysis was performed with SAS version 9.4, SAS Institute Inc., Cary, NC, and with R version 4.2.1, The R Foundation for Statistical Computing.

Results

Overall, 6,974 patients (20.7%) were non-adherent to at least one cardiovascular medication prior to PCI (PDC ≥0.80). Mean PDC for those classified as adherent was 0.96 (S.D. 0.05), while those classified as non-adherent had mean PDC of 0.58 (S.D. 0.19). Non-adherent patients were younger, more likely to be black, have lower rates of medical comorbidities, higher rates of depression and substance abuse, and were more likely to present emergently or urgently for PCI (Table 1).

Post-PCI non-adherence to $P2Y_{12}$ inhibitors was present for 6885 patients (20.4%) at 1 year. Patients who were non-adherent pre-PCI were more likely to be non-adherent post-PCI compared with pre-PCI adherent patients (33.0% vs 17.2%) (Figure 1). After adjustment for demographic and clinical factors, pre-PCI non-adherent patients had significantly lower odds of adherence post-PCI (OR 0.45 C.I. 0.41–0.46).

Patients who were non-adherent before PCI had a higher adjusted mortality rate within 1 year of PCI (HR 1.17 C.I. 1.03–1.33), though rates of the composites death/MI/stroke (HR 1.11 C.I. 0.99–1.25) and death/MI/stroke/repeat revascularization (HR 1.04 C.I. 0.97–1.12) were not significantly different compared with patients who were adherent before PCI.

Patients who were non-adherent to $P2Y_{12}$ inhibitors after PCI had significantly higher adjusted rates of death (HR 1.18 C.I. 1.06–1.32), death/MI/stroke (HR 1.20 C.I. 1.09–1.32), and death/MI/stroke/revascularization (HR 1.15 C.I. 1.09–1.23) within 1 year (Table 2) compared with patients who were adherent to $P2Y_{12}$ inhibitors after PCI.

Discussion

In this study of consecutive patients receiving PCI at VA hospitals from 2012 to 2018, two thirds of patients were evaluable for adherence to cardiovascular medications prior to PCI using the VA's integrated pharmacy system. Pre-procedure non-adherence was associated with post-procedure non-adherence to $P2Y_{12}$ inhibitors and increased rates of death. Automated assessment of medication use using pharmacy fills is a potential mechanism to identify patients at high-risk of non-adherence and poor outcomes.

Table 1 Patient Characteristics Associated with Adherence or Non-Adherence to Cardiovascular Medications Within 1 Year Prior to PCI

	Non-Adherent (N=6,974)	Adherent (N=26,731)	P-value	Standardized Difference
Age, mean (SD)	65.8 (8.9)	68.3 (8.26)	<0.01	0.205
Male	97.9	98.4	<0.01	0.038
Race				
White	77.5	86.3	<0.01	0.231
Black	20.6	11.8	<0.01	0.243
Asian	0.5	0.5	0.84	0.004
Native American	0.6	0.6	0.94	0.002
Hispanic ethnicity	6.0	4.3	<0.01	0.074
BMI, mean (SD)	30.2 (5.7)	31.2 (5.8)	<0.01	0.124
Diabetes	52.3	59.2	<0.01	0.138
Hyperlipidemia	93.6	95.9	<0.01	0.102
Hypertension	93.5	96.6	<0.01	0.143
CKD	22.8	25.9	<0.01	0.071
Dialysis	4.1	2.7	<0.01	0.076
Current/Former Tobacco use	69.3	66.9	<0.01	0.051
CVD	18.8	21.1	<0.01	0.059
PAD	21.9	24.0	<0.01	0.052
COPD	24.0	25.1	0.08	0.024
Atrial Fibrillation	10.7	15.3	<0.01	0.137
Depression	35.9	32.2	<0.01	0.077
PTSD	20.3	20.9	0.29	0.014
Prior MI	42.1	46.0	<0.01	0.079
Prior PCI	43.8	51.0	<0.01	0.146
Prior CABG	22.4	31.5	<0.01	0.206
Alcohol abuse	10.4	7.3	<0.01	0.110
Illicit drug use	6.9	3.6	<0.01	0.150
Baseline LDL, mean (SD)	104.2 (36.6)	86.5 (32.0)	<0.01	0.364
Baseline Systolic BP, mean (SD)	136.3 (14.3)	134.3 (13.6)	<0.01	0.103
Procedure status				
Elective	62.6	67.8	<0.01	0.109
Urgent	31.3	28.2	<0.01	0.069
Emergent	6.0	4.0	<0.01	0.094
Salvage	0.1	0.6	0.97	0.003

Medication non-adherence following PCI and myocardial infarction remains persistently high despite several decades of research and significant attention from the clinical community. Suboptimal adherence has been documented for several important medication classes, including statins and anti-platelet medications.[1] Multiple reasons for non-adherence have been observed,[20] so diverse interventions have been tested in randomized trials.[8] These include patient education, polypills, the reduction or elimination of medication copayments, and multifaceted interventions including pre-discharge education and post-discharge follow-up. Some of these interventions have improved patient adherence, though the overall impact has been modest and in most trials did not result in a reduction in clinical events.[21–26] Interventions may be more impactful if targeted to a high-risk population. Prospective adherence prediction is particularly important for PCI patients, since intervening after medication non-adherence occurs may be too late; the patient has already been exposed to higher risk of stent thrombosis and MI.

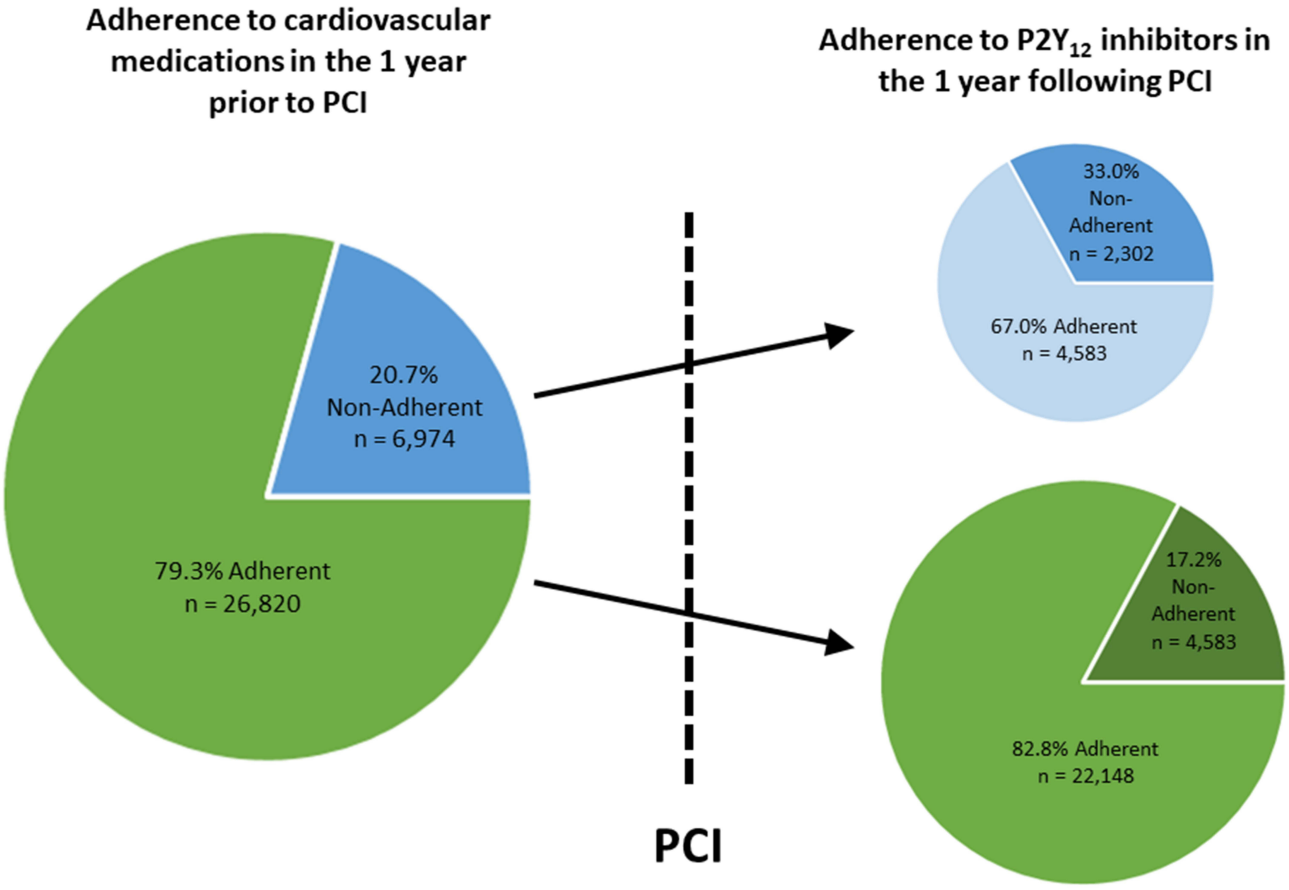

Figure 1 (Visual summary): Unadjusted rates of adherence to cardiovascular medications pre-PCI and adherence to $P2Y_{12}$ inhibitors post-PCI.

This study showed that patients who were adherent to their cardiovascular medications prior to PCI had 2.3 times greater odds of adhering to their anti-platelet therapy following PCI, compared with pre-PCI non-adherent patients. Importantly, a large, national, integrated health care system like the VA can provide evaluable adherence data for most patients at the bedside. A prior similar study of Medicare patients with MI could only assess 10% of patients due to reliance on Medicare Part D.[15] However, outpatient pharmacy data are increasingly available to hospitals through commercial services,[16] and with ongoing consolidation of healthcare systems and electronic health records in the US it is likely that point-of-care pharmacy data will be increasing available to clinicians. Our study provides one immediate application for these data.

Table 2 1-Year Outcomes Among Patients Who are Adherent and Non-Adherent to $P2Y_{12}$ Inhibitors After PCI

	Unadjusted			Adjusted HR* (95% CI)
	Adherent	Non-Adherent	p-value	
Death	4.6% (1228/26,820)	6.8% (466/6885)	<0.001	1.18 (1.06, 1.32)
Death/MI/Stroke	5.5% (1487/26,820)	8.2% (567/6885)	<0.001	1.20 (1.09, 1.32)
Death/MI/Stroke/Revascularization	16.5% (4417/26,820)	20.5% (1411/6885)	<0.001	1.15 (1.09, 1.23)

Notes: *Adjustment variables: age, race, sex, body mass index, body surface area, HF, hypertension, hyperlipidemia, diabetes, prior MI, prior cardiac catheterization, prior PCI, prior coronary artery bypass graft surgery, prior valve surgery, prior PCI, prior stroke/transient ischemic attack, PAD, chronic lung disease, chronic kidney disease, dialysis status, prior renal transplant, sleep apnea, atrial fibrillation, deep vein thrombosis, prior cancer diagnosis, liver disease, anxiety, depression, post-traumatic stress disorder, current or former smoker, current or former alcohol abuse, illicit drug abuse, family history of coronary artery disease, ST-segment elevation MI presentation, procedural status (elective, urgent, emergent, salvage), cardiogenic shock, cardiac arrest, surgical turn down, blood pressure, creatinine, total cholesterol, LDL, and HDL.

However, our study also highlights challenges in predicting non-adherence and intervening. Our model, including demographic and clinical factors in addition to fill-based adherence, had only modest discriminatory ability (c-statistic 0.64), consistent with prior studies.[13,14] Even if non-adherence can be accurately predicted, it is unclear if or how clinical care should be modified. Providing adherence data to clinicians is not effective as a standalone strategy,[27] so adherence prediction must be paired with other interventions. Interventions such as copayment reduction or pharmacist-led education may be effective for some patients but not others, regardless of pre-PCI adherence status. One promising potential strategy is digital health; adherence data could be integrated with personal electronic devices to promote healthy medication-taking behaviors. There is increasing evidence of the impact of digital health interventions on adherence and outcomes for patients with cardiovascular disease.[28,29] Future studies may test integrated solutions using data obtained from pharmacy systems, personal devices, and patient-reported symptoms.

Our study has several limitations. There are many potential ways to assess fill-based adherence; our method may underestimate non-adherence relative to other algorithms,[28] identifying a relatively small high-risk group (20% of patients). Specifically, for patients taking multiple medications we assigned the highest individual medication PDC as the overall patient PDC, under the assumption that this demonstrates the best adherence the patient has achieved. In addition, we could not assess for interruptions in treatment directed by physicians, which could result in some adherence misclassification. Our risk model included clinical data available at the time of PCI, but we could not assess for other factors that are associated with adherence, such as socio-economic status and social support. Subjects were primarily older and male, and our findings may not be fully generalizable to non-VA populations. In addition, VA copayments are low relative to private insurance or Medicare, all patients can receive mail order prescriptions, and there are multiple options for reordering medications.[29] This may explain why adherence was high after PCI compared with other studies, though still suboptimal at approximately 80%. Associations of adherence with favorable clinical outcomes in our study may be biased by the well-known "healthy adherer" effect if adherent patients are also more likely to engage in other health-promoting activities.

Conclusions

Adherence to cardiovascular medications prior to PCI can be assessed for most patients using pharmacy fill data, and non-adherence is associated with continued non-adherence and mortality after PCI. Use of integrated pharmacy data to identify patients at high-risk for non-adherence could improve patient outcomes and the cost-effectiveness of adherence interventions. This strategy should be tested in prospective trials.

Patient and Public Involvement

Patients and the public were not involved in the planning or interpretation of this study.

Funding

This study was supported by a pilot research grant from VA Puget Sound Health Care System.

Disclosure

TS is supported by NHLBI grant 5T32HL007828-25. PMH is supported by grants from the National Heart, Lung, and Blood Institute, the Veterans Affairs Health Services Research and Development, and University of Colorado School of Medicine. He serves as the Deputy Editor for *Circulation: Cardiovascular Quality and Outcomes*. SWW has received investigator-initiated research support from Abiomed, Cardiovascular Systems Incorporated, Janssen Pharmaceuticals, the National Institutes of Health, and VA HSR&D. JAD is supported by grants from the Veterans Affairs HSR&D. All other authors report no pertinent funding relationships or conflicts of interest in this work.

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