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ORIGINAL RESEARCH

Multifaceted Intervention to Improve P2Y12 Inhibitor Adherence After Percutaneous Coronary Intervention: A Stepped Wedge Trial

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BACKGROUND: P2Y12 inhibitor medications are critical following percutaneous coronary intervention (PCI); however, adherence remains suboptimal. Our objective was to assess the effectiveness of a multifaceted intervention to improve P2Y12 inhibitor adherence following PCI.

METHODS AND RESULTS: This was a modified stepped wedge trial of 52 eligible hospitals, of which 15 were randomly selected and agreed to participate (29 hospitals declined, and 8 eligible hospitals were not contacted). At each intervention hospital, patient recruitment occurred for 6 months and enrolled patients were followed up for 1 year after PCI. Three control groups were used: patients at intervention hospitals undergoing PCI (1) before the intervention period (preintervention); (2) after the intervention period (postintervention); or (3) at the 8 hospitals not contacted (concurrent controls). The intervention consisted of 4 components: (1) P2Y12 inhibitor delivered to patients' bedside after PCI; (2) education on importance of P2Y12 inhibitors; (3) automated reminder telephone calls to refill medication; and (4) outreach to patients if they delayed refilling P2Y12 inhibitor. The primary outcomes were as follows: (1) proportion of patients with delays filling P2Y12 inhibitor at hospital discharge and (2) proportion of patients who were adherent in the year after PCI using pharmacy refill data. Primary analysis compared intervention with preintervention control patients. There were 1377 (intent-to-treat) potentially eligible patients, of whom 803 (per protocol) were approached at intervention sites versus 5910 preintervention, 2807 postintervention, and 4736 concurrent control patients. In the intent-to-treat analysis, intervention patients were less likely to delay filling P2Y12 at hospital discharge (–3.4%; 98.3% CI, –1.2% to –5.6%) and more likely to be adherent to P2Y12 (4.1%; 98.3% CI, 1.0%–7.1%) at 1 year, but had more clinical events (3.2%; 98.3% CI, 2.3%–4.1%) driven by repeated PCI compared with preintervention patients. In post hoc analysis looking at myocardial infarction, stroke, and death, intervention patients had lower event rates compared with preintervention patients (–1.7%; 98.3% CI, –2.3% to –1.1%).

CONCLUSIONS: A 4-component intervention targeting P2Y12 inhibitor adherence was difficult to implement. The intervention produced mixed results. It improved P2Y12 adherence, but there was also an increase in repeat PCI.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01609842.

Key Words: clinical trial ■ medication adherence ■ P2Y12 inhibitor

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CLINICAL PERSPECTIVE

What Is New?

- Patients undergoing percutaneous coronary intervention (PCI) and receiving a multifaceted intervention to improve P2Y12 adherence were less likely to delay filling P2Y12 at hospital discharge.
- Patients undergoing PCI and receiving a multifaceted intervention were more likely to be adherent in the year after PCI.
- There were reductions in subsequent myocardial infarction, stroke, or death but an increase in repeated PCI among intervention patients.

What Are the Clinical Implications?

- A multifaceted intervention produced mixed results, with improved adherence to P2Y12 inhibitor medications but increased clinical events primarily attributable to repeated PCI.
- The observed increased event rate among intervention patients may be related in part to increased surveillance during the intervention period.
- Additional studies are needed to identify novel implementation strategies to improve adherence to P2Y12 and clinical outcomes after PCI.

Nonstandard Abbreviations and Acronyms

PP	per protocol
VA	Veterans Affairs

Percutaneous coronary intervention (PCI) is a common cardiovascular procedure performed in the United States, with >450 000 procedures annually.[1] Clinical practice guidelines recommend dual-antiplatelet therapy, including P2Y12 inhibitors, following PCI to reduce cardiovascular events.[2] Coordinated and complementary actions between providers (ie, prescribing and educating patients) and patients (ie, understanding rationale and taking medication as prescribed) are needed to ensure patients benefit from treatment.

Despite the importance of P2Y12 inhibitors, adherence to these medications is suboptimal.[3-13] Up to 1 in 5 patients delay filling their P2Y12 inhibitor following hospital discharge from PCI.[5] Furthermore, up to 1 in 3 patients discontinue their P2Y12 inhibitor prematurely before the intended treatment duration.[10] Patients who delay filling their P2Y12 inhibitor or discontinue prematurely have increased risk of adverse events.[4-9] These studies highlight the need to improve adherence to P2Y12 inhibitors following PCI. In a modified stepped wedge trial, we tested the effectiveness of a multifaceted intervention to improve P2Y12 inhibitor adherence following PCI.

METHODS

Study Setting

Veterans Affairs (VA) privacy regulations preclude overall release of study data. The objective of this study was to test the effectiveness of a multifaceted intervention to improve P2Y12 inhibitor adherence, defined by the following primary outcomes: proportion of patients who delay filling P2Y12 inhibitor at hospital discharge and proportion of patients who are adherent to P2Y12 inhibitor in the 12 months following PCI; and secondary outcomes of major adverse clinical events and adherence to other cardiovascular medications. The study was conducted within the VA health care system, where there were 76 medical centers with cardiac catheterization laboratories and 66 performing PCIs at the time of the study. These catheterization laboratories are part of the VA Clinical Assessment Reporting and Tracking Program, a national quality and safety program collecting data on all coronary angiography procedures performed in VA catheterization laboratories.[14]

Study Design

The study was designed as a modified stepped wedge study.[15] We stratified hospitals performing at least 20 PCI procedures annually between October 1, 2009, and September 30, 2012, into quintiles, determined by the proportion of patients who delay filling P2Y12 inhibitor during those years at each hospital. Hospitals in the quintile with the lowest proportion (quintile 1) of patients with P2Y12 inhibitor delay were excluded because they had little room to improve. Within each of the remaining 4 strata (quintiles 2–5), 4 hospitals were randomized to each of the 4 intervention waves.

There were 4 planned intervention waves, occurring every 6 months, and 4 hospitals in each wave. In practice, it was difficult to get hospitals to participate in the study. Some hospitals had long delays before implementing the intervention because of regulatory challenges (eg, getting institutional review board approval for study or team members completing required institutional review board training), staffing difficulties, or dropping out of the study before the start date. Hospitals that declined participation in any wave were replaced by another randomly selected hospital from the same stratum. In the fourth and final wave, none of the hospitals in quintile 4 agreed to implement the intervention, so only 3 sites were included. In total, 15 hospitals implemented the intervention. It was also difficult for hospitals to start at the assigned times for their wave, so actual start times for hospitals did

not align with planned start times (every 6 months). Because the sites began the intervention and ended the intervention at different times, we labeled this as a modified stepped wedge study. However, once the intervention began at an intervention hospital, the hospital implemented the intervention for 6 months and then entered a postintervention period (until the study ended in February 2018). The 8 sites remaining in the 4 strata that were eligible but not approached to participate served as concurrent control sites. Figure 1 shows the preintervention, intervention, postintervention, and concurrent control time periods.

Patient Population

During the study period from January 1, 2013, through February 24, 2018, patients who received PCI at 1 of the 15 intervention hospitals before the hospital started the intervention were considered preintervention controls, and patients who received PCI at an intervention hospital after the intervention ended were postintervention controls. Patients who received PCI during the study period at 1 of the 8 eligible but nonparticipating hospitals were concurrent controls (Figure 1). Intervention and control patients were followed up for 12 months following hospital discharge to assess medication adherence and clinical events.

Once a hospital began the intervention, all patients undergoing PCI with stent implantation and prescribed P2Y12 inhibitors (ie, clopidogrel, prasugrel, or ticagrelor) were potentially eligible. Study team members were informed about eligible patients through an automated alert sent by the study database. Patients were approached for the intervention after their PCI procedure once they were believed to be clinically stable and able to make decisions about study participation. A waiver of documentation of informed consent was obtained for the study. Patients provided verbal consent to either participate or opt out of the study. Patients were excluded if they filled their P2Y12 inhibitors outside of the VA or were discharged to an assisted care facility because we could not track medication refills. These exclusions were similarly applied to control group patients.

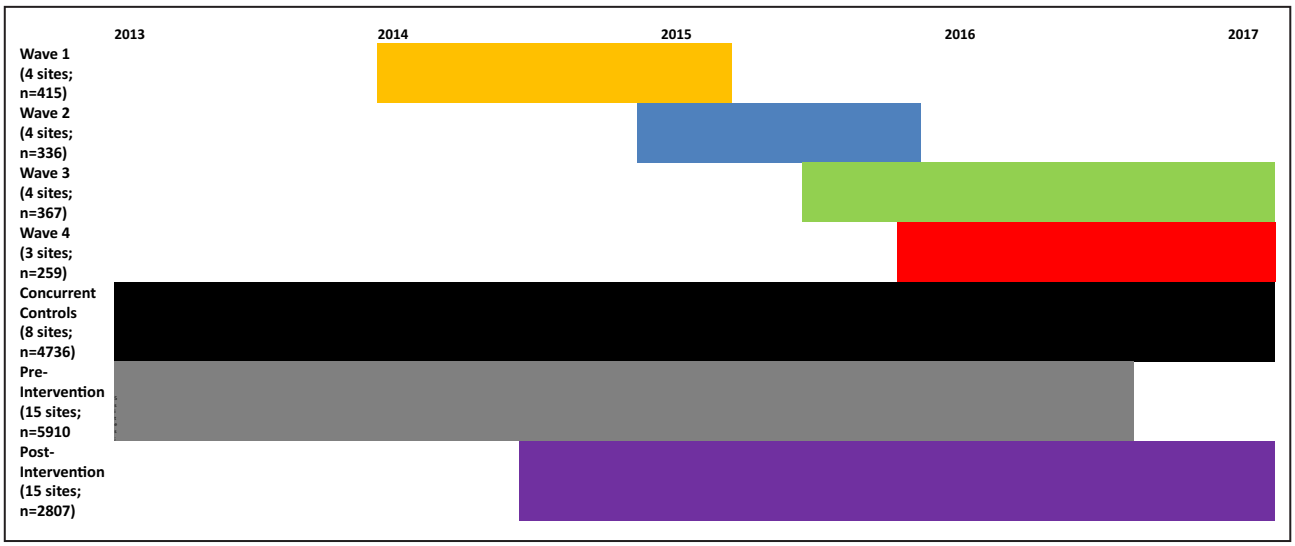

Figure 1. Dates of patient enrollment in waves and patient inclusion in the control groups (preintervention, postintervention, and concurrent controls).

1. Intervention sites: hospitals performing at least 20 percutaneous coronary intervention (PCI) procedures annually between October 1, 2009, and September 30, 2012, were grouped into quintiles based on the proportion of patients who delayed P2Y12 inhibitor pick up during those years at each hospital. Hospitals in the quintile with the lowest proportion (quintile 1) of patients with P2Y12 inhibitor fill delay were excluded from randomization to the intervention because they had little room to improve. Within each of the remaining 4 strata (quintiles 2–5), 4 hospitals were randomized to each of the 4 intervention waves. Hospitals that declined participation in any wave were replaced by another randomly selected hospital from the same stratum. There were 3 waves with 4 hospitals in each wave. In the fourth wave, none of the hospitals in quintile 4 agreed to implement the intervention, so only 3 sites implemented the intervention, resulting in a total of 15 intervention sites. The 8 sites remaining in the 4 strata that were eligible but not approached to participate served as concurrent control sites.
2. Preintervention period: patients undergoing PCI who were treated at an intervention hospital before the 6-month intervention period.
3. Postintervention period: patients undergoing PCI who were treated at an intervention hospital after the intervention period ended.
4. Concurrent controls: patients undergoing PCI and treated at hospitals that were eligible to participate in the intervention but were not invited to implement the intervention because enough hospitals within that stratum had already agreed to participate.

We estimated there would be at least 48 eligible sites, with 16 sites randomized to receive the intervention, and each intervention site contributing 90 patients during the intervention period. This would provide >80% power to detect a 2.7 percentage point decrease in the percentage of patients with P2Y12 delays at hospital discharge and an increase of 6.4 percentage points in medication adherence in the year after PCI. During intervention implementation, there were often logistical challenges for study team members to approach potentially eligible patients before hospital discharge. Only 58% (806/1397) of potentially eligible patients were approached for study participation. Patient recruitment for the intervention began in January 2014 and ended in March 2017.

Description of the Intervention

The multifaceted study intervention included 4 components: (1) bedside delivery of P2Y12 inhibitor medication before hospital discharge; (2) patient-focused education, including a pamphlet about managing medications and an individualized P2Y12 inhibitor prescription information card, specifying patient-specific reasons for P2Y12 inhibitor and intended duration; (3) use of interactive voice response automated telephone calls to remind patients to refill the P2Y12 inhibitor at 14 and 7 days before the medication refill date in the year after hospital discharge; and (4) nurse or pharmacist assistance with medication problems if they arose during the year. As this was a pragmatic study, each intervention component may not have been consistently delivered to patients because of competing clinical and/or research priorities of site personnel. Duration of P2Y12 inhibitor was left to the discretion of the providers.

Outcomes

The primary outcomes were as follows: (1) the proportion of patients who delayed filling P2Y12 inhibitor prescription at hospital discharge; and (2) the proportion of patients who were adherent to P2Y12 inhibitor based on pharmacy refill data in the year after PCI hospital discharge. Patients were categorized as having a delay if there was no record that a P2Y12 inhibitor medication was dispensed by the pharmacy on day of or anytime before hospital discharge during the same hospital admission. Adherent patients were defined on the basis of proportion of days covered >0.80 over 1 year. The proportion of days covered was calculated as the number of days of available supply of medication (medication on hand), divided by the number of days of follow-up during the 365 days following PCI. Secondary outcomes were as follows: (1) major adverse clinical events, including hospitalizations for revascularization, myocardial infarction, stroke, and bleeding, defined by administrative *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes, as well as mortality in the year after PCI; and (2) adherence to other cardiovascular medications (β-blockers, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers), defined as proportion of days covered >0.80 for that medication. Hospitalizations outside of VA but paid for by VA through fee basis were included.

Statistical Analysis

Three groups were used as controls for comparison to intervention patients: (1) patients undergoing PCI who were treated at an intervention hospital before the 6-month intervention period (preintervention), (2) patients undergoing PCI who were treated at an intervention hospital after the intervention period ended (postintervention), and (3) patients undergoing PCI and treated at hospitals that were eligible to participate in the intervention but were not invited to implement the intervention because enough hospitals within that stratum had already agreed to participate (concurrent controls). Patients from hospitals that were invited to participate in the intervention but declined were not included in the analyses.

In primary analyses, we conducted an intent-to-treat (ITT) analysis using as intervention patients all patients potentially eligible at intervention sites (n=1377) and a per-protocol (PP) analysis using as intervention patients all patients approached (n=803 for the intervention). In the ITT analysis, we included all potential eligible intervention patients rather than just those approached because, in the control groups, we were unable to apply this similar exclusion criterion during the control periods. Patients who were approached but refused to participate (n=97) were included in both ITT and PP intervention groups. These primary analyses compared intervention patients with the same set of preintervention control patients. In addition, both primary outcomes were of interest independently, and statistical significance in either would lead to a conclusion of a successful intervention for each individual outcome. In secondary analyses, we compared intervention patients with postintervention and concurrent control patients. In additional sensitivity analyses, we focused on the PP population given that most of these patients received the intervention and we could better assess the intervention treatment effect. In these analyses, we assessed the impact of the intervention on adherence to other secondary prevention medications and among specific patient subgroups: acute coronary syndrome, non–acute coronary syndrome, removing patients who received bare metal stents, and removing patients who may have received medications from outside VA pharmacies.

The 2 primary outcomes were analyzed separately with patient-level data to detect differences between the study arms. Unadjusted tests of binomial proportions for delay and adherence were examined between the intervention group and the control groups as a preliminary investigation, followed by separate logistic mixed regression models adjusted for significant risk factors. The full data with all potential variables (patient demographics, comorbidities, procedural data, process of care, and hospital characteristics) were bootstrapped 50 times using 80% of the data at random for each bootstrap iteration. Each iteration ran a logistic regression on the bootstrapped data using all covariates. Any covariate that had a $P \leq 0.05$ in any of the resulting bootstrap models was retained for the final mixed model. The logistic mixed models included terms for site (random effect, to account for correlation of patients within sites), an indicator for which study arm the patient belonged to (intervention, preintervention, postintervention, or concurrent controls), a B-spline term for time, to account for time trends and accommodate varying roll-out dates of the individual sites, and patient characteristics (listed in Table 1) and hospital characteristics (listed in Table S1).

To express results on a more interpretable risk difference scale, we used standardized or average predicted value estimators,[17-19] which compare probabilities of adherence among the groups, hypothesizing (in some cases counterfactually) that patients were in each of the 4 intervention/control groups. Inference was performed using bootstrap methods, and results were expressed as CIs for differences between groups. Risk differences and 98.3% CIs were obtained by implementing 1000 iterative bootstrap processes in which risk estimates were generated for all patients using counterfactuals. At each iteration, models were fit and risk estimates were obtained for all patients (1) coded as belonging to the intervention arm, (2) coded as belonging to the preintervention group, (3) coded as belonging to the postintervention group, and (4) coded as belonging to the group of sites used as concurrent controls. The estimated probabilities obtained from these 4 counterfactual cases were used to generate mean risk estimates and risk differences between the groups for each bootstrap iteration.

Secondary time to event outcomes required using Cox regression models. Survival risk differences for secondary outcomes, and 98.3% CIs at specified time points up to 1 year following hospital discharge, were generated using standardized estimates and bootstrapped CIs, similar to the logistic regression methods.[20,21]

All analyses were done in SAS 9.4 1M5 ©2016 (SAS Institute Inc, Cary, NC) and R: A Language and Environment for Statistical Computing 2018, version 3.4.2.

Data and Safety Monitoring

This research study was approved and overseen by VA Central Institutional Review Board and local research and development offices at each participating site (No. 12-12/12-1366). Any adverse events and protocol deviations were reported to VA Central Institutional Review Board, according to established regulations.

RESULTS

Of 52 eligible PCI hospitals, 29 declined, 15 agreed to participate, and 8 were eligible but not contacted to participate. There were no significant differences in measured hospital characteristics between hospitals that agreed to participate, hospitals that declined, and concurrent control hospitals (Table S1). At intervention hospitals during the intervention period, 1545 patients were potentially eligible for the intervention. Of these patients, 148 were ineligible, 20 did not have pharmacy data, 574 were not approached, and 803 were approached (Figure 2). This resulted in 1377 intervention patients for the ITT analysis and 803 intervention patients for the PP analysis. Among control groups, there were 1049 (15.1%), 726 (20.5%), and 646 (12.0%) patients excluded from the preintervention (final n=5910), postintervention (final n=2807), and concurrent (final n=4736) control groups, respectively.

Intervention patients were similar to patients undergoing PCI from the different comparison groups (Table 1 and Tables S2 and S3). Patients were mainly men, with average age of 66 years, and had a significant burden of comorbidities.

In the ITT analyses (n=1377 intervention patients), intervention patients were less likely to delay filling P2Y12 inhibitor at hospital discharge (risk difference, –3.4%; 98.3% CI, –1.2% to –5.6%) and more likely to be adherent (risk difference, 4.1%; 98.3% CI, 1.0%–7.1%). For the major adverse clinical event outcomes, intervention patients had higher event rates (3.2%; 98.3% CI, 2.3%–4.1%) (Tables 2 and 3), driven primarily by repeated PCI in the year following hospital discharge. In post hoc analysis, there was a reduction in myocardial infarction (MI), stroke, or death among intervention patients (–1.7%; 98.3% CI, –2.3% to –1.1%). In secondary analysis comparing ITT intervention patients with postintervention and concurrent control patients, there was a general trend that intervention patients were less likely to delay and more likely to be adherent, although the magnitude of effect was smaller (Tables S4 and S5).

In the PP analyses (n=803 intervention patients), the magnitudes of effects among intervention patients were greater. In adjusted analyses, intervention patients were less likely to delay (–4.6%; 98.3% CI, –2.2% to –6.9%), were more likely to be adherent (6.1%; 98.3% CI, 2.1%–9.8%), and had higher event rates (3.8%;

Table 1. Baseline Characteristics of Intervention Patients Compared With the Preintervention Control Patients

Variable	ITT intervention (N=1377)	PP intervention (N=803)	Preintervention (N=5910)	*P* value (ITT intervention vs preintervention)	*P* value (PP intervention vs preintervention)
Age, mean (SD), y	66.4 (8.9)	66.4 (9.2)	66.4 (8.7)	>0.99	>0.99
Male sex	1344 (97.6)	779 (97.0)	5799 (98.1)	0.77	0.15
Hispanic ethnicity	50 (3.6)	29 (3.6)	258 (4.4)	0.25	0.37
Black race	245 (17.8)	124 (15.4)	999 (16.9)	0.45	0.32
White race	1129 (82.0)	677 (84.3)	4891 (82.8)	0.52	0.29
Congestive heart failure	403 (29.3)	245 (30.5)	1710 (28.9)	0.83	0.76
Diabetes	720 (52.3)	421 (52.4)	3135 (53.0)	>0.99	>0.99
Hyperlipidemia	1264 (91.8)	746 (92.9)	5420 (91.7)	0.96	0.55
Hypertension	1280 (93.0)	747 (93.0)	5462 (92.4)	>0.99	>0.99
Chronic kidney disease	307 (22.3)	172 (21.4)	1361 (23.0)	0.71	0.41
Peripheral arterial disease	328 (23.8)	182 (22.7)	1288 (21.8)	0.33	>0.99
Cerebrovascular disease	231 (16.8)	130 (16.2)	1127 (19.1)	0.05	0.06
Dialysis	52 (3.8)	31 (3.9)	175 (3.0)	0.42	0.60
Prior myocardial infarction	603 (43.8)	329 (41.0)	2602 (44.0)	>0.99	0.22
Prior revascularization	830 (60.3)	477 (59.4)	3429 (58.0)	0.13	0.48
ACS indication	637 (46.3)	342 (42.6)	2571 (43.5)	0.07	>0.99
Non-ACS indication	740 (53.7)	461 (57.4)	3339 (56.5)	0.07	>0.99
Bare metal stent	89 (6.5)	47 (5.8)	600 (10.2)	<0.01	<0.01
P2Y12 inhibitor					
Clopidogrel	1184 (86.0)	681 (84.8)	5186 (87.8)	0.17	0.04
Prasugrel	60 (4.4)	45 (5.6)	402 (6.8)	<0.01	0.23
Ticagrelor	120 (8.7)	64 (8.0)	187 (3.2)	<0.01	<0.01
Missing	13 (0.9)	13 (1.6)	135 (2.3)	<0.01	0.67
Initial P2Y12, 90-d supply	1075 (78.1)	653 (81.3)	3830 (64.8)	<0.001	<0.01
Statin prescriptions	1335 (97.0)	777 (96.8)	5693 (96.3)	0.372	0.92
ACEi or ARB prescriptions	1048 (76.1)	611 (76.1)	4556 (77.1)	0.918	>0.99
β-Blocker prescriptions	1243 (90.3)	718 (89.4)	5426 (91.8)	0.218	0.08

Data are given as number (percentage), unless otherwise indicates. *P* values are adjusted for multiple comparisons of 3 tests using the Holm method.[16] ACEi indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; and ARB, angiotensin receptor blocker; ITT, intent to treat; and PP, per protocol.

98.3% CI, 0.6%–7.0%) (Tables 2 and 3). Again, the higher event rate was driven by repeated PCI as intervention patients had lower risk of MI, stroke, or death (–2.1%; 98.3% CI, –2.9% to –1.5%). The magnitudes of effects were smaller comparing PP intervention patients with postintervention and concurrent control patients (Tables S4 and S5).

In secondary analyses focusing on the PP population, intervention patients were more adherent to statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β-blockers compared with preintervention patients (Table S6). PP intervention patients remained more adherent when patients with bare metal stents were excluded because they may have shorter P2Y12 inhibitor treatment durations, when patients who filled their P2Y12 prescriptions outside the VA were excluded, and among patients with or without acute coronary syndrome (Table S7).

DISCUSSION

Our multifaceted intervention reduced delays to filling P2Y12 inhibitor medication at hospital discharge and increased adherence in the year after PCI. The findings were generally consistent in the ITT and PP analyses and across different comparison groups. Unexpectedly, intervention patients had a higher rate of 1-year major adverse clinical events, driven primarily by repeated PCI. There was a reduction in MI, stroke, or death among intervention patients. Although we focused on P2Y12 inhibitor medication in the study, our findings on medication adherence may have implications for noncardiovascular medications. With the prevalence of and the potential costs associated with medication nonadherence, there is an urgent need to identify new models to improve adherence and patient outcomes, such as the one demonstrated in this study.

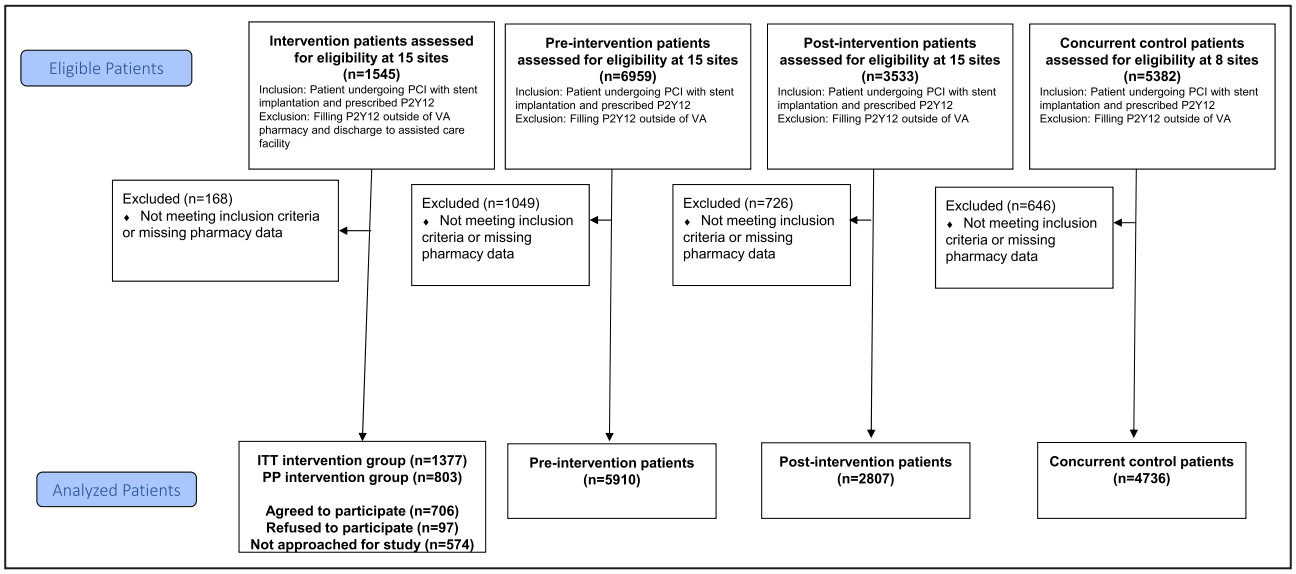

Figure 2. Participant flow diagram for intervention and control group patients.
ITT indicates intent to treat; PCI, percutaneous coronary intervention; PP, per protocol; and VA, Veterans Affairs.

The magnitude of adherence improvement is comparable to prior medication adherence interventions. In a prior intervention, we found that a multifaceted intervention, composed of medication reconciliation, patient education, collaborative care, and automated reminder calls, improved adherence to cardiovascular medications after acute coronary syndrome hospitalization.[22] The prior study was a patient-level randomized study, the intervention was more time and resource intensive, including patient visits at 1 week and 1 month after hospital discharge, and there was close monitoring of the delivery of intervention components. In contrast, the current study was designed to be more pragmatic, with cluster-level randomization. Furthermore, we designed the intervention package to be delivered at sites but did not specify who should deliver the intervention and did not keep track of whether each component was delivered. In the MI FREEE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation Trial) study, where copays to cardiovascular medications were eliminated after MI, intervention patients had higher adherence by 4% to 6% compared with usual care; however, the study did not focus on P2Y12 inhibitors.[23] In our study, we demonstrated ≈3% to 5% improvement in proportion of days covered to P2Y12 inhibitor medications, consistent with prior literature.

Table 2. Unadjusted Medication (P2Y12 Inhibitor Delay and Medication Adherence) and Clinical Outcomes

	ITT intervention (N=1377)	PP intervention (N=803)	Preintervention (N=5910)	*P* value (ITT intervention vs preintervention)	*P* value (PP intervention vs preintervention)
P2Y12 inhibitor delay	6.1 (84)	4.8 (39)	7.6 (449)	0.125	0.01
Adherent patients (PDC>0.80)	79.5 (1095)	82.2 (660)	74.8 (4418)	0.001	<0.01
PDC, mean (SD)	0.88 (0.20)	0.90 (0.18)	0.85 (0.23)	<0.001	<0.01
Death	4.9 (68)	4.6 (37)	6.3 (372)	0.197	0.22
Myocardial infarction	5.2 (72)	2.6 (21)	4.6 (273)	0.748	0.02
Stroke	3.0 (42)	1.0 (8)	1.7 (99)	0.001	0.59
Revascularization	16.0 (221)	14.6 (117)	10.4 (618)	<0.001	<0.01
CABG	0.9 (13)	0.5 (4)	1.1 (62)	1.00	0.39
PCI	15.1 (208)	14.1 (113)	9.4 (556)	<0.001	<0.001
Bleeding	13.8 (190)	12.3 (99)	11.6 (685)	0.069	1.00
Composite outcome	28.2 (388)	28.0 (225)	25.0 (1478)	0.50	0.22

Data are given as percentage (number), unless otherwise indicated. *P* values are adjusted for multiple comparisons of 3 tests using the Holm method[16] (intervention versus preintervention, intervention versus postintervention, intervention versus concurrent controls). CABG indicates coronary artery bypass grafting; ITT, intent to treat; PCI, percutaneous coronary intervention; PDC, proportion of days covered; and PP, per protocol.

Table 3. Risk-Adjusted Medication and Clinical Outcomes

Outcome measure	ITT intervention vs preintervention	PP intervention vs preintervention
Patients who delay, %	−3.4 (−5.6 to −1.2)	−4.6 (−6.9 to −2.2)
Adherent patients (PDC>0.80), %	4.1 (1.0 to 7.1)	6.1 (2.1 to 9.8)
MACE (hospitalizations for MI, bleeding, stroke, or coronary revascularization and death), %	3.2 (2.3 to 4.1)	3.8 (0.6 to 7.0)
MACE (hospitalization for MI or stroke and death), %	−1.7 (−2.3 to −1.1)	−2.1 (−2.9 to −1.5)

Data are given as risk difference (98.3% CI). Risk adjustment variables: patient-level characteristics: percutaneous coronary intervention status (elective, urgent, emergent, or salvage), race, atrial fibrillation, chronic kidney disease, prior coronary artery bypass grafting, blood pressure (diastolic), blood pressure (systolic), deep vein thrombosis, depression, sleep apnea, drug-eluting stent, posttraumatic stress disorder, hyperlipidemia, alcohol abuse, congestive heart failure, dialysis, peripheral artery disease, tobacco use, substance abuse/dependency, cholesterol, Framingham risk, prior MI, prior percutaneous coronary intervention, prior stroke/transient ischemic attack, prior renal transplant, and prior transcatheter valve; and site-level characteristics: average yearly percutaneous coronary interventions, yearly catheterizations, yearly patients, number of operating beds, and hospital complexity. ITT indicates intent to treat; MACE, major adverse clinical event; MI, myocardial infarction; PDC, proportion of days covered; and PP, per protocol.

In the MI FREEE study, there was a decrease in total major vascular events or revascularization in the full drug coverage arm, with an improvement of 4% to 6% in adherence to statins, β-blockers, and/or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker medications. In the current study, the findings were mixed on clinical events. There was a reduction in MI, stroke, or death but an increase in repeated PCI. Of the repeated PCIs in the intervention group, 62% were elective procedures. With the intervention, patients were contacted by a clinical team member if they did not refill their P2Y12 medication. It is possible that these additional clinical contacts led to greater surveillance of anginal symptoms and the subsequent clinical cascade leading to repeated PCI. Prior studies of home telemonitoring for patients with heart failure have demonstrated similar mixed results, with reductions in mortality but increases in emergency department visits.[24] Regardless of the clinical outcomes, it should be emphasized that P2Y12 inhibitors are recommended by clinical practice guidelines and performance measures.[25,26]

There are limitations that should be acknowledged. We used pharmacy refill and administrative data to assess outcomes of interest. In addition, we do not have medication information for medications filled outside of the VA or clinical events occurring outside of the VA in which the VA did not pay for that care. However, pharmacy refill data have been validated against more direct measures of medication adherence, and clinical events using VA administrative data have been validated with chart review and the national death index.[27,28] Second, our study comprised mainly male patients. Future studies may need to enroll more female patients as prior studies have noted differences in adherence by sex. Third, because of the pragmatic study design, many hospitals declined to participate after randomization because of the burden of implementing the intervention, hospitals from quintile 1 were not included because they were performing well with regard to P2Y12 inhibitor delay in the baseline period, and many patients were unable to be approached to receive the intervention so the sample size of enrolled patients was smaller than anticipated. Fourth, we included the postintervention time period as another control group, and it is possible that there may have been culture change impacting behavior during the postintervention period. Fifth, there are secular trends in P2Y12 treatment duration; however, we conducted several sensitivity analyses, and the findings were consistent in the intervention benefit. Sixth, we did not assess the impact of socioeconomic factors or education level on medication adherence. Finally, we did not assess the impact of any individual component of the multifaceted intervention. Prior studies have found that multimodal interventions are more likely to improve medication adherence than unimodal interventions, and we planned the intervention as a package to be delivered to patients.

In summary, our multifaceted intervention improved initiation and longitudinal adherence to P2Y12 inhibitor medication after PCI. There were reductions in subsequent MI, stroke, or death but an increase in repeated PCI. This may be related in part to increased surveillance of intervention patients. Implementation of the intervention was logistically challenging. Additional studies are needed to identify novel implementation strategies to improve adherence to P2Y12 and clinical outcomes after PCI.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al. on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139:e56–e528. doi: 10.1161/CIR.0000000000000659
2. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651. doi: 10.1161/CIR.0b013e31823ba622
3. Ho PM, Tsai TT, Maddox TM, Powers JD, Carroll NM, Jackevicius C, Go AS, Margolis KL, DeFor TA, Rumsfeld JS, et al. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation: implications for transitions of care. *Circ Cardiovasc Qual Outcomes*. 2010;3:261–266. doi: 10.1161/CIRCOUTCOMES.109.902031
4. Tuppin P, Neumann A, Danchin N, de Peretti C, Weill A, Ricordeau P, Allemand H. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. *Arch Cardiovasc Dis*. 2010;103:363–375. doi: 10.1016/j.acvd.2010.05.003
5. Roth GA, Morden NE, Zhou W, Malenka DJ, Skinner J. Clopidogrel use and early outcomes among older patients receiving a drug-eluting coronary artery stent. *Circ Cardiovasc Qual Outcomes*. 2012;5:103–112. doi: 10.1161/CIRCOUTCOMES.111.962704
6. Byrd JB, Maddox TM, O'Donnell CI, Grunwald GK, Bhatt DL, Tsai TT, Rumsfeld JS, Ho PM. Clopidogrel prescription filling delays and cardiovascular outcomes in a pharmacy system integrating inpatient and outpatient care: insights from the Veterans Affairs CART Program. *Am Heart J*. 2014;168:340–345. doi: 10.1016/j.ahj.2014.05.012
7. Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL, Investigators EDUCATE. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv*. 2015;8:404–410. doi: 10.1016/j.jcin.2014.10.017
8. Khalili H, Singh R, Wood M, Edwards A, Cooper M, Ayers C, Moss E, Berry JD, Vongpatanasin W, de Lemos JA, et al. Premature clopidogrel discontinuation after drug-eluting stent placement in a large urban safety-net hospital. *Am J Cardiol*. 2016;117:522–525. doi: 10.1016/j.amjcard.2015.11.037
9. Vigen R, Maddox TM, O'Donnell CI, Grunwald GK, Bhatt DL, Tsai TT, Rumsfeld JS, Ho PM. Hospital variation in premature clopidogrel discontinuation after drug-eluting stent placement in the veterans affairs (VA) healthcare system. *J Am Heart Assoc*. 2016;5:e001376. doi: 10.1161/JAHA.114.001376
10. Cho MH, Shin DW, Yun JM, Shin JH, Lee SP, Lee H, Lim YK, Kim EH, Kim HK. Prevalence and predictors of early discontinuation of dual-antiplatelet therapy after drug-eluting stent implantation in Korean population. *Am J Cardiol*. 2016;118:1448–1454. doi: 10.1016/j.amjcard.2016.07.073
11. Doll JA, Hellkamp AS, Thomas L, Fonarow GC, Peterson E, Wang TY. The association of pre- and posthospital medication adherence in myocardial infarction patients. *Am Heart J*. 2019;208:74–80. doi: 10.1016/j.ahj.2018.11.004
12. Cruden NL, Din JN, Janssen C, Smith R, Hilton JD, Klinke WP, Carere RG, Robinson SD, Siega AD. Delay in filling first clopidogrel prescription after coronary stenting is associated with an increased risk of death and myocardial infarction. *J Am Heart Assoc*. 2014;3:e000669. doi: 10.1161/JAHA.113.000669
13. Chua D, Shalansky S, Sinova A, Mackay M. Factors affecting delay in filling prescriptions for dual antiplatelet therapy after coronary stenting. *Can J Cardiol*. 2019;35:931–934. doi: 10.1016/j.cjca.2019.03.025
14. Maddox TM, Plomondon ME, Petrich M, Tsai TT, Gethoffer H, Noonan G, Gillespie B, Box T, Fihn SD, Jesse RL, et al. A national clinical quality program for Veterans Affairs catheterization laboratories (from the Veterans Affairs clinical assessment, reporting, and tracking program). *Am J Cardiol*. 2014;114:1750–1757. doi: 10.1016/j.amjcard.2014.08.045
15. McCreight MS, Lambert-Kerzner A, O'Donnell CI, Grunwald GK, Hebert P, Gillette M, Jneid H, Parashar A, Grossman PM, Helfrich C, et al. Improving anti-platelet therapy adherence in the Veterans Health administration: a randomized multi-site hybrid effectiveness-implementation study protocol. *Contemp Clin Trials*. 2019;77:104–110. doi: 10.1016/j.cct.2018.12.005
16. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist*. 1979;6:65–70.
17. Joffe MM, Greenland S. Standardized estimates from categorical regression models. *Stat Med*. 1995;14:2131–2141. doi: 10.1002/sim.4780141907
18. Zou GY. Assessment of risks by predicting counterfactuals. *Stat Med*. 2009;28:3761–3781. doi: 10.1002/sim.3751
19. Sjolander A. Regression standardization with the R package stdReg. *Eur J Epidemiol*. 2016;31:563–574. doi: 10.1007/s10654-016-0157-3
20. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol*. 2010;63:46–55. doi: 10.1016/j.jclinepi.2009.03.012
21. Zhang Z, Ambrogi F, Bokov AF, Gu H, deBeurs E, Eskaf K. Estimate risk difference and number needed to treat in survival analysis. *Annals of Translational Medicine*. 2018;6:120. doi: 10.21037/atm.2018.01.36

22. Ho PM, Lambert-Kerzner A, Carey EP, Fahdi IE, Bryson CL, Melnyk SD, Bosworth HB, Radcliff T, Davis R, Mun H, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA Intern Med*. 2014;174:186–193. doi: 10.1001/jamainternmed.2013.12944
23. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, Reisman L, Fernandes J, Spettell C, Lee JL, et al. for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365:2088–2097. doi: 10.1056/NEJMsa1107913
24. Pekmezaris R, Tortez L, Williams M, Patel V, Makaryus A, Zeltser R, Sinvani L, Wolf-Klein G, Lester J, Sison C, et al. Home telemonitoring in heart failure: a systematic review and meta-analysis. *Health Aff (Millwood)*. 2018;37:1983–1989. doi: 10.1377/hlthaff.2018.05087
25. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY, et al. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2017;70:2048–2090. doi: 10.1016/j.jacc.2017.06.032
26. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC, Dudley RA, Duffy PL, Faxon DP, Gurm HS, Hamilton LA, et al. ACC/AHA/SCAI/AMA–Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *J Am Coll Cardiol*. 2014;63:722–745. doi: 10.1016/j.jacc.2013.12.003
27. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119:3028–3035. doi: 10.1161/CIRCULATIONAHA.108.768986
28. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *J Gen Intern Med*. 1999;14:555–558. doi: 10.1046/j.1525-1497.1999.10198.x

SUPPLEMENTAL MATERIAL

TABLE S1: CHARACTERISTICS OF INTERVENTION SITES, SITES THAT REFUSED TO PARTICIPATE IN THE STUDY, AND CONCURRENT CONTROL SITES.

Hospital characteristic	**Intervention Sites N=15**	**Refused Sites N=29**	**Concurrent Control Sites N=8**	**p-value**
Operating beds	173.3	163.9	180.6	0.96*
Workload	65677	54607	61222	0.42*
Caths	634	513	519	0.34*
PCIs	215	180	191	0.57*
Hospital Complexity	'1a' =8; '1b'=5; '1c'=2; '2' = 0	'1a'=18; '1b'=6; '1c'=4; '2'=1	'1a'=5; '1b'=1; '1c'=2; '2'=0	0.89†

*Kruskall-Wallis; †Mehta-Patel

Hospital complexity designation:

Complexity 1a: Hospitals with the largest levels of volume and patient risk with significant teaching and research activities and have the highest volume and greatest breadth of specialty care. Complexity 1a facilities contain level 1 ICUs

Complexity Levels 1b and 1c: The levels of complexity decrease in Complexity Levels 1b and 1c, although these are still high volume hospitals with teaching and research missions

Complexity Level 2. These hospitals are considered medium complexity, with a medium patient volume and risk, some teaching and research, and level 2 and 3 ICUs.

TABLE S2: BASELINE CHARACTERISTICS OF INTERVENTION PATIENTS VERSUS POST-INTERVENTION AND CONCURRENT CONTROL PATIENTS

VARIABLE	ITT Intervention 1377 (%)	PP Intervention 803 (%)	Post-Intervention 2807 (%)	Concurrent 4736(%)	P-value (ITT Int vs Post)	P-value (ITT Int vs Conc)	P-value (PP Int vs Post)	P-value (PP Int vs Conc)
Age, mean (STD)	66.4 (8.9)	66.4 (9.2)	67.4 (8.9)	66.4 (8.6)	<0.01	1.00	0.02	1.00
Male gender	1344 (97.6)	779 (97.0)	2747 (97.9)	4642 (98.0)	0.81	0.81	0.20	0.18
Hispanic	50 (3.6)	29 (3.6)	146 (5.2)	394 (8.3)	0.06	<0.01	0.16	<0.01
Black	245 (17.8)	124 (15.4)	580 (20.7)	556 (11.7)	0.06	<0.01	<0.01	<0.01
White	1129 (82.0)	677 (84.3)	2223 (79.2)	4168 (88.0)	0.07	<0.01	<0.01	<0.01
Congestive heart failure	403 (29.3)	245 (30.5)	889 (31.7)	1287 (27.2)	0.37	0.37	0.76	0.17
Diabetes	720 (52.3)	421 (52.4)	1512 (53.9)	2512 (53.0)	1.00	1.00	1.00	1.00
Hyperlipidemia	1264 (91.8)	746 (92.9)	2548 (90.8)	4395 (92.8)	0.70	0.70	0.21	0.98
Hypertension	1280 (93.0)	747 (93.0)	2589 (92.2)	4369 (92.2)	1.00	1.00	1.00	1.00
Chronic kidney disease	307 (22.3)	172 (21.4)	777 (27.7)	1115 (23.5)	<0.01	0.71	<0.01	0.41
Peripheral arterial disease	328 (23.8)	182 (22.7)	699 (24.9)	1128 (23.8)	0.94	1.00	0.63	1.00
Cerebrovascular disease	231 (16.8)	130 (16.2)	618 (22.0)	962 (20.3)	<0.01	<0.01	<0.01	0.01
Dialysis	52 (3.8)	31 (3.9)	103 (3.7)	155 (3.3)	0.93	0.82	0.91	0.91
Prior myocardial infarction	603 (43.8)	329 (41.0)	1236 (44.0)	2105 (44.4)	1.00	1.00	0.22	0.22
Prior Revascularization	830 (60.3)	477 (59.4)	1519 (54.1)	2705 (57.1)	<0.01	0.08	0.03	0.48
ACS indication	637 (46.3)	342 (42.6)	1182 (42.1)	1906 (40.2)	0.02	<0.01	1.00	0.68
Non-ACS indication	740 (53.7)	461 (57.4)	1625 (57.9)	2830 (59.8)	0.02	<0.01	1.00	0.68
Bare Metal Stent	89 (6.5)	47 (5.8)	82 (2.9)	442 (9.3)	<0.01	<0.01	<0.01	<0.01

P2Y12 inhibitor								
Clopidogrel	1184 (86.0)	681 (84.8)	2372 (84.5)	4426 (93.4)	0.22	<0.01	0.88	<0.01
Prasugrel	60 (4.4)	45 (5.6)	79 (2.8)	124 (2.6)	0.01	<0.01	0<0.01	<0.01
Ticagrelor	120 (8.7)	64 (8.0)	288 (10.3)	107 (2.3)	0.13	<0.01	0.06	<0.01
missing	13 (0.9)	13 (1.6)	68 (2.4)	79 (1.7)	<0.01	0.07	0.67	1.00
Initial P2Y12 – 90 Day supply	1075 (78.1)	653 (81.3)	2196 (78.2)	3791 (80.0)	0.935	0.235	0.13	0.43
Statin prescriptions	1335 (97.0)	777 (96.8)	2697 (96.1)	4543 (95.9)	0.372	0.290	0.92	0.92
ACEi or ARB prescriptions	1048 (76.1)	611 (76.1)	2124 (75.7)	3669 (77.5)	0.918	0.918	1.00	1.00
Beta-blockers prescriptions	1243 (90.3)	718 (89.4)	2537 (90.4)	4335 (91.5)	0.952	0.319	0.46	0.12

P-values are adjusted for multiple comparisons of 3 tests.

ACS: acute coronary syndrome

ACEi: Angiotensin converting enzyme-inhibitor

ARB: Angiotensin receptor blocker

Statin: HMG CoA Reductase inhibitor

TABLE S3: BASELINE CHARACTERISTICS OF PATIENTS NOT APPROACHED FOR INTERVENTION COMPARED TO PP INTERVENTION PATIENTS AND PRE-INTERVENTION CONTROL PATIENTS.

Variable	Not Approached 574 (%)	PP Intervention 803 (%)	Pre-Intervention 5910 (%)	P-value Not-Approached vs Intervention	P-value Not-Approached vs Pre-intervention
Demographics					
Age, mean (STD)	66.5 (8.7)	66.3 (9.2)	66.4 (8.7)	1.00	1.00
Male	565 (98.4)	779 (97.0)	5799 (98.1)	0.26	0.72
Hispanic	21 (3.7)	29 (3.6)	258 (4.4)	1.00	0.98
Black	121 (21.1)	124 (15.4)	999 (16.9)	0.03	0.03
White	452 (78.7)	677 (84.3)	4891 (82.8)	0.03	0.04
CV Co-morbidities					
Congestive heart failure	158 (27.5)	245 (30.5)	1710 (28.9)	0.51	0.51
Diabetes	299 (52.1)	421 (52.4)	3135 (53.0)	1.00	1.00
Hyperlipidemia	519 (90.4)	746 (92.9)	5420 (91.7)	0.24	0.32
Hypertension	533 (92.9)	746 (92.9)	5462 (92.4)	1.00	1.00
Chronic kidney disease	135 (23.5)	171 (21.3)	1361 (23.0)	0.72	0.83
Peripheral arterial disease	145 (25.3)	181 (22.5)	1288 (21.8)	0.27	0.13
Cerebrovascular disease	100 (17.4)	131 (16.3)	1127 (19.1)	0.73	0.73
Dialysis	21 (3.7)	31 (3.9)	175 (3.0)	0.96	0.84
Prior myocardial infarction	274 (47.7)	327 (40.7)	2602 (44.0)	0.02	0.10
Prior Revascularization	353 (61.5)	477 (59.4)	3429 (58.0)	0.47	0.23
PCI details					
ACS indication	295 (51.4)	342 (42.6)	2571 (43.5)	<0.01	<0.01
Non-ACS indication	574 (48.6)	461 (57.4)	3339 (56.5)	<0.01	<0.01
Bare metal stent	42 (7.3)	47 (5.9)	600 (10.1)	0.33	0.07
Discharge medications					
P2Y12 inhibitor Clopidogrel Prasugrel Ticagrelor Missing	503 (87.6) 15 (2.6) 56 (9.8) 0 (0)	681 (84.8) 45 (5.6) 63 (7.8) 13 (1.6)	5186 (87.7) 402 (6.8) 187 (3.2) 135 (2.3)	0.32 0.01 0.25 0.01	0.99 <0.01 <0.01 <0.01
Initial P2Y12 – 90 Day supply	418 (72.8)	653 (81.3)	3820 (64.6)	<0.01	<0.01
Statin	558 (97.2)	777 (96.8)	5693 (96.3)	0.75	0.66
ACEi/ARB	437 (76.1)	611 (76.1)	4556 (77.1)	1.00	1.00
Beta-blockers	525 (91.5)	718 (89.4)	5426 (91.8)	0.48	0.83

P-values are adjusted for multiple comparisons of 2 tests.

ACS: acute coronary syndrome

ACEi: Angiotensin converting enzyme-inhibitor

ARB: Angiotensin receptor blocker
Statin: HMG CoA Reductase inhibitor

TABLE S4: UNADJUSTED MEDICATION (P2Y12 510 INHIBITOR DELAY AND MEDICATION ADHERENCE) AND CLINICAL OUTCOMES

	ITT Intervention % (N=1377)	**PP Intervention % (N=803)**	**Post-Intervention % (N=2807)**	**Concurrent % (N=4736)**
P2Y12 inhibitor delay	6.1 (84)	4.8 (39)	7.4 (209)	12.2 (578)
Adherent patients (PDC>0.80)	79.5 (1095)	82.2 (660)	77.0 (2162)	76.7 (3633)
Mean PDC (STD)	0.88 (0.20)	0.90 (0.18)	0.87 (0.22)	0.86 (0.23)
Death	4.9 (68)	4.6 (37)	6.4 (179)	5.3 (251)
Myocardial infarction	5.2 (72)	2.6 (21)	5.0 (139)	3.8 (180)
Stroke	3.0 (42)	1.0 (8)	1.4 (40)	0.80 (38)
Revascularization	16.0 (221)	14.6 (117)	10.8 (303)	10.6 (502)
CABG	0.9 (13)	0.5 (4)	1.1 (30)	1.5 (72)
PCI	15.1 (208)	14.1 (113)	9.7 (273)	9.1 (430)
Bleeding	13.8 (190)	12.3 (99)	14.0 (392)	11.5 (544)
Composite outcome	28.2 (388)	28.0 (225)	27.8 (780)	25.1 (1190)

Composite outcome: Accounts for the first event for each patient if they had multiple events

TABLE S5: RISK ADJUSTED MEDICATION AND CLINICAL OUTCOMES

Outcome measure	ITT Intervention vs. post-intervention Risk difference (98.3%% confidence interval)	ITT Intervention vs. concurrent control Risk difference (98.3%% confidence interval)	PP Intervention vs. post-intervention Risk difference (98.3% confidence interval)	PP Intervention vs. concurrent control Risk difference (98.3% confidence interval)
Percent of patients who delay	0.3% (-1.6% to 2.3%)	-2.8% (-5.1% to -0.5%)	-0.9% (1.5% to -3.4%)	-4.0% (-1.4% to -6.5%)
Percent of adherent patients (PDC>0.80)	2.7% (-0.8% to 6.2%)	3.0% (-0.5% to 6.4%)	+4.9% (1.0% to 8.7%)	+5.0% (0.6% to 9.0%)
MACE (Hospitalizations for MI, bleeding, stroke or coronary revascularization and death)	+1.2% (0.1% to 2.0%)	+4.8% (3.8% to 5.7%)	+1.8% (-1.7% to 4.9%)	+5.2% (1.8% to 8.3%)
MACE (Hospitalizations for MI or stroke, and death)	-1.6% (-2.2% to -1.0%)	0.04% (-0.5% to 0.6%)	-2.3% (-3.0% to -1.6%)	-0.4% (-1.2% to 0.2%)

Risk adjustment variables:
Patient level characteristics: PCI status (elective, urgent, emergent, salvage), Race, Atrial Fibrillation, Chronic Kidney Disease, Prior CABG, BP(diastolic), BP(systolic), Deep Vein Thrombosis, Depression, Sleep Apnea, Drug eluding stent, PTSD, Hyperlipidemia, Alcohol abuse, CHF, Dialysis, PAD, Tobacco use, Substance abuse/dependency, cholesterol, Framingham risk, Prior MI, Prior PCI, Prior stroke/TIA, Prior renal transplant, Prior transcatheter valve,
Site level characteristics: Average Yearly PCIs, yearly CATHs, Yearly Patients, number of operating beds, hospital complexity

TABLE S6: PERCENT ADHERENT TO OTHER CARDIOVASCULAR MEDICATION CLASSES
(PP INTERVENTION PATIENTS VERSUS CONTROL GROUPS)

% Adherent (Number Adherent / Number with Identified Rx)					**p-values (98.3% Confidence interval)**		
Medication Class	Intervention % (N)	Pre-Intervention % (N)	Post-Intervention % (N)	Concurrent Control % (N)	P-value Int v Pre	P-value Int v Post	P-value Int v Conc
STATIN	63.6 (494/777)	56.1 (3196/5693)	61.8 (1668/2697)	57.8 (2626/4542)	<0.01	0.40	<0.01
ACEi/ARB	65.0 (386/594)	56.5 (2505/4430)	63.1 (1300/2060)	57.7 (2057/3565)	<0.01	0.43	<0.01
Beta-Blocker	63.8 (445/698)	56.3 (2967/5266)	62.7 (1540/2455)	58.2 (2440/4194)	0.02	0.81	0.09

TABLE S7: SENSITIVITY ANALYSIS OF PERCENT OF ADHERENT PATIENTS AMONG DIFFERENT SUBGROUPS OF PP INTERVENTION PATIENTS

Subgroup	PP Intervention % (N)	Pre-intervention % (N)	Post-intervention % (N)	Concurrent control % (N)	P-value Int vs. pre	P-value Intvs. post	P-value Int vs. conc
ACS patients	80.7 (276/342)	73.5 (1889/2571)	76.8 (908/1182)	76.4 (1456/1906)	0.01	0.19	0.19
Non-ACS patients	83.3 (384/461)	75.7 (2529/3339)	77.2 (1254/1625)	76.9 (2177/2830)	<0.01	<0.01	<0.01
BMS patients excluded	84.1 (636/756)	77.6 (4119/5310)	77.8 (2119/2725)	79.0 (3394/4294)	<0.01	<0.01	<0.01
Outside VA pharmacy use patients excluded	82.3 (643/781)	75.0 (4281/5712)	77.4 (2090/2699)	77.0 (3503/4548)	<0.01	<0.01	<0.01
Patients refusing intervention excluded	83.6 (590/706)	74.7 (4418/5910)	77.0 (2162/2807)	76.7 (3633/4736)	<0.01	<0.01	<0.01