The association of pre- and posthospital medication adherence in myocardial infarction patients

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Background Nonadherence to optimal medical therapy following myocardial infarction (MI) is associated with adverse clinical outcomes such as stent thrombosis, recurrent cardiovascular events, and death. Whether adherence to medications prior to MI predicts post-MI medication adherence is unknown.

Methods We assessed adherence to $P2Y_{12}$ inhibitors and statins before and after admission for MI among 8,147 MI patients who had Medicare insurance with Part D prescription coverage. Adherence was defined as a proportion of days covered with medication fills ≥80%. Multivariable logistic regression was used to assess the association between pre- and post-MI $P2Y_{12}$ inhibitor adherence. As few patients were on $P2Y_{12}$ inhibitors pre-MI, we also examined the association of pre-MI statin adherence with post-MI $P2Y_{12}$ inhibitor and statin adherence.

Results Pre-MI medication nonadherence was observed in 427 of 2,633 (16%) patients on preadmission $P2Y_{12}$ inhibitors and 1,233 of 6,934 (18%) patients on preadmission statins. Nonadherent patients were more likely to be of nonwhite race and have multiple prior hospital admissions. Patients who were nonadherent to $P2Y_{12}$ inhibitors pre-MI were substantially less likely to adhere to $P2Y_{12}$ inhibitors at 90 days (adjusted odds ratio [OR] 0.33, 95% CI 0.25-0.43) and 1 year post-MI (adjusted OR 0.29, 95% CI 0.21–0.39) compared with patients who were adherent pre-MI. Pre-MI statin nonadherence was also associated with lower post-MI adherence to $P2Y_{12}$ inhibitors at 90 days (adjusted OR 0.65, 95% CI 0.53-0.79) and 1 year (adjusted OR 0.37, 95% CI 0.29-0.54).

Conclusions Prior medication adherence predicts post-MI adherence to $P2Y_{12}$ inhibitors. Increasing accessibility of medication adherence data in the medical record may be an important tool to identify patients at higher risk for post-MI medication nonadherence and target efforts to improve adherence. (Am Heart J 2019;208:74-80.)

Nonadherence to optimal medical therapy after myocardial infarction (MI) is common.[1,2] Adherence to $P2Y_{12}$ inhibitors is particularly critical because nonadherence can lead to stent thrombosis and recurrent MI with often fatal outcomes.[2-6] Hospitals use many strategies to improve patient medication adherence after discharge, but these interventions can be resource intensive, and some have only modest impact on adherence.[7,8] Targeting interventions to patients at high risk for nonadherence post-MI could yield greater impact and cost-effectiveness.[9]

Hospitalizations represent a teachable moment for patients with poor medication adherence[10] if providers can correctly identify these at-risk patients. Improvements in health information technology permit direct insights into past medication adherence.[11] Pharmacy fill data are routinely accessible in integrated health care systems such as the Veterans Affairs hospitals, and Meaningful Use initiatives have expanded that capability into other health care systems that use electronic health records.[12] We hypothesize that pre-MI medication adherence information from pharmacy fill data for $P2Y_{12}$ inhibitors and statins will predict post-MI $P2Y_{12}$ inhibitor adherence. In addition to accurately identifying patients most amenable to adherence-improving interventions, these data might also guide in-hospital

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treatment decisions such as the selection of revascularization strategy and stent type.[13,14]

Methods

Study population

We used administrative claims from a 5% random sample of Medicare beneficiaries aged greater than or equal to 65 years to assess clinical characteristics and pharmacy fill history of patients hospitalized with MI from 2007 to 2013. Patients were eligible for inclusion if admitted with primary or secondary diagnosis code for MI (410.*x*1) and enrolled in Medicare Part A (inpatient) and B (outpatient) for at least 1 year prior to admission.[15,16] Claims from the year preceding MI were used to define medical comorbid conditions. This project was supported by grant U19HS021092 from the Agency for Healthcare Research and Quality (AHRQ). The AHRQ had no role in the design and conduct of the study.

We assessed 101,983 MI hospital admissions among 83,075 beneficiaries at 4,246 hospitals in the United States. To evaluate the medication adherence of patients living at home after MI, we subsequently excluded hospitalizations for patients not discharged to home (47,868), who died or received hospice services within 3 months of discharge (4659), and who did not have Medicare Part D (prescription drug) coverage for at least 9 months before and 3 months after MI (24,311). We also excluded patients not evaluable for $P2Y_{12}$ inhibitor or statin adherence in the 6 months prior to MI (15,070) and any subsequent admissions for a patient admitted 2 or more times during the study period (928). Our final analysis cohort included 8,147 patients. Patients who were excluded from our analysis because they were not taking a $P2Y_{12}$ inhibitor or statin prior to admission (n = 13,536) were less likely to have Medicaid eligibility; had lower rates of comorbid diseases, prior MI, and prior percutaneous coronary intervention (PCI); and were less likely to have prior hospitalizations. They were also less likely to be discharged on a statin (eTable I).

Data definitions

Patient demographic data were obtained from the Medicare beneficiary summary file. Patients with unknown race (0.2%) were grouped with white race. Comorbid conditions and prior use of health services such as hospitalizations and nursing home care were identified from Part A and B claims from the year preceding MI hospitalization as previously described.[15,17] Index MI hospitalization features were obtained from Part A claims.

Medicare Part D pharmacy fill data were used to calculate the proportion of days covered (PDC), and adherence was defined as PDC $\geq$ 80%, consistent with prior analyses.[17-19] A patient was considered *evaluable* for pre-MI adherence if Part D coverage was available for at least 9 months prior to MI admission, a prescription fill provided some supply at the beginning of the 6-month pre-MI period of adherence evaluation, and the patient continued treatment (no gap of 30 days or more in supply) prior to admission. Patients were determined to be taking a medication after discharge (including statins and $P2Y_{12}$ inhibitors) if a pharmacy fill for that medication occurred within 30 days of discharge or the completion of the pre-MI supply for that medication. A patient was considered *evaluable* for post-MI adherence if they had Part D coverage for the full period of interest. Days spent as an inpatient in a hospital, nursing facility, or rehabilitation facility were not counted in the denominator.

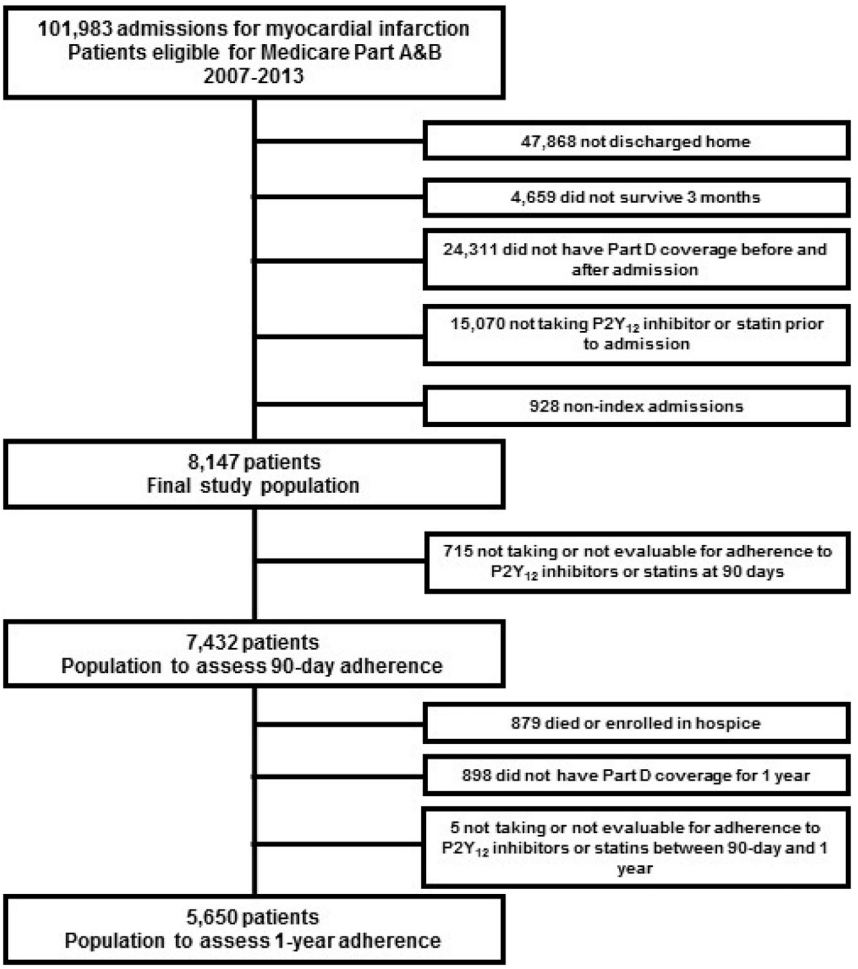
Because some patients may prematurely terminate medications in the post-MI period, we also assessed for the rate of medication gaps and discontinuations (30 days or greater without a prescription fill) for each period. In a sensitivity analysis, we assessed adherence rates (PDC $\geq$ 80%) among patients without a gap or discontinuation.

Statistical analysis

We compared demographic, clinical, and treatment characteristics among patients who were adherent versus nonadherent to statin and $P2Y_{12}$ inhibitor therapy using Wilcoxon rank sum tests for continuous variables and Pearson χ^2 tests for categorical variables.

To assess the association of pre-MI medication adherence with post-MI adherence, we included the 7,432 patients who were evaluable for at least 1 of the following 3 medication patterns: (1) $P2Y_{12}$ inhibitor treatment both pre- and post-MI, (2) statin treatment both pre- and post-MI, and (3) statin treatment pre-MI and $P2Y_{12}$ inhibitor treatment post-MI (Figure 1). To examine 1-year medication adherence, we further excluded patients who died or were enrolled in hospice between 90 days and 1 year (n = 879), did not have Part D coverage for the full year (n = 898), or were not evaluable for at least 1 of the 3 medication patterns noted above for the full year postdischarge (n = 5); this cohort included 5,650 patients (Figure 1). We performed multivariable logistic regression using generalized estimating equations to account for clustering within sites. A separate model was used for each of these 3 medication patterns at both 90-day and 1-year follow-ups, including only patients evaluable for each medication of interest at each time point. Covariates in the models were selected a priori as potentially unbalanced between groups or associated with medication adherence. These included demographics (age, sex, race, Medicare/Medicaid dual eligibility, geographic region), comorbid medical conditions (hypertension, diabetes, dyslipidemia, chronic kidney disease, cerebrovascular disease, congestive heart failure, peripheral arterial disease, prior MI, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery [CABG]), health services used in the prior 6 months (number of prior hospitalizations, stay at skilled

Figure 1



Consort diagram showing patients included in each of the analyses.

nursing facility or long-term care facility), presentation and in-hospital treatment characteristics (cardiogenic shock, cardiac arrest, percutaneous coronary intervention, drug-eluting stent use, CABG, length of stay), and number of cardiovascular medications filled at discharge. Model fit was assessed with *c*-index (ranging from 0.59 to 0.70 for the 6 models), and the strength of association of pre-MI adherence to post-MI adherence was ranked with other covariates by χ^2 values. A P value $\leq .05$ was considered statistically significant for all tests. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC).

Results

Among 8,147 MI patients in the final study population, 2,633 were taking a $P2Y_{12}$ inhibitor in the 6 months prior to admission and 6,934 were taking a statin (including 1420 who were taking both). Pre-MI nonadherence was 16% for $P2Y_{12}$ inhibitors and 18% for statins. Nonadherent patients were more likely to be of nonwhite race and more likely to have hospitalizations or nursing facility admissions in the 6 months prior to admission. Comorbid medical conditions and Medicare/Medicaid dual eligibility status were not associated with pre-MI adherence (Table I). During the index hospitalization, 37% underwent PCI, 5% underwent CABG, and 58% were medically managed without revascularization. Among patients treated with PCI, 65% received a drug-eluting stent.

In the 30 days after index hospital discharge, 4,695 (58%) patients filled a prescription for a $P2Y_{12}$ inhibitor; these included 4,462 for clopidogrel, 169 for prasugrel, 51 for ticagrelor, and 13 for ticlopidine. Additionally, 5,116 (63%) patients filled a statin prescription, including 3,288 for a generic statin, 1,338 for a branded statin with a generic option, and 490 for a statin that did not yet have a generic option.

$P2Y_{12}$ inhibitor adherence was 82.1% at 90 days and 72.3% at 1 year among patients continuing treatment at

Table I. Characteristics of older adults admitted for MI, stratified by preadmission medication adherence to $P2Y_{12}$ inhibitors and statins

	$P2Y_{12}$ inhibitor			Statin		
Variable	Adherent	Nonadherent	*P*	Adherent	Nonadherent	*P*
n	2206	427		5701	1233	
Demographics						
Age, y, median (IQR)	78 (72-84)	76 (70-81)	<.01	77 (71-83)	77 (71-83)	.29
Female	59%	56%	.21	56%	59%	.07
Race			<.01			<.01
White	84%	75%		87%	79%	
Black	9%	16%		7%	13%	
Other	7%	9%		6%	8%	
Medicaid dual eligible	37%	34%	.20	31%	31%	.88
Region			.29			<.01
Northeast	20%	19%		21%	19%	
Midwest	25%	26%		26%	24%	
South	44%	41%		39%	43%	
West	10%	13%		14%	14%	
US territory	<1%	<1%		<1%	<1%	
Medical history*						
Hypertension	97%	96%	.43	96%	96%	.26
Diabetes	61%	59%	.44	56%	55%	.51
Dyslipidemia	92%	93%	.35	96%	96%	.85
Chronic kidney disease	38%	42%	.11	34%	34%	.74
Cerebrovascular disease	42%	45%	.37	32%	33%	.65
Congestive heart failure	63%	61%	.47	55%	52%	.07
Peripheral arterial disease	49%	55%	.02	39%	40%	.80
MI in prior year	44%	42%	.54	34%	35%	.91
PCI in prior year	13%	11%	.37	5%	6%	.02
CABG in prior year	1%	1%	.12	1%	2%	.01
Health service use in prior 6 m						
Number of hospitalizations			<.01			<.01
0	69%	61%		75%	71%	
1	19%	20%		16%	17%	
2+	12%	19%		8%	12%	
SNF, IRF, or LTC stay	4%	10%	<.01	5%	8%	<.01
Index MI hospitalization features						
Cardiogenic shock	2%	2%	.63	2%	2%	.99
Cardiac arrest	4%	4%	.91	4%	5%	.04
PCI	38%	40%	.48	37%	40%	.06
Drug-eluting stent	26%	28%	.38	24%	26%	.07
CABG	3%	2%	.10	6%	5%	.14
Length of stay, d, mean (SD)	6.1 (3.6)	6.1 (4.0)	.55	6.2 (3.8)	6.0 (3.7)	.07
Medications taken after discharge						
Statin	59%	52%	.01	67%	60%	<.0001
$P2Y_{12}$ inhibitor	65%	60%	.05	57%	57%	.70
No. of cardiovascular meds,† mean (SD)	2.5 (1.2)	2.3 (1.2)	<.01	2.5 (1.2)	2.4 (1.2)	.05

IQR, interquartile range; *SNF*, skilled nursing facility; *IRF*, inpatient rehabilitation facility; *LTC*, long-term care.
*Occurring in 1 year prior to admission or during index admission. For prior MI, PCI, and CABG, occurring prior to admission only.
† Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, statin, or $P2Y_{12}$ inhibitor.

least 1 year. Statin adherence was higher at 86.5% at 90 days and 81.2% at 1 year. Patients who were nonadherent to $P2Y_{12}$ inhibitors pre-MI had lower observed rates of adherence at 90 days post-MI compared with patients who were adherent pre-MI (unadjusted 67.1% vs 87.4%) (Table II). This persisted after multivariable adjustment: adjusted odds ratio (OR) 0.33 (95% CI 0.25-0.43). For patients who continued treatment, pre-MI nonadherence remained associated with poorer post-MI adherence at 1 year (unadjusted 53.7% vs 80.1%; adjusted OR 0.29 [95% CI 0.29-0.39]). Among 24 demographic and clinical variables included in the multivariable model, preadmission $P2Y_{12}$ inhibitor adherence was most strongly associated with post-MI adherence at 90 days.

Similar associations were noted for statin adherence pre- and post-MI (Table II). As few patients were on $P2Y_{12}$ inhibitors pre-MI, we also evaluated if pre-MI adherence to the more commonly used statins was associated with post-MI adherence to $P2Y_{12}$ inhibitors. Patients who were nonadherent to statins pre-MI were less likely to adhere to

Table II. Association of preadmission medication adherence (PDC ≥ 80%) to postdischarge medication adherence after MI

Analysis				Post-MI Adherence		
Pre-MI	Post-MI	Follow-up	n	Among pre-MI nonadherent	Among pre-MI adherent	Adjusted OR (95% CI)
$P2Y_{12}$ inhibitor	$P2Y_{12}$ inhibitor	90 d	2192	67.1%	87.4%	0.33 (0.25-0.43)
		1 y	1639	53.7%	80.1%	0.29 (0.21-0.39)
Statin	Statin	90 d	5991	73.6%	88.9%	0.35 (0.29-0.42)
		1 y	4562	64.0%	84.5%	0.33 (0.28-0.40)
Statin	$P2Y_{12}$ inhibitor	90 d	4283	76.1%	83.2%	0.65 (0.53-0.79)
		1 y	3323	64.6%	74.7%	0.37 (0.29-0.54)

$P2Y_{12}$ inhibitor therapy at both 90 days (76.1% vs 83.2%; adjusted OR 0.65 [95% CI 0.53-0.79]) and 1 year (64.6% vs 74.7%; adjusted OR 0.37 [95% CI 0.29-0.54]).

Because temporary interruptions and premature discontinuations of indicated medications could impact patient outcomes after MI, we also examined the rates of gaps of 30 days or more in medication prescription fills. Patients with pre-MI medication nonadherence were more likely to have fill gaps at both 90 days and 1 year (eTable II). When we excluded these patients from the overall cohort in a sensitivity analysis, medication adherence rates improved, but relationships with pre-MI adherence were unchanged (eTable III).

Discussion

Our study demonstrated suboptimal medication adherence before and after hospitalization for MI. Examining pre-MI patient medication adherence, whether to $P2Y_{12}$ inhibitors or to another cardiovascular medication, can yield insight into post-MI adherence to $P2Y_{12}$ inhibitor therapy.

Prior studies have identified multiple patient factors associated with nonadherence. The most predictive factors, including barriers related to communication (low health literacy, substance abuse, mental illness), socioeconomic status (financial hardship, poor social support), and motivation (poor patient activation, lack of perceived benefit, fear of adverse effects),[20,21] are not routinely assessed during a typical short hospitalization for MI care.[22] Our study, limited to variables obtained from Medicare claims, identified only nonwhite race, prior hospitalizations, and prior nursing facility admission as significant factors associated with nonadherence prior to MI. This highlights the paucity of objective measures to assess nonadherence risk. Outpatient pharmacy fill data provide an objective measure of prior medication-taking behavior that may be useful to guide in-hospital treatment strategies or use of interventions to improve adherence.

Medication nonadherence after MI is associated with recurrent MI and death.[1,23,24] Although MI guidelines recommend 1 year of $P2Y_{12}$ inhibitor therapy, fill rates were low post-MI (58%) even among patients previously taking $P2Y_{12}$ inhibitors (64%). Additionally, 18% of patients filling a $P2Y_{12}$ prescription were shown to be nonadherent to $P2Y_{12}$ inhibitor as early as 90 days after discharge. This is consistent with other studies that have described a vulnerable period after hospitalization.[21,24] Therefore, adherence immediately after MI may be a key target for interventions. Adherence rates declined between 90 days and 1 year, resulting in only 72% of patients filling a $P2Y_{12}$ prescription after discharge ultimately completing the recommended 1 year of $P2Y_{12}$ treatment with good adherence.

Association of pre-MI and post-MI medication adherence

A strong association of pre-MI adherence with post-MI adherence was present in all analyses and time points, including comparisons within the same medication class ($P2Y_{12}$ inhibitor/$P2Y_{12}$ inhibitor, statin/stain) and between medication classes (statin/$P2Y_{12}$ inhibitor). Post-MI adherence was notably poor among patients with prior nonadherence to $P2Y_{12}$ inhibitors; only 67.1% adhered at 90 days. Prior studies have identified the importance of past medication-taking behavior for predicting future adherence.[25-27] However, these studies have been performed among stable outpatients, and admission for MI presents an opportunity to alter adherence behavior. Kronish et al examined adherence to statin therapy before and after MI. They reported that MI hospitalization was frequently associated with a change in adherence to statins, although this could be either positive or negative.[10] Of nonadherent patients, 37.7% became adherent (PDC ≥ 80%) after discharge. However, 32.6% of previously adherent patients subsequently were nonadherent (PDC < 80%). Our study confirms that adherence behavior may change in the setting of an MI admission, but prior adherence behavior is nonetheless strongly associated with future adherence.

Clinicians may be particularly interested in predicting adherence to $P2Y_{12}$ inhibitor therapy. However, relatively few patients in our cohort presented with pre-MI $P2Y_{12}$ inhibitor use. It is therefore notable that pre-MI adherence to statins (a more commonly used medication class) was also associated with $P2Y_{12}$ adherence post-MI, and adherence predictions across medication classes may be

reasonable. Although we only assessed statins and $P2Y_{12}$ inhibitors in this study, clinicians may also choose to consider the patient's adherence history with other drugs.

Potential for clinical use

Knowledge of prior adherence behavior could alter care, but clinician assessment of adherence is often inaccurate.[28] In addition, although several interventions have improved adherence rates in randomized trials, costs may be high.[7,8,29,30] Interventions targeting high-risk populations and tailored to prior adherence barriers could result in greater clinical benefit and cost-effectiveness. If pharmacy data were more fully integrated into the electronic medical record, detection of poor adherence could trigger point-of-care notifications at the time of medication reconciliation or cardiac catheterization, prompting clinicians to investigate adherence barriers. Poor adherence could also trigger additional services from pharmacists or case managers. Finally, pharmacy fills could serve as outcomes for evaluation of local quality improvement initiatives or clinical trials that target medication adherence.

Prediction of future $P2Y_{12}$ inhibitor adherence may also influence in-hospital treatment decisions such as revascularization strategy and stent selection because poor adherence is associated with stent thrombosis, MI, and death,[4,6,23] especially after PCI. Nonadherent patients in particular may benefit more from CABG than PCI in the setting of multivessel coronary disease, as described by a recent retrospective study.[14] Additionally, because of stent thrombosis concerns, some clinicians may prefer bare metal stents to drug-eluting stents for patients at high risk for nonadherence.[4,13,31] However, nonadherence is associated with MI and death among patients treated with bare metal stents, drug-eluting stents, and CABG, emphasizing the importance of adherence for all MI patients.[14,31]

Limitations

Our analysis included only patients with Medicare Part D coverage who were discharged home from MI admission and had prior use of statin and/or $P2Y_{12}$ inhibitors. This population is older, has more prior cardiac and vascular disease, and is less likely to receive revascularization than patients with MI in other studies.[32] Patterns of adherence may differ for younger patients, patients with other methods of payment for medication costs, and patients with conditions other than MI. In addition, we included only patients with documented prescription supply within 30 days of the MI admission and at least 1 fill postdischarge, potentially enriching our population with patients with superior medication-taking habits. This may explain why adherence rates in our study, although suboptimal, were generally higher than in other analyses using Medicare data. We also assessed only statin and $P2Y_{12}$ inhibitor therapy. Although our findings were consistent within and between these medications classes, it is unknown if other medication classes would show similar associations of preadmission and postdischarge adherence. PDC as calculated from pharmacy fill records is an indirect assessment of adherence and may overestimate adherence relative to more direct methods such as observed therapy and pill counts. However, the correlation of pharmacy records to other measures has been well established.[32,33] Any adherence misclassification should be systematic, thereby not altering the relationship of pre-MI to post-MI adherence. A sensitivity analysis accounting for medication interruptions and discontinuations revealed consistent results. Finally, our analysis was limited to data obtained from Medicare claims and therefore could not assess nor adjust for psychosocial, economic, and motivational factors that may influence adherence. These factors may be critical for assessing risk of nonadherence for individual patients and may be considered in concert with fill-based adherence measures.

Conclusions

There is a strong association between preadmission and postdischarge medication adherence among older adults hospitalized for MI. Pharmacy fill records can identify patients at high-risk for nonadherence. Future quality improvement efforts and clinical trials should consider targeting patients with poor preadmission adherence for interventions to improve adherence after MI.

Disclosures

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Dr Doll had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.004.

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