ORIGINAL RESEARCH

Association of Diabetes Mellitus Status and Glycemic Control With Secondary Prevention Medication Adherence After Acute Myocardial Infarction

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***Background*—**Cardioprotective medication adherence can mitigate the risk of recurrent cardiovascular events and mortality after acute myocardial infarction (AMI). We examined the associations of diabetes mellitus status and glycemic control with cardioprotective medication adherence after AMI.

***Methods and Results*—**We performed a retrospective observational cohort study of 14 517 US veterans who were hospitalized for their first AMI between 2011 and 2014 and prescribed a beta-blocker, 3-hydroxy-3-methyl-glutaryl-CoA-reductase inhibitor, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The primary exposure was a diagnosis of type 2 diabetes mellitus; in diabetes mellitus patients, hemoglobin A1c (HbA1c) was a secondary exposure. The primary outcome was 1-year adherence to all 3 medication classes, defined as proportion of days covered ≥0.8, assessed using adjusted risk differences and multivariable Poisson regression. Of 14 517 patients (mean age, 66.3 years; 98% male), 52% had diabetes mellitus; 9%, 31%, 24%, 15%, and 21% had HbA1c <6%, 6% to 6.9%, 7% to 7.9%, 8% to 8.9%, and ≥9%, respectively. Diabetes mellitus patients were more likely to be adherent to all 3 drug classes than those without diabetes mellitus (adjusted difference in adherence, 2.1% [0.5, 3.7]). Relative to those with HbA1c 6% to 6.9%, medication adherence declined with increasing HbA1c (risk ratio of achieving proportion of days covered ≥0.8, 0.99 [0.94, 1.04], 0.93 [0.87, 0.99], 0.82 [0.77, 0.88] for HbA1c 7–7.9%, 8–8.9%, and ≥9%, respectively).

***Conclusions*—**Although diabetes mellitus status had a minor positive impact on cardioprotective medication adherence after AMI, glycemic control at the time of AMI may help identify diabetes mellitus patients at risk of medication nonadherence who may benefit from adherence interventions after AMI. **(*J Am Heart Assoc*. 2019;8:e011448. DOI: 10.1161/JAHA.118.011448.)**

Key Words: diabetes mellitus • medication adherence • myocardial infarction

Individuals with diabetes mellitus are at increased risk of cardiovascular disease compared with those without diabetes mellitus.[1] In fact, myocardial infarction is the leading cause of death among individuals with diabetes mellitus,[2] and patients with diabetes mellitus are at increased risk of recurrent cardiovascular events and mortality after acute myocardial infarction (AMI).[3,4] Although coronary heart disease (CHD) mortality rates have declined over the past few decades, CHD remains responsible for nearly 1 of every 6 deaths in the United States.[5] Cardioprotective medications, including aspirin, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), renin-angiotensin-aldosterone system modulators (angiotensin-converting enzyme [ACE]-inhibitors [ACEis] and angiotensin receptor blockers [ARBs]), and beta-blockers (BBs), have been shown to significantly reduce mortality following AMI in individuals without and with diabetes mellitus.[6–10] As a result, these medications are recommended by the American Heart Association and European Society of Cardiology for secondary prevention of CHD after AMI, especially among those with reduced cardiac function.[11,12]

A major barrier to effective management following AMI is medication nonadherence, which is associated with increased morbidity,[6,10] mortality,[6,8–10] and healthcare cost.[13] A large meta-analysis estimated that approximately one third of patients were nonadherent to medications after a cardiac

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Accompanying Tables S1 through S7 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011448

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Clinical Perspective

What Is New?

- Patients with diabetes mellitus had a slightly higher rate of adherence to cardioprotective medications than those without diabetes mellitus after acute myocardial infarction (AMI), though the difference may not be clinically significant.
- Among those with diabetes mellitus, worsening glycemic control and low hemoglobin A1c (<6%) were associated with a higher likelihood of cardioprotective medication nonadherence compared with individuals with hemoglobin A1c 6% to 6.9%.
- Those without and with diabetes mellitus demonstrated suboptimal adherence to medications following AMI.

What Are the Clinical Implications?

- In the first year after AMI, there remains an opportunity to improve outcomes through targeted interventions addressing cardioprotective medication adherence among those without and with diabetes mellitus.
- In those with diabetes mellitus, hemoglobin A1c at the time of AMI may help identify individuals at particularly high risk for cardioprotective medication nonadherence who may benefit from interventions that target secondary medication adherence to reduce recurrent events.
- Patients with diabetes mellitus with hemoglobin A1c <6% at the time of AMI may also be a high-risk population for cardioprotective medication adherence who may benefit from additional adherence resources.

event, irrespective of the type of drug prescribed.[14] Similarly, a retrospective analysis of 4591 patients with AMI found that ≈20% had not filled their cardiovascular medications at 4 months after discharge.[15] Collectively, these studies highlight that improving cardioprotective medication adherence after AMI represents an opportunity for improving cardiovascular outcomes.[6–10,13–16] Thus, predictors of medication nonadherence at the time of AMI could be valuable for identifying a vulnerable patient population amenable to medication adherence interventions. Although previous studies have examined predictors of diabetes mellitus medication adherence in patients with diabetes mellitus,[17–20] little is known specifically about predictors of cardioprotective medication adherence in the high-risk population of patients with diabetes mellitus after AMI.

Accordingly, the aim of this study was 2-fold: to analyze whether cardioprotective medication adherence after AMI differs based on diabetes mellitus status or based on glycemic control, as indicated by hemoglobin A1c (HbA1c), in those with diabetes mellitus. Determining whether diabetes mellitus status or glycemic control can help identify those at an increased risk of cardioprotective medication nonadherence could inform interventions that address barriers to medication adherence after AMI and potentially reduce preventable recurrence of cardiovascular events or mortality.

Methods

The data and study materials cannot be made publicly available because of Department of Veterans Affairs privacy policies and are limited to groups operating on behalf of the Department of Veterans Affairs. Statistical code is available upon reasonable request to the corresponding author.

Study Population

We studied US veterans who were hospitalized with their first AMI between January 1, 2011 and September 30, 2014. AMI hospitalization was based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) primary diagnosis codes for AMI from inpatient visits as described previously.[21] Because we were interested in cardioprotective medication adherence, we included patients who were either already taking or were prescribed at hospital discharge an ACEi or ARB, a BB, and a statin. To be included in the study, patients had to have data in the Veterans Affairs (VA) electronic health record for at least 2 years before and 1 year following AMI hospitalization. To avoid confounding attributed to acute illnesses, overall decline in health, or other causes of treatment interruption that might not be captured in the electronic health record, we included only individuals who survived for 1 year after AMI hospitalization (Figure S1). Because the study involved only secondary analysis of data collected routinely in the course of clinical care, the requirement for informed consent from study participants was waived. The local VA Research and Development Committee and the Colorado Multiple Institutional Review Board provided approval for this study.

Exposures

The primary exposure for this study was diabetes mellitus status. We defined patients with diabetes mellitus as those with at least 1 *ICD-9-CM* type 2 diabetes mellitus diagnosis code from an inpatient hospitalization or at least 2 *ICD-9-CM* type 2 diabetes mellitus diagnosis codes from 2 separate outpatient visits occurring within the 24 months before presentation for AMI.[22] In secondary analyses of individuals with diabetes mellitus, we examined HbA1c at the time of AMI as an exposure. HbA1c at the time of AMI was defined as the measurement occurring nearest in date to the date of admission for AMI and occurring between 1 year before the

admission date to 3 days after the admission date. To accommodate nonlinearity in the association between HbA1c and outcomes, HbA1c was classified into clinically meaningful categories: <6% (<42 mmol/mol), 6% to 6.9% (42–52 mmol/mol), 7% to 7.9% (53–63 mmol/mol), 8% to 8.9% (64–74 mmol/mol), or ≥9% (≥75 mmol/mol).

Outcomes

The primary outcome for this study was adherence to cardioprotective medications: ACEi or ARB, BB, and statin therapy. Adherence to each medication class was assessed as the proportion of days covered (PDC) over the first year after AMI hospitalization as previously described.[23] Briefly, PDC was calculated as the total number of days of medication supplied for filled prescriptions, divided by the total observation period (1 year). For each participant, we calculated PDC for each medication class and estimated a summary PDC for all 3 medications by taking the average PDC for all 3 medications. We dichotomized adherence using a threshold PDC of ≥0.8, consistent with previous medication adherence literature.[23]

Statistical Analysis

Patient demographics, comorbidities, smoking status, and body mass index (calculated as the weight in kilograms divided by the height in meters squared) were collected and compared between those without and with diabetes mellitus and between HbA1c categories. We used chi-square tests to compare categorical data and Mann–Whitney–Wilcoxon nonparametric tests for continuous or ordinal data.

We estimated unadjusted associations of diabetes mellitus status and HbA1c with medication adherence using Mann–Whitney–Wilcoxon nonparametric tests for PDC as a continuous variable and using chi-square tests for PDC dichotomized at a threshold of 0.8. We estimated standardized associations of diabetes mellitus status and HbA1c with medication adherence after adjusting for age, race, sex, comorbidities (congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, post-traumatic stress disorder, chronic kidney disease, dialysis use, and depression), smoking status, and body mass index. Comorbidities were measured based on the presence of *ICD-9-CM* diagnosis codes present in the patient problem list at the time of AMI. Smoking status was estimated using health factors recorded in the VA electronic health record at the time of AMI hospitalization, and body mass index was based on height and weight recorded at the time of AMI hospitalization. We also compared achievement of PDC exceeding 0.8 across HbA1c categories using multivariable Poisson regression to estimate incidence rate ratios because the outcome rate was too frequent to accurately estimate rate ratios using logistic regression. As a sensitivity analysis, we examined the distribution of time between HbA1c measurement and hospitalization for AMI, and repeated the incidence rate ratio analysis comparing adherence across HbA1c categories including only individuals with an HbA1c measurement occurring within 90 days or within 180 days of the index AMI hospitalization. In analyses comparing individuals without and with diabetes mellitus, non-diabetes-mellitus status was the reference group; in analyses comparing HbA1c categories, 6% to 6.9% (42–52 mmol/mol) was the reference category. We applied a significance threshold of $P<0.05$ for all comparisons. All analyses were conducted in SAS software (version 9.4; SAS Institute Inc, Cary, NC).

Results

Study Population Characteristics

A total of 7491 (52%) patients in our population carried a diagnosis of diabetes mellitus at the time of AMI, while 7026 (48%) did not. Of those with diabetes mellitus, 9%, 31%, 24%, 15%, and 21% had HbA1c <6% (<42 mmol/mol), 6% to 6.9% (42–52 mmol/mol), 7% to 7.9% (53–63 mmol/mol), 8% to 8.9% (64–74 mmol/mol), and ≥9% (≥75 mmol/mol), respectively. Patients with and without diabetes mellitus were primarily non-Hispanic white (77% in both groups) and male (98% in both groups); those with diabetes mellitus were slightly older at baseline (66.7 versus 65.9 years; $P<0.0001$; Table 1). While generally similar regarding age, sex, and race, individuals with and without diabetes mellitus diverged with regard to prevalence of comorbidities. Congestive heart failure co-occurred in 2553 (34%) of those with diabetes mellitus, but only 1544 (22%) of those without ($P<0.0001$). Similar trends were observed in peripheral artery disease (21% in those with versus 14% in those without diabetes mellitus; $P<0.0001$), chronic kidney disease (27% in those with versus 13% in those without diabetes mellitus, $P<0.0001$), dialysis (3% in those with versus 1% in those without diabetes mellitus; $P<0.0001$), depression (29% in those with versus 24% in those without diabetes mellitus; $P<0.0001$), and post-traumatic stress disorder (15% in those with versus 12% in those without diabetes mellitus; $P<0.0001$; Table 1).

Association Between Diabetes Mellitus Status and Medication Adherence

The mean PDC for all 3 cardioprotective medications was higher in patients with diabetes mellitus (86.5 versus 85.0; $P=0.0001$; adjusted between-group difference, 1.2 [95% CI, 0.6–1.8]; Table 2). Similarly, the mean PDC for each medication class was higher for patients with diabetes mellitus than for those without diabetes mellitus (84.3% versus 82.8% for statins, 87.3% versus 85.5% for BBs, and 88.0% versus 86.5%

Table 1. Baseline Characteristics of Study Population

	No Diabetes Mellitus (n=7026)	Diabetes Mellitus (n=7491)	*P* Value
Age (y), mean (SD)	65.9 (10.8)	66.7 (9.5)	<0.0001
Sex, n (%)			
Male	6877 (98)	7327 (98)	0.78
Female	149 (2)	164 (2)	
Race, n (%)			
Non-Hispanic white	5376 (77)	5801 (77)	0.002
Black	1200 (17)	1289 (17)	
Asian	344 (5)	269 (4)	
Hawaiian/Pacific Islander	58 (1)	70 (1)	
American Indian/Alaskan Native	48 (1)	62 (1)	
CHF, n (%)	1544 (22)	2553 (34)	<0.0001
PAD, n (%)	982 (14)	1575 (21)	<0.0001
CKD, n (%)	915 (13)	2005 (27)	<0.0001
Dialysis, n (%)	67 (1)	236 (3)	<0.0001
COPD, n (%)	1634 (23)	1805 (24)	0.24
PTSD, n (%)	833 (12)	1136 (15)	<0.0001
Depression, n (%)	1716 (24)	2186 (29)	<0.0001
Smoking, n (%)			
Current smoker	2666 (41)	2181 (31)	<0.0001
Past smoker	2154 (33)	2826 (40)	
Never smoker	1666 (26)	2095 (30)	
BMI, n (%)			
Underweight (BMI <18)	57 (1)	13 (0.2)	<0.0001
Normal weight (18 ≤BMI <25)	1340 (22)	708 (10)	
Overweight (25 ≤BMI <30)	2408 (39)	2188 (31)	
Obese (BMI ≥30)	2309 (38)	4189 (59)	

BMI indicates body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease; PTSD, post-traumatic stress disorder.

for ACEi/ARB; Table 2). When adherence was dichotomized at a PDC threshold of 0.8, participants with diabetes mellitus were slightly more likely to be adherent to all 3 medications than those without diabetes mellitus (56% versus 54%; *P*=0.002; adjusted risk difference, 2.1% [0.5, 3.7]; Table 2). The same trend was observed for each medication individually (adjusted risk difference of achieving PDC, ≥0.8, 2.0 [0.5, 3.6] for statins, 2.7 [1.2, 4.2] for BBs, and 1.4 [0.01, 2.8] for ACEi/ARB; Table 2). Finally, although the mean PDC for each medication class exceeded 80% in all patients and ≈70% of the participants achieved a PDC ≥0.8 for each medication, fewer than 60% of patients exceeded a PDC of 0.8 for all 3 medications.

Glycemic Control and Medication Adherence in Patients With Diabetes Mellitus

We next examined whether rates of adherence to cardioprotective medications in those with diabetes mellitus varied across HbA1c levels at the time of AMI. At baseline, there were small, but statistically significant, differences in demographics and comorbidities across HbA1c categories. Individuals with poorly controlled diabetes mellitus (HbA1c, ≥9% [≥75 mmol/mol]) were younger and less likely to have peripheral artery disease, chronic kidney disease, or use dialysis (Table S1). In contrast, individuals with lower HbA1c, <6% (<42 mmol/mol) or 6% to 6.9% (42–52 mmol/mol), were less likely to be obese and more likely to be normal weight or overweight (Table S1). Most patients (59%) with diabetes mellitus had an HbA1c measurement recorded within 30 days of AMI, 79% within 90 days, and 93% within 180 days (Table S2).

Among diabetes mellitus patients, those with an HbA1c ≥9% (≥75 mmol/mol) had the lowest PDC for each of the medication classes as well as for all 3 medication classes combined (Table S3). In multivariable models, adjusting for comorbidities and demographics, individuals with HbA1c <6% (<42 mmol/mol) had lower average PDC for ACEi/ARB and statin compared with individuals with HbA1c 6% to 6.9% (42–52 mmol/mol; Figure 1). In addition, PDC for each of the 3 medication classes individually and all 3 classes combined declined as HbA1c increased (Figure 1). Relative to individuals with HbA1c 6% to 6.9% (42–52 mmol/mol), those with HbA1c ≥9% (≥75 mmol/mol) had 3% [1.6, 4.2], 3.3% [2.0, 4.5], 2.9% [1.5, 4.3], and 3% [2.0, 4.1] lower adherence to ACEi/ARB, beta-blocker, statin, and all 3 medications combined (Figure 1). The same pattern of association was observed when medication adherence was dichotomized at a threshold PDC of 0.8. Individuals with HbA1c <6% had nonsignificantly lower likelihood of achieving a PDC ≥0.8 for each medication and for all 3 medications combined relative to those with HbA1c 6% to 6.9% (42–52 mmol/mol), and the likelihood of achieving PDC ≥0.8 declined with increasing HbA1c >7% (53 mmol/mol; Figure 2; Table S4). Individuals with HbA1c ≥9% (≥75 mmol/mol) were 18% less likely to be adherent to all 3 medication classes than those with HbA1c 6% to 6.9% (42–52 mmol/mol; *P*<0.0001). Results were similar in sensitivity analyses restricted to individuals with an HbA1c measurement within 90 or 180 days of AMI except for slightly wider CIs owing to reduced sample size (Tables S5 and S6).

VA quality measures for diabetes mellitus care define poorly controlled diabetes mellitus based on an HbA1c ≥9% (≥75 mmol/mol),[24] so we compared cardioprotective medication adherence after AMI between individuals with and without poorly controlled diabetes mellitus based on the VA

Table 2. Achievement of Secondary Prevention Medication Adherence for Individuals Without Versus With Diabetes Mellitus

	Unadjusted				Adjusted*
	No Diabetes Mellitus	Diabetes Mellitus	Between-Group Difference (95% CI)	*P* Value	Between-Group Difference (95% CI)
Medication adherence, mean PDC, % (SD)					
Statin	82.8 (22)	84.3 (21)	1.4 (0.7, 2.1)	0.0003	1.2 (0.4, 1.9)
Beta-blocker	85.5 (21)	87.3 (20)	1.8 (1.1, 2.5)	<0.0001	1.3 (0.7, 2.0)
ACEi or ARB	86.5 (22)	88.0 (19)	1.5 (0.8, 2.2)	0.008	1.2 (0.5, 1.9)
Mean	85.0 (18)	86.5 (16)	1.5 (1.0, 2.1)	0.0001	1.2 (0.6, 1.8)
Dichotomized adherence PDC ≥0.8, n (%)					
Statin	4825 (69)	5341 (71)	2.6 (1.1, 4.1)	0.0006	2.0 (0.5, 3.6)
Beta-blocker	5177 (74)	5777 (77)	3.4 (2.0, 4.8)	<0.0001	2.7 (1.2, 4.2)
ACEi or ARB	5378 (77)	5880 (78)	1.9 (0.6, 3.3)	0.005	1.4 (0.01, 2.8)
All 3 medications	3761 (54)	4205 (56)	2.6 (1.0, 4.2)	0.002	2.1 (0.5, 3.7)

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PDC, proportion of days covered; Statin, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor.
*Adjusted for age, race, sex, and comorbidities (congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, post-traumatic stress disorder, chronic kidney disease, dialysis use, and depression).

clinical guidelines. Those with poorly controlled diabetes mellitus (HbA1c ≥9% [≥75 mmol/mol] at the time of AMI) were less likely to adhere to all 3 cardioprotective medication classes than those with HbA1c <9% (<75 mmol/mol; 49% versus 58% in those with versus without poorly controlled diabetes mellitus; $P<0.0001$; adjusted risk difference 8.9% [6.0, 11.8%]). Additionally, they were less likely to achieve a PDC exceeding 0.8 for each medication class individually (adjusted risk difference of 6.2 [3.5, 9.0] for statins, 7.7 [5.2, 10.3] for BBs, and 6.7 [4.2, 9.2] for ACEi/ARB; Table S7).

Discussion

In this study, we found that patients with diabetes mellitus had a higher rate of adherence to guideline concordant secondary prevention medications after AMI than patients without diabetes mellitus, mirroring previous associations between diabetes mellitus status and antihypertensive medication adherence.[25] However, among individuals with diabetes mellitus, HbA1c <6% (<42 mmol/mol) or ≥8% (≥64 mmol/mol) was associated with worse medication adherence. Individuals with poorly controlled diabetes mellitus (HbA1c ≥9% [≥75 mmol/mol]) had the lowest adherence rates to each cardioprotective medication individually as well as to all 3 classes together. Collectively, these results suggest that diabetes mellitus status alone may not be an informative marker of medication adherence after AMI, but that HbA1c at the time of event may be helpful in identifying individuals with diabetes mellitus at increased risk of medication nonadherence.

Previous studies have demonstrated associations of cardioprotective medication adherence with morbidity and mortality after AMI in individuals with and without diabetes mellitus.[6–10, 13–15] Multiple studies have also shown an inverse relationship between HbA1c following CHD diagnosis and risk for recurrent cardiovascular events.[26–28] Furthermore, higher diabetes mellitus medication adherence has previously been shown to be associated with lower HbA1c,[17–20] higher cardiovascular medication adherence,[29] and fewer physician visits, emergency room visits, and hospitalizations.[17] Taken together, the existing literature demonstrates relationships between HbA1c and recurrent cardiovascular events after AMI, between HbA1c and diabetes mellitus medication adherence, and between cardioprotective medication adherence and mortality among individuals with diabetes mellitus.

Our study builds on the previous work in several ways. First, by examining the year after AMI, we focus on a population of individuals at particularly high risk of cardiovascular events. Second, we found that diabetes mellitus status only modestly impacted cardioprotective medication adherence and, surprisingly, that diabetes mellitus patients had slightly higher adherence rates than individuals without diabetes mellitus. Although the modest difference in adherence (2%) was statistically significant, it is unlikely to be clinically significant. Rather, our study suggests that diabetes mellitus status alone does not provide clinically actionable information relevant to cardioprotective medication adherence after AMI. Notably, the frequency with which patients achieved 80% adherence to all 3 classes of cardioprotective medications was low (<60%), irrespective of diabetes mellitus status, suggesting that an opportunity remains to improve care after AMI through medication adherence interventions for individuals without and with diabetes mellitus. Third, HbA1c not only predicts diabetes mellitus

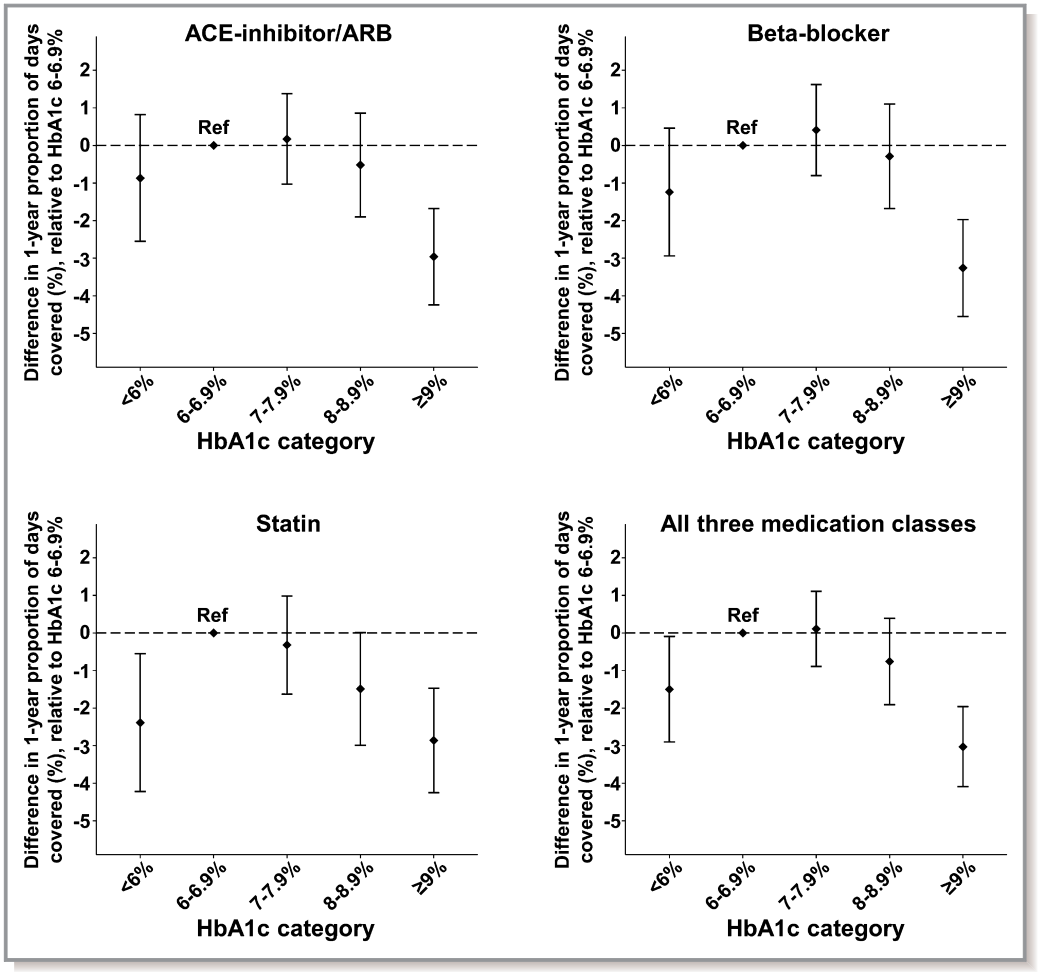

Figure 1. Difference in 1-year proportion of days covered for cardioprotective medications across levels of baseline glycemic control. Adjusted difference in proportion of days covered (PDC) over the first year after acute myocardial infarction of ACEi/ARB, beta-blockers, statins, and all 3 medication classes combined in individuals with diabetes mellitus and hemoglobin A1c (HbA1c) of <6% (<42 mmol/mol), 7% to 7.9% (53–63 mmol/mol), 8% to 8.9% (64–74 mmol/mol), and ≥9% (≥75 mmol/mol), relative to those with HbA1c 6% to 6.9% (42–52 mmol/mol). Differences in PDC adjusted for demographic variables and comorbidities. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

medication adherence (as shown in previous studies), but also predicts adherence to guideline-concordant cardioprotective medications after AMI. Finally, we found that low HbA1c (<6%) was associated with lower cardioprotective medication adherence compared with HbA1c 6% to 6.9%, a relationship not previously observed in correlations between HbA1c and diabetes mellitus medication adherence.

In the context of previous work, this study provides new insights into medication adherence in patients with diabetes mellitus and AMI and suggests future research. The correlations between HbA1c and diabetes mellitus medication adherence,[17–20,29] between HbA1c and cardioprotective medications (this study), and between diabetes mellitus medication adherence and cardioprotective medication adherence,[29] raise the question of whether a medication adherence intervention targeting either diabetes mellitus medications or cardiovascular medications would have secondary effects on adherence to the other medication class, glycemic control, or recurrent cardiovascular events after AMI. That is, disease-specific medication adherence interventions may positively impact multiple diseases in patients with comorbidities. Interestingly, some of the cardioprotective medications evaluated in this study (ACEi/ARB and BBs) have been associated previously with improved glycemia,[30] whereas statin therapy can have negative glycemic impacts.[31–34] Thus, our findings motivate further research into whether improving medication adherence for one disease, CHD, may have positive secondary effects on diabetes mellitus. At minimum, the generalizability of HbA1c as an easily measured proxy of medication adherence—to all types of chronic medications rather than just diabetes mellitus

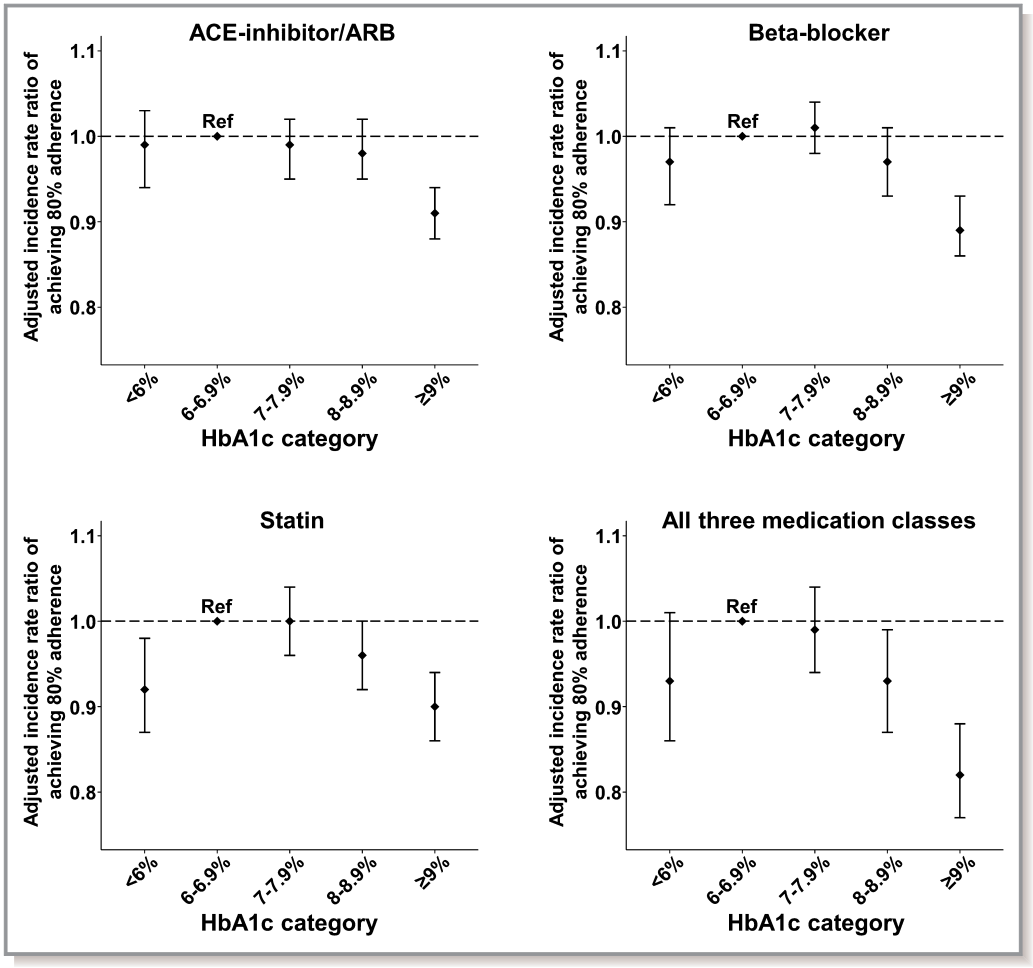

Figure 2. Incidence rate ratios of achieving a threshold of at least 80% adherence to cardioprotective medications over 1 year across levels of baseline glycemic control. Adjusted incidence rate ratios from multivariable Poisson regression models for achieving a minimum proportion of days covered (PDC) ≥0.8 over the first year after acute myocardial infarction across HbA1c categories (with 6–6.9% [42–52 mmol/mol] as reference category) among individuals with diabetes mellitus. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

agents or cardioprotective drugs—in patients with diabetes mellitus warrants further evaluation. Our results suggest that HbA1c at the time of AMI hospitalization is informative regarding potential medication nonadherence, but we do not provide data to support a mechanism for this association. Future work is needed to evaluate the potential mechanisms through which HbA1c is associated with cardioprotective medication nonadherence, determine whether medication nonadherence is a mediator of associations between HbA1c and clinical outcomes, and examine mechanistically guided interventions to address adherence across levels of HbA1c. Specifically, whether HbA1c can be used to detect those at higher risk for nonadherence and target cardioprotective medication adherence interventions after AMI remains to be studied.

The association between HbA1c <6% (<42 mmol/mol) and lower cardioprotective medication adherence was unexpected. Individuals with HbA1c <6% at the time of AMI differed from the remainder of diabetes mellitus patients in the study in that they were more likely to have chronic kidney disease or be on dialysis and were less likely to be overweight or obese. Though our multivariable model accounted for these potential confounders, there may be residual confounding if individuals with low HbA1c differ from other diabetes mellitus patients in a systematic way. Interestingly, several observational studies have found a J-shaped association between HbA1c and mortality among individuals with diabetes mellitus that is not completely explained by increased hypoglycemia risk among those with low HbA1c.[27,35–37] Our results raise the question of whether differential medication adherence across HbA1c levels could contribute to the paradoxical association between low HbA1c and mortality. In addition, our findings support the notion that HbA1c values correlate with more than merely glycemia, and that HbA1c-guided diabetes mellitus treatment may fail to

recognize important health behaviors, such as non-diabetes-mellitus medication adherence, associated with important clinical outcomes.[38] Indeed, recent evidence suggests that diabetes mellitus treatment intensification based solely on HbA1c measurements may be ineffective if medication adherence and other factors related to high HbA1c are not taken into consideration.[39] In addition, the correlation between HbA1c and non-diabetes-mellitus medication adherence suggests potential confounding by health behaviors in association studies of HbA1c with cardiovascular outcomes.

Our study has several important limitations. As an observational study, the data represent association, not causation, and we are susceptible to bias from residual confounding. In particular, we did not adjust for socioeconomic factors, which can impact medication adherence; however, socioeconomic variables are not uniformly available among VA patients and so could not be included in this study. We also were unable to address putative mediators of the association of HbA1c with cardioprotective medication adherence. The study is most relevant to the US veteran population, limiting generalizability to older white men who comprise the majority of our study. That said, there are no a priori reasons to expect that the pattern of association between diabetes mellitus status or HbA1c and medication adherence would differ in other populations. By categorizing patients with diabetes mellitus based on HbA1c values, we assume homogeneity within HbA1c categories. There are also limitations to using PDC to assess adherence, most important, that PDC assumes that filling a prescription is associated with taking a medication, which is not directly verifiable in our data. Finally, this study includes only survivors 1 year after AMI, which could induce selection bias that affects adherence estimates. However, we imposed a 1-year survival criterion for inclusion to avoid misestimation of medication adherence attributed to decline in health or other interval events.

In spite of these limitations, our study has several important clinical implications. First, the low rate of cardioprotective medication adherence in the first year after AMI, irrespective of diabetes mellitus status, suggests a care gap that can be targeted to reduce recurrent events. Second, although patients with diabetes mellitus are at increased risk of recurrent cardiovascular events after AMI, they are, on average, slightly more adherent to secondary prevention medications. Third, HbA1c at the time of AMI can help predict cardioprotective medication adherence among individuals with diabetes mellitus and might be leveraged to target medication adherence interventions. Finally, individuals with poorly controlled diabetes mellitus and AMI may benefit from medication adherence interventions focused on cardioprotective medications to reduce recurrent events, rather than solely optimizing diabetes mellitus treatment to improve glycemia.

Author Contributions

Adamek, Ramadurai, and Raghavan conceived of and designed the study; Gunzburger, Plomondon, and Ho contributed to data acquisition and availability; Raghavan and Gunzburger performed all data analysis. All authors contributed to interpretation of results, as well as drafting and critical revision of the manuscript. All authors approve of the version submitted for review and publication. S.R. is the guarantor of the data and analysis in this study, as well as of the manuscript.

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Disclosures

Ho served on a Steering Committee for a clinical trial on medication adherence for Janssen, Inc., and is the Deputy Editor for Circulation: Cardiovascular Quality and Outcomes, but reports no conflicts of interest with this study. The remaining authors have no disclosures to report.

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Supplemental Material

Association of diabetes status and glycemic control with secondary prevention medication adherence after acute myocardial infarction

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Table S1. Baseline characteristics of individuals with diabetes, stratified by baseline hemoglobin A1c.

	HbA1c <6% n= 640	**HbA1c 6-6.9% n= 2226**	**HbA1c 7-7.9% n= 1753**	**HbA1c 8-8.9% n= 1128**	**HbA1c ≥9% n= 1522**	**p-value**
Age (years), mean (SD)	68.0 (9.3)	68.1 (9.6)	67.9 (9.2)	66.5 (8.7)	62.9 (8.9)	<0.0001
Sex, n (%)						0.04
Male	624 (98)	2184 (98)	1724 (98)	1102 (98)	1474 (97)	
Female	16 (2)	42 (2)	29 (2)	26 (2)	48 (3)	
Race, n (%)						0.48
Non-Hispanic White	492 (77)	1795 (77)	1394 (80)	890 (79)	1154 (76)	
Black	120 (19)	398 (18)	270 (15)	174 (15)	283 (19)	
Asian	20 (3)	84 (4)	57 (3)	42 (4)	57 (4)	
Hawaiian / Pacific Islander	5 (0.8)	23 (1)	17 (1)	10 (1)	12 (1)	
American Indian / Alaskan Native	3 (0.5)	16 (0.7)	15 (0.9)	12 (1)	16 (1)	
CHF, n (%)	229 (36)	711 (32)	592 (34)	422 (37)	522 (34)	0.03
PAD, n (%)	141 (22)	489 (22)	375 (21)	258 (23)	273 (18)	0.01
CKD, n (%)	201 (31)	559 (25)	511 (29)	343 (30)	348 (23)	<0.0001
Dialysis, n (%)	51 (8)	75 (3)	50 (3)	25 (2)	29 (2)	<0.0001
COPD, n (%)	176 (28)	574 (26)	401 (23)	253 (22)	348 (23)	0.02
PTSD, n (%)	114 (18)	345 (16)	251 (14)	171 (15)	229 (15)	0.33
Depression, n (%)	197 (31)	595 (27)	499 (28)	339 (30)	494 (32)	0.003
Smoking, n (%)						0.0003
Current smoker	202 (33)	697 (33)	435 (26)	320 (30)	460 (32)	
Prior smoker	224 (40)	846 (40)	713 (43)	417 (39)	551 (38)	
Never smoker	180 (30)	573 (27)	507 (31)	337 (31)	433 (30)	
Body mass index (BMI), n (%)						<0.0001
Underweight (BMI < 18)	1 (0.2)	6 (0.3)	1 (0.1)	1 (0.1)	3 (0.2)	
Normal weight (18 <= BMI < 25)	114 (19)	254 (12)	137 (8)	82 (8)	92 (7)	
Overweight (25 <= BMI < 30)	213 (35)	678 (31)	527 (31)	310 (29)	413 (30)	
Obese (BMI >= 30)	284 (46)	1216 (56)	1040 (61)	692 (64)	877 (63)	

Abbreviations: HbA1c, hemoglobin A1c; **CHF**, congestive heart failure; **PAD**, peripheral arterial disease; **CKD**, chronic kidney disease; **COPD**, chronic obstructive pulmonary disease; **PTSD**, post-traumatic stress disorder; **BMI**, body mass index.

Table S2. Distribution of diabetes patients in the study based on time between HbA1c measurement and hospitalization for acute myocardial infarction.

Days between HbA1c measurement and AMI	Number of patients N (%)
≤30	4290 (59.0%)
31-60	863 (11.9%)
61-90	621 (8.5%)
91-180	1004 (13.8%)
>180	491 (6.8%)

Table S3. Unadjusted medication adherence across HbA1c categories among individuals with diabetes.

	Hemoglobin A1c category					
	<6%	**6-6.9%**	**7-7.9%**	**8-8.9%**	**≥9%**	**p-value**
Medication adherence, mean PDC, % (SD)						
Statin	83.0 (22)	85.6 (21)	85.4 (21)	84.1 (21)	82.0 (22)	<0.0001
Beta blocker	86.7 (21)	88.1 (20)	88.7 (19)	88.1 (18)	84.6 (20)	<0.0001
ACEi or ARB	87.8 (20)	88.8 (19)	89.1 (19)	88.5 (18)	85.6 (20)	<0.0001
Mean	85.8 (17)	87.4 (16)	87.8 (15)	86.9 (15)	84.0 (17)	<0.0001
Dichotomized Adherence, PDC ≥0.8, n (%)						
Statin	437 (68)	1654 (74)	1307 (75)	805 (71)	992 (65)	<0.0001
Beta blocker	488 (76)	1767 (79)	1411 (80)	875 (78)	1071 (70)	<0.0001
ACEi or ARB	509 (80)	1798 (81)	1408 (80)	899 (80)	1110 (73)	<0.0001
All three medications	352 (55)	1331 (60)	1045 (60)	631 (56)	740 (49)	<0.0001

Abbreviations: PDC, proportion of days covered; **Statin**, HMG-CoA reductase inhibitor; **ACEi**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker.

Table S4. Association between HbA1c category and likelihood of achieving 1-year proportion of days covered of at least 0.8 after acute myocardial infarction.

	Hemoglobin A1c category									
	<6%		6-6.9%		7-7.9%		8-8.9%		≥9%	
	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value
Medication category										
Statin	0.92 (0.87, 0.98)	0.008	Ref	-	1.00 (0.96, 1.04)	0.98	0.96 (0.92, 1.00)	0.08	0.90 (0.86, 0.94)	<0.0001
Beta blocker	0.97 (0.92, 1.01)	0.16	Ref	-	1.01 (0.98, 1.04)	0.60	0.97 (0.93, 1.01)	0.12	0.89 (0.86, 0.93)	<0.0001
ACEi or ARB	0.99 (0.94, 1.03)	0.56	Ref	-	0.99 (0.95, 1.02)	0.56	0.98 (0.95, 1.02)	0.32	0.91 (0.88, 0.94)	<0.0001
All three medications	0.93 (0.86, 1.01)	0.07	Ref	-	0.99 (0.94, 1.04)	0.69	0.93 (0.87, 0.99)	0.02	0.82 (0.77, 0.88)	<0.0001

Abbreviations: IRR, incidence rate ratio; **PDC**, proportion of days covered; **Statin**, HMG-CoA reductase inhibitor; **ACEi**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker.

Table S5. Association between HbA1c category and likelihood of achieving 1-year proportion of days covered of at least 0.8 after acute myocardial infarction among individuals with HbA1c measurement within 90 days of cardiac catheterization.

	Hemoglobin A1c category									
	<6%		6-6.9%		7-7.9%		8-8.9%		≥9%	
	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value
Medication category										
Statin	0.90 (0.84, 0.96)	0.003	Ref	-	1.00 (0.96, 1.04)	0.99	0.97 (0.93, 1.02)	0.25	0.89 (0.85, 0.94)	<0.0001
Beta blocker	0.98 (0.92, 1.03)	0.37	Ref	-	1.01 (0.98, 1.05)	0.49	0.97 (0.93, 1.02)	0.22	0.88 (0.84, 0.92)	<0.0001
ACEi or ARB	0.97 (0.92, 1.02)	0.23	Ref	-	0.99 (0.95, 1.02)	0.50	0.99 (0.95, 1.03)	0.58	0.90 (0.87, 0.94)	<0.0001
All three medications	0.91 (0.83, 1.00)	0.06	Ref	-	0.99 (0.93, 1.04)	0.62	0.94 (0.88, 1.01)	0.08	0.81 (0.76, 0.87)	<0.0001

Abbreviations: IRR, incidence rate ratio; **PDC**, proportion of days covered; **Statin**, HMG-CoA reductase inhibitor; **ACEi**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker.

Table S6. Association between HbA1c category and likelihood of achieving 1-year proportion of days covered of at least 0.8 after acute myocardial infarction among individuals with HbA1c measurement within 180 days of cardiac catheterization.

	Hemoglobin A1c category									
	<6%		6-6.9%		7-7.9%		8-8.9%		≥9%	
	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value	IRR	p-value
Medication category										
Statin	0.92 (0.87, 0.98)	0.01	Ref	-	1.01 (0.97, 1.04)	0.76	0.97 (0.93, 1.01)	0.18	0.90 (0.86, 0.94)	<0.0001
Beta blocker	0.96 (0.92, 1.01)	0.16	Ref	-	1.01 (0.98, 1.04)	0.58	0.97 (0.93, 1.01)	0.09	0.89 (0.85, 0.92)	<0.0001
ACEi or ARB	0.98 (0.94, 1.03)	0.43	Ref	-	1.00 (0.96, 1.03)	0.77	0.99 (0.95, 1.02)	0.42	0.91 (0.87, 0.94)	<0.0001
All three medications	0.93 (0.86, 1.01)	0.09	Ref	-	0.99 (0.94, 1.05)	0.83	0.93 (0.87, 0.99)	0.03	0.82 (0.77, 0.87)	<0.0001

Abbreviations: IRR, incidence rate ratio; **PDC**, proportion of days covered; **Statin**, HMG-CoA reductase inhibitor; **ACEi**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker.

Table S7. Achievement of secondary prevention medication adherence for those without versus with poorly-controlled diabetes.

	Unadjusted			Adjusted*	
	HbA1c < 9%	**HbA1c ≥ 9%**	**p-value**	**Between-group difference**	**95% CI**
Medication adherence, mean PDC, % (SD)					
Statin	85.0 (21)	82.0 (22)	< 0.0001	2.2	1.0, 3.4
Beta blocker	87.8 (20)	84.6 (20)	< 0.0001	3.2	2.1, 4.3
ACEi or ARB	88.6 (20)	85.6 (20)	< 0.0001	2.8	1.7, 3.9
Mean	87.1 (16)	84.0 (17)	< 0.0001	2.7	1.8, 3.7
Dichotomized Adherence, PDC ≥0.8, n (%)					
Statin	4203 (73)	992 (65)	< 0.0001	6.2	3.5, 9.0
Beta blocker	4541 (79)	1071 (70)	< 0.0001	7.7	5.2, 10.3
ACEi or ARB	4614 (80)	1110 (73)	< 0.0001	6.7	4.2, 9.2
All three medications	3349 (58)	740 (49)	< 0.0001	8.9	6.0, 11.8

Abbreviations: PDC, proportion of days covered; **Statin**, HMG-CoA reductase inhibitor; **ACEi**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker.

* Adjusted for age, race, sex, comorbidities (congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, post-traumatic stress disorder, chronic kidney disease, dialysis use, and depression)

Figure S1. Flow chart of study cohort development from VA electronic health record