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# Impact of hospitalization on medication adherence estimation in claims data

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## Summary

**What is known and objective:** Pharmacy claims are commonly used to assess medication adherence. It is unclear how different approaches to handling hospitalizations compare to the gold standard of using outpatient and inpatient drug data. This study aimed to compare the impact of different approaches to handling hospitalizations on medication adherence estimation in administrative claims data.

**Methods:** We identified β-blocker initiators after myocardial infarction (MI) and statin initiators regardless of hospitalization histories in the population-based, Taiwan database, which includes outpatient and inpatient drug claims data. Adherence to β-blockers or to statins during a 365-day follow-up period was estimated in outpatient pharmacy claims using the proportion of days covered (PDC) in three ways: ignoring hospitalizations (PDC1); subtracting hospitalized days from the denominator (PDC2); and assuming drug use on all hospitalized days (PDC3). We compared these to an approach that incorporated inpatient drug use (PDC4). We also used a hypothetical example to examine variations across approaches in several scenarios, such as increasing hospitalized days.

**Results and discussion:** Mean 365-day PDC was 74% among 1729 post-MI β-blocker initiators (range: 73.1%-74.9%) and 44% among 69 435 statins initiators (range: 43.5%-44.0%), which varied little across approaches. Differences across approaches increased with increasing number of hospitalized days. For patients hospitalized for >28 days, mean difference across approaches was >15%. PDC3 consistently yielded the highest value and PDC1 the lowest.

**What is new and conclusions:** On average, different approaches to handling hospitalizations lead to similar adherence estimates to the gold standard of incorporating inpatient drug use. When patients have many hospitalization days during follow-up, the choice of approach should be tailored to the specific setting.

KEYWORDS

β-blockers, adherence measures, hospitalizations, proportion of days covered, statins

## 1 | WHAT IS KNOWN AND OBJECTIVE

Medication non-adherence is a pressing public health issue.[1] Medication non-adherence is responsible for up to 70% of all medication-related hospital admissions and approximately $US 100 billion in potentially avoidable healthcare spending each year.[2] Administrative claims data are commonly used to identify predictors of non-adherence, examine impacts of policies and other interventions on changes in medication adherence, and target individuals for adherence improvement interventions.[3,4]

Prescription claims data have a number of strengths for assessing medication adherence, including the large size, the ability to follow patients longitudinally and the availability of detailed dispensing information, including measures of how long a prescription will last if used as prescribed.[5-8] Among a variety of measures for assessing adherence in pharmacy claims data, the proportion of day covered (PDC) is the most common metric.[9] PDC is defined as the number of days of medication supply dispensed in a period (numerator) divided by the number of days in the period, such as 365 days (denominator).[9,10]

In many automated healthcare databases, inhospital drug data are not available,[10] which leads to difficulties in accurately classifying hospitalized days in PDC calculation. Researchers have used different approaches to account for hospitalization periods, such as ignoring hospitalizations, subtracting hospitalized days from the denominator and assuming drug use on all hospitalized days, although research publications often do not explicitly describe which approach was used.[9-11] One study has shown that, in hypothetical situations, lack of inpatient drug use information can have a major impact on claims-based estimates of medication adherence.[12] However, it is unclear what impact this limitation has in practice and which approach to handling this deficiency best approximates the gold standard of using both outpatient and inpatient drug claims data.

The National Health Insurance Research Database (NHIRD) in Taiwan, which is based on the comprehensive national health insurance programme, captures inpatient drug use, which provides an unique opportunity to evaluate the impact of hospitalization periods on the calculation of adherence measures.[13] In this study, we assessed adherence to β-blockers for patients who experienced incident, acute myocardial infarction (MI) and adherence to statins among all initiators during a 365-day follow-up period. Adherence to both drug classes has been widely examined in claims databases,[3,14,15] and both drug classes are typically used in older individuals for conditions associated with events requiring hospitalization. We specifically restricted use of β-blockers to patients recently discharged from hospitalization to further focus on a population with high probability of hospitalization during follow-up. We aimed to compare various approaches to handling hospitalizations when measuring medication adherence.

## 2 | METHODS

### 2.1 | Data source

A single-payer and compulsory national health insurance programme was implemented in Taiwan in 1995, with an enrolment rate of 99% by 2014.[13] The NHIRD is a research data environment developed by the National Health Research Institute, with linked data from demographic and enrolment records, outpatient and inpatient diagnoses and procedures, and outpatient and inpatient pharmacy dispensings. For outpatient pharmacy dispensings, the database includes information on dispensed prescription drugs, including quantity dispensed and days supply, which is a pharmacist-estimated measure of how long a prescription will last if used as prescribed. For inpatient drug use, the database provides information on drugs dispensed from the hospital pharmacy, including the total quantity dispensed.

The Longitudinal Health Insurance Database 2005 (LHID2005) is a random sample of one million subjects from the NHIRD with longitudinally linked data for individuals starting from 1997 and updated annually. The source population for this study included all beneficiaries from the LHID2005. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

### 2.2 | Study cohorts

We assembled two cohorts—β-blocker initiators after incident, acute MI and all statin initiators (with or without prior hospitalizations)—between 1 January 2001 and 31 December 2009.

For incident post-MI β-blocker initiators, we identified patients who were hospitalized for acute MI using a validated algorithm (International Classification of Diseases, 9th Revision, Clinical modification [ICD-9-CM] code 410.xx in any position on an inpatient claim, with antiplatelet drugs during hospitalization)[16] and who initiated a β-blocker (Anatomical Therapeutic Chemical [ATC] classification system codes provided in Table A1) within 90 days following hospital discharge. The index date was defined as the dispensing date of the first outpatient post-discharge β-blocker prescription. We excluded patients without continuous enrolment in the database for at least 365 days before the acute MI admission date, defined as having no inpatient or outpatient visits during this time, those with prior MI (ICD-9-CM codes 410.xx and 412.xx in any position on inpatient or outpatient claims) in 365 days before the acute MI admission date and those with any β-blocker prescriptions in 365 days before the index date.

For statin initiators, we identified patients who initiated a statin (ATC classification system codes provided in Table A1) regardless of their hospitalization history; the index date was defined as the dispensing date of the first outpatient statin prescription during the study period. We excluded patients without 365 days of continuous enrolment and those with any statin prescriptions within 365 days before the index date.

From both cohorts, we excluded those younger than 20 years (due to specific data policies) or older than 120 years of age on the index date, those with missing or ambiguous sex information, and those with last resource utilization records (outpatient visit or hospitalization discharge) within 365 days of the index date. From the statin cohort, we excluded those with a dispensing of another type of lipid-lowering drugs (fibrates, bile acid sequestrants or ezetimibe) within 365 days of the index date. Patients in both cohorts were followed for 365 days from the index date.

For both study cohorts, we also captured information on demographic characteristics and cardiovascular-related comorbidities based on outpatient and inpatient diagnoses occurring within 365 days before the index date (ICD-9-CM codes provided in Table A2).

### 2.3 | Adherence estimation

Using dispensing dates and the days supply variable from the outpatient pharmacy claims data, we created longitudinal medication

supply diaries to determine whether patients had drug available on each follow-up day. If a patient filled a prescription before exhausting the days supply from the previous prescription, use of the subsequent prescription was assumed to begin the day after the end of the prior prescription dispensation.[14,17] For prescriptions dispensed with days supply that exceeded the end of the follow-up window, we truncated the days supply at the end of the follow-up window. We considered all medications within the class of β-blockers and statins as interchangeable when creating the supply diaries. We capped PDC at 100%.

PDC was calculated in three ways using only outpatient pharmacy claims: (i) ignoring hospitalizations (PDC1); (ii) subtracting hospitalized days from the denominator (PDC2); and (iii) adding all hospitalized days to the numerator (PDC3). We used information on inpatient drug administration available in the Taiwan database to calculate the gold standard PDC (PDC4) by including hospitalized days in the denominator and adding them to the numerator only when patients took β-blockers or statins during the hospitalized period. When patients had an inpatient dispensing of a drug of interest, we assumed that they used it on every day of the corresponding hospitalization. Figure 1 illustrates the PDC calculations using the different approaches to handling hospitalizations. To examine the sensitivity of the gold standard, PDC4, to lack of days supply information on inpatient dispensings, we also estimated hospitalized days with inpatient drug use using the total quantities dispensed and assuming that patients took one tablet per day. We capped the number of hospitalized days with drug use at the total length of stay for each hospitalization.

## 2.4 | Statistical analyses

For each cohort, we tabulated the mean number of outpatient prescriptions and total days supply for β-blockers and statins during the follow-up window. We also tabulated the number of patients who were hospitalized during follow-up, the mean number of hospitalized days and the mean number of hospitalized days with inpatient use of the drugs of interest. PDCs and proportions of patients with 'full' adherence were compared across the different approaches to handling hospitalization. For each measure, we defined 'full' adherence as a PDC ≥80%, which is the most commonly used cut-point in the literature.[9,10,18] We also categorized patients based on their total number of hospitalized days during follow-up: 0, 1-7, 8-14, 15-21, 22-28 and >28 days. We calculated mean PDCs and proportions of patients with 'full' adherence using the different approaches to handling hospitalization across the subgroups.

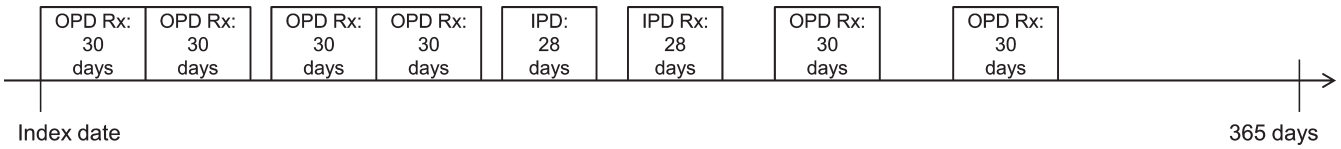
## 2.5 | Hypothetical example varying outpatient drug use, number of hospitalized days and inpatient drug use

To expand our findings beyond the characteristics of two specific examples, we used the different PDC calculations to plot expected PDC for each metric across the full range of numbers of days hospitalized during follow-up (ie 0 to 365). We created plots under six different scenarios with varying total days supply of medication in the follow-up period (ie 30, 60, 120, 180, 240 and 300 days). For the gold standard PDC4, we assumed two scenarios in which patients received the drug of interest on 20% or 80% of hospitalized days.

# 3 | RESULTS

## 3.1 | Eligible patients

We identified a total of 1729 incident post-MI β-blocker initiators and 69 435 statin initiators (Table 1; Figure A1a,b). The mean age of the incident post-MI β-blocker cohort was 63 years (standard deviation [SD], 13), and 70% were male. Most initiators also had a history of




| Adherence measure | Approaches to handling hospitalizations | Calculation | % |
|---|---|---|---|
| PDC1 | Ignoring hospitalizations | = (180) / (365) | = 49.3 |
| PDC2 | Subtracting hospitalized days from the denominator | = (180) / (365-28-28) | = 58.3 |
| PDC3 | Adding all hospitalized days to the numerator | = (180+28+28) / (365) | = 64.7 |
| PDC4[a] | Incorporating inpatient drug use ('gold standard') | = (180+28) / (365) | = 57.0 |

"OPD Rx" and "IPD Rx" represent prescriptions from outpatient settings and inpatient settings, respectively. "IPD" indicates that there is no inpatient drug use during the corresponding hospitalization.
Total days supply of outpatient prescriptions : 30X6=180 days
Total no. hospitalized days: 28+28=56 days
Total no. hospitalized days with inpatient drug use: 28 days
[a]Assumed that patients used the drug of interest through the entire hospitalization for the PDC4 approach

**FIGURE 1** Example for proportion of days covered (PDC) calculation using different approaches to handling hospitalizations

**TABLE 1** Baseline and follow-up characteristics of two cohorts

| | β-Blocker initiators after incident, acute myocardial infarction, n=1729 | Statin initiators, n=69 435 |
|---|---|---|
| At baseline | | |
| Age, year, mean (SD) | 62.9 (12.7) | 58.6 (12.6) |
| Male, n (%) | 1208 (69.9) | 32 287 (46.5 |
| Year of index date, n (%) | | |
| 2001-2003 | 418 (24.2) | 19 075 (27.5) |
| 2004-2006 | 571 (33.0) | 24 771 (35.7) |
| 2007-2009 | 740 (42.8) | 25 589 (36.8) |
| Cardiovascular or cerebrovascular diseases, n (%) | | |
| Hypertension | 1256 (72.6) | 40 059 (57.7) |
| Ischaemic heart disease | 1579 (91.3) | 16 258 (23.4) |
| Myocardial infarction | 1729 (100.0) | 1780 (2.6) |
| Stroke | 196 (11.3) | 5670 (8.2) |
| Diabetes mellitus | 729 (42.2) | 25 620 (36.9) |
| Hyperlipidaemia | 914 (52.9) | 52 358 (75.4) |
| During the 365-day follow-up | | |
| In total cohort | n=1729 | n=69 425 |
| No. of outpatient prescriptions for drugs of interest, mean (SD) | 10.9 (5.1) | 6.1 (4.5) |
| Total outpatient days supply for drugs of interest, mean (SD) | 266.9 (122.2) | 159.4 (120.0) |
| No. of patients with hospitalization, n (%) | 942 (54.5) | 11 190 (16.1) |
| Total no. of hospitalized days, mean (SD) | 7.9 (20.0) | 2.2 (11.4) |
| No. of patients with inpatient drug use, n (%) | 690 (39.9) | 3241 (4.7) |
| Among patients with hospitalization | n=942 | n=11 190 |
| Total no. of hospitalized days, mean (SD) | 14.4 (25.3) | 13.3 (25.5) |
| Total no. of hospitalized days with inpatient drug use[a] mean (SD) | 7.8 (16.7) | 3.3 (11.7) |
| Proportion of hospitalized days with inpatient drugs use, % | 54.4 | 24.4 |

SD, standard deviation.
[a]Assumed that patients used the drug of interest through the entire hospitalization.

ischaemic heart disease (91%), hypertension (73%) and hyperlipidaemia (53%). The mean age of the statin cohort was 59 years (SD, 13), and 47% were male. Most initiators had a history of hyperlipidaemia (75%), hypertension (58%) and diabetes mellitus (37%); 3% had had a prior MI.

One average, incident post-MI β-blocker initiators filled 11 outpatient β-blocker prescriptions and statin initiators filled six outpatient statin prescriptions during the 365-day follow-up window (Table 1). The mean total days supply in the follow-up year was 267 and 159 days, respectively. In the incident post-MI β-blocker cohort, 55% of patients were hospitalized during follow-up; 16% of statin initiators were hospitalized. The mean (SD) number of hospitalized days was 8 (2) and 2 (11), respectively. Among incident post-MI β-blocker initiators hospitalized during follow-up, patients received β-blockers on 54% of days in the hospital; hospitalized statin initiators received statins on 24% of hospitalized days during follow-up.

## 3.2 | Comparisons of different approaches to handling hospitalization

### 3.2.1 | Results from β-blocker and statin cohorts

The gold standard approach yielded mean PDC4 of 74.1% for β-blockers and 43.6% for statins. For the other measures, mean PDC ranged from 73.1% (PDC1) to 74.9% (PDC3) for β-blockers and 43.5% (PDC1) to 44.0% (PDC3) for statin initiators. All approaches to handling hospitalizations produced similar results as compared to the gold standard approach (Table 2). Little variation was also observed across methods for proportions of patients classified as having 'full' adherence (Figure A2).

As expected, results from the PDC estimates from the four different approaches were identical among patients who were not hospitalized during follow-up as the PDC formulae are equivalent in the absence of hospitalizations. Conversely, the mean PDC diverged across the approaches in subgroups of patients with increasingly large numbers of days hospitalized during follow-up. For patients hospitalized for >28 days (7% of incident post-MI β-blocker initiators and 2% of statin initiators), absolute differences between mean PDC3 and mean PDC1 were >15% in both cohorts (64.7% vs 49.0% for incident post-MI β-blockers; 52.7% vs 35.3% for statins) (Table 2). The proportion of patients with 'full' adherence based on PDC3 and PDC1 was 41.0% and 24.8%, respectively, for incident post-MI β-blocker initiators and 22.0% and 10.1%, respectively, for statin initiators (Figure A3).

The two approaches to handling inpatient drug use information provided similar estimates for PDC4 in the total cohort and in each subgroup of patients with varying hospitalized days (Table A3).

### 3.2.2 | Results from the hypothetical example

As expected, when using the PDC formulae to directly calculate PDC across numbers of days hospitalized during follow-up in

scenarios defined by different numbers of outpatient days supply and proportions of hospitalized days with inpatient drug use, PDC3 always yielded the highest value and PDC1 the lowest (Figure 2). Under certain conditions, PDC2 was smaller than PDC4 with both 20% and 80% of hospitalized days with inpatient drug use, and under other conditions, PDC2 was larger than PDC4 in both inpatient drug use scenarios. When the number of hospitalized days during follow-up was <28, the difference between PDC3 and PDC1 was less than 7.7% (ie 28 days divided by 365 days). This increased with greater number of hospitalized days. The relative performance of each approach compared to the gold standard PDC4 depended on total days supply of outpatient prescriptions during follow-up, number of hospitalized days and proportions of hospitalized days with inpatient drug use. In general, in the scenario in which patients had shorter days supply of outpatient prescriptions (left-hand plots in Figure 2), PDC2 was usually closest to PDC4 when the proportion of hospitalized days with inpatient drug use was low (ie 20%) and PDC3 tended to be closest to PDC4 when the proportion of hospitalized days with inpatient drug use was high (ie 80%). However, in the scenario in which patients had longer days supply of outpatient prescriptions (right-hand plots in Figure 2), PDC1 was closest to PDC4 when the proportion of hospitalized days with inpatient drug use was low and PDC2 was closest to PDC4 when the proportion of hospitalized days with inpatient drug use was high.

## 4 | DISCUSSION

Our analyses demonstrate that, in two realistic, empirical scenarios, different approaches to handling hospitalizations led to average adherence estimates that were very similar to the gold standard of incorporating both outpatient and inpatient drug use. Even when hospitalization days were entirely ignored, the difference between the estimated PDC and the gold standard PDC was trivial. However, variations across different approaches, which were bounded by the approach assuming drug used on all hospitalization days and the approach ignoring hospitalization, increased across subgroups of patients with more hospitalized days during follow-up. Among patients with >28 hospitalized days during follow-up, we observed >15% absolute differences in mean PDC among approaches and large variations in proportions of patients classified as having 'full' adherence.

Some of the most effective interventions to improve adherence to cardiovascular medications have been reported to increase measures of adherence by up to 30%.[19] Most interventions, including those that have been shown not only to increase adherence but also improve clinical outcomes,[4,20] increase PDC by less than 10%.[19] Hence, the 15% difference in PDCs that we observed across methods in patients with large numbers of hospitalized days is meaningful and requires attention in practice.

**TABLE 2** Mean proportion of days covered (PDC) calculated using different approaches to handling hospitalization

| Adherence measure | PDC1, mean (SD) Ignoring hospitalizations | PDC2, mean (SD) Subtracting hospitalized days from the denominator | PDC3, mean (SD) Adding all hospitalized days to the numerator | PDC4[a], mean (SD) Incorporating inpatient drug use ('gold standard') |
|---|---|---|---|---|
| β-blocker initiators after incident, acute myocardial infarction, n=1729 | | | | |
| Total cohort | 73.1 (33.5) | 74.1 (33.5) | 74.9 (32.4) | 74.1 (33.2) |
| Among patients with varying no. of hospitalized days (n) | | | | |
| 0 days (n=793) | 77.5 (32.1) | 77.5 (32.1) | 77.5 (32.1) | 77.5 (32.1) |
| 1-7 days (n=521) | 77.2 (31.5) | 77.6 (31.6) | 77.8 (31.3) | 77.6 (31.5) |
| 8-14 days (n=155) | 65.7 (34.7) | 66.9 (35.0) | 67.9 (34.0) | 66.9 (34.7) |
| 15-21 days (n=82) | 68.6 (32.0) | 70.9 (32.6) | 72.4 (31.0) | 70.7 (32.4) |
| 22-28 days (n=61) | 52.1 (37.3) | 54.7 (38.5) | 57.8 (35.9) | 54.7 (37.7) |
| >28 days (n=117) | 49.0 (32.6) | 57.3 (35.0) | 64.7 (29.9) | 57.1 (34.1) |
| Statin initiators, n=69 435 | | | | |
| Total cohort | 43.5 (32.6) | 43.7 (32.7) | 44.0 (32.5) | 43.6 (32.6) |
| Among patients with varying no. of hospitalized days (n) | | | | |
| 0 days (n=58 310) | 43.3 (32.5) | 43.3 (32.5) | 43.3 (32.5) | 43.3 (32.5) |
| 1-7 days (n=6417) | 47.2 (33.5) | 47.6 (33.7) | 48.2 (33.3) | 47.4 (33.6) |
| 8-14 days (n=2259) | 41.8 (32.5) | 42.8 (33.1) | 44.5 (32.1) | 42.4 (32.8) |
| 15-21 days (n=878) | 43.6 (31.4) | 45.5 (32.5) | 48.2 (30.9) | 44.8 (32.1) |
| 22-28 days (n=435) | 41.7 (31.0) | 44.4 (32.7) | 48.2 (30.4) | 43.3 (31.8) |
| >28 days (n=1136) | 35.3 (27.5) | 43.0 (31.7) | 52.7 (27.6) | 39.5 (29.9) |

SD, standard deviation.
[a]Assumed that patients used the drug of interest through the entire hospitalization for the PDC4 approach.

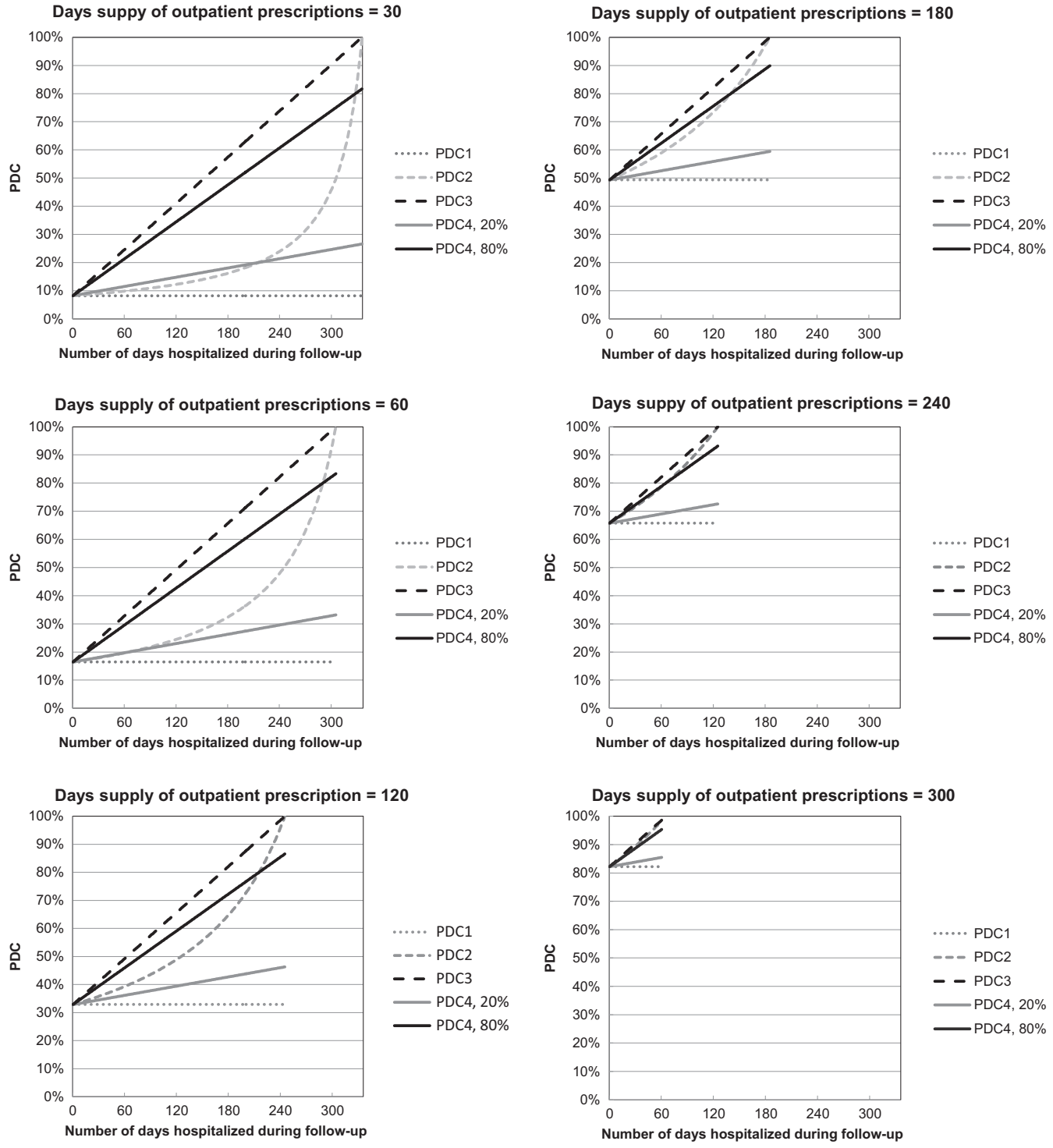



**FIGURE 2** Proportion of days covered (PDC) for a hypothetical example varying outpatient drug use and number of hospitalized days, assuming proportion of hospitalized days with inpatient drug use (assumed that patients used the drug of interest through the entire hospitalization for the PDC4 approach) equal to 20% or 80%

Our empirical findings were supported by a hypothetical example in which we directly examined estimated PDC as a function of number of hospitalized days during follow-up across metrics and in varying scenarios. As claims-based adherence studies are common[5-8] and most claims databases lack information on inhospital drug use,[10] our findings have wide-ranging implications. In particular, our hypothetical data example indicates that no single approach to handling hospitalizations is optimal in the absence of inpatient drug data. For example, in the scenario in which patients had 60 days supply of outpatient prescriptions, the approach subtracting hospitalized days from denominators (ie PDC2) was usually closest to the gold standard PDC (ie PDC4) when the proportion

of hospitalized days with inpatient drug use was low. The finding, however, varied with longer days supply of outpatient prescriptions, longer hospitalized days and higher proportion of hospitalized days with inpatient drug use. The approach used to generate the hypothetical results can be used to determine which method would most closely approximate the gold standard in a specific study with certain conditions. In such studies, the number of days supply can be estimated from pharmacy claims data and the number of hospitalized days can be estimated from medical data. The only unknown parameter is the proportion of hospitalized days with inpatient drug use; our two empirical examples provide estimates of this in realistic scenarios.

Although more than 50% of incident post-MI β-blocker initiators were hospitalized during follow-up, the mean number of days hospitalized during follow-up was small in the two empirical examples (eight days for post-MI β-blocker initiators and two days for statin initiators), which resulted in trivial differences in PDC estimates across approaches to handling hospitalizations. However, as the hypothetical data example showed, different approaches to handling hospitalizations will produce estimates that differ substantially in patient populations with much larger percentages of follow-up days hospitalized, such as patients with terminal illnesses who require frequent and long hospitalizations. As can be appreciated from the PDC formulae and as shown in the hypothetical example, the approach assuming drug used on all hospitalization days (PDC3) always overestimates the gold standard PDC, whereas the approach ignoring hospitalization (PDC1) always underestimates the gold standard PDC.

This study has several limitations that relate to the challenges of assessing medication adherence using automated healthcare data. First, prior studies have demonstrated that medication adherence measured using pharmacy claims records is correlated with other more direct measures, such as serum drug levels or self-reported information.[5,21,22] However, although pharmacy claims data provide information about the prescriptions that patients fill, they do not necessarily reflect whether and when patients consume the medications. Second, although inpatient drug data in the Taiwan database allowed us to determine whether patients used drugs of interest during hospitalization, the inpatient data do not include information on days supply and exact points in time at which patients start or stop medications during hospitalization.[13] Therefore, there may still be misclassification of inpatient drug use in what we called the gold standard approach. Although we assumed use of a drug of interest on all hospital days if an inpatient drug claim appeared, incorporating information on quantities dispensed produced highly similar results, which may imply that the influence of misclassification of inpatient drug use was negligible. Third, we focused on PDC, which is the most commonly used adherence measure in claims data, but we did not examine the impact of different approaches to handling inpatient drug use on other metrics, such as continuous measure of medication acquisition or continuous measure of medication gaps. Finally, although most claims databases themselves lack information on inpatient drug use, investigators are increasingly linking claims data to electronic medical record data, which can provide more comprehensive inpatient drug information than claims data alone.

## 5 | WHAT IS NEW AND CONCLUSIONS

In conclusion, different approaches to handling hospitalizations will usually lead to PDC estimates that are very similar to the gold standard of incorporating inpatient drug use for patient populations with small proportions of follow-up days spent in the hospital. In populations with greater proportions of follow-up days hospitalized, the approaches can yield substantially different results and the choice of approach should be tailored to the specific study conditions.

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### CONFLICT OF INTEREST

Joshua J. Gagne is Principal Investigator of a grant from Novartis Pharmaceuticals Corporation to the Brigham and Women's Hospital for work unrelated to this study and is a consultant to Aetion, Inc., a software company, and to Optum Inc. All other authors declared no conflict of interest.

### AUTHOR CONTRIBUTION

Yaa-Hui Dong and Joshua J. Gagne designed the study. Mei-Shu Lai acquired data. Yaa-Hui Dong and Li-Chiu Wu analysed data. Yaa-Hui Dong, Niteesh K. Choudhry, Alexis Krumme, Moa Lee, Li-Chu Wu, Mei-Shu Lai and Joshua J. Gagne interpreted data. Yaa-Hui Dong and Joshua J. Gagne drafted the manuscript. Niteesh K. Choudhry, Alexis Krumme, Moa Lee, Li-Chu Wu and Mei-Shu Lai provided critical suggestion on the manuscript.

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## APPENDIX

**TABLE A1** Anatomical therapeutic chemical (atc) classification system codes used to identify B-blocker initiators after acute myocardial infarction and statin initiators

| ATC classification system codes | Therapeutic chemicals |
|---|---|
| | β-blockers |
| C07AA01 | Alprenolol |
| C07AA02 | Oxprenolol |
| C07AA03 | Pindolol |
| C07AA05 | Propranolol |
| C07AA06 | Timolol |
| C07AA07 | Sotalol |
| C07AA12 | Nadolol |
| C07AA14 | Mepindolol |
| C07AA15 | Carteolol |
| C07AA16 | Tertatolol |
| C07AA17 | Bopindolol |
| C07AA19 | Bupranolol |
| C07AA23 | Penbutolol |
| C07AA27 | Cloranolol |
| C07AB01 | Practolol |
| C07AB02 | Metoprolol |
| C07AB03 | Atenolol |
| C07AB04 | Acebutolol |
| C07AB05 | Betaxolol |
| C07AB06 | Bevantolol |
| C07AB07 | Bisoprolol |
| C07AB08 | Celiprolol |
| C07AB10 | Epanolol |
| C07AB11 | s-Atenolol |
| C07AB12 | Nebivolol |
| C07AB13 | Talinolol |
| C07AG01 | Labetalol |
| C07AG02 | Carvedilol |
| C07B-C07F | β-blocker combinations |
| | Statins |
| C10AA01 | Simvastatin |
| C10AA02 | Lovastatin |
| C10AA03 | Pravastatin |
| C10AA04 | Fluvastatin |
| C10AA05 | Atorvastatin |
| C10AA07 | Rosuvastatin |
| C10AA08 | Pitavastatin |
| C10BA, C10BX | Statin combinations |

**TABLE A2** International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM) diagnostic codes used to identify comorbidities among bronchodilator initiators at baseline

| Comorbidities | ICD-9-CM Codes |
|---|---|
| Hypertension | 401–404 |
| Ischemic heart disease | 411, 413, 414 |
| Myocardial infarction | 410, 412 |
| Stroke | 430, 431, 432, 433, 434, 436 |
| Diabetes mellitus | 250 |
| Hyperlipidemia | 272 |

**TABLE A3** Mean PDC4 (proportion of days covered) calculated using two assumptions to estimate hospitalized days with inpatient drug use

| Assumption | Assuming that patients used the drugs of interest through the entire hospitalization, mean (SD) | Estimating hospitalized days with inpatient drug use using total quantities, mean (SD) |
|---|---|---|
| β-blocker initiators after incident, acute myocardial infarction, n=1729 | | |
| Total cohort | 74.1 (33.2) | 73.8 (33.3) |
| Among patients with varying no. of hospitalized days (n) | | |
| 0 days (n=793) | 77.5 (32.1) | 77.5 (32.1) |
| 1-7 days (n=521) | 77.6 (31.5) | 77.5 (31.5) |
| 8-14 days (n=155) | 66.9 (34.7) | 66.7 (34.8) |
| 15-21 days (n=82) | 70.7 (32.4) | 70.5 (32.3) |
| 22-28 days (n=61) | 54.7 (37.7) | 54.2 (37.7) |
| >28 days (n=117) | 57.1 (34.1) | 54.1 (34.1) |
| Statin initiators, n=69 435 | | |
| Total cohort | 43.6 (32.6) | 43.6 (32.6) |
| Among patients with varying no. of hospitalized days (n) | | |
| 0 days (n=58 310) | 43.3 (32.5) | 43.3 (32.5) |
| 1-7 days (n=6417) | 47.4 (33.6) | 47.4 (33.6) |
| 8-14 days (n=2259) | 42.4 (32.8) | 42.3 (32.8) |
| 15-21 days (n=878) | 44.8 (32.1) | 44.6 (32.0) |
| 22-28 days (n=435) | 43.3 (31.8) | 42.9 (31.8) |
| >28 days (n=1136) | 39.5 (29.9) | 38.3 (29.4) |

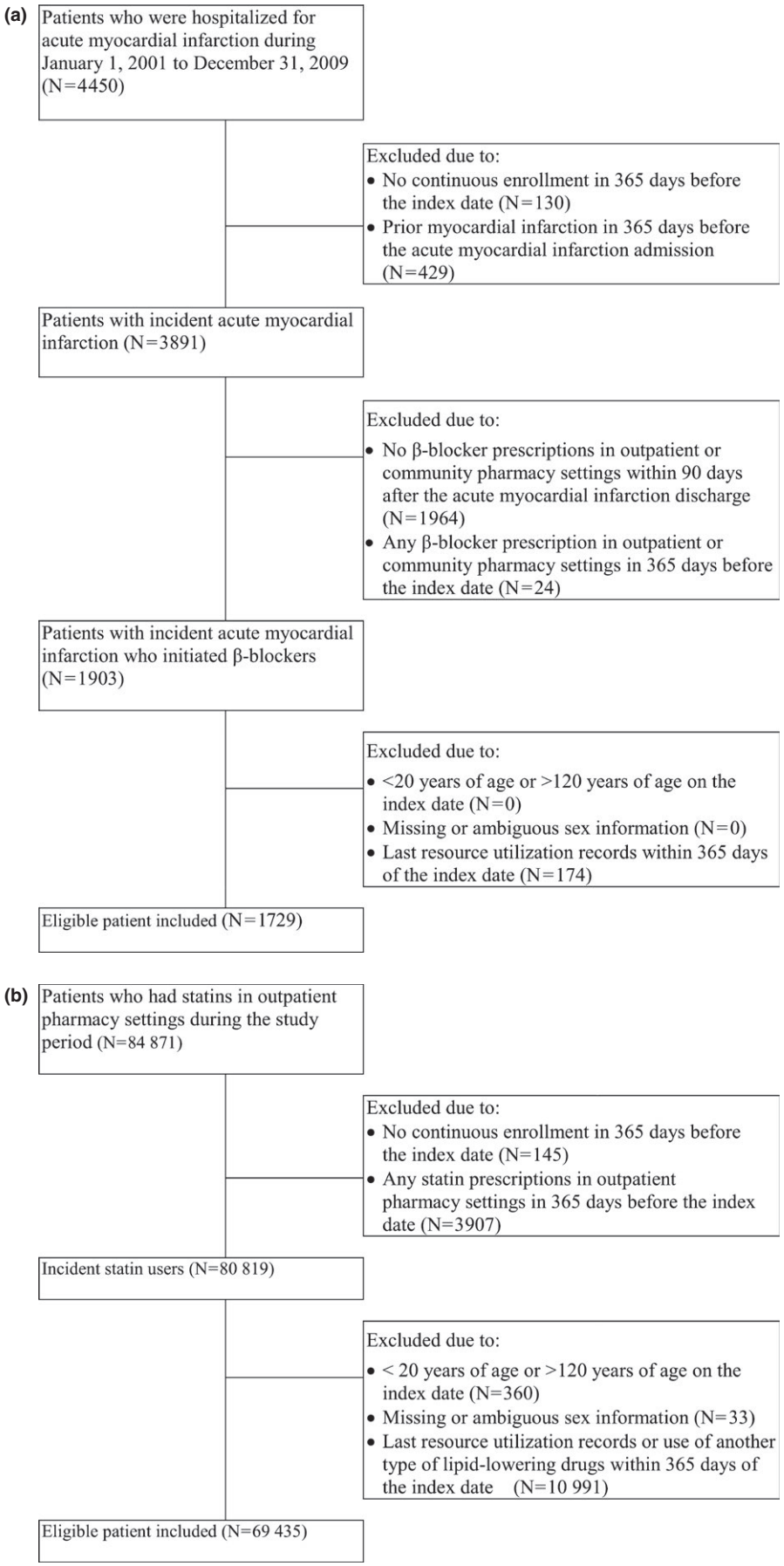


Figure A1 Flowchart of the study cohort assembly - (a) β-blocker initiators after acute myocardial infarction, (b) statin initiators

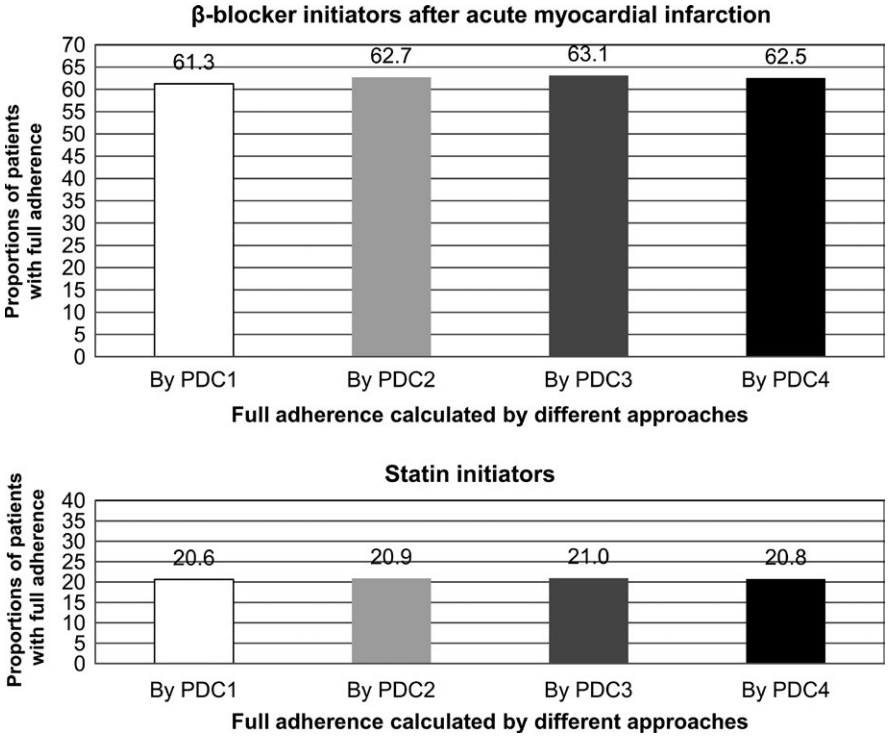


Figure A2 Proportions of patients with full adherence[a] calculated using different approaches[b].
[a]Full adherence: PDC>=80%.
[b]Assume that patients used the drug of interest through the entire hospitalization for the PDC4 approach.

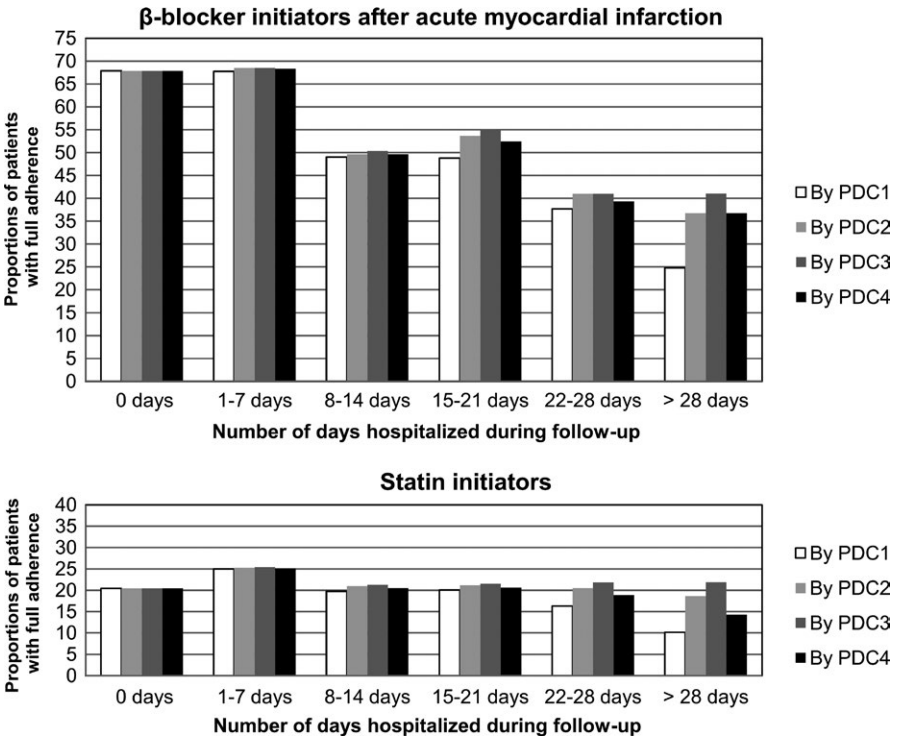


Figure A3 Proportions of patients with full adherence[a] calculated using different approaches[b], stratified by number of hospitalized days during follow-up.
[a]Full adherence: PDC>=80%.
[b]Assumed that patients used the drug of interest through the entire hospitalization for the PDC4 approach.