ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2021) **7**, 141–147
doi:10.1093/ehjcvp/pvaa010

**ORIGINAL ARTICLE**
*Prevention and epidemiology*

# Low adherence to statin treatment during the 1st year after an acute myocardial infarction is associated with increased 2nd-year mortality risk—an inverse probability of treatment weighted study on 54 872 patients

**Kani Khalaf [1]*, Kristina Johnell [2], Peter C. Austin [3,4,5], Patrik Tyden [6], Patrik Midlöv [7,8], Raquel Perez-Vicente [1], and Juan Merlo [1,8]**

[1]Unit for Social Epidemiology, Department of Clinical Sciences, Faculty of Medicine, Lund University, Jan Waldenströms gata 35, 20502 Malmö, Sweden; [2]Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet (KI), Nobels väg 12A, 17165 Solna, Sweden; [3]ICES, Toronto, Ontario, Canada; [4]Institute of Health Management, Policy and Evaluation, University of Toronto, Toronto, Ontario, Canada; [5]Schulich Heart Research Program, Sunnybrook Research Institute, Toronto, Ontario, Canada; [6]Department of Cardiology, Skåne University Hospital, Faculty of Medicine, Lund University and Region Skåne, Lund, Sweden; [7]Unit for Family Medicine and Community Medicine, Department of Clinical Sciences, Faculty of Medicine, Lund University, Jan Waldenströms gata 35, 20502 Malmö, Sweden; and [8]Center for Primary Health Care Research, Region Skåne, Jan Waldenströms gata 35, 20502 Malmö, Sweden

*Received 4 December 2019; revised 13 January 2020; editorial decision 4 February 2020; accepted 6 February 2020; online publish-ahead-of-print 14 February 2020*

**Aims** Experiencing an acute myocardial infarction (AMI) is a life-threatening event and use of statins can reduce the probability of recurrence and improve long-term survival. However, the effectiveness of statins in the real-world setting may be lower than the reported efficacy in randomized clinical trials. Therefore, we aimed to investigate whether low statin treatment adherence during the year following an AMI episode is associated with increased 2nd-year mortality.

**Methods and results** We analysed all 54 872 AMI patients aged ≥45 years, admitted to Swedish hospitals between 2010 and 2012, and who survive at least 1 year after the AMI episode. We defined low adherence as a medication possession ratio <50% or non-use of statins. Applying inverse probability of treatment weighting (IPTW), we investigated the association between low adherence and all-cause, cardiovascular disease (CVD), and non-CVD mortality during the 2nd year. Overall, 20% of the patients had low adherence during the 1st year and 8% died during the 2nd year. In the IPTW analysis, low adherence was associated with an increased risk of all-cause [absolute risk difference (ARD) = 0.048, number needed to harm (NNH) = 21, relative risk (RR) = 1.71], CVD (ARD = 0.035, NNH = 29, RR = 1.62), and non-CVD mortality (ARD = 0.013, NNH = 77, RR = 2.17).

**Conclusion** In the real-world setting, low statin adherence during the 1st year after an AMI episode is associated with increased mortality during the 2nd year. Our results reaffirm the importance of achieving a high adherence to statin treatment after suffering from an AMI.

**Keywords** AMI • Statin • Effectiveness • Adherence • Inverse probability of treatment weighting • Propensity score

* Corresponding author. Tel: 0046700367154, Email: kani.khalaf@med.lu.se

# Introduction

The efficacy of statins in secondary cardiovascular disease (CVD) prevention has been widely demonstrated in randomized clinical trials (RCTs).[1,2] According to both the Swedish national guidelines[3] and the European Society of Cardiology (ESC) recommendations,[4] all patients suffering from acute myocardial infarction (AMI) should be prescribed statins regardless of their cholesterol level if these drugs are tolerated.

It is known that today the proportion of patients using statins the year after an AMI episode is high but not satisfactory.[3] However, there is less information on the degree of adherence to the treatment and to what extent low adherence is associated with increased later mortality in the real-world setting. In recent observational studies[5–7] on patients with atherosclerotic CVD or AMI,[8–10] low adherence to statins was associated with increased risk of mortality. However, previous studies have not included primary non-adherence in the low-adherence group, which is relevant when investigating the effectiveness of statins.

Suffering from an AMI is a life-threatening event for the patient and the preventive efficacy of statin has been proved in RCTs.[1,2] However, their effectiveness in the real-world setting might be lower than the reported. Therefore, we aimed to answer the question: Is low adherence to statin treatment during the year following an AMI episode associated with increased 2nd-year mortality risk? To do so, we analysed 54 872 AMI patients admitted to Swedish hospitals between 2010 and 2012 and survived at least 1 year after the AMI episode.

# Methods

## Study population

We obtained information about pharmacy dispensing from the Swedish Prescribed Drug Register (SPDR),[11] which records information on all drug dispensations made at Swedish pharmacies, excluding those from hospitals or nursing home storerooms. For each dispensation, there is information on the date of dispensation, the Anatomical Therapeutic Chemical (ATC) code, the prescribed amount of the dispensed medication, and the number of defined daily doses (DDDs). The DDD is a World Health Organization-defined statistical measure of drug consumption. It represents the assumed average maintenance dose required by an adult when the drug is used for its main indication.[12,13]

Using the Swedish unique personal identification number,[14] the SPDR was linked to the Swedish Patient Register,[15] which records all inpatient stays and outpatient visits from hospitals in Sweden as well as to the Cause of Death Register.[16] All diagnoses were coded according to the International Classification of Diseases and Causes of Death, 10th Edition (ICD-10). The National Board of Health and Welfare administers both the SPDR and the Patient Register. Thereafter, the research database was merged with the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) register,[17] which is administrated by Statistics Sweden and combines information from several other registers recording data on demographic and socioeconomic factors as well as on living conditions.

Both the data safety committees of the Swedish authorities and the ethics committee at Lund University (Reference No. 2014/856) approved the construction of the database. To ensure the anonymity of the subjects, the Swedish authorities transformed the official personal identification number into an arbitrary personal code before delivering the research databases to us.

The initial inclusion criteria for the study consisted of patients aged 45 years or older with an AMI (defined as discharge diagnosis code I21) and admitted to Swedish hospitals between 2010 and 2012. This yielded an initial study population of 67 936 patients. We excluded all patients who died during the first 365 days following discharge from hospital ($N = 12\,584$), those residing in Sweden for <5 years prior to the index AMI hospitalization ($N = 434$), those who emigrated from Sweden during the 1st year after discharge from the index AMI hospitalization ($N = 20$), and those who emigrated during the follow-up period ($N = 26$). The final sample consisted of 54 872 AMI patients. In these patients, we observed their dispensation of statins during the first 365 days, to give a long enough period for dispensation and evaluation of adherence,[18] as well as their mortality between the 366th and the 730th days after discharge from the hospital.

## Assessment of variables

### Outcome variable

The outcome variables measured were all-cause mortality, CVD mortality (ICD: 10 codes I00–I99) as underlying or contributing causes of death, and mortality for causes other than CVD (non-CVD).

### Adherence to statin treatment

The statins (ATC codes) prescribed in Sweden during the study period were, Simvastatin (C10AA01), Pravastatin (C10AA03), Fluvastatin (C10AA04), Atorvastatin (C10AA05), Rosuvastatin (C10AA07), and Pitavastatin (C10AA08), and Simvastatin in combination with Ezetimib (C10BA02).

As a measure of statin adherence, we computed a medication possession or medication coverage ratio (MPR) expressing the percentage of days during the year following the AMI episode covered by dispensed statins.[19] First, we calculated the number of DDDs of statins during the 1st year following discharge from hospital. Thereafter, we divided the number of DDDs by 365. We categorize low statin adherence as a coverage ratio <50%,[5] which is a more strict cut-off value for low adherence. Acute myocardial infarction patients without any statin dispensation during the 1st year following the AMI episode (i.e. potentially primary non-adherence) were included in the low-adherence group. For the rest of the article, the term 'adherence' refers to the above definition.

### Demographical and socioeconomic variables

We classified the age of the patients into nine categories using 5-year intervals (45–49, 50–54, and so on) except the last category that included patients 85 years or older. We dichotomized sex as man or woman according to the register.

In order to obtain a stable measure of socioeconomic position, we combined information on household disposable income from three occasions 2010, 2005, and 2000. Thereafter, using tertile values, we divided the study population into high, medium, and low income.

We classified all patients into living alone or cohabiting (i.e. married, registered partnership, unregistered partnership with a common child, or living in a household with at least one other adult).

## Statistical methods

### Propensity score of low statin treatment adherence and inverse probability of treatment weighting

Demographic, socioeconomic, and clinical characteristics may differ between those with high and low adherence to statin treatment. If so, systematic differences between those with low and high adherence may

preclude a direct comparison of outcomes between these two groups.[20] Therefore, to account for possible confounding due to these differences, we computed a propensity score (PS) for low statin treatment adherence.[21]

In a first step, based on a previous publication investigating the utilization and adherence of statins in the Swedish population,[22] we identified a number of previous diagnoses and medications (see *Table 1*) within a period of 5 years prior to the admission date for the index AMI diagnosis. Then, using a logistic regression, we calculated the predicted probability, or, PS of low adherence to statin treatment based on the variables indicated in *Table 1*. Finally, for every patient, we calculated an inverse probability of treatment weighting (IPTW) for low adherence to statin treatment as IPTW = 1/PS for patients with low statin adherence and IPTW = 1/(1-PS) for those with high adherence to statins. Thereafter, we used the IPTW to estimate the average treatment effect of low statin adherence on mortality.

We compared the distribution of the PS between the low- and high-adherence groups (*Figure 1*). We then identified the common support region or the intersection of both density distributions and, thereafter, we excluded five individuals outside this common support region by using the maxima–minima method.[23]

We compared the balance of baseline covariates between the two groups by calculating the standardized mean difference (SMD).[24,25] We did so with and without weighting by IPTW. If the IPTW were effective for balancing the exposure groups, the SMD should be close to zero. As a rule of thumb, the SMD should be lower than 0.1.[24]

### Low statin treatment coverage and mortality risk

The follow-up was short, the mortality registration coverage was complete, and we excluded the few patients who emigrated from Sweden during the follow-up period. Therefore, to investigate the association between low statin adherence and all-cause, CVD, and non-CVD mortality, we directly estimated absolute risk difference (ARD), the relative risk (RR), and the number needed to harm (NNH) as the inverse of the ARD. The NHH indicates how many persons on average need to be exposed to low statin adherence to cause harm (i.e. death) in one person who would not otherwise have been harmed. We used the inbuilt Stata command *teffects ipw* to obtain a robust variance estimation and 95% confidence intervals when performing the IPTW-adjusted analysis.[26,27]

Additionally, we conducted a sensitivity analysis applying a double robust approach (IPTW with regression adjustment).[26,28]

## Results

Overall, 20.2% (11 081/54 872) of the patients had low adherence during the 1st year after the AMI episode, and 8% (4629/54 872) of the patients who survived the 1st year died during the 2nd year. The crude mortality rate in the high- and low-adherence groups was 5.3% (2309/43 791) and 20.9% (2320/11 081), respectively.

*Table 1* shows the means and proportions of the covariates in the low- and high-adherence groups, as well as the SMD before and after IPTW weighting. The large SMDs indicated that before the weighting, there was a considerable imbalance between the two groups. Only diabetes presented a similar prevalence in both groups. However, after the IPTW weighting, we obtained a rather satisfactory balance with very small SMD values (*Figure 1* shows that the density distributions of PS become almost fully overlapped after IPTW weighting). However, the SMD for previous use of statins was 0.14 after IPTW adjustment, which is larger than the 0.1 absolute value considered as a potentially unacceptable level of imbalance.[24] As a sensitivity analysis, and because of this finding, we repeated the analysis after stratification by previous statin use and re-estimated the PS model and the risk differences in the two groups separately.

*Table 2* informs that low adherence was clearly associated with all-cause, CVD, and non-CVD mortality. The unadjusted risk difference for all-cause mortality (ARD= 0.156, 95% CI: 0.149–0.165) was reduced three-fold but remained after IPTW adjustment (ARD = 0.048, 95% CI: 0.041–0.055) with a (RR= 1.71, 95% CI: 1.59–1.83) and a (NNH = 21). The results were similar concerning CVD and non-CVD mortality. However, the risk difference for CVD mortality was larger than the risk difference for non-CVD mortality. The association between low statin adherence and all-cause mortality similarly remained in the sensitivity analysis using the double robust approach.

We also found similar results after stratification by previous use of statins. Low statin adherence was associated with higher ARD and RR of mortality in both those with [ARD = 0.043 (95% CI: 0.32–0.054), NNH = 23.42 (18.56–31.73), RR= 1.51 (1.37–1.65)] and those without previous statin use [ARD = 0.055 (0.046–0.064), NNH = 18.15 (15.69–21.52), RR= 1.99 (1.78–2.22)]. However, the risk difference for mortality was higher in those without previous statin use.

## Discussion

This nation-wide observational study indicates that the preventive effectiveness of statin treatment is in concordance with the efficacy showed in RCT. Low adherence with statin treatment during the 1st year following an AMI episode is associated with increased 2nd-year mortality risk in the real-world setting. Compared with RCTs, observational studies are less suitable to investigate treatment effects and making valid causal inference. However, the investigation of adherence to medication can hardly be done using an RCT.[29] Therefore, our study provides added evidence on the effectiveness of statins. Our results are in line with previous publications.[5,8,9,30–32] However, our study focuses on patients with overt AMI and addresses a specific and relevant clinical question. Our results support the clinician's advice and may motivate the patient to start and maintain a good adherence with the statin treatment.

Overall, adherence to statins after AMI was suboptimal during the study period, with as much as 20% of the study population having an MPR <50%, and only 69% of the patients having an MPR above 80%, which is a widely used cut-off point for good adherence.[33] The rates of low adherence were higher in our study compared with other studies,[5,8] as we included patients with primary non-adherence who did not fill any statin prescription after the AMI episode in the low-adherence group. Rodriguez *et al.*[5] report a 6% rate of low adherers, but these investigators only included patients who filled at least one statin prescription. Similar inclusion criteria have been used in other studies investigating medication adherence and mortality following AMI, where patients have to fill at least one prescription.[8–10] When we excluded patients without statins during the 1st year after AMI in a sensitivity analysis, the prevalence of low adherence (i.e. 7.2%) was in line with previous studies. However, we think our definition of low adherence is more suitable from a clinical perspective, because prescription of statins at discharge from hospital and life-long

**Table 1 Standardized mean differences in baseline variables**

| | Unadjusted | | | IPTW adjusted | | |
|---|---|---|---|---|---|---|
| | Adherence | | SMD | Adherence | | SMD |
| | Low | High | | Low | High | |
| Demographic and socioeconomic characteristics | | | | | | |
| Age (years) | | | | | | |
| 45–49 | 1.3 | 4 | -0.17 | 3.3 | 3.4 | -0.01 |
| 50–54 | 2.2 | 6.7 | -0.22 | 5.9 | 5.8 | 0.01 |
| 55–59 | 2.8 | 9.5 | -0.28 | 8.2 | 8.2 | 0.00 |
| 60–64 | 4.9 | 14 | -0.31 | 12.2 | 12.2 | 0.00 |
| 65–69 | 6.2 | 16.3 | -0.32 | 14.0 | 14.3 | -0.01 |
| 70–74 | 7.6 | 15.2 | -0.24 | 13.9 | 13.8 | 0.00 |
| 75–79 | 10.9 | 14.1 | -0.10 | 14.0 | 13.6 | 0.01 |
| 80–84 | 19.6 | 12.4 | 0.20 | 13.9 | 13.9 | 0.00 |
| ≥85 | 44.4 | 7.9 | 0.91 | 14.7 | 14.9 | -0.01 |
| Women | 56.6 | 32.5 | 0.50 | 37.7 | 37.2 | 0.01 |
| Income | | | | | | |
| Low | 39.6 | 25.3 | 0.31 | 29.2 | 28.1 | 0.03 |
| Middle | 38.9 | 36.9 | 0.04 | 37.5 | 37.3 | 0.00 |
| High | 21.5 | 37.8 | -0.36 | 33.3 | 34.6 | -0.03 |
| Living alone | 63.9 | 42.2 | 0.45 | 47.0 | 46.4 | 0.01 |
| Diabetes, cardiovascular, and urinary system diseases (ICD-10 code) | | | | | | |
| Diabetes (E10–E13) | 17.5 | 15.6 | 0.05 | 18.0 | 16.2 | 0.05 |
| Transient cerebral ischaemic (G45 and G46) | 4.1 | 2.5 | 0.09 | 3.1 | 2.8 | 0.02 |
| Cerebrovascular diseases (I60–I69) | 12.7 | 7.3 | 0.18 | 9.1 | 8.4 | 0.02 |
| Hypertensive diseases (I10–I15) | 44.8 | 32.6 | 0.25 | 37.3 | 35.2 | 0.04 |
| Previous myocardial infarction (I21) | 11.5 | 8.3 | 0.11 | 10.9 | 9.0 | 0.06 |
| Ischemic heart diseases (I20–I25) | 34.5 | 27.4 | 0.16 | 32 | 28.9 | 0.07 |
| Other forms of heart disease (I30–I52) | 36 | 18.2 | 0.41 | 22.3 | 21.8 | 0.01 |
| Arteriosclerosis/aorta aneurysm (I70–I71) | 6.2 | 4.7 | 0.07 | 6.4 | 5.1 | 0.06 |
| Peripheral arterial disease (I73.9) | 2.5 | 2.3 | 0.01 | 2.8 | 2.4 | 0.02 |
| Arterial embolism (I74) | 0.6 | 0.4 | 0.03 | 0.6 | 0.5 | 0.02 |
| Vascular disorders of the intestine (K55) | 0.4 | 0.2 | 0.03 | 0.3 | 0.2 | 0.00 |
| Glomerular diseases (N00–N08) | 0.9 | 0.7 | 0.02 | 0.7 | 0.7 | -0.01 |
| Renal tubulo-interstitial diseases (N10–N16) | 2.8 | 1.4 | 0.09 | 1.8 | 1.8 | 0.00 |
| Acute kidney failure and CKD (N17–N19) | 6.9 | 3.3 | 0.16 | 4.2 | 4.0 | 0.01 |
| Mental diseases (ICD-10 code) | | | | | | |
| Related to psychoactive drug use (F10–F19) | 3.2 | 3.3 | 0.00 | 3.7 | 3.3 | 0.02 |
| Schizophrenia and related disorders (F20–F29) | 0.9 | 0.5 | 0.05 | 0.5 | 0.6 | -0.01 |
| Mood disorders (F30–F39) | 4.7 | 3.1 | 0.09 | 3.4 | 3.4 | 0.00 |
| Neurotic and related disorders (F40–F48) | 3.8 | 2.9 | 0.05 | 3.3 | 3.1 | 0.01 |
| Other diseases (ICD-10 code) | | | | | | |
| Cancer (C1–C97) | 16.1 | 11.4 | 0.14 | 12.8 | 12.5 | 0.01 |
| Respiratory diseases (J) | 26.6 | 15.9 | 0.27 | 18.8 | 18.2 | 0.02 |
| Cardiovascular medication (ATC code) | | | | | | |
| Previous statins (C010AA 01. 03. 04. 05. 07 and C10BA02) | 34.5 | 47.8 | -0.27 | 52.7 | 46.0 | 0.14 |
| Diabetes medication (A10) | 18.7 | 19.1 | -0.01 | 20.8 | 19.2 | 0.04 |
| Platelet aggregation inhibitors (B01AC04. 05. 07. 30) | 17.5 | 16 | 0.04 | 19.6 | 16.5 | 0.08 |
| Cardiac therapy (C01) | 46.2 | 33.3 | 0.27 | 38.6 | 35.8 | 0.06 |
| Antihypertensives (C02) | 2.4 | 2.2 | 0.01 | 2.4 | 2.2 | 0.01 |
| Low and high ceiling diuretics (C03A–C) | 59.1 | 35.5 | 0.49 | 40.4 | 40.1 | 0.01 |
| Peripheral vasodilators (C04) | 0.2 | 0.1 | 0.03 | 0.1 | 0.1 | 0.00 |
| Vasoprotectives (C05) | 10.1 | 7.1 | 0.11 | 8.1 | 7.7 | 0.01 |

*Continued*

**Table I** *Continued*

| | Unadjusted | | | IPTW adjusted | | |
|---|---|---|---|---|---|---|
| | Adherence | | SMD | Adherence | | SMD |
| | Low | High | | Low | High | |
| Beta blocking agents (C07) | 60.3 | 48.9 | 0.23 | 53.9 | 51.3 | 0.05 |
| Calcium channel blockers (C08) | 38.2 | 32.3 | 0.12 | 36 | 33.7 | 0.05 |
| Agents on the renin-angiotensin system (C09) | 55.4 | 49.3 | 0.12 | 53.3 | 50.7 | 0.05 |
| Psychotropics and analgesics (ATC code) | | | | | | |
| Psychoanaleptics (N06) | 31.2 | 19.6 | 0.27 | 21.5 | 21.9 | -0.01 |
| Neuroleptics (N05) | 55.3 | 34.4 | 0.43 | 38.7 | 38.5 | 0.01 |
| Analgesics (N02) | 69.4 | 52.8 | 0.35 | 55.7 | 56.0 | -0.01 |

Mean values/proportions and standardized mean differences (SMD) between patients with low vs. high adherence to statin treatment in relation to the baseline variables used to obtain the propensity score (PS) for low adherence to statin treatment. The results are presented unadjusted and adjusted by inverse probability of treatment weighting (IPTW). Values are percentages if not otherwise indicated. SMD are expressed as standard deviation units.

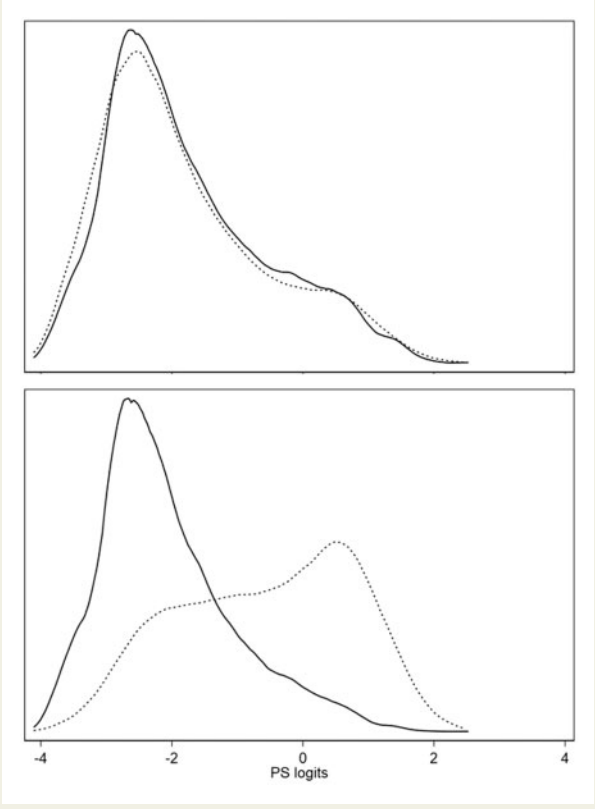


**Figure 1** Density distribution of the estimated propensity score (PS) for low statin adherence during the 1st year after acute myocardial infarction in patient with low (dashed line) and high (solid line) adherence, after (top figure) and before (bottom figure) adjustment for inverse probability of treatment weighting.

maintenance of statin treatment subsequent is recommended for all AMI patients younger than 80 years, when statins are tolerated and in absence of severe side effects that are associated with statins. This process indicator is fundamental for the evaluation of the quality of AMI care in Sweden with a target level of 90% according to the latest guidelines.[3,34] We did not have information on side effects[35] but in any case, patients who were unable to use statins because of justified medical reasons were not exposed to the potential protective effect of statin. From a clinical perspective, eventual side effects need to be evaluated in relation to the benefits of statins in this patient group, so relatively mild or presumed side effects should not prevent statin treatment.

When performing a sensitivity analysis excluding patients without any statin during the 1st year (primary non-adherers) after AMI episode, the association between low adherence and mortality during the 2nd year remained but was smaller (ARD = 0.023, NNH = 43.98, RR = 1.40) compared with the primary analysis. The sensitivity analysis suggests that any use of statins is associated with decreased mortality risk. However, the risk difference decreases as adherence increases.

When constructing the PS model, we aimed to cover the five dimensions of medication adherence according to the World Health Organization, i.e. socioeconomic factors, condition-related factors, patient-related factors, therapy-related factors, and healthcare system factors.[36] Among predictors of adherence, we found that female sex and living alone were associated with low adherence to statins. This is in line with the studies by both Rasmussen *et al.*[8] and Rodriguez *et al.*,[5] who found female sex being associated with lower adherence. Affordability of statin therapy should not affect adherence, as most of the prescribed medications are reimbursed with an annual Swedish co-payment ceiling of SEK 1800 (~EUR 180) by 2011 and the relatively low cost of statins. Despite this, we observed an income gradient with increased odds of low adherence as income decreases.

Adherence to statin treatment could be related to other behaviours and medical conditions (e.g. disease severity) that might confound the association between low statin adherence and mortality.[37] However, other studies have investigated this question more thoroughly and concluded that the association is dependent on the pharmacological effect.[5,8,30] To control for confounding, we used IPTW and stratified the analysis for previous use of statins in a sensitivity analysis. However, since our study is observational, part of the observed effect of statin adherence on mortality after AMI might be

**Table 2 Average treatment effect of low statin adherence**

| | ARD | NNH | RR | Mortality rate % (cases/patients) | |
|---|---|---|---|---|---|
| | | | | High adherence | Low adherence |
| All-cause mortality | | | | | |
| Unadjusted | 0.156 (0.149–0.165) | 6.4 (6.1–6.7) | 3.97 (3.76–4.19) | 5.3 (2309/43 791) | 20.9 (2320/11 081) |
| IPTW adjusted | 0.048 (0.041–0.055) | 20.9 (18.2–24.4) | 1.71 (1.59–1.83) | | |
| Specific causes of mortality | | | | | |
| Unadjusted | | | | | |
| CVD | 0.131 (0.124–0.139) | 7.6 (7.2–8.1) | 4.04 (3.80–4.29) | 4.3 (1893/43 791) | 17.5 (1935/11 081) |
| Non-CVD | 0.025 (0.022–0.029) | 39.5 (34.7–46.1) | 3.66 (3.19–4.20) | 0.9 (416/43 791) | 3.5 (385/11 081) |
| IPTW adjusted | | | | | |
| CVD | 0.035 (0.029–0.041) | 28.6 (24.3–34.7) | 1.62 (1.50–1.75) | | |
| Non-CVD | 0.013 (0.009–0.017) | 77.3 (60.5–106.9) | 2.17 (1.82–2.59) | | |

Average effect of low statin adherence during the year following an AMI episode on all-cause, cardiovascular disease (CVD), and non-CVD mortality, the 2nd year after the AMI episode in 54 867 patients. Values are absolute risk difference (ARD), number needed to harm (NNH), relative risk (RR), and 95% confidence interval (CI) unadjusted and adjusted by inverse probability of treatment weighting (IPTW).

due to the healthy-adherer effect.[38] Furthermore, we cannot exclude the existence of confounding by indication (i.e. patients with a higher mortality risk may be more adherent just because they have a higher risk). If this is true, our results may underestimate the protective effects of statins.

A further limitation of this study is the lack of detailed clinical information including data on AMI types, laboratory parameters, and information on adverse effects of statin therapy that may act as confounders. Another limitation is that we rely on dispensation coverage as a proxy for actual adherence. However, we do not think that this issue affects our results to a fundamental extent.

While we excluded patients residing in Sweden <5 years because of missing register information, we believe that our result is generalizable to this patient group. Moreover, when excluding patients younger than 45 years, we lose patients with familial hypercholesterolaemia; however, this group has a different physiopathology and a higher cardiac risk even when treated with lipid-lowering drugs.[39,40]

Our study found that low adherence to statin treatment the year following an AMI episode is associated with increased later mortality risk in the real-world setting. Our findings support the importance of using and achieving a high adherence to statin treatment after suffering from an AMI.

## Funding

This study was supported by grants from the Swedish Research Council (Vetenskapsrådet) to Prof. Dr J.M. [2013-2484 and 2017-01321]. Dr P.C.A. was supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation. The sponsors did not influence the study.

**Conflict of interest:** none declared.

## References

1. Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson P. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 2014;**129**:S1–S45.
2. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte Op Reimer WJM, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
3. Socialstyrelsen. Nationella riktlinjer – Utvärdering 2015 – Hjärtsjukvård – Rekommendationer, bedömningar och sammanfattning. Socialstyrelsen; 2015. Report No.: 2015-12-5.
4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
5. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiology* 2019;**4**:206–213.
6. Alsabbagh MW, Eurich D, Lix LM, Wilson TW, Blackburn DF. Does the association between adherence to statin medications and mortality depend on measurement approach? A retrospective cohort study. *BMC Med Res Methodol* 2017;**17**:66.
7. Shin S, Jang S, Lee TJ, Kim H. Association between non-adherence to statin and hospitalization for cardiovascular disease and all-cause mortality in a national cohort. *Int J Clin Pharmacol Ther* 2014;**52**:948–956.
8. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;**297**:177–186.
9. Tuppin P, Neumann A, Danchin N, de Peretti C, Weill A, Ricordeau P, Allemand H. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. *Arch Cardiovasc Dis* 2010;**103**:363–375.
10. Hickson RP, Robinson JG, Annis IE, Killeya-Jones LA, Fang G. It's not too late to improve statin adherence: association between changes in statin adherence from before to after acute myocardial infarction and all-cause mortality. *J Am Heart Assoc* 2019;**8**:e011378.
11. Wettermark B, Hammar N, MichaelFored C, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**:726–735.

12. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2013. http://www.whocc.no/atc_ddd_index/ (26 February 2020).
13. Merlo J, Wessling A, Melander A. Comparison of dose standard units for drug utilisation studies. *Eur J Clin Pharmacol* 1996;**50**:27–30.
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–667.
15. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
16. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R. The Swedish cause of death register. *Eur J Epidemiol* 2017;**32**:765–773.
17. Statistics Sweden. Longitudinal integrated database for health insurance and labour market studies (LISA) SCB. 2018. https://www.scb.se/en/services/guidance-for-researchers-and-universities/vilka-mikrodata-finns/longitudinella-register/longitudinal-integrated-database-for-health-insurance-and-labour-market-studies-lisa/ (26 February 2020).
18. Johnson ES, Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. *Am J Manag Care* 2002;**8**(Suppl):S249–S254.
19. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int* 2015;**2015**:1–12.
20. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;**168**:656–664.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;**46**:399–424.
22. Anveden-Berglindm I, Kieler H, Linder M, Sundström A, Wettermark B, Citarella A, Andersen M. *Värdet av statiner – användningsmönster och följsamhet vid behandling: Rapport från SNS forskningsprogram Värdet av nya läkemedel. Stockholm: SNS;* 2013.
23. Caliendo M, Kopeinig S. *Some Practical Guidance for the Implementation of Propensity Score Matching.* Bonn: IZA; 2005.
24. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;**38**:1228–1234.
25. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;**34**:3661–3679.
26. StataCorp. *Treatment-Effects Reference Manual: Potential Outcomes/Counterfactual Outcomes.* Texas: Stata Press; 2019.
27. Williamson EJ, Forbes A, White IR. Variance reduction in randomised trials by inverse probability weighting using the propensity score. *Stat Med* 2014;**33**:721–737.
28. Słoczyński T, Wooldridge JM. A general double robustness result for estimating average treatment effects. *Econom Theory* 2018;**34**:112–133.
29. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;**312**:1215–1218.
30. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol* 2014;**78**:684–698.
31. McGinnis BD, Olson KL, Delate TM, Stolcpart RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. *Am J Manag Care* 2009;**15**:689–695.
32. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart* 2002;**88**:229–233.
33. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;**25**:2303–2310.
34. Regions NBoHaWatSAoLAa. Open comparisons of health care quality and effectiveness. Comparisons between county councils in (Öppna jämförelser av hälso- och sjukvårdens kvalitet och effektivitet. Jämförelser mellan landsting). Sveriges Kommuner och Landsting wwwsklse/publikationer. 2010.
35. Ward NC, Watts GF, Eckel RH. Statin toxicity. *Circ Res* 2019;**124**:328–350.
36. World Health Organization. Adherence to *Long-Term* Therapies: Evidence for Action. *Geneva: World Health Organization*; 2003.
37. Ladova K, Vlcek J, Vytrisalova M, Maly J. Healthy adherer effect—the pitfall in the interpretation of the effect of medication adherence on health outcomes. *J Eval Clin Pract* 2014;**20**:111–116.
38. Lavikainen P, Helin-Salmivaara A, Eerola M, Fang G, Hartikainen J, Huupponen R, Korhonen MJ. Statin adherence and risk of acute cardiovascular events among women: a cohort study accounting for time-dependent confounding affected by previous adherence. *BMJ Open* 2016;**6**:e011306.
39. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan J-K, Veierød MB, Leren TP, Retterstøl K. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. *J Am Heart Assoc* 2014;**3**:e001236.
40. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc* 2019;**8**:e013225.